Treatment of Multi resistant Gram-negative Infection: Report of a Working Party of the British Society of Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party

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Table of Contents

Executive Summary

Infections due to multi-drug-resistant (MDR) Gram-negative bacteria (GNB) have become prevalent in many countries. Moreover, increased use of broad-spectrum agents selects organisms with resistance and, by increasing their numbers, also increases their chance of spread. This Report describes best practice for the UK in antimicrobial prescribing in treatment of infections caused by these organisms. Methods for systematic review 1946-2014 were in accordance with the SIGN 50 Handbook (Scottish Intercollegiate Guidelines Network and the Cochrane Collaboration)[1]; critical appraisal was applied using AGREE II [2]. Accepted guidelines were used as part of the evidence base and to support expert consensus. Questions for review were derived from the Working Party Group, which included patient representatives, in accordance with Patient Intervention Comparison Outcome. Recommendations for specific organisms are given where there are species differences.

Lay Summary

Multi-drug resistant (MDR) Gram-negative bacteria (GNB) are bacteria (or germs) that remain susceptible to only one or two antibiotics. Gram-negative bacteria usually live in the gut (or in the environment), where they do no harm, but can appear and cause infection at other body sites that normally lack any bacteria, for example in the bladder or blood. This especially occurs in patients who are made vulnerable by underlying disease, injury or hospitalization.. MDR GNB may be acquired from other patients who have received antibiotics. Infections caused by MDR GNB are difficult to treat and so may cause more prolonged symptoms in the site of infection and can cause additional complications such as pneumonia or infection in the blood. This can prolong the length of stay in hospital, and in some cases, can cause death. Some types of MDR GNB e.g. *Acinetobacter spp.* can be carried on the skin rather than the gut, again with no obvious signs or symptoms. 'Colonization' describes carriage of bacteria on body surfaces or in the gut without infection. When patients develop infection and require antibiotic treatment, selecting the correct antibiotic can be difficult. This report provides advice on the best choice of antibiotics currently available.

1 Introduction

This guidance has been prepared by a jointWorking Party of the British Society for Antimicrobial Chemotherapy, the Healthcare Infection Society and the British Infection

Association to advise on the treatment of infections caused by MDR GNB. It also describes best practice in antimicrobial prescribing. There is an accompanying guideline describing appropriate infection prevention and control precautions, including hand hygiene, equipment and environmental cleaning and guidance on screening for MDR GNB [3]. The infection control and prevention guideline should be used in conjunction with the present document. There is a glossary for technical terms (See Appendix 1).

The Working Party comprised a group of medical microbiologists and scientists, infectious disease physicians, infection control practitioners, epidemiologists, and patient representatives nominated by the Societies. The patient representatives were lay members and had direct experience of the treatment of healthcare-associated infections through personal experience, membership of SURF (Healthcare-acquired Infection Service Users Research Forum), patient charities or through involvement in the development of NICE guidelines. The representatives were:

Susan Bennett, Member of Health Care Acquired Infections, Service Users Research Forum, Leicester, UK

Jennifer Bostock, Member of Health Care Acquired Infections, Service Users Research Forum, Leicester, UK

Maria Cann, Trustee, MRSA Action, Kirkham, UK

They were involved in the preparation of the remit of the Working Party remit (Appendix 3), were invited to all meetings, invited to comment on the final draft prepared by the authors and endorsed the final version.

2 Guideline Development Team

4.1 Guideline Advisory Group

Phil Wiffen, Cochrane Pain, Palliative and Supportive Care Group Pain Research, Churchill Hospital Oxford, Nuffield Dept. of Clinical Neurosciences, Oxford.

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4.2. Responsibility for Guidelines

The views expressed in this publication are those of the authors and have been endorsed by the three sponsoring societies following consultation. Patient representatives confirmed the guidelines addressed the questions raised in setting the Working Party's remit.

3 The Working Party report

Date of publication: TBC 2017 (Published online TBC)[CD1]

1.1 What is The Working Party report?

This Report is a set of recommendations covering the treatment of infections caused by MDR GNB (i.e. susceptible to only to one or two different antibiotics). Strains internationally defined as MDR GNB by possession of resistance to 3 or more classes of antibiotics can nevertheless be treated with a wide range of antibiotics so we argue the case for a re-definition below (See Section 6.2.).

The Working Party recommendations have been developed systematically through a multi-professional group based on published evidence. They should be used in the to develop local protocols for acute and long-term healthcare settings.

3.1 Why do we need a Working Party Report for these infections?

MDR GNB have become more prevalent internationally, including in the UK and Europe. The increased use of broad-spectrum agents encourages their proliferation[4] . The spread of these bacteria causes infections that can increase the length of hospital stay and adversely affect the quality of life of patients. Public awareness has been increasing, and the relative lack of new antimicrobial agents to treat infections due to Gram-negative bacteria has resulted in the formulation of the five-year Antimicrobial

Resistance Strategy by the UK Department of Health [5]. Outbreaks are associated with considerable, physical, psychological and financial costs. Evidence-based treatment regimens . are effective in improving the outcome of infections due to these bacteria.

3.2 What is the purpose of the Report's recommendations?

The Report describes appropriate antimicrobial chemotherapy for infections due to MDR Gram –negative bacteria.

3.3 What is the scope of these guidelines?

We examine the background information on the mechanisms, global spread, and the UK prevalence of resistance, prescribing, and then discuss treatment i) in hospitals using antibiotics intravenously and ii) in primary care using agents given orally, ending with a consideration of antibiotic stewardship. Data (and doses, where given) usually refer to adults as there are few data for children and neonates. Extrapolation from adult data for β-lactams seems reasonably secure but this is not necessarily the case for other agents. Another set of guidelines considers appropriate infection control principles, best practice hand hygiene, screening and environmental cleaning[3] . For the detailed scope for this guideline see Appendix 2.5 and for the review questions see Appendix 3.7

3.4 What is the evidence for these guidelines?

In the preparation of these recommendations, systematic reviews were performed of peer-reviewed research using the searches show in Appendix 4. Expert opinion was also derived from published guidelines subjected to validated appraisal[2]. Evidence was assessed for methodological quality and clinical applicability according to protocols of the Scottish Intercollegiate Guidelines Network (SIGN) initially using SIGN2011[1] guidelines and then updating this as the working party continued to comply with the SIGN 2014 guidance[6].

3.5 Who developed these guidelines?

A group of medical microbiologists, scientists, infectious disease physicians, infection control practitioners, epidemiologists, and patient representatives.

3.6 Who are these guidelines for?

Any hospital or general practitioner can use these guidelines and adapt them for local use. Expected users include clinical medical, nursing, antimicrobial pharmacy and paramedical staff. Paediatric licenses and formulation may limit the suitability of some of the discussed agents for children and neonates. . Where there are specific issues relating to dosage, outcome or toxicity that are outside current license information, these are discussed. The guidelines should be used to improve the treatment of both presumptive and confirmed cases of infection by MDR GNB.

3.7 How are the guidelines structured?

Most areas (defined by questions) comprise an introduction, a summary of the evidence base with levels and a recommendation graded according to the available evidence. The guidelines are not organised by clinical indication.

3.8 How frequently are the guidelines reviewed and updated?

The guidelines will be reviewed and updated every 4 years if warranted by sufficient changes in the evidence or by the availability of new agents or formulations.

3.9 Aim

The primary aim of the review was to assess the current evidence for antimicrobial prescribing in the treatment of MDR Gram-negative infections. The secondary aims were: (a) to evaluate the efficacy of antibiotics to treat community, and hospital infections caused by MDR GNB (b) to evaluate the impact of educating and providing support to professionals and patients to reduce unnecessary use of antibiotics leading to a reduction in the selective pressure for resistance, thereby assisting antibiotic stewardship.

4 Summary of Guidelines

The guidance has been derived from current best peer-reviewed publications and expert opinion. Each recommendation is graded according to standard grades [1] and is associated with a class of supporting evidence, or it is presented as a Good Practice Point. General recommendations for stakeholders, including prescribers are made in Table 1. Specific antibiotic recommendations are made in Table 2.

4.1 How can the guidelines be used to improve clinical effectiveness?

The Guidelines can be used to direct and formulate antibiotic policies. They provide a framework for clinical audit tools for quality improvement.

4.2 How much will implementation of the guidelines cost?

The majority of antimicrobial agents that are described in these guidelines are generic and are currently widely used. Newer β-lactam/β-lactamase inhibitors (BL/BLI) are more expensive than older BL/BLIs and most alternatives to carbapenems against MDR GNB are also more expensive. Extra financial support will be required for the surveillance of outcomes of bacteraemia. Implementation of these guidelines should enable better-focused therapy, with no increase in drug utilization and possibly a modest decrease.

4.3 Summary of suggested audit measures

Patients with infections with MDR GNB, should receive empirical (best guess) or definitive (i.e. after results of laboratory tests) appropriate antibiotic treatment (alone or in combination) and the former should be active in at least 80% of cases. It is important to note that the basis on which resistance was defined was changed by EUCAST from predicting failed clinical response to deviation from the normal susceptibility of the species. In an era of multiple resistance, continuing to select for such resistant strains even when the patient has clinically responded to apparently

resistant isolates is undesirable. Control groups with infections at the same site and caused by the same species, but not MDR, or infections without known aetiology should not receive definitive treatment reserved for patients with MDR GNB. This audit should be conducted first for bacteraemias.

Reducing total antibiotic consumption, in defined daily doses.

Quarterly use of carbapenems and piperacillin/tazobactam should be reduced if either is in the top quintile/1000 patient days as assessed in each quarter. Specialist and tertiary care units may have special needs and should be excluded from the quintile assessment. Reductions of use in such units should be undertaken but should be tailored by consideration of their speciality case mix. .

Trimethoprim use should be reduced and nitrofurantoin use increased in primary care.

Risk assessment tools for colonization and infection with MDR GNB in patients should be developed for the UK and put in place in all settings. Only infected patients known to be, or at risk of being (by these assessments), colonized with these bacteria should receive empirical treatment with drugs reserved for MDR GNB.

No antibiotic prescriptions for treating the elderly with asymptomatic bacteriuria (ASB),or urinary tract infection (UTI) in the presence of a urinary catheter unless bacteraemia or renal infection suspected.

No antibiotic prophylaxis for urinary catheter insertion or change unless previous history of symptomatic urinary infection (UTI) associated with a change of catheter or if there is trauma during catheter insertion.

Gram-negative bacteraemia incidence should be decreased and outcome should be improved both in cases which developed in primary care, wider healthcare settings, and secondary and tertiary units.

Enhancements to surveillance should be planned and supported by information technology (IT) that allows record linkage and simplification of surveillance from the laboratory to national level.

4.4 How can the guidelines be used to improve clinical effectiveness?

The Guidelines can be used to direct and formulate antibiotic policies and to aid the prescribing practice of infection specialists and other clinicians. They provide a framework for clinical audit tools for quality improvement.

4.5 E-learning tools

Continuing Professional Development questions and model answers are listed for self-assessment in Appendix 5.

5 Methodology

5.1 Evidence appraisal

Methods were in accordance with SIGN 50 and Cochrane Collaboration criteria [1, 7] and critical appraisal was applied using AGREEII[2] Accepted guidelines were used as part of the evidence base and to support expert consensus. Questions for review (See Appendix 3.7.) were derived from the Working Party Group which included patient representatives in accordance with Patient Intervention Comparison Outcome (PICO)[6]

K Soares-Wiesner of Enhance Reviews Ltd. and Dr P Wiffen of Pain Research and Nuffield Department of Clinical Neurosciences, Oxford University used a systematic review process. Guidelines and research studies were identified for each search question. Systematic reviews, randomized controlled trials (RCT) and observational

studies were included. The latter comprised cohort non-RCT, controlled before -and after -studies, and interrupted time series. All languages were searched. Search strategies for each area are given in the sections below and in Appendix 4. MeSH headings and free text terms were used in the Cochrane Library (Issue 11 2012), Medline (1946-2012), Embase (1980-2012) and Cumulated Index of Nursing and Allied Health Literature (CINAHL) (1984-2012). On 23rd May 2014, an update search was conducted on Medline alone using the same strategy for references after 1st January 2013. Reference lists of included studies were searched. Additional references were added in octpber 2016 and June 2017 to cover specific issues. Two review authors independently screened all citations and abstracts identified, and screened full reports of potentially eligible studies (those that addressed the review questions in primary or systematic secondary research or a clinical, *in vitro*, or in use study). Disagreements were resolved by discussion, and rationales for exclusion of studies were documented. Pre-tested data extraction forms were used, and study characteristics and results collected. Data were extracted from observational studies for multiple effect estimates: these included the number of cases analyzed, adjusted and unadjusted effect estimates, with standard error or 95% confidence interval (CI), confounding variables and methods used to adjust the analysis. If available, data were extracted from contingency tables. Risk of bias was assessed using SIGN critical appraisal checklists. Interrupted time series were assessed using the Cochrane Effective Practice and Organisation of Care (EPOC) Group[6, 8]. Quality was judged by report of details of protection against secular changes (intervention independent of other changes) and detection bias (blinded assessment of primary outcomes and completeness of data). For outbreak patterns associated with particular pathogens, the Working Party made additional searches of descriptive studies to extract effective treatments for infections caused by bacteria with specific resistance.

5.2 Data analysis and interpretation

Clinical outcomes were mortality, effectiveness of treatment, and length of hospital stay. Microbial outcome measures were decreases in the prevalence of MDR GNB, or decreases in colonization or infection by specific GNB. Risk ratios (RR) were used for dichotomous variables, and mean differences with 95% CI were used for continuous variables[9].Analyses were performed in Revman 5.22 [10]. SIGN summary tables were used. Evidence tables and judgment reports were presented and discussed by the Working Party and the guidelines were prepared according to the nature and applicability of the evidence, patient preference and acceptability and likely costs. The level of evidence was as defined by SIGN (Table 3), and the strength of recommendation was based upon GRADE (Grading of Recommendations Assessment, Development and Evaluation) (Table 4) [11]. The grading relates to the strength of the supporting evidence and predictive power of the study designs, rather than the importance of the recommendation. Any disagreements between members were resolved by discussion. For some areas and recommendations, only expert opinion is available; in such cases, a good practice recommendation has been made. A flow chart of the systematic review process is given in Figure 1.

5.3 Consultation process

These guidelines were opened to consultation with circulation to the stakeholders listed (See Appendix 6). The draft report was placed on the BSAC website for one month in June 2016 for open consultation. Views were invited on format, content, local applicability, patient acceptability and recommendations. The Working Party considered and collated comments, and agreed revisions

6 Rationale for recommendations

6.1 Usage

It is beyond the scope of this guideline to define optimal quantitative usage of antibiotics by hospital beds or community populations and the UK is not an exceptionally high user in international terms. Equally measures to reduce antibiotic usage will depend on what apparent over usage is occurring in any community or hospital department. For this reason, the assessment of reduction measures whilst based on comparative epidemiology must also consider both clinical outcome measures and usage at the local level. Suggestions for reducing overall usage must therefore be largely implemented at the local level where risk to patients and benefit can be adequately assessed and lie beyond the practical scope of this guideline.

6.2 What is the Definition of Multidrug-resistant Gram-negative bacteria?

Multidrug resistant (MDR) is a vexed term. From 1980 it was used to mean, 'resistant to multiple agents' without the number or types of agents being specified. More recently the European Centre for Disease Prevention and Control (ECDC) has attempted to formalise the term as 'resistant to three or more antibiotic classes' whilst extremely drug resistant (XDR) is 'susceptible only to one or two drug classes. These definitions, based on those for tuberculosis, are epidemiologically attractive, but run into the sands of practicality. An international consensus is difficult to achieve, as not all products are .available and tested by laboratories in all countries and there is no universal testing policy for laboratories which make pragmatic decisions on what to test. Some antibiotic resistances are now very common and stable e.g. to ampicillin and sulphonamides so they are seldom tested, but if they are present the organism needs only one further resistance to count as MDR GNB by the "3 classes of resistance" rule. There also is scope for disagreement on which antibiotics should be considered as separate classes, for

example, monobactams behave similarly to oxyimino cephalosporins in respect of most resistance mechanisms but very differently in the case of metallo-B-lactamases (MBL).

Difficulties arise also if *in vitro* "susceptibility" is poorly defined e.g. with the absence of EUCAST breakpoints as, for example, for i) *Acinetobacter spp.* and sulbactam, and ii) for temocillin. Furthermore differences between European (EUCAST) and US (CLSI or FDA) breakpoints can affect fundamentally whether isolates are regarded as MDR or XDR and recruitment to, and results in, clinical trials. Separate breakpoints for urinary isolates although needed to take account of high urinary concentrations with some antibiotics also complicate assessments. Lack of laboratory uniformity in breakpoints can make comparisons and data aggregation meaningless. For example, EUCAST and CLSI breakpoints differ for piperacillin/tazobactam and amoxicillin/clavulanate. EUCAST defines Enterobacteriaceae isolates as piperacillin/tazobactam susceptible if they have an MIC<=8mg/L (R>16mg/L) compared with <=16+4mg/L (R>=128+4 mg/L) in CLSI guidance. For amoxicillin/clavulanate susceptibility is defined by EUCAST as <=8+2mg/L (R>8mg/L (or 32+2mg/L for uncomplicated UTI) and by CLSI as <=8+4mg/L (R>=32+16mg/L) The FDA regard *Pseudomonas aeruginosa* isolates as susceptible to piperacillin/tazobactam if the MIC is <=64mg/L (the historical CLSI breakpoint for piperacillin) whereas EUCAST and CLSI now consider the breakpoint should be S<=16+4mg/L . The EUCAST and CLSI definitions have changed with time and from previous national guidelines e.g. the pre-EUCAST BSAC breakpoint for amoxicillin/clavulanate in systemic infections was 8+4mg/L Cefepime is a further example of an antibiotic with breakpoint changes: the old CLSI breakpoint for Enterobacteriaceae was =<8mg/L but is now =<2mg/L based on 1g.twice dailydoses. Organisms with MICs of 4or 8mg/L are viewed as being "susceptible but dose-dependent" by CLSI. EUCAST categorises an MIC =<1mg/L as susceptible and >4mg/L as resistant. A failure rate of 83% in a prospective trial of cephalosporins for "susceptible"

serious infections due to ESBL-producing *Klebsiella spp*. and *E. coli* partly reflected the use of high breakpoints [12]. Breakpoint differences and changes over time in the categorization of isolates with the same MIC as "susceptible" or "resistant" profoundly challenge conclusions in the clinical literature, including reports of regulatory trials on the response to be expected of infections due to "susceptible" or "resistant" strain or indeed which patients have been included in trials where susceptibility of the organism is a selection criterion.

For all these reasons, the international definitions have not lead to better surveillance of MDR strains and their usefulness must still be questioned. In our literature search routines, we have employed the international definitions but have had to augment these with literature on specific resistances. A useful pragmatic approach to the definition of MDR is to consider oral and parenteral drugs separately as, in the UK, these will be largely used in primary, and secondary with tertiary, care respectively, with multi resistance constituting different challenges in each setting. Furthermore, one should base definitions on susceptibility rather than resistance as the former is more likely to be sought clinically by further testing with MDR strains. This gives a basis for alternative definitions for MDR which we would advocate. For oral drugs, multi-resistance can usefully be defined as an organism susceptible to only one or no readily available oral agent active against infections systemically or in the upper urinary tract. This definition is vulnerable to the introduction of new, or newly re-licensed, oral agents, but this is appropriate and may emphasise the importance of new agents to the licensing authorities. By this definition the following would be classed as multi-resistant isolates for the community:

i) Escherichia coli resistant to co-amoxiclav[RE2], oral cephalosporins, quinolones, trimethoprim but susceptible to nitrofurantoin, mecillinam and fosfomycin. Although providing options in cystitis these oral agents lack evidence of achieving systemically

active concentrations and efficacy in upper and complicated UTIs, which is particularly relevant if these are caused by ESBL- and AmpC-producing strains *ii)P. aeruginosa* resistant to quinolones.This approach could be modified to exclude agents where the mutation frequency is sufficiently high so that resistance commonly emerges during treatment.

For parenteral antibiotics a similar approach can be considered. Susceptibility to oral agents that have no licensed, or available, parenteral form e.g. pivmecillinam and nitrofurantoin should not be taken into account. Specific agents to which impaired susceptibility might be significant include carbapenems, relevant cephalosporins (cefotaxime for Enterobacteriaceae, ceftazidime for *P. aeruginosa*), aztreonam, ceftolozane/tazobactam, ceftazidime/avibactam , temocillin, piperacillin/tazobactam, colistin, quinolones, fosfomycin, tigecycline and aminoglycosides (including amikacin). Given this greater number of agents and the paucity of new pipeline antibiotics active against Gram-negative bacteria, it is pragmatic to consider 'multi-resistant' as isolates where only two, or fewer, unrelated antibiotics are active against the bacterium. By such a definition the following would be considered multi-resistant isolates in hospitals.

i) *Acinetobacter baumannii* susceptible to two or fewer of meropenem or imipenem, (third generation cephalosporins), piperacillin/tazobactam, (tigecycline), aminoglycosides, quinolones, (trimethoprim), colistin. Bracketed agents lack EUCAST breakpoints,
ii) *Klebsiella spp., Enterobacter spp*., *Serratia spp.* and *Citrobacter spp.* that are susceptible to two or fewer of carbapenems, third-generation cephalosporins, including with B-lactamase inhibitors, piperacillin/tazobactam, temocillin, tigecycline, aminoglycosides, quinolones, trimethoprim or colistin.

iii) Proteus spp., Morganella spp. and *Providencia spp.* that are resistant to third-generation cephalosporin, piperacillin/tazobactam, and aminoglycosides and susceptible only to carbapenems, and the new beta-lactam/beta-lactam inhibitors (BL/BLI) combinations (ceftolozane/tazobactam or ceftazidime/avibactam). Unlike the species considered in ii) above, these Proteeae are inherently resistant to tigecycline and colistin.The following would not be regarded as multi-resistant:

E. coli that is susceptible to carbapenems, ceftolozane/tazobactam, ceftazidime/avibactam, colistin and fosfomycin but resistant to unprotected third-generation cephalosporins, co-amoxiclav, piperacillin/tazobactam, quinolones, and trimethoprim.The effect of new parenteral antibiotic introductions on the definition of MDR GNB in hospitals is illustrated by the licensing of ceftazidime/avibactam and the availability of parenteral fosfomycin. Both drugs join temocillin, tigecycline or colistin, as potentially effective agents against some Enterobacteriaceae with KPC carbapenemases. Such strains would no longer be classified as MDR GNB by our definition. Clearly acquired resistance of KPC-producing strains to colistin, ceftazidime/avibactam, fosfomycin and tigecycline may all arise so some will be MDR GNB and some will not. From a therapeutic view this is probably appropriate although all should remain major targets for infection control, given the cost of new agents and the need to conserve their usefulness, along with plasmid-mediated transmission of *bla* $_{KPC}$ gene, and transmission of their host strains. The use of alternative B-lactams or new BL/BLIs rather than carbapenems may be expensive but might reduce the selective-pressure for carbapenem-resistant MDR GNB. These antimicrobials, with activities against different B-lactamases, may have differential effects on the prevalence of particular B-lactamases and other carbapenem-resistant bacteria. They may select more for MBLs which are particularly resistant to B-lactams which will limit their ultimate

usefulness in a locality. The activity of different B-lactamase inhibitors against, and stability of B-lactams to, different B-lactamases is shown in Table 5.

The difficulty in international surveillance of MDR GNB need not preclude the establishment of surveillance for specific organism-antibiotic resistance combinations. This has been adopted by Public Health England for the English Surveillance Programme for Antibiotic Use and Resistance (ESPAUR) and is weighted towards resistance to third-generation cephalosporins, quinolones and carbapenems of *E. coli*, *Klebsiella spp.,* and *P. aeruginosa.*

6.3 What is the global epidemiology of MDR GNB?

6.3.1 Origins and impact of multi-resistance

Resistance to multiple agents can develop via successive mutations, through the dissemination of multi resistance plasmids/genes (e.g. transposons), or through a combination of both processes. Resistance narrows antibiotic choices for definitive therapy. More critically, it increases the likelihood that empirical therapy will prove ineffective, increasing mortality in septic patients. Plasmids are the main source of multidrug resistance in Enterobacteriaceae and *Acinetobacter spp.*, except for mutations in DNA gyrase genes *gyr* A/B conferring fluoroquinolone resistance, mutational up-regulation of *arc*A/B-mediated efflux compromising tigecycline, and for mutational derepression of AmpC β-lactamases giving resistance to third -generation cephalosporins in *Enterobacter spp.* , *Citrobacter spp.*, *Serratia spp.*, *Morganella morgani* [13] [14]. By contrast, sequential accumulation of mutations is paramount in *Pseudomonas spp..*

A recent review has discussed the emergence of specific resistance lineages and the role of different plasmid groups in emerging resistance problems in *E. coli* [15]. Some clones have spread widely for reasons that are not clear. Resistance may increase their

competitiveness, but some strains are adept at acquiring multidrug resistance. Several strands of evidence support this view. First, some 'high-risk clones', e.g. *E. coli* ST131, frequently acquire diverse resistance determinants, including different extended-spectrum β-lactamases (ESBLs), AmpC and even carbapenemases[16]. Secondly, there is co-selection of hypermutability with resistance in *P. aeruginosa* in patients with cystic fibrosis, facilitating development of further resistance. Thirdly, it is commonplace for plasmids and resistance islands to carry multiple genes encoding resistance to an antibiotic via two or more different mechanisms not all of which can remain under effective selection pressure. Fourthly the presence of toxin-antitoxin systems in plasmids may prevent loss of plasmids even when selective pressure is removed[17]. Fifthly, integrons, which provide efficient gene-capture and expression systems, and which are now frequent in plasmids but were not present prior to the widespread use of antibiotics, provide a mechanism whereby resistance acquisition has accelerated. Finally, the presence of MDR GNB in the environment including foodstuffs and water sources provides important pathways for amplification and the spread of some resistance genes to man [18] [19] [20-23].

Until recently, environmental sources of carbapenemase genes did not appear to exist but the description of high levels of NDM-producing *E. coli* in chicken in China[24] suggests this position will not be maintained with current international practices and biosecurity of food as a source. Surprisingly, the ST131 clone of *E. coli* did not seem to have significant environmental sources in its initial spread although it has now been described occasionally in chickens[25, 26].

6.3.2 Epidemiological trends among multidrug resistant Enterobacteriaceae - cephalosporin and quinolone resistance

Countries historically varied in the prevalence of different CTX-M ESBLs conferring cephalosporin resistance and in the plasmids encoding these enzymes [27]. The

prevalence of different CTX-M enzymes has changed with time and latterly in Europe and North America CTX-M-15 has become the dominant enzyme, often associated with *E. coli* ST131[28]. Whole genome sequencing suggests that the acquisition of CTX-M enzymes occurred a number of times in clade C of *E. coli* ST131[29]. Frequent co-carriage of OXA-1 penicillinases impairs susceptibility to combinations of clavulanate and tazobactam with penicillins. Ceftolozane appears stable to this OXA-1 enzyme. Other factors associated with the rise of multidrug resistant Enterobacteriaceae include the spread of plasmids encoding AmpC B-lactamase. These seem around 10-fold less frequent than plasmids encoding ESBLs in the UK[30] although more recently, in Canada a plasmid-mediated AmpC enzyme (CMY-2 which shares a promoter gene, ISEcp1, with CTX-M-15) was almost half as common as ESBL production and one third of such strains belonged to E*. coli* ST131[31]. Distinguishing AmpC and ESBL cephalosporin-resistant strains is important epidemiologically and in routine testing, although both EUCAST and CLSI do not recommend it for guiding treatment[32]. However early information on AmpC/ESBL status in Enterobacteriaceae may predict respectively ceftolozane/tazobactam resistance/susceptibility. Mutations can augment multidrug resistance: for example, porin loss can engender resistance to ertapenem (and, sometimes, other carbapenems) in ESBL- and AmpC- producing Enterobacteriaceae.

6.3.3 Carbapenem resistance

Carbapenem resistance was initially slow to emerge in Enterobacteriaceae but is now steadily increasing, and mediated more and more by acquired carbapenemases (predominantly by KPC, VIM, IMP, NDM and OXA-48-like types) [33-36]. Internationally there has been a considerable spread of *K. pneumoniae* clonal complex (CC) 258 isolates with KPC carbapenemases. The rise of NDM and OXA-48 carbapenemases is more often associated with the spread of their encoding plasmids or transposons among bacterial strains. Carbapenem resistance due to ESBL or AmpC enzymes combined with Omp

K35 porin loss, may lead to treatment failure but is often unstable and may impose a fitness cost on bacteria, meaning that spread of such strains among patients is rare, though not unknown [33]. Omp K36 porin-loss conferred resistance to new carbapenem-B-lactamase inhibitor combinations (relebactam with imipenem/cilastatin[37] and meropenem with vaborbactam[38]) entering clinical trial. Resistance conferred by acquired carbapenemases is of much greater concern, and is generally associated with considerable resistance to other agents.

Data from EARS-Net suggest that the prevalence of carbapenem-resistant Enterobacteriaceae causing bacteraemia markedly increased in most parts of Europe between 2013and 2015 [39] . European prevalence of carbapenem-resistant K.pneumoniae was higher than 5% in 2015 (and much higher in some of the countries)[40] in Greece, Italy, Cyprus and Romania. In Greece, the proportion of bloodstream *K. pneumoniae* isolates resistant to carbapenems increased from 27.8% in 2005 to 62.3% in 2014. VIM enzymes dominated early in this period but were replaced by KPC types, often carried by CC258. The rise of carbapenem-resistant *K. pneumoniae* in Italy has been dramatic and recent: from 1% of bacteraemias in 2009, to 15% in 2010 to 32.3% in 2014. This increase again is mainly due to CC258 *K. pneumoniae* with KPC enzymes [41]. This clone also spread widely earlier in the USA[42] and then in Israel[43] - where an aggressive, nationwide infection control intervention was successful in bringing it under control[44, 45]. In Romania the major problem is *K. pneumoniae* producing OXA-48 ESBL[46].

Outbreaks of carbapenemase-producing Enterobacteriaceae (CPE) have been reported in many other parts of the world, including all US states[47] (where KPC enzymes dominate), South Asia (predominantly NDM enzymes), the Middle East (OXA-48), Brazil and Colombia (KPC) [36, 48]. The MBL IMP-4 has spread widely in China - often together with KPC-2: IMP-4, without KPC, is the dominant carbapenemase in Australia. Further

global spread is to be expected [49] as now reported in South London. In the absence of comprehensive international prevalence data for infection and carriage, risk factors for CPE are difficult to derive, but seem to include travel to high prevalence areas, notably including the Indian subcontinent for NDM-producers and exposure to healthcare and antimicrobials[33]. Travel locations are becoming convergent with those where ESBLs are prevalent. Case-number trigger points for carbapenem-resistant isolates and regional coordination in control action has recently been modeled in the USA to show the high importance of early intervention with effective control measures[50] for K. *pneumoniae* strains and other Enterobacteriaceae. Carbapenem resistance in Enterobacteriaceae has been associated with increased attributable mortality probably owing to the greater likelihood that initial empirical therapy proves inadequate [Gupta et al.33, 51, 52].

6.3.4 Global resistance issues with oral drugs with low resistance rates in the UK

A 2008 study of clinical isolates from women aged 18–65 years with symptoms of uncomplicated lower UTI in ten countries, found susceptibility rates above 90% only for fosfomycin (98%), mecillinam (96%), and nitrofurantoin (95%)[53]. Nitrofurantoin resistance in E. coli as assessed on European and Canadian isolates made in 1999-2000 and 2007-8 was associated with a very diverse range of sequence types although many strains showed multiple resistances: mecillinam resistance was similarly diverse but not associated with multiple-resistance[54]. A further study from Munster and Seattle suggests nitrofurantoin resistance is particularly common in ST58 [55]. Nitrofurantoin resistance is now described in 11% of the dominant H30 sub-clone of ST131[56] suggesting the drug may be selective in the upper intestine although this drug does not usually eliminate Enterobacteriaceae from the faecal flora of patients receiving it. In Canada, nitrofurantoin resistance rates in ESBL-producing *E. coli* were 16% but in ESBL-producing *Klebsiella spp.* were 71% (nosocomial) and 93% (non-nosocomial) [57].

Well-described mutations in nitrofuran reductases confer resistance and plasmid-mediated resistance due to an efflux pump (*oqxAB*) has recently been described from Hong Kong [58]. This efflux pump and its encoding plasmid (with the *oqxAB* gene flanked by IS26 insertion sequences) was found in 26/103nitrofurantoin resistant or intermediate human isolates (by CLSI criteria) and was commoner in ESBL-producing isolates. The combination of *oqxAB* with the nitroreductase genes caused high-level nitrofurantoin resistance. This two level resistance process is analogous to the hypothetical role of AAC-6'-1b-cr in aiding the emergence of quinolone resistance by chromosomal mutation. Notably *oqxAB* also mediates resistance to mequindox, which is used in China as a growth promoter in animal feed. In China 322/1123 veterinary isolates of E. coli carried this gene but these mainly belonged to phylogroups A and B1 that are less associated with extra intestinal pathogenicity in man[59],

Fosfomycin use has been complicated by the emergence of resistance in some populations[60]. In Spain when use increased some fifty percent between 2005 and 2008, resistance rates in CTX-M-15 ESBL producing *E. coli* rose to 16% and among all ESBL-producing isolates increased from 4.4% in 2005 to 11.4% in 2009. The increase was particularly associated with nursing homes[61]. Fosfomycin resistance developed in *E. coli* ST131 (previously present there but not typed)[62] and was not associated with described mutational mechanisms of fosfomycin resistance[63]. Such mutations involve inactivation of genes encoding the hexose and triose sugar phosphate transport impairing drug uptake. A different mechanism is present in the acquired *fosA* gene, which encodes a drug-inactivating metalloglutathione transferase[60]. Fosfomycin resistance was present in 2009-2010 in 7.8% human *E. coli* in mainland China and approximately half of this was due to *fosA*$_3$[64]. A recent survey of food animals in Hong Kong found plasmid-mediated *fosA* to be increasing in frequency and associated with CTX-M ESBL-encoding plasmids [65]. A recent Chinese survey of isolates collected from 2010 to 2013 detected

fosfomycin resistance in 12% of ESBL-producing *Klebsiella* and 169/278 (61%) of KPC-producing *Klebsiella pneumoniae*: 94 KPC-producing strains carried fosA $_3$ flanked by two IS26 insertions and were clonally related[66]. Similar genetic findings were made in non-clonally related *E. coli* and *Klebsiella sp.* in Korea[67].

Mecillinam resistance is said to remain uncommon in the clinic – at 5-7% of ESBL-producing *E coli* in Sweden[68]. In a wider European study, overall susceptibility was similar with 4.8% resistance in *E coli* from uncomplicated UTI, although gradually rising [69], notably in Spain where the resistant proportion of strains rose from1% in 2000 to 6.5% in 2014.

6.4 How do Multi-Resistant Enterobacteriaceae differ from non-fermenters in terms of their prevalence and associated resistance genes?

Carbapenem resistance is more common in non-fermenting Gram-negative bacteria than in Enterobacteriaceae. In *A. baumannii*, it was common by the year 2000, to see isolates resistant to all treatment options except carbapenems, colistin and tigecycline. Subsequently, carbapenem resistance has proliferated, reaching *c.* 30% of bloodstream isolates. It is largely associated with acquired OXA-23, -40 or 58-like carbapenemases or with insertion-sequence mediated upregulation of the chromosomal OXA-51-like carbapenemase. The strain structure of *A. baumannii* is extremely clonal, making it difficult, without a history of patient transfers, to distinguish place-to-place spread from repeated independent selection of lineage variants that were previously circulating at low frequency. UK *A. baumannii* isolates producing OXA-23 carbapenemases often co-produce *ArmA* encoded 16S ribosomal methyltransferases conferring pan-aminoglycoside resistance. Multidrug resistant *Acinetobacter spp.* largely cause outbreaks in ICU settings [70-72], whereas carbapenem-resistant Enterobacteriaceae, principally *E. coli* and *Klebsiella spp.*, cause infection in a wider group of patients, and

have far greater potential to spread rapidly when introduced into wider patient populations [36, 44, 45, 48, 73, 74].

Most UK *P. aeruginosa* remain susceptible to β-lactams, including ceftazidime, piperacillin/tazobactam and carbapenems, aminoglycosides and fluoroquinolones, with resistance rates of 5-10% for these agents; and fewer than 1% for ceftolozane/tazobactam [75] . Nevertheless, single multidrug resistant lineages, some with carbapenemases, have persisted in a few UK hospitals for up to 9 years, causing multiple infections widely scattered over time and possibly reflecting colonisation of the hospital water systems. The most frequently encountered carbapenemase is VIM, which may be plasmid-mediated, with multiple gene copies conferring high level meropenem resistance [76] but is usually integron associated. IMP-9, another MBL is as common as VIM in China [77], and has been shown to be derived (as probably are many carbapenemase genes) from environmental bacteria by horizontal gene transfer [78]. Multidrug resistance is also a major problem in *P. aeruginosa* from cystic fibrosis (CF), with resistance increasing over time in the individual patient's lung microflora. Multidrug resistance profiles are extremely variable even within widely successful CF lineages, e.g. the Liverpool Epidemic Strain, which has circulated in multiple CF patients and units. Rates of carbapenem-resistance in *P. aeruginosa* vary greatly across Europe, with high rates in Eastern Europe – Lithuania, Poland, Slovakia, Hungary, Croatia, Romania, Bulgaria and Greece all having rates of resistance >25% and sometimes >50%)[40]. More generally, rates of resistance show a gradient, rising from NW to SE Europe, with extensive spread of carbapenemase-producing clones in Belarus, Kazakhstan and Russia [79][CD3]. In contrast to Enterobacteriaceae rates of resistance to carbapenem are generally higher than those to ceftazidime, piperacillin/tazobactam or aminoglycosides.

6.5 Prevalence of antibiotic resistance in Gram negative bacilli in the UK and relevant antibiotic prescribing

There are no epidemiological reports in the UK that specifically study defined MDR GNB. In this section, we discuss information on resistance to individual antibiotics and, where available, their associated resistances. Analysis is complex. Different reports from English, Welsh, Northern Irish and Scottish devolved administrations need drawing together to give a UK summary: bacteria and antibiotic resistances do not respect national boundaries.

Reduced prescribing may be followed by reduced resistance (See 11.1) but this is not invariable at a national level. Such reduced resistance has not occurred as older antibiotics (e.g. sulphonamides and streptomycin) have been abandoned [80], perhaps because of resistance linkage and for reasons already discussed in (See 6.3.) Reduced prescribing may reduce the likelihood of new resistance becoming prevalent but this is only a hypothesis set within the modern issues of travel and migration, which may import and spread resistance. Overall antibiotic consumption in England has fallen by 4.5% between 2012 and 2015 to 21.8 DDD/1000 population/day. It has yet to decline in general practice to the levels seen in 2010. After 5 years of increases in prescribing, hospital antibiotic use declined by 5% in 2014 from 5190 to 4933 DDD/1000 admissions and is now at approximately 2010 and 2011 levels. This decrease is concentrated in teaching hospitals which may reflect their case-mix or different pressures in other hospitals [4] .

In Scotland antibiotic use in primary care fell for the third consecutive year in 2015 (by 2.4%) and is now 9.5% lower than the peak rate of use in 2012. The level of prescribing was related to population deprivation scores and to residence in nursing homes where antibiotic use among those aged over 65 years was 83% than for similarly-aged patients not resident in nursing homes[81]. Since 2012, antibiotic use in Scottish nursing homes

has fallen by 7.8% compared with 5.1% in all patients aged >65 years. Nevertheless, hospital use rose by 3.5% and is now 9.9% higher than it was in 2012. The rate of 5880 DDDs/1000 admissions is now 19% higher than in England[81]. Of course, this may reflect use of less selective combination regimens such as penicillin, metronidazole and gentamicin rather than the number of days a patient receives antibiotics which is a weakness both of using Defined Daily Doses and the number of admission to estimate the number of people exposed to an individual antibiotic. Although England has the lowest antibiotic consumption in the UK, Scottish hospitals show significantly less consumption of carbapenems and piperacillin/tazobactam.

Information on primary and secondary care prescribing for Wales for 2015 [82, 83] is only available at the level of health board and hospital respectively, and has not been reported as aggregate totals .

An overview of current antibiotic-resistance in Gram-negative serious infections in the UK can be secured in various ways. The BSAC Bacteraemia Surveillance Programme (http://www.bsacsurv.org) provides historical and current information with a marked time lag for centrally-tested isolates from a restricted sample of 24-40 hospitals and can be examined on a national or regional basis by species. It has an archive of organisms that can be studied in retrospect, which is an important strength. Other surveillance depends on collection of local data rather than isolates. In England reporting is mandatory for all cases of *E. coli* bacteraemia with an improvement in case ascertainment. However mandatory data are needed for *Klebsiella*, other Enterobacteriaceae and Proteeae, *Acinetobacter spp.* and *P. aeruginosa* if early national interventions in emerging problems are to be reliably detected. Mandatory reporting of MRSA bacteraemia in England was established in 2001 and has improved with more comprehensive data capture from 2005 onwards. Health Protection Scotland now has mandatory reporting of *E. coli* bacteraemia but other species of Gram negative bacilli

are only reported across the UK on a voluntary basis. Such voluntary laboratory reporting of all bacteraemias has been in place since the Devonport incident of contaminated intravenous infusions in 1972 and is believed now to capture data for 82% of all bacteraemias. This data includes antibiotic susceptibility data which has not been present in mandatory data. The collection of voluntary and mandatory data suggest that voluntary reporting should be replaced by mandatory reporting as soon as possible to reduce the laboratory workload. Most laboratories in England and Wales examining human samples now download bacteria identified and their antibiotic susceptibilities irrespective of anatomical site to regional and national repositories where trends but not additional information e.g. demographic details of patients' residence etc. can be analysed.

Bacteraemia due to *E. coli* has increased over the last ten years in England and Wales, and analysis of the data-set showed that receipt of antibiotics in the 4 weeks preceding bacteraemia was the most important risk factor, followed by age over 65 years, and occurrence during summer months[84] A study by the *E. coli* subgroup of the UKs DH Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcarel Associated Infection on the first 891 cases of *E coli* bacteraemia with enhanced surveillance data are available in Committee papers for 28 March 2014 on line [85]. This showed that urinary catherisation was a factor in only 10% of cases but that in 72% of episodes from a urogenital source involved individuals aged >=65 years. A urogenital infection had been treated in 310/891 (34.8%) cases in the 4 weeks preceding bacteraemia and this sub-population differed very significantly in its antibiotic resistances. Resistance in this subpopulation to ciprofloxacin was 80% vs. 17% overall, 76.9% vs. 39% to trimethoprim, and 49.3% vs. 45% to co-amoxiclav. The 3rd generation cephalosporin resistance rate in the population overall was 10% but no figure was provided for the resistance rate in this sub-population treated. Although the rates for

ciprofloxacin seem surprising, the figures show a marked selection for multiply resistant, if not necessarily MDR, strains because of either failed treatment that did not cover the multi-resistant organisms or selection of resistant organisms in the gut flora that subsequently caused a urinary infection which then progressed to bacteraemia. Approximately half of the bacteraemias appeared to be associated only with a lower UTI but this probably represents symptomatically silent upper UTI giving rise to bacteraemia, either initially, or through spread to the upper tract despite treatment. The implication of this important study is that failure to give effective antibiotics may be the reason for 70% *of E. coli* bacteraemias whilst 30% of cases are associated with antibiotic resistance and, possibly, directly with treatment failure. The former requires detailed study which is beyond the scope of this guideline. The consistent use of an active antibiotic regimen for those either aged over 65 years or with signs and symptoms of an upper UTI, would make a sizeable contribution to the target of a 50% reduction in the rate of in *E. coli* bacteraemias by 2020 that was announced as a target by the then UK Prime Minister at the Japan 2016 G7 meeting [86]. This enhanced surveillance study has now been analysed and published[87]. Most patients (69.6%) were aged over 65 years. Most patients (68.3%) had a positive blood culture taken within 24 hours of admission but 46.7% of these had a healthcare exposure within the previous month and 546 out of these 930 (58,7% of this subgroup, 31.5% overall) had received antibiotics in te orededing month, In 281 there was a clear urinary focus for the bacteraemia for which 145 had received antibiotics (most commonly trimethoprim or co-amoxiclav). The largest independent risk factor for a bacteraemia's focus being the urogenital tract was previous treatment for UTI within 4 weeks of the bacteraemia's onset (adjusted Odds Ratio:10.7&(95% CI 3.6-8.1) but details of antibiotic resistance in this subpopulation for the whole study was not given. Twenty one per cent of patients had either a urinary catheter in situ or had one inserted, removed or manipulated in the

previous 7 days. Since the 2014 initial report, Public Health England has changed its recommendation for first line treatment of UTI in all but those under 50 years from trimethoprim to nitrofurantoin which is a urinary antiseptic that is only effective for treating lower UTI although it can be effective for preventing pyelonephritis associated with bacteriuria of pregnancy. It is too early to tell whether this will be effective in reducing bacteraemia or whether an oral combination regimen that attains systemically active concentrations will be necessary to achieve the desired outcome. APRHAI (The UK Advisory Committee on Antimicrobial Prescribing, Resistance, and Healthcare Associated Infection) on 28th March 2014 opined that in suspected pyelonephritis or upper UTI, the patient should be admitted if a) ciprofloxacin, piperacillin/tazobactam or co-amoxiclav had been used in the previous 2 months and b) the patient's symptoms worsened or did not improve in the 12-48 hours after prescription. In UK strains of *E. coli* ST131from various sources collected in 2011-2, when O16 and non- typeable strains are excluded, there is evidence that trimethoprim resistance occurs in at least 69% of CTX-M positive strains which comprised 32% of recent UK strains studied but 39%, at most, of CTX-M-negative strains [88]. All CTX-M producers were ciprofloxacin resistant and 71% of non-CTX-M producers were quinolone resistant. Quinolones are not therefore useful if ST131 strains are prevalent even if these strains are not ESBLs.

A study reported that sequence typed *E. coli* isolates from the BSAC Bacteraemia Surveillance Programme showed that the significant change in *E. coli* bacteraemia was almost exclusively due to an increase in clonal complexes 12, 69, 73, 95 and 131[84]. This reflects the sequence types in these clonal complexes. The clonal complexes, which each may contain more than one sequence type, belong to phylogroups B2 and D that have the virulence factors associated with extraintestinal spread. Phylogroup A and B1 strains, which may be more antibiotic resistant are usually confined to the gut and lack these virulence factors. Clonal Complex 131 unlike the other clonal complexes includes

multi-resistant isolates (of ST131) hosting CTX-M ESBLS with almost invariably now, resistance to quinolones [84]. In a 2010-2012 Yorkshire study of bacteraemias 129/768 - 39/129 ESBL producers - were ST131 confirming the importance of ST131 strains even in the absence of production of ESBls. 142/768 were ST73 (3/142ESBL producers), 81 were ST69 (1 an ESBL producer), 73 were ST95 (1 an ESBL producer), 31 were ST12 (no ESBL producer quinolone resistance), 27 ST127 (no ESBL producers or quinolone-resistant strains) [89] . Phylogroup D-ST69 strains (which include the previously designated clonal group A) were not fluoroquinolone resistant in a recent Italian study [90] although they were commonly detected in Italy in a previous cystitis study [91]. ST69 is usually ampicillin, trimethoprim and suphamethoxazole resistant. Quinolone-resistant D-ST69 strains were also uncommon in a Spanish survey with isolates from 2009 accounting for 3% of quinolone-resistant strains respectively, compared with 26% for O25:H4-B2 ST131 strains [92]. We did not consider it feasible to introduce control measures for ST 131 when preparing our earlier guidance on infection control[3] and indeed cephalosporin resistance has spread into many other STs [93].

More recent data from 2012 to 2014 on antibiotic resistance in *E. coli* bacteraemia in England were collected on 82% (54,301/66,512) of cases recorded by mandatory surveillance by record-linking with the national records of all bacterial isolates. 74% were classified as community onset whereas 16% of cases occurred 7 or more days after hospital admission. Antibiotic resistances reported were 8439(18.4%) to ciprofloxacin, 4256 (10.4%) to third generation cephalosporin, 4694 (10.2%) to piperacillin/tazobactam, 4770 (9.7%) to gentamicin and 91 (0.2%) to carbapenems[94] . Non-susceptibility to quinolones and cephalosporins decreased by 10% and 11% respectively over the two years in hospital onset cases whereas third-generation cephalosporin resistance increased by 10% in community onset cases. Trends in

hospital or community onset changes in antibiotic susceptibility in other species such as *Klebsiella* are precluded by lack of mandatory surveillance of bacteraemia.

A 12 year single centre-study in England suggested that the increase in *E. coli* bacteraemias was essentially confined to ciprofloxacin, co-amoxiclav, cefotaxime and aminoglycoside resistance and accompanied a similar change in urinary isolates[95]. The major rise in cephalosporin and multi-drug resistant *E. coli* in the UK occurred between 2000 and 2007 largely reflecting the spread of IncF (pEK499 or similar) plasmids, and was associated initially with the internationally-successful *E. coli* ST131 lineage with chromosomal fluoroquinolone resistance. These *IncF* plasmids encoding the CTX-M-15 B-lactamase, along with resistances to trimethoprim, sulphonamides, tetracyclines and aminoglycosides (often associated with *aac(6')*-Ib –cr also augmenting ciprofloxacin resistance) also spread in other *E. coli* Sequence types and other Enterobacteriaceae notably *K. pneumoniae*. Since approximately 2007 (the date varies with the species and resistance) the rise of cephalosporin- and fluoroquinolone-resistant Enterobacteriaceae has slowed and fluctuated (*E. coli*) or reversed (*Klebsiella spp.* and *Enterobacter spp*.) in the UK, though not in continental Europe [96] . This shift in percentage resistance may reflect the reduction in prescribing of cephalosporins and quinolones in the UK, predicated not only by the Enterobacteriaceae problem but also by concern about *Clostridium difficile*. It is important to know if this reflects an absolute decrease in numbers. Some data suggests that increased quinolone use largely mirrored the selection of such strains [97]. An increase in quinolone resistance in bacteraemias preceded the arrival of ESBL-producing strains. Cephalosporin use in England is now reported to be the lowest in Europe [4, 98][RE4]. Cephalosporin usage fell by a further 9.2% between 2012 and 2015 following larger previous declines from a peak in 2006-7 because of the national *C. difficile* problems. From 2012-5, oral cephalexin use fell by 25.7% but parenteral cefotaxime use by only 1.6%, whilst parenteral ceftriaxone use

increased by 37.4% probably reflecting use of this once daily antibiotic in outpatient parenteral antibiotic therapy [4]. The microbiological need for preferring this broad-spectrum agent to teicoplanin or daptomycin, which are only active against Gram-positive bacteria, should be critically reassessed.

General practice quinolone use in terms of DDDs/1000 inhabitants/day has fallen consistently since 2012 reducing by 3.6% between 2014 and 2015. However the national overall usage of ciprofloxacin has declined only slightly from approximately 0.48 DDDs/1000 inhabitants/day in 2012 to 0.43 in 2015: quinolone use in hospitals has increased despite an 18.4% incidence of ciprofloxacin resistance in E. coli bacteraemia[94]. A 53.6% rise in the respiratory quinolone levofloxacin which is the L isomer of ofloxacin seems unjustifiable but reflects a recommendation for use in penicillin-allergic patients with pneumonia. A similar increase (50.3%) was seen in Scotland accompanied by a 17% increase in ofloxacin use. An English target of a 10% reduction on 2013-4 levels of cephalosporin, quinolone ,and co-amoxiclav use in primary care or a reduction in use to be below the 2013-4 median value(11.3%) of Clinical Commissioning Groups (CCGs) for antibiotic prescribing of these agents, was achieved in 189/209 CCGs [4]. Prescribing of these antibiotics is substantially lower in Scotland and is not the subject of targets. Scottish reductions in primary care use in 2015 were 4.9% for co-amoxiclav, 5.8% for fluoroquinolones, and 6.0% for cephalosporins, with an 8% overall reduction in use[81].

Despite these reductions, cephalosporin and quinolone resistances continues to be seen frequently in UK bloodstream and urinary *E. coli* and *K. pneumoniae* isolates, with significant circulation in older patients who move between hospitals, nursing homes, and the community and who have frequent exposure to cross-infection and antibiotics. Resistance to both quinolones and third generation cephalosporins in *E. coli* bacteraemias is concentrated in those aged over 65 years and over and in England is at

least twice as prevalent in those aged over 74 years compared with those aged 65 to 74 years [4]. An Italian scoring system for carriage of ESBL-producing organisms has not been tested in the UK or modeled to see if the group of patients at risk of carrying these strains on admission to hospital is increasing [99].

The total number of *E. coli* bacteraemias in England and therefore the absolute burden of resistance , continues to rise – by 4.6% from 35659 to 37310 between 2014 and 2015 in England [4]. The same publication notes an increase in *Klebsiella* bacteraemias by 9% over the same period. Over the period from 2000 to 2014 the incidence of *E. coli* bacteraemia in England has risen inexorably from 20 to 50 cases/100,000 population [94].

In England, rates of resistance to piperacillin/tazobactam are said to have increased in *E. coli* bacteraemias from 8.5% to 11.7% and in *Klebsiella ssp.* bacteraemias from 12.6% to 18.5% over the period from 2011 to 2015 [4]. Equivalent rises in resistance to co-amoxiclav from 31% to 42% in *E. coli* bacteraemias and 18.7% to 28.2% in *Klebsiella spp.* bacteraemias over the same period have occurred.

Record linkage for *E. coli* bacteraemias between 2012 and 2014 showed piperacillin/tazobactam resistance increasing by 15.1% for hospital onset cases compared with 8.7% for community-onset cases[94]. This study also revealed significant variations in resistance rates by age and sex. Similar trends were seen in Scotland with an 8.6% increase for piperacillin tazobactam resistance and 6.1% for co-amoxiclav resistance in *E. coli* bloodstream isolates and 14.8% and 28.7% respectively in *Klebsiella sp.* in 2015. Changes from CLSI to EUCAST criteria may have produced these large rises in resistance in Scotland (See 6.2.) but there were no changes in EUCAST criteria for these antibiotics between 2013 and 2015 [81] and in England few laboratories use CLSI criteria In Wales 11/18 hospitals in 2015 recorded an increase in piperacillin/tazobactam resistance in *E. coli* in 2015[100]. In England

piperacillin/tazobactam use rose linearly by 62% between 2010 and 2015 to 135 DDD/1000 admissions across all hospital types [4]. In Scotland, use fell by 7.9% in 2015[81].

These changes are important. The main antibiotics used in a recent prospective study in 10 English hospitals of treatment of Gram negative bacteraemia were co-amoxiclav in 32% of patients and piperacillin/tazobactam in 34% [101]. Despite empirical therapy being inactive against responsible organisms based on *in vitro* tests in 34% of cases, all-cause mortality was said to be low - 8% assessed at 7 days and 15% at 30 days. Given the increasing resistance rates and use, explorations of comparative outcome in relation to resistance and use are needed at each national level and also by source of infection(See 11.2). Mortality in *E. coli* bacteraemia throughout England was measured between July 2011 and June 2012 as 18.2% at 30 days or 10.34/100,000 population in 1 year. These data were derived by record linkage of *E coli* bacteraemia cases mandatorily reported to Public Health England; voluntary reporting of antibiotic susceptibilities on all isolates to Public Health England, and records at the Office for National Statistics Death Registrations and at the NHS Spine. [102] Mortality is high as compared with Finland (8%), and inpatient only mortality in Canada (11%), and New Zealand (9%) Analysis showed important associated features. 30% of deaths occurred on, or on the day, after the blood sample was taken and 76.3% within 14 days making the separate mortality analysis of community-onset and hospital-onset bacteraemia important. Overall 19,174/26216 (73.1%) patients had their bacteraemia recorded within 1 day of admission. Mortality was higher (34.0%) if a respiratory focus of infection was diagnosed or the focus of infection was unknown (25.9%) than if a urogenital focus was diagnosed (13.2%). No information was available on the antibiotics prescribed precluding any test of whether higher mortality was correlated with failure to provide adequate Gram-negative cover in suspected respiratory or unknown foci of infection; moreover, there was no audit data to show if the reported foci of infection was

supported by evidence. A recent audit of coding and diagnosis of pneumonia by the British Thoracic Society did not support the diagnosis in 15.8% of cases and noted a 14.3% rate of mortality in this group [103]. At a population level the high burden of urogenital-related infection for *E. coli* was such as to make this the largest cause of deaths, even though mortality in this group was lower. The lower rate of mortality with urogenital infection correlates with information in an earlier study which showed that the excess mortality for bacteraemia with ESBL-producting Enterobacteriaceae was confined to non-urinary infections[RE5] [104]. The study by Abernethy and colleagues[102] identified a urogenital source for 55.3% of community-onset cases of bacteraemia and 45.1% of healthcare-onset cases. In 17.3% of cases the source was unknown. Mortality was lowest in those aged 1 to 44 years (5.4%) versus those aged 45-84 (17.9%) and >85 years (25.2%). Mortality rates varied by the susceptibility of the isolated causative bacterium; Ciprofloxacin S 17.0% (95%CI 16.4% -17.5%) ciprofloxacin I or R 21.9% (95%CI 20.5%-23.2%); Cephalosporin S 17.5% (95%CI 16.9%-18.1%), Cephalosporin I or R 21.3% (95%CI 19.4%-23.2%). The inclusion of a factor in the adjusted model to allow for hospital and case mix related mortality eliminated any significance to the difference in mortality by cephalosporin susceptibility. Cephalosporins are unlikely to have been used in infections due to ESBL-producing organisms in England, but piperacillin/tazobactam may have been used and the absence of a difference in mortality may reflect some improved outcome in urinary infection, despite the presence of bacteraemia. Different cephalosporins are not equally associated with *C. difficile* [105]. Oral first generation cephalosporins would be useful in early treatment. It might be appropriate, whilst keeping *C. difficile* under review, to abandon downward pressure on the whole class of antibiotics and introduce a cephalosporin-specific approach. There were no data on mortality in relation to susceptibility to piperacillin/tazobactam-, co-

amoxiclav-, or aminoglycosides: carbapenem-resistance rates were too low for robust assessment.

Resistance to any one of quinolones, cephalosporins or carbapenems was associated with a 30% increase in mortality. The association of increased mortality in quinolone-resistant strains needs explanation and it is not clear if this relates to hospital case-mix. Furthermore, if reduced use of oral quinolones is attempted, care is needed in the controversial area of prophylaxis in neutropenia where quinolones are widely used. Studies of withdrawing quinolones for this indication show an increase in Gram negative bacteraemia with susceptible strains without any diminution at least initially in resistant strains [106-108] and recent Cochrane reviews support the efficacy of quinolone prophylaxis[109, 110].

Rates of carbapenemase-production by Enterobacteriaceae (<2%) remain low in the UK but reference laboratory submissions of these organisms are growing annually (Figure 2), with many of the isolates coming from clinical rather than screening samples. It is noteworthy that surveillance of carbapenem-resistant strains depends on voluntary submission to reference laboratories and that regional molecular testing necessary for rapid turnaround has not been converted into national surveillance [4]. Given the importance of reducing carbapenem resistance, consideration should be given to introducing mandatory reporting of all isolates of carbapenem-resistant Enterobacteriaceae so the evolving picture can be properly assessed English data suggests the proportion of carbapenem-resistant *Klebsiella sp.* rose from 0.2% to 1.1% between 2011 and 2015 [4]. There are pockets of local endemicity, especially of *K. pneumoniae* and other Enterobacteriaceae with KPC enzymes around Manchester or with VIM and OXA-48 in north Cheshire. These have persisted for 5-6 years (D.M. Livermore, unpublished data). Many other sites, notably London teaching hospitals, are currently being repeatedly challenged with a diversity of carbapenemase producers,

many imported from overseas. Clonal complex 258 *K. pneumoniae* with KPC carbapenemase remains rare in the UK, despite repeated introduction, and the greater issue, particularly in NW England is dissemination of plasmids encoding KPC carbapenemases among different *K. pneumoniae* and Enterobacteriaceae. Carbapenem-resistant isolates submitted to reference laboratories in Scotland increased from 47 in 2014 to 63 in 2015[81].The dual loss of both quinolone and cephalosporin susceptibility has driven increased usage of carbapenems particularly meropenem from some 75 DDD/1000 admissions in 2010 to 104 DDD/1000 admissions in 2015 in England, a 38.6% increase, but in 2015 the increase was only 1%[4, 81]. In Scotland the picture is different: there was a 6.5% increase in use of carbapenems between 2014 and 2015 but this is now only 9.3% higher than in 2012 .

Phenotypic information on aminoglycoside susceptibility is available. Frequent gentamicin-resistance was noted in ESBL-producing strains of *E. coli* from all sites in one region, representative of the UK, with resistance rates of 48.7% for *E. coli* ST131 and 55.1% for *E. coli* non-ST131 [93]. The record linkage data previously discussed shows that overall gentamicin-resistance rates (i.e. irrespective of ESBL production) varied by region between 5.5% and 15.4% in the years 2012 to 2014 and that the overall rate in community-onset cases was 8.6%[94]. The region with lowest rate of resistance had a 34% higher incidence of *E. coli* bacteraemias than that with the highest rates, which suggests the possibility of dilution of the denominator by an increase in more susceptible bacteraemias (e.g.ST73 in northern England). In Wales in 2015 only 5/18 hospitals reported gentamicin resistance rates less than 8.6% in *E. coli* bacteraemia and two had rates over 20% [100]. Rates of 8.6% to 15% would seem too high for empirical use of gentamicin alone. However, the 8.6% rate of gentamicin resistance in community onset bacteraemia is very similar to the 8.7% resistance rate to piperacillin/tazobactam which is widely used alone [94]. National data on amikacin are hard to interpret because

fewer laboratories test it as well as gentamicin and the amount of testing that is second line because of resistance on first line testing remains unresolved, potentially skewing the data Nevertheless, as expected, amikacin resistance is rarer than gentamicin resistance (2% in 2015) in England[4].

Rates of co-resistance in bacteraemia isolates for 2015 for gentamicin and third generation cephalosporins were 4.6% for *E. coli* and 5.9% for *Klebsiella sp*. compared with resistance rates to third-generation cephalosporins alone of 7.5% and 5.2% suggesting some useful activity for gentamicin against ESBL-producing *E. coli* but less against ESBL-producing *Klebsiella sp*. Rates of co-resistance in bacteraemia isolates for 2015 to gentamicin with co-amoxiclav are 7.8% in both *E. coli* and *Klebsiella sp*. compared with resistance rates to co-amoxiclav alone of 35.2% and 19.3% [4]. This confirms the potential utility of an aminoglycoside compared with co-amoxiclav alone for both *E. coli* and *Klebsiella spp.* bacteraemias. The same data source indicates a somewhat different situation with ciprofloxacin-gentamicin combinations. For E coli and *Klebsiella spp*. rates of co-resistance were respectively 6.8% and 5.8% whereas resistance to ciprofloxacin alone occurred in 11.8% and 5.0% suggesting that addition of an aminoglycoside was seldom advantageous in *Klebsiella* infection. Overall this co-resistance data[4] suggests only a modest improvement on gentamicin monotherapy and the benefit compared with the harm of continuing selection of resistance by the non-aminoglycoside may not be great.

Consumption of aminoglycosides is now low in England in hospital inpatients (approximately 0.08 DDD/1000 population/day) and fell in 2015. By contrast use rose in Scotland by 5.9% becoming 16.9% more frequent than in 2012. Falls in use are likely to reflect concern about resistance in ESBL-producers and about potential toxicity; they may also reflect a change in clinical contacts with microbiologists as antibiotic assays

are increasingly undertaken by clinical chemistry departments. A comparison with Scotland to understand the differences would be informative.

Bacteraemia represents a group of community infections selected for virulence factors sometimes but not always by antibiotics. Antibiotic resistance in Gram-negative infections in the community was thought, even a decade ago, to be quite uncommon in the UK. A historical European study of acute, community-acquired, uncomplicated, non-recurrent UTI in 2008 caused by *E. coli* involved 12 GP practices in the UK and enrolled 200 unselected women aged 18-65 years. Resistance was rare to mecillinam (1%), nitrofurantoin (0%), fosfomycin (0.5%) amoxicillin/clavulanic acid (2.0%) and ciprofloxacin (0.5%), but commoner to amoxicillin (32%), sulfamethoxazole (26%), trimethoprim (15%) and trimethoprim/sulfamethoxazole (14%) [111]. In this survey the co-amoxiclav resistance rate seems low in relation to the amoxicillin resistance rate. Reported resistance rates to co-amoxiclav in lower urinary infections have increased since the time of this study partly because of the substitution of EUCAST's (32+2mg/L) breakpoint for the previous BSAC (16+8mg/L) value. A contemporaneous UK study with a large community sample reported 12.0% resistance to co-amoxiclav versus 54% for ampicillin [112]. Welsh data in 2014 reports the following resistance rates in "coliforms" from urine in different communities:: co-amoxiclav 12.9% (Range:5.1% to 25.4%) , third-generation cephalosporin (ESBL) 6.8% (Range 3.3% to 17..9%), nitrofurantoin 10.0% (range 8.7% to 22.4%), trimethoprim 36.7% (Range:30.3 to 41.8%) and fluoroquinolone 10% (range 7.6% to 16.4% [113]. A 2010-3 large UK study [114] of all community urinary isolates from a UK region with a population of 5.6 million found that by 2013 resistance to third generation cephalosporins in *E. coli* had risen to 5.5% and ciprofloxacin resistance to 15.5%; for *Klebsiella spp.* the cephalosporin resistance rate was higher at 10.1%. Only 0.06% of the *E. coli* isolates were reported as resistant to one or more carbapenems as were 0.32% of the *Klebsiella spp. isolates.* In this regional

survey, VIM enzymes were found in *Pseudomonas spp.* whereas among *E. coli* and *Klebsiella spp.*, 16 had NDM genes, 5 KPC and 2 OXA-48.... These findings support the view that carbapenemases are rare in the community in the UK. A further study of isolates in the same English region over the period 2007-2014 showed, after deduplication 69 with *bla*NDM, 26 with *bla* KPC, 16 with *bla*OXA-48-like, and 7 with *bla*-VIM[115] .

A historical audit of urine samples taken at presentation from primary and secondary care in South London before the widest dissemination of ESBL positive *E. coli* ST131 occurred, found that 22.6% of isolates were resistant to trimethoprim, 43.3% to amoxicillin, and 10.3% nitrofurantoin [116]. Since this audit resistance to trimethoprim has slowly risen across the UK, and in Wales is significantly commoner in isolates from patients over 65 years. Trimethoprim resistance rates vary widely by CCG in England. In 2011 it ranged in these from 16.3% to 66.7% but by 2015 86% showed >25% resistance with an almost uniform median of 29% in CCGs [4, 82]. The reason for these variations in a minority of CCGs remains uncertain. In Wales resistance rates of 38.2% overall are currently reported. A caveat is that high resistance rates may reflect selective testing of previously treated patients in the community and different local policies for submitting samples, and the true rate of resistance to trimethoprim in patients presenting in the community with uncomplicated UTI may be lower than current figures suggest [117]. Trimethoprim use in England fell by 14.5% between 2014 and 2015 reversing the increase seen between 2012 and 2014. This fall should be many times larger in 2016 if there is expeditious compliance with the Public Health England recommendation in 2014 to substitute nitrofurantoin for trimethoprim as the first line antimicrobial for cystitis in the older patient. A Swedish trimethoprim-sparing switch in one region resulted in an 86% decline in trimethoprim use between 2004 and 2006 [118]. In 2015 in England rates of trimethoprim prescribing were approximately

1.1DDDs/1000 population/day compared with 0.8DDDs/1000 population for nitrofurantoin[4].

UK data on resistance to nitrofurantoin, fosfomycin and mecillinam is scanty. In a single centre study nitrofurantoin resistance was commoner in *Klebsiella spp.* of community origin (around 15%) than *E. coli* (3%) [119]. English national data for the 2nd quarter of 2016 suggests resistance in *E. coli* in community UTIs varied with CCG between 0.3% and 12.8% with a median of 3.8% [4] whilst in Scotland, 5.9% of isolates tested in 2015 showed nitrofurantoin resistance[81]. Nitrofurantoin resistance is also common in UK CPE isolates[120]. Proteeae are inherently resistant to nitrofurantoin and data on their prevalence in UTI and resistance linkage for nitrofurantoin resistance in England is needed given the recommendation to use this antimicrobial first-line (See 9.1 for previous experience of changes in prevalent phylogroups and STs of *E. coli*). There are no recent data on fosfomycin resistance in the UK. A survey of fosfomycin resistance in Leeds found *fosA* in 2 urinary tract isolates collected months after its UK introduction in 1994 despite a lack of use in the study hospital [121]. In the same publication, a study of foods in Leeds in 1995 identified 2 Enterobacteriaceae isolates carrying *fosA* in vegetables imported from Spain. Fosfomycin resistance (MIC>=64mg/L was present in 32/81 strains of CPE in 2011; 27 of these were *Klebsiella spp.* [120]. In Wales, only 6.2% of cefpodoxime-resistant *E coli* (i.e. probably ESBL- and AmpC-producing strains) were apparently resistant to mecillinam [122] but this is discussed further later in the article (See 9.4.).

The impact of the successful clone ST131 clone of *E. coli* on multiple resistances has been assessed. In one 2011 UK study, resistance rates in ESBL-producing *E. coli* ST131 (mostly with CTX-M-15 enzyme) compared with non ST131 (producing CTX-M-15 or CTX-M-14) were respectively 99% versus 83% respectively for ciprofloxacin, and 92% vs. 86% for trimethoprim [93]. Fluoroquinolone resistance alleles *gyr*A/B and *par*C are

characteristic on whole genome sequencing of the Clade C of *E. coli* ST131, which is almost exclusively the clade carrying CTX-M ESBLs [29].

There is no reliable information on acquired colistin resistance. Usage sharply increased by 30% between 2013 and 2015 in England , entirely in specialist and teaching hospitals[4]. Given i)the growing use of colistin as a drug of last resort, ii) the prevalence of colistin resistance in KPC-producing *Klebsiella pneumoniae*, especially in Italy, but also in the USA. iii) the lack of mandatory surveillance of *Klebsiella sp.* and iv) the recognition of plasmid-mediated colistin resistance due to *mcr1* and *mcr2*, there is an urgent need for enhanced surveillance of colistin resistance at a national level [4]. Mcr-1 has been isolated from British pigs [123] but is widespread in the European food chain including additionally turkeys and veal calves [124] and Mcr-2 has been found in pork and cattle products [125].

6.6 What impact have returning travelers made on UK epidemiology?

Whilst mutational resistances often emerge locally, strains with acquired resistance genes are often clearly imported to the UK from other countries. Examples include multidrug resistant *K. pneumoniae* with OXA-48 carbapenemases with Libyan conflict casualties and with patient transfers from elsewhere in the Middle East; *K. pneumoniae* with KPC carbapenemases from Greece, and Israel and, also most significantly, Enterobacteriaceae with the NDM MBL, from south Asia and China [126]. Colonisation of travellers may be frequent, although precise rates are largely unknown. A systematic review confirms travel to certain areas is a significant risk factor [127]. Most data concerns ESBL-producing strains and there is a notable dearth of information on other important resistances including aminoglycosides, carbapenems, colistin, and fosfomycin. Nevertheless an Australian study suggests that travel associated aminoglycoside- and quinolone- resistance may be even commoner than travel associated cephalosporin

resistance[RE6] [128]. Interestingly prolonged carriage was significantly associated with the pathogenic phylogroups B2 and D rather than A and B1 but strains of St131 were rare even with Asian travel. A Canadian study showed that bacteraemia due to CTX-M-14 ESBL-producing *E. coli* was associated with travel to Europe and Africa whilst CTX_M-15-producing strains were associated with travel to Asia [129], Analysis of risk factors in Norway for new cases of ESBL-producing infection was undertaken in a case-control study of adults who had been resident for 1 year or more, with no previous hospital or nursing home residence >24 hours in the previous 31 days. It identified as risk factors travel to Asia, the Middle East or Africa within the past 6 weeks (OR=21 95% CI 4.5-97) or 6weeks to 24 months (OR=2.3 95% CI1.1-4.4), recent use of fluoroquinolones (OR=16 95%CI3.2-80) or recent use of B-lactams other than pivmecillinam (OR=5.0 95%CI 2.1-12, diabetes (OR-3.2 95%CI 1.0-11), and freshwater swimming in the last year (OR=2.1 95%CI 1.0-4.0) were associated with UTI due to ESBL-producing *E. coli* or *Klebsiella spp.*. Factors associated with decreased risk were the number of fish meals/week (OR=0.68/fish meal 95%CI 0.51-0.90) and increasing age (OR=0.89/5 year increase 95% CI 0.82-0.97). Almost 1 in 4 (23%) ESBL-positive patients had travelled to the risk countries within the previous 6 weeks and 39% in the 6 week to 24 month period compared with 1% and 19% respectively. Travel to Europe (11% and 67% in ESBL producers and 7% and 57% non ESBL producers) or America of Oceania (including Japan) was not a risk factor [130]. This emphasises that there is a longer-term effect of travel or migration that is often not considered. A placebo-controlled trial of ciprofloxacin to prevent traveller's diarrhoea showed that the prophylaxis selected for quinolone- and other-drug resistant GNB suggesting that such practices need review [131]. Previous travel to destinations where resistance is prevalent is a risk factor for acquired multidrug resistant bacteria and should be considered in respect of empirical therapy However many patients with multidrug resistant organisms lack any relevant travel and

it is not known if their organisms represent spread from carriers, especially in the same household, who have a history of high risk travel [132-134], or who have asymptomatically acquired the organism in hospital.

The most significant impact that the movement of people can have on the problem of resistance in Gram-negative bacteria is the maintenance of higher levels of resistance in commensal bacteria after return from high incidence areas. Data on faecal carriage rates may mislead when compared with correlates of clinical infection since it will include phylogroup A and B1 strains of lower pathogenicity than the B2 and D strains seen commonly in urinary and bacteraemia [135] Tangden in Sweden showed that 7/8 previously uncolonised travellers to South Asia and 10/32 to East Asia returned with gut carriage of ESBL *E. coli* [136]. One study in Birmingham showed that 22% of individuals with names of Middle Eastern or south Asian origin had faecal carriage of CTX-M ESBL-producing *E. coli* compared with 8.1% in those with names of European origin [137]. Hence, the choice of antibiotics for empirical treatment may need to take into account recent travel history and cultural background. The 2nd ESPAUR report (2016)[4] includes details from a research study of faecal carriage rates of ESBL-producing Enterobacteriaceae in England. This showed variations in carriage from 4.9% in Shropshire to 16% in Heart of Birmingham Primary Care Trust with intermediate rates in Southampton and Newham (East London). Risk factors in this study, which is yet to be published in full, included birth in India, Pakistan, Bangladesh, Sri Lanka, Afghanistan (which collectively accounted for 24% of all carriage) or the Middle East (including Egypt, Iraq, Saudi Arabia and other countries in the Persian Gulf) and travel in the last year to Africa, South Asia (Indian sub-continent and Afghanistan), South East Asia (Thailand, Burma, Cambodia, Laos, Malaysia, Singapore or Pacific Asia (including Vietnam, Koreas, China), South or Central America,(WHO regions). Until control measures reduce prevalence and at present only, (given the rate of change) travel to,

and most particularly healthcare in, the following countries are also risk factors for either ESBL carriage or carbapenemase acquisition or both: the Eastern Mediterranean (the Balkans, Greece, Cyprus, Turkey, Syria) and Eastern Europe and Russia, Belarus and Kazakhstan, and Italy.

There is a need for further studies with controls (non-travellers from different households of the same ethnic background) on the carriage of antibiotic-resistant *E. coli,* with strain typing and phylogroup allocation to better predict the potential for extraintestinal infection. This is further reviewed in elsewhere. Studies are needed also of *Klebsiella sp*. and on the time elapsed since travel to specified locations of high prevalence. Information on healthcare and antibiotic exposure is required as well as details of many non-ESBLantibiotic resistance mechanisms.

Evidence:

There is a clear indication of association of infection with ESBL-producing *E. coli* and travel. There is no information on other antibiotic resistances in association with travel and minimal information on carriage duration after travel.

Evidence level: 3

Recommendation:

Need to quantify risks of infection with/ carriage of, extraintestinal pathogenic *E. coli* and of *Klebsiella sp.* resistant to all antibiotics and relate to time since travel to countries with high prevalence of MDR GNB and incorporate in risk assessments for clinical infection with MDR GNB in the community and on admission to hospital to guide therapy

Grading: Strong recommendation for

6.7 What is the clinical importance of carbapenemase- versus CTX-M- and AmpC-producing strains

ESBL-producing Enterobacteriaceae, multidrug-resistant *P. aeruginosa* and *A. baumannii* are associated with increased mortality, length of stay and expense in most but not all studies evaluating the impact of antibiotic resistance in Gram-negative bacteria [138, 139]. Nevertheless, variability in the setting (mainly ICU), study design, organisms included (most notably, which Enterobacteriaceae species), resistance profile, and site of infection make the studies difficult to compare[138, 139]. Fluoroquinolone resistance in *P. aeruginosa* was associated with increased hospital costs, and, if associated with imipenem resistance (MDR strains), increased mortality [140]. Four of eight studies in one review of MDR strains of *P. aeruginosa* showed increased mortality [138]. With *A. baumannii,* carbapenem-resistance was generally associated with increased length of stay and expense of care; mortality was generally increased, most clearly if blood-stream infection was involved [138, 139]. However, two studies of MDR, but carbapenem-susceptible, *A. baumannii* did not identify a significant increase in mortality, whereas studies of carbapenem-resistance in *A. baumannii* consistently identify a significant increase in mortality only partly due to use of inactive carbapenems [139, 141-143]

More recently, studies have emerged evaluating the impact of carbapenem resistance in Enterobacteriaceae [144]. Pooled analysis of nine studies comparing mortality in Enterobacteriaceae infections including bacteraemia found that mortality was more than two fold higher when infections were caused by CPE. Broad-spectrum antibiotics other than carbapenems can select for colonization (detectable by active surveillance) that precedes later infection with bacteria resistant to a range of other antibiotics because of linkage of with multiple resistance factors [145-149]. Carbapenem resistance in *Acinetobacter spp.* is similarly linked with multiple resistances that can be selected for

by antibiotics that are not carbapenems, and can be detected as colonization prior to development of infection [150] and this is likely to be the case with Enterobacteriaceae.

Carbapenem resistance is an increasing problem in *Enterobacter spp.* in the absence of carbapenemases. In *Enterobacter aerogenes* ertapenem resistance is associated with loss of Omp35, a porin, and meropenem resistance with loss of Omp36 together with derepressed overproduction of AmpC [151].

Bacteria producing CTX-M are of international importance. In the community they are usually MDR with few and hitherto little used antibiotics offering the sole effective treatment. The spread of these strains requires widespread changes in primary care prescribing practice which can be slow to take effect. Further, systemic infection with these strains usually requires parenteral drugs involving additional hospital admissions or outpatient parenteral antibiotics. Particular successful clones such as *E. coli* ST131 and ST69 are frequently involved. The fundamental reason for the success of these clones remains obscure and strategies to counter their spread nationally and internationally have so far been based on antibiotic restriction alone.

AmpC-producing strains of Enterobacteriaceae were a problem when third generation cephalosporins and monobactams were widely used because stable derepression of this enzyme occurred by mutation at the regulatory gene *ampD* [13] in *Enterobacter spp., Serratia spp., Citrobacter freundi* and *Morganella morganii*. Selection of such mutants during cephalosporin treatment of bacteraemia with these species can cause treatment failure [152, 153]. Amoxicillin/clavulanate, both components of which are strong inducers of AmpC in such species is not active against such species but piperacillin although inactive against derepressed mutants seems less prone than third generation cephalosporins to select such strains from the induced population. Genes encoding AmpC enzymes have also escaped to plasmids that have spread into *E. coli*; such

plasmid carrying strains are widespread in food stuffs. The main enzyme is CMY-2. In the UK it remains considerably rarer than ESBLs [30] . Cefepime is more stable than other third-generation cephalosporins to AmpC but in *E. cloacae* high-level cefepime resistance is associated with mutation in AmpC [151]. Carbapenems and temocillin are active against *AmpC*-B-lactamase whether of chromosomal or plasmid origin but ertapenem is more labile and, if OmpK35 porin loss occurs, resistance arises from this enzymes action.

7 Intravenous treatment options for MDR GNB: What is the efficacy of carbapenems,, temocillin, fosfomycin, colistin and other antibiotics against specific MDR GNB and what are the recommended antibiotics for secondary/tertiary care?

7.1 The evidence base (and grading) for all agents is generally weak, as most studies were retrospective case series, only rarely including a comparator agent. Our suggestions for intravenous treatment are summarized in the algorithm in Figure 3. Each intravenous agent is individually further considered.Carbapenems

Carbapenems should be regarded as the drugs of choice for serious infections with ESBL-producing Enterobacteriaceae[154] and they are the drugs of choice for the empirical therapy of patients with serious sepsis caused by Gram-negative bacteria, depending on local resistance rates and clinical experience.

Meropenem was found to be narrowly superior to imipenem/cilastatin (cilastatin prevents degradation of imipenem by urinary and ileal dehydropeptidase) in both clinical and bacteriological outcomes in one meta-analysis of 27 RCTs [155]. The clinical response rates (complete remission or improvement in signs and symptoms of sepsis) for meropenem and imipenem were 91.4% and 87.2%, whereas bacteriological response rates were 85.1% and 82.8% respectively. There was no significant difference in mortality in the nine trials reporting data (7.4% for meropenem, 9.7% for

imipenem).Meropenem and imipenem (sometimes referred to as 'Group 2' carbapenems, based upon activity against Gram-negative non-fermentative bacteria) are typically preferred to ertapenem for the empirical treatment of bacteraemiass (often arising from the urinary tract) because of the broader spectrum (see below). A switch to ertapenem may be rational with susceptible isolates if it leads to earlier discharge with OPAT but without this, is not a mechanism for reducing selection for carbapenem resistance. In Singapore, de-escalation of meropenem-regimens by ID physicians (including in a small proportion to ertapenem) was associated with no increased in clinical failure rates or hospital mortality, reduced duration of carbapenem treatment from 8 to 6 days, less diarrhoea and *C. difficile* infection and less carbapenem-resistant Acinetobacter baumannii acquisition [156].

Meropenem or imipenem select respectively for carbapenem-resistant Gram-negative organisms including pre-existing carbapenem-resistant *A. baumannii* [157], and porin oprD mutants, the commonest mechanism of imipenem resistance, arising during imipenem treatment of *P. aeruginosa* [158]. Overproduction of AmpC type enzymes , and efflux pumps which are common, are implicated, in meropenem resistance in *P. aeruginosa:* MBLs usually of a VIM type occur but are much less common [159] A multi-centre Spanish study of isolates in 2008 from P. aeruginosa bacteraemia showed similar resistance rates to piperacillin/tazobactam, ceftazidime and meropenem. Meropenem resistance was more commonly associated with *mexB* or *mexY* and *AmpC* overexpression whereas resistance to piperacillin/tazobactam and ceftazidime was more commonly associated with AmpC overexpression alone, making non-carbapenems preferable agents for avoidance of MDR strains. Nevertheless, AmpC overexpression was associated with quinolone resistance, which with aminoglycoside resistance is already known to be associated with efflux pumps [160]. Whilst both imipenem and

meropenem have a similar spectrum of activity, use of imipenem has declined and meropenem is now the most widely prescribed carbapenem in the UK[154] .

Widespread usage particularly internationally, has driven the emergence of resistance and careful and considered empirical usage is essential. If the bacteria responsible for the infection are subsequently shown to produce neither ESBLs nor AmpC B-lactamase, carbapenem use reasonably should be stepped down to narrower spectrum agents. An Italian cohort study across 5 hospitals showed that rectal carriage of KPC-producing *Klebsiella* was predictive of bacteraemia with such strains in the subsequent 2 years; sensitivity and specificity were 93% and 42% respectively; positive and negative predictive values were 29% and 93% respectively. Bacteraemia was associated with ICU admission, invasive abdominal procedures, cancer chemotherapy or radiation therapy and the number of colonization sites [161]. This suggest that screening may play a role in anticipating a requirement for treatment other than carbapenems active against such strains but this will not necessarily apply to other bacteria with carbapenemases.

The ominous changes and increase in meropenem resistance in Enterobacteriaceae in the UK (Evidenced in 8.4), and the clinical importance of such resistance and the need to know the resistance mechanism to use appropriate chemotherapy, mean that an accurate overall view of the emerging picture is essential so appropriate action can be taken. We include recommendations on this epidemiological matter because of its importance. We recommend the introduction of both mandatory reporting of carbapenem-resistant Enterobacteriaceae from all anatomical sites and specimens and that such isolates should be tested at once to determine the responsible carbapenemase and precise level of meropenem resistance, and submitted to agreed reference laboratories to determine susceptibility to a further range of appropriate agents where susceptibility testing I technically demanding such as colistin or ceftazidime-avibactam, or where ongoing surveillance or quantitative methodology may be

important such as temocillin, aminoglycosides, fosfomycin and tigecycline. The determination of these susceptibilities is a part of essential surveillance. Appropriate patient treatment also depends on performing these susceptibilities in an expeditious manner but the methodology required may be beyond the scope of most routine diagnostic laboratories.

Ertapenem is licensed in Europe for the treatment of intra-abdominal and gynecological infections and community-acquired pneumonia. In the rest of the world, including in the USA, it is also licensed for skin and skin structure infections and for complicated urinary tract infections (for which it is widely used 'off-label' in the UK). Ertapenem shares the broad spectrum of imipenem and meropenem against Enterobacteriaceae, some Gram-positive species .and anaerobes, but is inactive against *Acinetobacter spp.* and *P. aeruginosa* [162]. It is sometimes called a Group 1 carbapenem on this basis. Its main benefit is its once-daily mode of administration.

Use of ertapenem for the treatment of infections caused by Enterobacteriaceae is less well established than for imipenem or meropenem but it has good *in vitro* activity. A retrospective cohort study compared outcomes of bacteraemias due to ESBL-producing *E. coli* and *K. pneumoniae* treated with ertapenem and group 2 carbapenems. Outcomes were equivalent between patients (mortality rates of 6% and 18%, respectively; *P*=0.18). However, more patients treated with group 2 carbapenems had severe sepsis / septic shock / multi-organ failure - 5/49 (10.2%) for ertapenem versus 36/109 (33.3%) for other carbapenems (odds ratio of 0.23; 95% confidence intervals 0.08–0.62; p< 0.002), suggesting clinicians were more likely to treat "sicker" patients with a group 2 carbapenem than ertapenem [163]. A retrospective study in Taiwan evaluated 251 patients with bacteraemia caused by ESBL-producing *E. coli* and *Klebsiella pneumoniae* isolates treated with a carbapenem[164] Two hundred and thirty patients received carbapenems appropriately – 57 ertapenem, 136 imipenem and 37 meropenem: 21

received carbapenems inappropriately - 18 received ertapenem and 3 imipenem when the MICs were respectively >0.5mg /L and >1mg/L. Among the isolates, rates of susceptibility to ertapenem (MIC ≤0.5 mg/L EUCAST) were 83.8% in *E. coli*, and 76.4% in *Klebsiella spp.*, respectively and those to meropenem were 100% and 99.3%. Sepsis-related mortality varied if the lower breakpoint CLSI breakpoint, for susceptibility (≤0.25mg/L) was used. By this criterion, mortality was 5.3% (3/57) in those patients infected with an ertapenem-susceptible strain versus 33% (6/18) for an ertapenem non-susceptible isolate if they were treated with ertapenem. If categorisation was based on the EUCAST breakpoints MIC <=0.5mg/l or >0.5mg/l, there was no significant difference in mortality. Propensity matching of patients showed that patients with isolates that were ertapenem non-susceptible by CLSI criteria had a similar raised mortality if treated with imipenem or meropenem but numbers were small. A recently published multinational retrospective cohort study of 195 patients given empirical carbapenem and 509 given targeted therapy for bacteraemia with ESBL producing Enterobacteriacea*e* found ertapenem to be equivalent to other carbapenems [165]. The authors recognized that as in other similar studies ertapenem was more frequently used in lower risk patients and that more studies are needed in the severely ill patient populations.

Resistance (MIC=>1mg/L) and high-level resistant (taken here as MIC>16mg/L) by EUCAST breakpoints to ertapenem in *Klebsiella spp.* and *Enterobacter spp*. were well recognised before CPE began to spread and were associated with combinations of a β-lactamase (often a CTX-M ESBL in *Klebsiella spp.* or AmpC in *Enterobacter spp.)* plus impermeability due to omp K35 porin loss. Despite the results of[164] imipenem and meropenem appear to remain active against most isolates with low-level ertapenem resistance caused by these mechanisms but with raised MICs compared with normal levels for the species. An *in vitro* study showed the frequent emergence of this type of

resistance in ESBL-producing *E. coli* in a pharmacokinetic model [166] but most resistant isolates are *Klebsiella spp.* or *Enterobacte*r spp. not E. coli. In a survey of UK isolates in 2007 only one of 95 ertapenem-resistant isolates of *Klebsiella pneumoniae* produced a defined carbapenemase, namely IMP-1with the remainder inferred to have impermeability (porin-loss) mediated resistance[167]. However, this situation has changed radically as KPC, OXA-48 and NDM are enzymes now regularly encountered in the UK [168, 169] . A retrospective case-control study from the Eastern USA found that risk factors for infection caused by ertapenem-resistant Enterobacteriaceae with such impermeability-mediated resistance included exposure to any antibiotic (not just β-lactams and carbapenems) during the 30 days before a positive culture result, [170]. A study from Singapore found that hospitalization and fluoroquinolone treatment were predictors for the appearance of ertapenem resistant imipenem susceptible variants [171].

The use of ertapenem has no detrimental effect in terms of selecting for *P. aeruginosa* [172]. Results from ten clinical studies showed that use of ertapenem did not result in decreased susceptibility to carbapenems in Pseudomonas. This was confirmed in study of hospitals in Queensland [173].A further study found that one hospital's use of ertapenem was balanced by less use of imipenem and ciprofloxacin, and this may have contributed to a reduced prevalence of resistance of *P. aeruginosa* to imipenem [174]. In contrast to these findings a study in Singapore associated increasing consumption of ertapenem with a rising incidence density of carbapenem-resistant *P. aeruginosa* [175]. Ertapenem use had no impact on the susceptibility of *A. baumannii* to imipenem [176].

Prolonged infusion therapy with meropenem for MDR GNB including carbapenem resistant organisms has been advocated on pharmacokinetic grounds in children for *A. baumannii*, *P. aeruginosa* and Enterobacteriaceae with meropenem MICs up to 8mg/l. [177]. There is a general trend towards considering continuous infusion of beta-lactams in critically ill patients with severe Gram-negative sepis (See 7.18) [178]. Continuous infusion

meropenem has been assessed in 375 obese patients for its ability to produce steady state levels above the MIC at levels from 2mg/L to >16mg/L [179] . Dosing nomograms to sustain this had previously been constructed in critical care patients [180].

Meropenem combined with vaborbactam (RPX7009); a boronic acid derived B-lactamase inhibitor is progressing through Phase 111 trials and may cover Enterobacteriaceae strains with KPC producing carbapenemases but not those with MBLs or OXA-48-like enzymes. Some isolates with ompK36 porin loss (See 6.3.3 & 6.7.) are resistant [38]. Relebactam in combination with imipenem/cilastatin is entering Phase 3 trials with trials against imipenem-resistant bacteria compared with a combination of colistin and imipenem/cilastatin and a comparative study against piperacillin/tazobactam in ventilator-associated pneumonia. Phase 2 studies are as yet unpublished. In vitro studies show no enhanced activity against *Acinetobacter spp.* but activity against KPC-producing K. pneumoniae (unless it has an OmpK36 porin loss which is responsible for meropenem resistance (See 6.3.3 & 6.7), and many but not all P. aeruginosa with enhanced AmpC production and depressed oprD[37].

Evidence

Carbapenems are drug of choice for treatment of serious infection with Enterobacteriaceae including those producing ESBLs or AmpC.

Evidence level: 1+

Imipenem use is associated with emergence of resistance in *P. aeruginosa*

Evidence level: 3

Ertapenem treatment is associated with emergence of resistance via porin loss in ESBL- and AmpC-producing Klebsiella *spp.* and *Enterobacter spp.*

Evidence level 3

Recommendations

- Use meropenem, imipenem or ertapenem to treat serious infections with ESBL and AmpC-producing Enterobacteriaceae.

  Grading: Strong recommendation for

- Apply antibiotic stewardship to use of all carbapenems to minimize the risk of developing resistance either by acquisition of carbapenemase-producing strains or, with ertapenem, by porin loss.

  Grading: Strong recommendation for

- Do not use imipenem to treat susceptible Pseudomonas infections

  Grading: Conditional recommendation for

- Introduce in the UK mandatory reporting of meropenem- or imipenem- resistant Enterobacteriaceae from all anatomical sites and specimens.

  Grading: Strong recommendation for

- Test immediately for the precise level of meropenem resistance and for an indication of the responsible class of carbapenemase (e.g. MBL/KPC/OXA48-like) all meropenem- or imipenem- resistant isolates of Enterobacteriaceae. Submit to agreed reference laboratories to determine susceptibility to a wide range of potentially active agents including, as appropriate colistin, ceftazidime/avibactam, temocillin, aminoglycosides, fosfomycin and tigecycline.

  Grading: Strong recommendation for

- Prefer ertapenem for outpatient antibiotic treatment (OPAT) of susceptible infections in view of the once daily dosing regimen.

Grading: Conditional recommendation for

7.2 Ceftazidime

Observational studies of ceftazidime-susceptible ESBL-producing *E. coli* and *Klebsiella spp.* infections treated with ceftazidime frequently show treatment failure, mainly during bacteraemias [12, 181-184]. One study of 7 patients treated with ceftazidime in China suggested useful activity but this may reflect the type of ESBL; CTX-M-14. -27 and -9 enzymes predominate in parts of China (and Spain) and have weak activity against ceftazidime as compared with CTX-M-15 enzymes with lower ceftazidime MICs. The higher CLSI susceptible breakpoint (<=4mg/L was found to classify 34% of CTX-M positive *E. coli* as susceptible to ceftazidime with normal inocula. Most CTX-M-14 isolates became resistant at higher inocula [185]. The EUCAST breakpoint for susceptibility is <1mg/L reducing this problem, Early problems arose with apparent ceftazidime susceptibility by disc testing of CTX-M-15-producing *E. coli* ST131 isolates in the UK down regulated by an IS26 insertion between promoter and structural gene[186]. Ceftazidime is active against some OXA-48-producing CPE principally those that do not co-produce ESBLs or AmpC enzymes. Ceftazidime retains activity against many isolates of *P. aeruginosa* including in the presence of mutation to imipenem or ciprofloxacin resistance [187]. However strains with derepressed class C (AmpC) β-lactamases or strongly upregulated efflux mechanisms are resistant, as are strains producing MBLs, other carbapenemases or ESBLs.

Evidence

Ceftazidime is usually ineffective in treating multi-resistant infections with Enterobacteriaceae except against some OXA-48 carbapenemase-producing strains.

Evidence level: 3

Ceftazidime remains useful for infections due to quinolone or imipenem resistant h *P. aeruginosa*

Evidence level: 3

Recommendations

- Use ceftazidime for susceptible infections with *P. aeruginosa* including quinolone- or some imipenem- resistant strains

  Grading: Strong recommendation for

- Do not use ceftazidime to treat infections due to ESBL-or AmpC-producing Enterobacteriaceae or CPE (other than OXA-48 producers), even if *in vitro* tests suggest the isolate is susceptible.

  Grading: Conditional recommendation against use

7.3 Ceftazidime/avibactam

Ceftazidime has recently been combined with the β-lactamase inhibitor avibactam. This combination has broad Gram-negative activity including Enterobacteriaceae and *P. aeruginosa.* Ceftazidime-susceptible bacteria remain susceptible to the combination, but avibactam protects additionally against class A (TEM, SHV, CTX-M, KPC) class C (AmpC) and some class D (OXA) β-lactamases [188-192]. Avibactam has no inhibitory activity against the MBLs (NDM-1, IMP and VIM) but it is the first BL/BLI combination to retain activity against KPC-2 carbapenemase-producing and most OXA-48 carbapenemase

producing strains. Ceftazidime/avibactam has minimal activity against *Acinetobacter spp.,* anaerobic or Gram-positive organisms [190, 193, 194]. A recent susceptibility study that included 120 KPC-producing Enterobacteriaceae collected from US hospitals found that ceftazidime/avibactam had $MIC_{50/90}$ values of 0.5/2mg/L [195]. The first case series of use of ceftazidime/avibactam against carbapenem-resistant Enterobacteriaceae has recently been published [196]. Among 37 patients with severe infections due to these organisms 31 had strains with KPC carbapenemases. Resistance to ceftazidime/avibactam emerged independently in 3 cases infected by *K. pneumoniae* ST258 with KPC-3 enzymes. In 2 of these isolates meropenem MICs were reduced >=4-fold to the susceptible range in parallel with the rise in ceftazidime-avibactam MICs. The overall clinical success rate was 59% of patients whilst microbiological failure occurred in 10 patients, including the 3 patients where resistant mutants were selected. An earlier epidemiological study had shown that ceftazidime/avibactam median MICs of ceftazidime/avibactam are higher for KPC3-producing isolates than those with KPC-2 enzymes although it was unclear if this represents enzyme specificity or quantity [197]. Isolates that produce KPC3 enzyme are internationally widespread including in South America and Southern Europe. Ceftazidime/avibactam resistant isolates with similar or identical mutations can be selected *in vitro* [198]. The mechanism involves the enzyme becoming a stronger ceftazidime-destroying enzyme, not in it becoming avibactam resistant. The licensing of avibactam –a non-B-lactam B-lactamase inhibitor with ceftazidime offers a new choice where organisms that produce both AmpC and an ESBL, or KPC2 carbapenemase cause systemic infection.

In phase II double-blind randomized trials, the efficacy of ceftazidime/avibactam was similar to imipenem/cilastatin in treatment of complicated urinary tract infection, (19/27) and (21/35) respectively [199]. A Phase 3 RCT of doripenem versus ceftazidime avibactam in complicated UTI or pyelonephritis, with patients not selected for antibiotic

resistance, showed equivalence with microbiological eradication in 304/393 (77.4%) in the ceftazidime/avibactam arm and 296/417 (71%) in the doripenem arm [200]. Efficacy combined with metronidazole was similar to meropenem in a RCT of 203 patients with intra-abdominal infection [201]. A Phase 3 RCT comparison of meropenem against ceftazidime/avibactam with metronidazole in 1066 complicated intra-abdominal infection, with the exclusion of a standardised set of highest mortality surgical indications, again showed equivalence [202]. On intention to treat analysis response rates were 82.5% to the ceftazidime/avibactam-metronidazole combination and 84.9% to meropenem. There was no difference in patient outcome in the combination arm if a ceftazidime-resistant strain of Enterobacteriaceae was present or absent. Only 1 case of *C. difficile* was recognised in either arm of the study. A RCT of ceftazidime/ avibactam and metronidazole against meropenem of 333 patients largely with patients with complicated UTI, but with some patients treated for intra-abdominal infections, all with infections with ceftazidime-resistant Enterobacteriaceae or *P. aeruginosa* showed 91% response rates at a test of cure visit [203]. None of these patients were infected with carbapenemase-producing strains.

Evidence

Ceftazidime/avibactam has similar efficacy to carbapenems in abdominal and complicated UTI, the former requiring combination of ceftazidime/avibactam with metronidazole.

Evidence level: 1+

Although clinical experience is limited in MDR GNB largely to ceftazidime-resistant organisms in complicated urinary tract infection, it would be expected to be effective when OXA-48 producing MDR GNB cause infection.

Evidence level: 4

Clinical experience against *Klebsiella spp.* producing KPC-carbapenemase is limited but ominously efficacy is only some 60% with resistance emerging in 10% of treated patients.

Evidence level: 2+

Recommendations

- Could use ceftazidime/avibactam as an alternative to carbapenems for infection with ESBL- and AmpC- producing Enterobacteriacea*e* but alternatives may be cheaper

  Grading: Conditional recommendation for

- Evaluate further ceftazidime/avibactam use alone or in combination when non-MBL carbapenemase-producing organisms cause infection. KPC-3 producing *Klebsiella spp.* are vulnerable to mutations in the enzyme causing resistance

  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

- Do not use for treating infection with anaerobes or bacteria producing MBLs: these are resistant

  Grading: Strong recommendation against

7.4 Ceftolozane/tazobactam

Ceftolozane is an oxyimino-cephalosporin that has been combined with tazobactam. Ceftolozane/tazobactam is active against many Gram-negative organisms, including Enterobacteriaceae and *P. aeruginosa* [193, 204, 205]. It is active against *P. aeruginosa* isolates

that are resistant to standard agents such as ceftazidime because of derepressed AmpC β-lactamases or upregulated efflux. In terms of MIC, ceftolozane is the most active β-lactam against *P. aeruginosa*, with resistance (MIC >4 mg/L EUCAST) largely confined to those with metallo-β-lactamases or unusual ESBLs such as VEB and GES types. MIC50/90 values against 310 multidrug resistant isolates of *P. aeruginosa* were 2/8mg/L [205]. Activity against *Acinetobacter spp.* is variable [193]. Ceftolozane/tazobactam has *in vitro* activity against Enterobacteriaceae producing ESBLs including most TEM, SHV, and CTX-M types [205-207]. Since oxyimino-cephalosporins are stable to the inhibitor-resistant OXA-1 enzyme, ceftolozane is not compromised by co-production of this enzyme in CTX-M-15 producing Enterobacteriaceae as happens with piperacillin/tazobactam, Activity is less against ESBL-producing *Klebsiella spp.,* possibly owing to high ESBL levels arising from production of additional SHV enzymes [208]. Activity against Enterobacteriaceae with copious AmpC enzyme is variable, but many *Enterobacter spp.* with derepressed AmpC are resistant. The combination has no activity against strains with MBLs (NDM-1, IMP, and VIM) or against those with KPC carbapenemases. Ceftazidime-resistant strains with OXA-48-like enzymes are mostly resistant: ceftazidime-susceptible OXA-48 producers are susceptible to ceftolozane/tazobactam (D.M. Livermore –unpublished data.

Ceftolozane/tazobactam therefore has potentially different uses from ceftazidime/avibactam and should not be used in infections due to AmpC- or KPC-producing Enterobacteriaceae. The absence of clinical comparisons of piperacillin/tazobactam and ceftolozane/tazobactam mean that choices must be made on *in vitro* grounds. The apparent enhanced activity of ceftolozane/tazobactam against strains that co-produce the enzyme OXA-1, including the internationally prevalent *E. coli* ST131 lineage, needs full laboratory and clinical verification but may make this drug more likely to produce clinical cure. Caution on clinical outcome is necessary because of

the potential, as with ceftazidime/avibactam for superinfection with *C. difficile*. Ceftolozane activity against *P. aeruginosa* including ceftazidime-resistant strains *in vitro* may offer clinical advantages where MDR Pseudomonas infections are a problem such as in cystic fibrosis [209] but this needs confirmation in a clinical trial. Optimal dosing in cystic fibrosis needs to be established but the drug's pharmacokinetics appears to be the same as in unaffected patients [210].

Ceftolozane/tazobactam is licensed, at present, for complicated intra-abdominal infection and complicated urinary tract infection [211]. In a prospective, randomised, double-blind trial, 993 hospitalised patients with complicated intra-abdominal infection received either ceftolozane/tazobactam (1.5g 8h iv) plus metronidazole, or meropenem (1g 8h iv) for 4–14 days [212]. Non-inferiority was demonstrated overall and MIC was not related to outcome. In fifty patients an ESBL-producing organism was isolated. In these patients, the clinical cure rate was 95.8% (23/24) in the ceftolozane/tazobactam plus metronidazole group and 88.5% (23/26) in the meropenem group. In patients with CTX-M-14/15 ESBL-producing Enterobacteriaceae, clinical cure was observed in 13 of 13 (100%) and 8 of 11 (72.7%) patients, respectively. A double-dummy, double-blinded RCT compared ceftolozane/tazobactam against levofloxacin in 1083 patients with complicated UTI [213]. Patients received ceftolozane /tazobactam (1.5g iv 8h) or intravenous levofloxacin (750mg od iv). The majority of participants (82%) had pyelonephritis. Overall, ceftolozane/tazobactam was found to be non-inferior in clinical, and superior in microbiological, outcome to levofloxacin therapy. In the intention to treat population, 20 (2·7%) of 731 Gram-negative pathogens were resistant to ceftolozane/tazobactam at baseline, whereas 195 (26·7%) of 731 were resistant to levofloxacin. Two (0·3%) of 594 of *E. coli* isolates were resistant to ceftolozane/tazobactam and 144 (24·2%) of 594 were resistant to levofloxacin. For patients with levofloxacin-resistant uropathogens (based on CLSI criteria) clinical cure

was seen in 90 (90·0%) of 100 patients in the ceftolozane/tazobactam group compared (surprisingly) with 86 (76·8%) of 112 in the levofloxacin group. In patients with ESBL-producing uropathogens, cure with ceftolozane/tazobactam was 55 (90·2%) of 61 compared with 42 (73·7%) of 57 for levofloxacin (95% CI 2·6–30·2). Treatment choice in complicated UTI and pyelonephritis involving MDR GNB between piperacillin/tazobactam, carbapenems, ceftolozane/tazobactam, temocillin or ceftazidime-avibactam depends on the bacteria present and their patterns of susceptibility.

Evidence

Ceftolozane/tazobactam is not active against CPE strains, excepting ceftazidime-susceptible OXA-48-producers, but otherwise, when combined with metronidazole, is non-inferior to meropenem in intra-abdominal infection

Evidence level: 1+

Ceftolozane/tazobactam is non-inferior to intravenous levofloxacin in complicated UTI including those caused by ESBL-producing *E. coli* (most of which are resistant to levofloxacin)

Evidence level: 2-Ceftolozane/tazobactam is the most active β-lactam *in vitro* against *P. aeruginosa*

Evidence level: 4

Recommendations

- Use ceftolozane/tazobactam to treat susceptible *P. aeruginosa* infections resistant to ceftazidime

  Grading: Conditional recommendation for

- Conduct clinical trials in *P. aeruginosa* infections in cystic fibrosis

  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

- Use ceftolozane- tazobactam as an alternative to carbapenems to treat urinary or intra-abdominal infection involving ESBL-producing *E. coli*. Caution may be needed when treating infection due to ESBL-producing *Klebsiella spp.* owing to a higher resistance rate.

  Grading: Conditional recommendation for

- Do not use for infections due to AmpC- or carbapenemase- producing Enterobacteriaceae or MBL/ESBL- producing *P. aeruginosa*.

  Grading: Strong recommendation against

7.5 Aztreonam

Aztreonam is labile to AmpC and ESBL enzymes. It is stable to MBLs and OXA-48–like carbapenemases but most Enterobacteriaceae with these enzymes also express ESBLs or AmpC which confer resistance [214, 215]. Isolates with MBLs or OXA 48 and no ESBL- or AmpC- production may be susceptible (those with OXA-48 alone are likely also to be susceptible to ceftazidime and ceftolozane/tazobactam). At EUCAST breakpoints (S <=1, R >16) most *P. aeruginosa* are intermediate in susceptibility and the drug is usually less active than ceftazidime or ceftolozane/tazobactam except against MBL-producers resistant to all other B-lactams which may be intermediate (rarely susceptible) to aztreonam.

An aztreonam-avibactam combination is in Phase 11 development. This creates a combination with very promising activity against Enterobacteriaceae with MBLs, OXA-

48, AmpC, ESBLs and other B-lactamases (including AmpC, OXA-1 and CTX-M class)[214, 215 216] .

Evidence

Aztreonam is not active against Gram-negative bacteria producing ESBLs, AmpC or KPC carbapenemase; it is only moderately active against *P. aeruginosa*.

Evidence level: 4

It is stable to MBLs but strains possessing these often have ESBL or AmpC as well resulting in resistance. Similar limitations apply to strains with OXA-48-like enzymes.

Evidence level; 3

Combination with a B-lactamase inhibitor such as avibactam would potentially make aztreonam useful against MBLs (NDM, IMP and VIM)-producing bacteria that also have ESBLS or Amp C enzymes.

Evidence level: 4

Recommendations

- Do not use aztreonam alone empirically if MDR GNB or Gram-positive or anaerobic pathogens are suspected.

  Grading: Strong recommendation against

- Do not use aztreonam for CTX-M ESBL- or AmpC- producing bacteria even if these appear susceptible *in vitro*

  Grading: Strong recommendation against

- Use aztreonam for MBL- or OXA-48- producing strains if it is certain that they do not produce ESBLs or AmpC

  Grading: Conditional recommendation for

- Research usefulness of aztreonam in combination with avibactam for bacteria producing MBLs with ESBL/AmpC enzymes and for those with other carbapenemases.

  Grading: Recommendation for research

7.6 Cefepime

Cefepime is not available in the UK. It appeared to be active *in vitro* against ESBL-producing *Enterobacteriaceae* especially when the old NCCLS-CLSI breakpoint of =<8mg/l was used. A retrospective, case-controlled study compared the clinical and microbiologic responses for 10 infections due to ESBL-producing *Klebsiella spp.* and *E. coli* from a non-urinary source with 20 matched controls receiving cefepime for non-ESBL strains. Four patients with ESBL-producers had strains that were resistant to cefepime by broth microdilution MIC, one of whom responded: Three of the remaining six with strains then regarded as susceptible (NCCLS -CLSI- breakpoint MIC =<8mg/l), failed on treatment Patients receiving cefepime for infection with ESBL-producing bacteria were 9.7 times more likely to have an unsuccessful clinical and microbiological response than those with non-ESBL-producing bacteria [217]. A randomised evaluator-controlled trial of ICU patients compared cefepime with imipenem for the treatment of hospital acquired pneumonia. The failure rate was 31% in the cefepime group compared to 0% in the imipenem group. Cefepime MICs of 2-4mg/l, then interpreted as susceptible by the NCCLS_(CLSI) breakpoint of =<8mg/l but now regarded as susceptible dose-dependent by CLSI and intermediate by EUCAST criteria were noted in

strains from treatment failures [218]. A retrospective case-control study of cefepime-susceptible bacteraemia caused by ESBL-producers in the period 20012-7 compared 30 day mortality amongst 17 patients treated with cefepime versus 161 cases treated with a carbapenem [219]. Mortality in the cefepime group was 58.8% versus 16.8% for carbapenem treatment and, in multi variate analysis cefepime treatment was strongly associated with mortality (OR, 9.9; 95% CI, 2.8-319; p 0.001). Mortality with cefepime in definitive treatment also related to MIC being 16.7% (1/6) in those with an MIC=<1mg/l, 45% (5/11) in those with an MIC of 2-8mg/l and 100% (4/4) in those with an MIC of =>16mg/L [220]. In a retrospective study of 305 adults with monomicrobial *Enterobacter cloacae* infections, those with MICs of 4-8mg/l (i.e. with CLSI dose-dependent susceptibility and straddling the EUCAST I/R breakpoint) had significantly higher mortality than those treated with carbapenem 71.4% vs. 18.2% (= 0.045) [14]. Fifty eight percent of strains in the cefepime-treated group produced an ESBL in addition to AmpC. In those definitively treated with cefepime, ESBL-production (16/40 vs. 3/32 p=0.006) and susceptible dose-dependent strains (10/16 vs. 9/56 p=<0.001) were independently associated on multivariate analysis with increased mortality [14]. ESBL production was more frequent in those strains with cefepime MICs of 4-8 mg/l (32/36 compared with 61/138 with MIC=<2mg/l p=<0.001). Mortality was not reduced even when high dose regimens (2g 8h iv) were used. Mortality in infections due to ESBL non-producers (with median MICs of 0.5mg/l) treated with definitive cefepime was similar to those who received definitive carbapenem therapy (9/56 vs. 16/72 p=0.5). This study demonstrates the efficacy of cefepime against the presumptive AmpC producer *E. cloacae* but only in the absence of additional ESBL-production or absence of MIC >2mg/L Nevertheless, in another retrospective study between 2005 and 2007, of bacteraemia due to ESBL-producing pathogens, receipt of empirical cefepime alone (n=43) was associated with increased mortality compared with cefepime

combination(n=69) or carbapenem combination (n=44) regimens: mortality was unlinked to MIC being 5/13 with those with organisms MIC=<2mg/L, 2/6 with MICs of 4 or 8mg/L and 10/24 with MICs =>16mg/:L [221].

The concept of susceptible dose dependent isolates of Enterobacteriaceae was suggested by CLSI In order to maximise cefepime use and spare carbapenems but these findings suggest this is unwise A recent systematic review did not support the use of cefepime in empirical therapy of critically-ill patients when ESBL-producing *E coli* or *Klebsiella sp.* infection is suspected. Even in patients with ESBL strains susceptible to cefepime (≤2mg/l CLSI; < 1mg/L EUCAST), treatment failure can be seen [220].

Evidence

Cefepime has a higher failure rate in treatment of infections due to ESBL-producing GNB than carbapenems unless cefepime MICs were =<1mg/L

Evidence level: 2+

Bacteraemias due to *E. cloacae* strains without ESBLs and with MIC =>2mg/l <8mg/L can be successfully treated with cefepime

Evidence level 2+

Recommendations

- Could use cefepime to treat infection caused by ESBL- or Amp-C-producing bacteria if susceptible to the EUCAST breakpoint of MIC =<1mg/L

  Grading: Conditional recommendation for

- Do not use cefepime even at increased dose for isolates with i) MIC of 2-8 mg/l (CLSI "susceptible dose dependent") or ii) MIC 2-4mg/L (EUCAST intermediate, or iii) strains that produce both AmpC and ESBLs.

  Grading: Strong recommendation against

- Do not use cefepime to treat infection caused by carbapenemase-producing Enterobacteriaceae.

  Grading: Strong recommendation against

7.7 Cefoxitin

Cefoxitin, the original parenteral cephamycin, was developed by Merk and is now a generic. It is no longer available in Europe but has several suppliers in the USA. Cefoxitin was licensed at the same time as second-generation cephalosporins like cefuroxime but differs in having activity against gut *Bacteroides sp.* but minimal activity against *Haemophilus influenzae*. Cefoxitin is on the list of forgotten antibiotics that may be useful against MDR GNB [222]. It is active against ESBL-producing *E. coli* but is not active against AmpC-inducible species of *Enterobacteriacea*e e.g. *Enterobacter spp.*, *Citrobacter freundi*, *Serratia spp*., *Morganella morganii* and *Providencia stuartii*, nor against *P. aeruginosa*. Cefoxitin differs from temocillin (which has a 6-alpha methoxy group corresponding to the 7-alpha methoxy group of cefoxitin) in having activity against Gram-positive bacteria including penicillin-susceptible *Streptococcus pneumoniae* and methicillin-susceptible *Staphylococcus aureus*, which may be advantageous if a urinary infection is diagnosed but the patient actually has infection due to these organisms elsewhere.

EUCAST no longer cites MIC breakpoints but BSAC had a breakpoint of S<8mg/L and resistant >8mg/L Typical MICs for *E. coli* and *Klebsiella sp.* are slightly below this level

meaning that small reductions in susceptibility can confer resistance. These can arise by reductions in permeability or, (in *E. coli* only) by mutation in promoter or attenuator sequences for *amp*C. Cefoxitin resistance is very common in the Middle East, India and China. In a multicentre study of 1762 isolates from urinary infection in the Asia-Pacific region 50.3% of strains were resistant to cefoxitin [223] . Resistance also occurs in *E. coli* and *Klebsiella sp*., from plasmid-mediated Amp-C production. Porin loss combined with other mechanisms of B-lactam resistance such as ESBL-production is described as emerging during treatment of some Klebsiella infections (See 6.3.3 & 6.7).

Cefoxitin is used in selective media for *C. difficile* and would be expected to trigger infection with this pathogen. In one recent study antibiotic prophylaxis with cefoxitin was an independent risk factor for *C. difficile* infection [224]. The absolute frequency at which this will occur relative to other antibiotics is not known.

In murine models of pyelonephritis cefoxitin was effective against an OXA-1- and CTX-M-15- producing transconjugant *E. coli* [225] and in combination with fosfomycin prevented selection for fosfomycin-resistant mutants [226]. Only one human trial of cefoxitin against current ESBL-producers has been reported. In this 2015 French study largely of urinary and catheter-related bacteraemia 30/33 patients responded in the first 48 hours and 20/24 evaluable patients at follow-up. Six microbiological failures were documented with emergence of resistance in 2 patients with Klebsiella infection [227]. A pharmacological model suggests 1 h. infusion of 2g four times daily would be effective [228].

Although cefoxitin appears active against CTXM-15-producing *E. coli* and *Klebsiella spp.,* it lacks temocillin's activity against strains with copious inducible, derepressed [229] or plasmid-mediated, AmpC. Cefoxitin may be more prone than temocillin to select *C. difficile* [230]. Temocillin unlike cefoxitin has no Gram-positive spectrum so in empirical

use in the elderly where it is not clear if the urinary tract or the chest/skin is the source of infection, it may need supplementation with another antibiotic. It is not clear if cefoxitin's reintroduction would offer any sustainable or competitive advantage apart from its carbapenem-sparing capacity as its four-times daily intravenous dosing makes it only usable in inpatient treatment not OPAT.

Evidence:

Cefoxitin is an intravenous cephamycin antibiotic, formerly licensed in the UK. Inducible, derepressed or plasmid-mediated AmpC-production confers resistance as does porin loss, especially in association with ESBL-production. Nevertheless, in *vitro*, animal and human studies indicate activity against ESBL-producing strains of *E. coli* and *Klebsiella spp.* Treatment can be complicated by emergence of resistance due to porin loss.

Grading: Level 3.

Recommendations

- Could use as a carbapenem-sparing agent for infections caused by CTX-M-15-producing *E. coli* but is only suitable for inpatient use not OPAT because of the short serum half-life. Narrower Gram-negative spectrum than temocillin so less suitable for empirical use in UTI .

  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

7.8 Temocillin

Temocillin is a semi-synthetic 6-alpha-methoxy derivative of ticarcillin that is highly stable to most β-lactamases except MBLs (e.g. IMP, NDM, and VIM) and OXA-48-like

enzymes. It lacks activity against anaerobes, Gram positive bacteria and most Gram-negative non-fermenters such as *P. aeruginosa* and *Acinetobacter spp.* It retains *in vitro* activity against ESBL- and AmpC-producing Enterobacteriaceae [231, 232], and some KPC-producing *E. coli* and *Klebsiella pneumoniae* [233], and *Burkholderia cepacia* complex [234]. It is active against Enterobacteriaceae strains whose AmpC –production is stably derepressed [235]. No EUCAST breakpoint for susceptibility to the drug has yet been published but the BSAC had a systemic value of S <8, R>8mg/L MICs for temocillin of KPC-producing bacteria are in the range of 4-32mg/L (mode 16mg/L).In a lethal mouse model of intra-abdominal infection using strains of KPC producing *E. coli* temocillin was effective against KPC-2 [236]. Temocillin has poor activity against carbapenem-resistant isolates of Enterobacteriaceae lacking carbapenemases – presumptively due to porin loss [237]. This antibiotic has no activity against OXA-48 or MBL-producing strains [238]. Caution is also needed in predicting results of treatment of systemic infections from *in vitro* susceptibility and further trials of temocillin alone at defined and possibly greater doses than the licensed 2g twice dailyare necessary. Outcomes should be correlated with MIC.

At present, clinical studies are limited to non-comparative series. The largest multi-centre study (non-randomised retrospective case series) involved 92 patients who were treated with at least 3 days of therapy [239]. Urinary tract and bacteraemia (42 episodes each) were the most frequent indications followed by hospital acquired pneumonia. Dosages of ≥4g/day, rather than 1g twice daily, were associated with improved outcome. Patients with strains producing Amp C or ESBL enzymes responded microbiologically in 23/27 or 18/22 cases in respectively UTI or bacteraemia. Higher dosage regimens, including 2g three times dailyand 6g by continuous infusion and use in veno-venous haemofiltration are reported in the literature with suggestions that these improve efficacy [240].In a retrospective case review of bacteraemia caused by KPC

producing Enterobacteriacae, 14/14 patients treated either alone or in combination with temocillin survived, whereas 6/30 treated similarly with tigecycline died [241]. Two studies have been published on the use of temocillin in cystic fibrosis patients with *B. cepacia* complex and sometimes *P. aeruginosa*. Both were retrospective non-randomised audits the first showing equivalence of combinations of temocillin with tobramycin versus other agents with tobramycin against *B. cenoepacia* and the second showing that 18/32 courses of temocillin resulted in improvement in the patient's infection [242, 243].

Evidence

Temocillin at a dose of 2g twice daily is an effective and well tolerated drug for urinary tract infection with AmpC- or ESBL-producing bacterial infection.

Evidence Level: 3

Although *in vitro* work suggests activity against many KPC-producing bacteria, there is little published clinical evidence to support this. Respiratory infections, including cystic fibrosis infections with *Burkholderia cepacia*, and other sites of systemic infection requires further clinical trials.

Evidence Level: 4

Recommendations

- Use alone for UTIs and associated bacteraemia caused by AmpC- or ESBL-producing Enterobacteriaceae.

  Grading: Conditional recommendation for

- Continuous infusion or thrice-daily dosing may be desirable for systemic infections with ESBL- or Amp-C producing bacteria

Grading: recommendation: for research and possible conditional recommendation for use restricted to trials

- Could use for UTIs with KPC-producing Enterobacteriaceae but not for OXA-48 or MBL-producers, on basis of published in-vitro data.

  Grading: Recommendation for research and possible conditional recommendation for use restricted to trials

7.9 Ampicillin/sulbactam

Sulbactam has *in vitro* microbiological activity against some strains of *A. baumannii*, including some carbapenem-resistant lineages. Microbiological studies showed that sulbactam alone (without ampicillin) was active against these bacteria [244]. In an uncontrolled study, forty-two patients with infections caused by multidrug –resistant *A. baumannii* were treated with sulbactam or ampicillin/sulbactam. Eighteen received sulbactam alone and 24 received ampicillin/sulbactam; no difference in cure rate was observed between the two groups. Another study compared ampicillin/sulbactam to colistin therapy in a retrospective review of patients who had nosocomial infections caused by carbapenem-resistant *Acinetobacter spp.* from 1996 to 2004 [245]. Eighty-two patients received polymyxins and 85 were treated with ampicillin/sulbactam. The authors concluded that ampicillin/sulbactam appeared to be more efficacious than polymyxins. More generally, and predictably, multivariate analysis found that prognostic factors for in-hospital mortality were older age, septic shock and higher APACHE II score. A small retrospective non-blinded trial compared treatment with ampicillin-sulbactam to imipenem and tried also to address the benefit of combining ampicillin/sulbactam with colistin. There was no difference in outcome [246, 247]. Two small RCTs have tried to assess differences in dosing regimens and efficacy compared with colistin [248, 249]. Overall the evidence base is poor and interpretation is difficult

without consideration of the MIC for the organism. In context sulbactam MICs for most UK isolates of carbapenem-resistant *A. baumannii* are 16-32mg/L implying poor rates of susceptibility (D,M. Livermore, unpublished data).

Evidence

Ampicillin/sulbactam appears effective in treating infections due to some carbapenem-resistant, *Acinetobacter spp*. but many isolates in the UK have relatively high sulbactam MICs.

Evidence level: 3

Recommendations

- Could use against some carbapenem-resistant apparently sulbactam-susceptible *A. baumannii* isolates, Caution needed in the UK because of a higher range of MICs. Absence of a breakpoint prevents categorisation as susceptible/resistant.

  Grading: Conditional recommendation for

7.10 Amoxicillin- clavulanate

Co-amoxiclav is known to select for Enterobacteriaceae resistant to the clavulanate component as well as amoxicillin in the gastrointestinal flora [250]. Co-amoxiclav has been successfully used to treat urinary tract infections due to ESBL-producers, as described in case reports and an observational study [251, 252]. The cure rate among 37 patients with cystitis treated with co-amoxiclav was 93% for those with susceptible isolates (minimum inhibitory concentration ≤8 mg/L) and 56% for those with intermediate or resistant isolates (minimum inhibitory concentration ≥16 mg/L) (P=0.02)[251]. The study was performed in Spain, where many ESBL-producers have CTX-M-14 enzyme; in the UK more have CTX-M-15 and many of these co-produce OXA-1, an inhibitor-resistant

penicillinase, raising co-amoxiclav MICs to the intermediate or resistant range. Furthermore MIC determinations were done with a β-lactam: β-lactamase inhibitor ratio of 2:1 and higher MICs would likely be obtained using the fixed clavulanate concentration of 2 mg/L now advocated by EUCAST. The outcomes for bacteraemias treated with co-amoxiclav or piperacillin/tazobactam have been reviewed and the findings are discussed in the section on piperacillin/tazobactam [253].

Evidence

These studies suggest that co-amoxiclav is effective in lower UTIs caused by ESBL-producing bacteria but efficacy was only reliably predicted in strains where these organisms were fully susceptible *in vitro* and lacked co-production of OXA-1 B-lactamase.

Evidence level: 3

Recommendations

- Use for lower UTI due to known ESBL-producing bacteria only if current isolates, or, if using empirically, recent isolates, are fully susceptible.

  Grading: Conditional recommendation for

7.11 Piperacillin/tazobactam

Different susceptibility standards are used worldwide and so correlations of mortality with in-vitro susceptibility cannot be reliably transferred between countries. EUCAST regards more isolates as resistant than CLSI. Some countries such as the UK have a higher prevalence of Enterobacteriaceae with CTX-M-15 and, in *E. coli*, OXA-1 β-lactamase and these are more resistant than the CTX-M-14 ESBL producers circulating, for example, in Spain. This may critically affect the validity of evidence collected from

different laboratories and hospitals about the adequacy of these combinations against ESBL-producing bacteria.

The use of piperacillin/tazobactam for treating bacteraemias caused by ESBL-producing bacteria remains consequently contentious. One recent retrospective analysis of 331 patients in a US hospital with bacteraemia due to ESBL-producing bacteria suggested carbapenems were superior to piperacillin/tazobactam [254]. One hundred three (48%) patients received piperacillin/tazobactam empirically and 110 (52%) received carbapenems empirically. The adjusted risk of death was 1.92 times higher for patients receiving empiric piperacillin/tazobactam compared with empiric carbapenem therapy. Another retrospective study of bacteraemic patients with ESBL-producing *P. mirabilis* compared the outcomes of patients treated by piperacillin/tazobactam or a carbapenem for at least 48 hours [255]. Forty-seven patients with available clinical data were studied of whom 34 were included. Only 11% of strains were imipenem susceptible but MICs of the drug for Proteeae typically cluster around the breakpoint. The overall 30-day mortality rate was 29.8%. 3/21 patients treated with carbapenems (all imipenem) died within 30 days (all in hospital) versus 4/13 treated with piperacillin-tazobactam – a non-significant difference. Furthermore, among those treated by piperacillin/tazobactam, the mortality rate was lower in those infected by the isolates with lower piperacillin/tazobactam MICs (≤0.5/4 mg/L) when compared with isolates with MICs of ≥1/4 mg/L (0/7 versus 3/5; P = 0.045). A study of 39 episodes of bacteraemia due to ESBL-producing *E. coli* from Spain found a statistically significant reduction in 30 day mortality in infections from non-urinary sources if the MIC ≤ 2 mg/L (0/11) compared with those strains with higher MIC (7/17)[256]. This suggests that even the current EUCAST breakpoints (S<8mg/L, R>16mg/L) are too high to give guidance on clinical response. An analysis of patients with bacteraemias due to ESBL-producing E. coli was performed to assess the efficacy of combinations of

piperacillin/tazobactam or co-amoxiclav compared with carbapenems [253]. Mortality in patients treated with such BL/BLI combinations or carbapenem was compared in two cohorts: empirical therapy and definitive therapy. Mortality rates at day 30 for those treated with BL/BLI versus carbapenems were 9.7% versus 19.4% for empirical therapy and 9.3% versus 16.7% for definitive therapy respectively. After adjustment for confounders, no association was found between either empirical therapy or definitive therapy and increased mortality. The study suggested that co-amoxiclav and piperacillin/tazobactam may be suitable alternatives to carbapenems for treating patients with bacteraemias due to ESBL-E coli but only in the minority that were susceptible in vitro. The study was not randomized, and confounding due to unmeasured variables may have occurred. This retrospective observational study has been repeated on a multi-national basis and extended to 627 patients with results that BL/BLI combinations were statistically as effective as carbapenems in empirical and directed therapy against ESBL-producing Gram-negative bacteraemia [257] A subset of 207 patients had their ESBL genes of their pathogens examined by PCR:42 were identified as CTX-M-15, 27 as CTX-M-1, 31 CTX-M-14 and 18 as CTX-M-9. No details were given of response rates in relation to the presence of specific resistance genes and co-production of OXA enzymes was not sought. In another study co-amoxiclav and piperacillin/tazobactam susceptibility of the bacteria causing bacteraemia, particularly for E. coli ST 131, were not correlated: 51% of the isolates also had OXA-1 and 90% of isolates were reported susceptible to piperacillin/tazobactam versus 26% susceptible to co-amoxiclav by CLSI criteria [258]. Such discrepancies with different BL/BLI may relate to whether the EUCAST or CLSI breakpoints are used as the MICs for many isolates with a combination of CTX-M-15 and OXA-1 enzymes cluster around 16mg/L. The relationship of the BL/BLI used and its MIC for infecting strain to efficacy in lower UTIs (where urinary concentrations are higher than in serum) or bacteraemia needs to be

established. More generally, individual drug/inhibitor combinations must be separately studied for efficacy, and related to both the β-lactamase genes present and in vitro susceptibility. As American commentators have pointed out [259], it is important to note the dosing regimen when considering response to piperacillin-tazobactam of many ESBLs. Many Spanish studies used piperacillin-tazobactam at 4.5g 6-hourly not the usual licensed UK dose of 4.5g 8- hourly. With B-lactams increasing the time above the MIC substantially decreases mortality [260]. It is possible that more frequent dosing would achieve this. More materially this can be achieved with continuous infusion, albeit with higher daily drug dosage (which might breach targets to reduce use) and could be considered to increase efficacy of piperacillin-tazobactam. It cannot be anticipated with biliary excretion whether this will change selection pressure for superinfecting organisms or *C. difficile* in the gastrointestinal flora.

A retrospective case review of empirical treatment of bacteraemia caused by ESBL-producing *E. coli* or ESBL-producing Klebsiella sp. showed a mortality rate of 18/70 (25.7%) when patients received carbapenems. If they received piperacillin/tazobactam 8/44 (18.2%) died if the strain retrospectively was susceptible by CLSI criteria but 3/6 died if the strain was resistant or intermediate Similarly, if they received co-amoxiclav 3/40 (7.5%) died if the strain retrospectively was susceptible by CLSI criteria but 10/27 (37%) died if the strain was resistant or intermediate[261] piperacillin/tazobactam. Data on the genotypes of the ESBL producers present was not provided.

The findings of all these studies cannot be simply applied to the UK where many ESBL-producing strains are more resistant than CTX-M-14 as they co-produce CTX-M-15 and OXA-1 β-lactamases, with the latter enzyme compromising susceptibility to piperacillin/tazobactam. Variable dosing further complicates the picture

Piperacillin/tazobactam is commonly used to treat infections caused by *P. aeruginosa*. A retrospective cohort study of bacteraemic patients showed that in 34 episodes of bacteraemia caused by strains with a MIC of 32 or 64 mg/L piperacillin/tazobactam , the 30-day mortality was significantly greater than controls given other appropriate therapy [262]. At the time, CLSI defined strains as susceptible if they had an MIC of ≤64mg/L whereas EUCAST, then as now, has a breakpoint for susceptibility of <= 16+4mg/L and for resistance >16+4mg/L

Evidence

Could use piperacillin/tazobactam in some blood stream infections where ESBL-producers appear susceptible *in vitro* but mortality may be higher than with carbapenems.

Evidence level 2-

Mortality when piperacillin/tazobactam is used in blood stream infection due to ESBL-producing Enterobacteriaceae without regard to *in vitro* susceptibility appears higher than with carbapenems.

Evidence level 2+

In vitro susceptibilities by EUCAST and CLSI recommendations on what is a susceptible organism differ for Enterobacteriaceae but only two-fold. There is no good analysis of the impact of this difference in relation to i) strain MIC ii) clinical outcome of infections at different sites and iii) different ESBL genotypes

Evidence level: 4 .

Breakpoints for piperacillin/tazobactam against Enterobacteriaceae have changed with time. Better outcomes may be seen with isolates much more susceptible (MIC <=2mg/L)

than the currently agreed piperacillin/tazobactam Enterobacteriaceae breakpoints (EUCAST Sensitive if MIC<=8+4mg/L resistant if MIC>16+4mg/LCLSI Sensitive if MIC <=16+4mg/l/, resistant if MIC >=128+4mg/L.

Evidence level: 3

Recommendations

- Use for infections with known ESBL-producing bacteria only if current isolates, or, if using empirically, isolates from the recent past, are fully susceptible.

  Grading: Conditional recommendation for

- Consider definitive use of piperacillin/tazobactam to treat infections caused by *P. aeruginosa* if susceptible by EUCAST standards.

  Grading: Conditional recommendation for

7.12 Aminoglycosides

Parenteral broad-spectrum aminoglycosides are potentially important carbapenem-sparing drugs for infections due to MDR-GNB. Three such antibiotics, gentamicin, tobramycin and amikacin remain available in the UK following withdrawal of netilmicin and sisomicin. These antibiotics have intrinsic activity against all *P. aeruginosa*, *Acinetobacter spp*. and Enterobacteriaceae but plasmid-borne resistance (and chromosomal resistance in *Providencia spp.* and *Serratia spp.*) now limits their spectrum. Resistance is mostly due to i) bacterial aminoglycoside-modifying enzymes which acetylate, phosphorylate or adenylate vulnerable hydroxyl or amino groups or ii) to 16s ribosomal methyltransferases which alter the binding site for aminoglycosides. The latter mechanism produces pan-resistance to aminoglycosides except the veterinary product apramycin [263]. By contrast, the vulnerability of aminoglycosides to

modifying enzymes varies, with amikacin inactivated by fewer enzymes than gentamicin or tobramycin [264]. Initially aminoglycoside-modifying enzymes were restricted to certain species but integron and transposon carriage have mediated their wide dissemination.

Amikacin evades AAC (3) and AAC (2') enzymes but remains vulnerable to AAC (6')-I as does tobramycin. AAC(6')-1b-cr arose from AAC(6')-1b by the substitutions Trp102Arg and Asp179Tyr and can acetylate ciprofloxacin (not levofloxacin) as well as aminoglycosides causing deactivation. This enzyme, formerly rare in the UK [265] is commonly found in *E. coli* ST131. Amikacin MICs typically are raised to just below the susceptible breakpoint. Such reductions nevertheless may be important since efficacy of aminoglycosides is proportional to the ratio of peak concentration to MIC [266]. EUCAST currently suggests that reports on isolates with this enzyme are edited to amikacin-resistant but this is under review. In contrast to other common aminoglycoside modifying enzymes AAC (6')-1 spares gentamicin. Aminoglycoside-nucleotidyl transferases (ANT-6, ANT-9, ANT-4', ANT-2", and ANT-3") do not confer amikacin resistance nor – except APH (3)-V1 which is mostly confined to *A. baumannii* - do aminoglycoside phospho-transferases in Gram-negative species.

Overall resistance rates to gentamicin in community-onset *E. coli* bacteraemia in 2012-2014 was 8.6%. This is a similar figure to the 8.7% resistance rate to piperacillin/tazobactam in community-onset cases. Such data must be considered when empirically treating probable Gram-negative bacteraemia of likely urinary or unknown origin [94]. In the 1980s, parenteral aminoglycoside therapy rarely selected for resistant Enterobacteriaceae in the gut flora [267] but oral aminoglycosides given for selective digestive decontamination in haematological malignancy frequently did so [268] and continued to do so over a 20 year period once resistance emerged - even when combined with oral colistin [269].

There is limited surveillance of the genotypic distribution of aminoglycoside-modifying enzymes except in specific strains and in those with other resistances (e.g. ESBL-producers). Little is known of travel associations beyond those to gentamicin and tobramycin (but to a lesser extent amikacin) associated with acquisition of ESBL- or carbapenemase producers for which there are clear travel links [270].

Aminoglycoside activity against *P. aeruginosa* varies between patients with cystic fibrosis where aminoglycosides continue to be heavily used and patients with other comorbidities. Resistance due to efflux pumps and permeability defects are common, as well as aminoglycoside-modifying enzymes. Tobramycin which has greater intrinsic activity than gentamicin against this species (off-setting its lower activity against Enterobacteriaceae) and which causes less toxicity than gentamicin, continues to be the aminoglycoside most likely to remain active. A recent meta-analysis continues to suggest that use of B-lactam aminoglycoside combinations in the absence of cystic fibrosis offers no statistically significant advantage in terms of outcome compared to use of an active B-lactam alone [271].

A new aminoglycoside plazomicin (ACHN 490, Achaeogen)[272, 273 274] has completed clinical trials. This evades modification by almost all aminoglycoside modifying enzymes except the AAC(2') chromosomal enzymes of *Providencia spp*. It is however compromised by the plasmid mediated ArmA and Rmt 16S ribosomal methyltransferases which are currently rare in UK MDR GNB except in Enterobacteriaceae strains producing NDM-1 carbapenemase [263] or OXA-23 carbapenemase-producing *A. baumannii* which have spread globally over the last 10 years.

Aminoglycosides have a narrow margin between being effective and toxic to the auditory and vestibular apparatus or to the kidneys. They fell from favour as broader –

spectrum B-lactams were developed. For acceptably safe use, intervals between doses are increased usually to a minimum of once daily but with doses related to renal clearance and MIC and the presumption of a post-antibiotic effect. If the dosage is based on the patient's weight it is possible, using a nomogram, to model the likely blood concentration at varying intervals after the dose. Measuring plasma levels between 6 and 14 hours after the dose, usually now by immunoassay, and relating these levels on to the nomogram permits more precise dosing intervals than by measuring renal function. Nomograms for gentamicin and tobramycin at doses of 7mg/kg [275] and 5mg/Kg [276] in adults have been constructed and their use is associated with a low incidence of detected ototoxicity (3/2184 cases in the former). The dosage recommendation for amikacin is 15mg/kg/day reflecting that, amikacin MICs are 2 to 4 fold higher than gentamicin MICs for susceptible strains. Much higher incidences of toxicity with all aminoglycosides are well recorded and it is still common to encounter in the UK deficiencies in i) weight-related dosage ii) dosage interval especially if there is renal impairment, iii) measuring levels in every case, and iv) taking blood for assay at the correct interval after dosage and recording both the time of administration and time of sample collection to enable later interpretation of assay results by other staff. Validation of expected and achieved serum levels has been undertaken for 7mg/kg dose but not 5mg/kg doses which are based on exclusion of some patients considered in the former study. There is no validated nomogram for amikacin [277] and immunoassays for this antibiotic are not widely available on automated immunoassay platforms. There are no trial data on amikacin use in *E. coli* ST131. Vestibular toxicity with all aminoglycosides commonly presents after the drug has stopped and the patient has left hospital [278, 279]. Toxicity can occur after normal courses of 5 daily doses or even a single dose [278]. Auditory toxicity is initially often subclinical requiring audiograms to detect. The true incidence of toxicity is difficult to determine. Renal toxicity can be measured by

quantitative renal function tests or qualitative urinary renal tubular enzymes. These critical steps to safe use as determined by case follow-up after the patient has left hospital, have not yet been assessed for plazomicin although there are no described cases of toxicity yet in clinical trials. In older studies before the adoption of once daily regimens and weight-related dosage, auditory toxicity appears to have been commoner with amikacin than gentamicin whilst vestibular toxicity rates were not significantly different [280]: toxicity was commoner with increasing age paralleling a decline in renal function [281]. This creates an issue, insofar as infections with MDR GNB and ESBL-producers occur more frequently among those aged over 65 years and especially over 75 years of age. It is noteworthy that one recent Scottish national intervention in surgery as part of targeted antimicrobial stewardship measures to reduce the incidence of *C. difficile* by 30% in 2 years was to substitute use of gentamicin for cephalosporins in prophylaxis in surgery. In Tayside, a interrupted time series with segmented regression in 7666 patients undergoing orthopaedic surgery (excluding fractured neck of femur),where 2 doses of flucloxacillin 1G and one dose of 4mg/Kg gentamicin were substituted for cefuroxime was performed. An unacceptable 94% increase in acute kidney injury in gentamicin-treated patients occurred and the gentamicin use was stopped [282]. Patients undergoing implant surgery had a mean age of 71 years and 36% had received non-steroidal anti-inflammatory drugs in the last year and 38% received a diuretic which are known cofactors for gentamicin nephrotoxicity but this was adjusted for in the study. One year mortality was higher in the acute kidney injury group (20.8% vs. 8.2%). There was no association of acute kidney injury in a further 4816 patients in other surgical specialties where gentamicin was substituted. It is not certain whether the effect was due to gentamicin, flucloxacillin, or the combination or whether all patients additionally received gentamicin bone cement.

Evidence:

Aminoglycosides retain activity against a similar proportion of Enterobacteriaceae to piperacillin/tazobactam (8.6-8.7%). However approximately 50% of ESBL-producing *E. coli* in the UK are resistant to gentamicin and more to tobramycin.

Evidence level: 3

Overall resistance rates to amikacin are lower than to gentamicin and tobramycin in the UK. However bacteria producing AAC(6') are usually amikacin resistant and bacteria producing the AAC(6')-1b-cr enzymes including many E. coli ST131 often have reduced amikacin susceptibility. Strains producing NDM-carbapenemase often carry 16S ribosomal methyltransferases which confer high-level pan-resistance to aminoglycosides including amikacin and plazomicin. 16S ribosomal methyltransferases are also frequent in UK A. baumannii.

Evidence level: 3

Plazomicin, a new aminoglycoside evades almost all aminoglycoside-modifying enzymes but is inactive if 16s ribosomal methyltransferases are present. It has recently completed a phase 3 RCT with superiority to meropenem in complicated UTI so far reported only in a press release.

Evidence level: 3

Historically parenteral aminoglycosides rarely proved selective for resistance among Enterobacteriaceae in the faecal flora. However, because of resistance linkage and carriage on transposons and integrons aminoglycoside resistance may be selected by use of other antibiotics.

Evidence level 3

Evidence from travel-associated ESBL-producers suggests that aminoglycoside-resistance may also be travel-associated. The co-carriage of 16S ribosomal methyltransferases by strains with NDM-carbapenemase linked to the Indian sub-continent is noteworthy.

Evidence level: 3

The narrow therapeutic index of aminoglycosides demands attention to the detail of weight-related dosing and frequency of doses, collection of blood at an appropriate time for assays, and the careful interpretation of antibiotic assays by nomograms. These actions are essential for adequately safe management of patients treated with gentamicin and tobramycin. Similar modern safety measures are likely to be necessary for amikacin and plazomicin but nomograms are not, and assays may not be, widely available.

Evidence level: 4

When strains are susceptible and safety measures are well-organised and reviewed in hospitals, gentamicin and tobramycin are useful carbapenem-sparing agents for definitive treatment.

Evidence level: 4

Recommendations

- Could use gentamicin empirically in the UK if the likelihood of MDR GNB is low.

  Grading Conditional recommendation for

- Could use gentamicin as a carbapenem sparing agent for urinary, intra-abdominal and bacteraemic infections due to ESBL-producing E. coli when

susceptibility is confirmed but do not use empirically if the risk of MDR GNB is raised

Grading: Conditional recommendation for.

- Could use gentamicin in combinations for urinary, intra-abdominal and bacteraemic infections due to gentamicin-susceptible KPC-producing Klebsiella *spp*. if strain is resistant to colistin and meropenem (See Section 7.18).

Gradingl: Conditional recommendation for

- Use once daily dosage of gentamicin if no renal impairment followed by measurement of levels 6 to 14 hours post dose and adjust repeat dosage by reference to the appropriate 7mg/kg or 5mg/kg nomogram. Consider increased risks of toxicity if there is co-administration of nephrotoxic or ototoxic drugs.

Grading: Strong recommendation for.

- Avoid tobramycin for MDR Enterobacteriaceae because of risk of resistance due to AAC (6')1 and AAC (6')-1b-cr

Grading: Conditional recommendation against

- Use tobramycin in preference to other aminoglycosides for susceptible Pseudomonas infection

Grading: Conditional recommendation for

- Use once daily dosage of tobramycin if no renal impairment followed by measurement of levels 6 to 14 hours post dose and adjust repeat dosage by reference to nomogram.

Grading: Strong recommendation for

- Modernise use of amikacin, which has improved activity, with development of validated nomograms. Ensure assays are readily available before repeat doses and consider, because of the risks of toxicity, the practicality of monitoring with audiograms.

  Gradingl: Conditional recommendation for.

7.13 Polymyxins

The polymyxins are a group of five chemically different bactericidal antibiotics (polymyxins A to E). Only polymyxin B and polymyxin E (colistin) have been used in clinical practice. Intravenously administered colistin methane sulphonate is most widely used, and requires conversion in the body to the active colistin molecule. Polymyxins have a wide spectrum of activity against Gram-negative organisms, including most Enterobacteriaceae, *A. baumannii, P. aeruginosa* and *S. maltophilia*, but are inactive against *B. cepacia*, *Proteus spp.*, *Providencia spp.*, *Morganella spp.* and *Serratia marcescens.* Resistance to colistin occurs in some *P. aeruginosa* isolates [283]but remains rare and almost exclusive to cystic fibrosis isolates. Acquired colistin resistance is generally rare but has become common in *K. pneumoniae* in Italy. Colistin heteroresistance is defined as the emergence of resistance to colistin in a subpopulation of an otherwise susceptible (MIC of ≤2 mg/L) population [284]. This may be related to exposure to suboptimal polymyxin concentrations. Detection of resistance or hetero-resistance is difficult and requires MIC-testing either by broth microdilution, or agar dilution: Etest®, disc diffusion, Microscan [285] and VITEK2 are currently unreliable [286] and no data are published for Phoenix. The difficulty of detecting colistin resistance in routine laboratories and its widespread presence (13%) in KPC-producing Klebsiella when tested in reference laboratories was evident in a recent US study [287] Resistance to gentamicin was rarer and tigecycline resistance commoner in colistin-resistant isolates.

Colistin resistance was associated with increased hospital mortality. Most colistin resistance is chromosomally mediated, involving various mutations that modulate two component regulatory systems (e.g. *pmrAB*, *phoPQ* and its negative regulator *mgrB* in the case of *K. pneumoniae*), leading to modification of lipid A with moieties such as phosphoethanolamine or 4-amino-4-arabinose, or in rare instances to total loss of the lipopolysaccharide [288]. Of concern is the recent reporting of plasmid-mediated polymyxin-resistance lipid A-modifying enzymes (MCR-1 and 2) that confer resistance in Enterobacteriaceae [24]. MCR-1 was first found in China but is now being detected worldwide mainly in Enterobacteriaceae of animal origin but also in occasional human isolates. It remains much rarer than mutational resistance. China plans to stop use of 8000 tons of colistin in animal feed from April 2017. A recent study shows MCR genes are very widespread (50-100%) in chicken in hatcheries, commercial farms and supermarkets and a slaughterhouse in Shandong, Although testing of hatcheries was negative, NDM-carbapenemase-producing E. coli were recovered from 21.8% of samples. 23% of carbapenem-resistant E. coli tested MCR-1 positive and multiple sequence types and NDM subtypes were found[289]. There are widespread reports of MCR-1 in the European (including UK) food-chain.

Synergy studies suggested many years ago [290-294] that polymyxins, trimethoprim and sulphonamides might be useful together in therapy and these studies need repeating with other agents and newer strains.

Pharmacokinetic and pharmacodynamic data have been limited, particularly in critically ill patients. Polymyxins were developed before the advent of contemporary drug evaluation. Colistin methanesulfonate is an inactive pro-drug converted in vivo to the active drug and different brands may produce different concentrations of active drug. Data suggested drug concentrations are very variable and dosing in excess of data-sheet recommendations may be required commonly on the basis of pharmacokinetic

parameters [295]. Recently the FDA and European medicines agency have made new, but different, recommendations for intravenous colistin in patients with various degrees of renal function. These have been assessed using data from 162 adult critically ill patients with varying renal function. A comparison showed that adequate serum levels with impaired renal function were more likely to be attained with European guidelines and a later paper suggests that in the critically ill target concentrations are difficult to achieve if creatinine clearance =>80ml/min/1.73m$^{2.}$ [296, 297]. Data are also now available on the implications of haemodialysis [298]. Therapeutic drug monitoring is advisable, if available and depends critically on maintaining stability of the drug in separated plasma.

Colistin can be given intravenously, or in respiratory infection via the aerosol route (typically in patients with CF; either alone or combined with IV administration), or intrathecal.

Polymyxin B or colistin sulphate can be given orally as a non-absorbed major component of selective digestive decontamination regimens. Selective digestive decontamination has been widely used for general infection prevention in neutropenia and intensive care. Polymyxins orally were widely added in haematology to aminoglycosides, trimethoprim-sulfamethoxazole [299] or ciprofloxacin [269] to prevent emergence of resistance and in intensive care units to parenteral cephalosporins and oral tobramycin [300]. Recent findings that colistin resistance is difficult to detect accurately and it's frequency is usually underestimated, the clear emergence in China and elsewhere of plasmid mediated resistance and the emergence of colistin resistance in KPC-producing *Klebsiella spp*. in Italy, China and the USA imply that it can no longer be relied on to prevent emergence of resistant strains in patients who have strains that are already frequently resistant to the drugs it was added to protect. Use of colistin in all patients in such a unit might well become a mechanism now for selection for XDR GNB or indeed pan-drug resistant MDR GNB in the critical care and haematology units where

it is used. This is an enduringly controversial area [301] which we do not have space to fully review but such selection of colistin resistance in ESBL-producing *Klebsiella spp.* in an ICU has already been reported [302]. We consider continued use of colistin-containing decontamination regimens should be reviewed urgently within specialties [303]and at the local level, and in our judgement is now unwise.

Clinical reports and reviews of experience with colistin are relatively encouraging, with side effects (principally nephrotoxicity and neurotoxicity) observed less often than expected from historical data [304-309]. These studies are summarized in Table 6. In Italy strict rules for the use of colistin are advocated to stop the spread of colistin resistant KPC-producing *Klebsiella spp.*, which have increased three fold in 4 years among bacteraemic patients. A case-control study of this guidance showed associations of resistance with previous colistin therapy, previous colonization or infection with KPC-producing *Klebsiella spp.*, and a Charlson comorbidity score >3 (all of which were associated with mortality) and also with neutropenia and >3 hospitalisations [310].

The addition of aerosolized to IV colistin has been compared to IV colistin alone for the treatment of VAP in several studies. Korbila and colleagues demonstrated an improvement in outcome with the addition of aerosolized colistin [311] but no benefit was demonstrated in another study [312]. Both had methodological flaws. NICE has recently reviewed the usefulness of aerosolised colistin or tobramycin dry powders in patients with cystic fibrosis and concluded there were some patients who would benefit from colistin dry powder with cost reduction [313].

Polymyxin B is more toxic than colistin (polymyxin E) but has the advantage of not requiring subject-variable conversion to an active form, A recent retrospective cohort study compared 45 patients with *P. aeruginosa* bacteraemia treated with polymyxin B at a median dose of 141+/-54 mg/day usually in 2 divided doses: 11 received

>200mg/day. Eighty eight patients were treated with a comparator (typically a β-lactam). The in-hospital mortality was 66% in the arm treated with polymyxin B versus 28% for those treated with a comparator, even when matched for mechanical ventilation and sepsis score suggesting polymyxin B was inferior [314]. This was regardless of dosing regimens. A higher dose (≥200mg/day) of polymyxin B was found to be associated with reduced mortality but increased renal impairment in another retrospective cohort study [315]. We do not recommend use of polymyxin B in the light of these results.

Combinations including colistin are more effective than monotherapy in treating *K. pneumoniae* carbapenemase (KPC) infections (See 7.18) [316, 317].

Nephrotoxicity and neurotoxicity are the principal side effects associated with parenteral administration of polymyxins. The toxicity demonstrated in earlier studies was almost certainly related to lack of understanding of the drug's PK/PD and the use of inappropriate doses [318]. Studies now suggest that age, high doses, prolonged courses, concomitant vancomycin, hypoalbuminaemia and non-steroidal anti-inflammatory drugs, are independent risk factors for nephrotoxicity [319, 320] and it is likely that other nephrotoxic drug are also associated. Monitoring renal function closely is essential for patients receiving colistin. Recent expert opinion suggests the risk benefit ratio should be carefully considered with strategies applied to reduce toxicity[321]. There is no information on the dose-relationship of reversible neurotoxicity or encephalopathy: in a recent large paediatric series they occurred in 2% of patients [322]

There are gaps in our knowledge about these agents. Although they were developed some seventy years ago . they have only recently been used extensively. Much of the current knowledge is summarised in the Prato consensus report [323].

Dosing of intravenous colistin remains contentious. In adult cystic fibrosis (CF) patients, colistin is typically given at a standard dose of 2MU 8-hourly. However, evidence is emerging that higher-dose regimens may be more appropriate in the ICU setting (with therapeutic drug monitoring: to target a peak of 5-15mg/L and a trough of 2-6mg/L). A recent study of significant infections caused by a range of MDR GNB suggested that a loading dose of 9MU followed by 4.5MU twelve hourly reduced in renal impairment was effective (23/28 responses) and resulted in a reversible mild renal injury in only 5 patients [324]. Further clinical and PK/PD studies are required to confirm appropriate regimens including in relation to a loading dose, combination therapy and the need for monitoring. In the meantime European medicines agency guidance should be followed.

Evidence

Colistin is effective in treatment of infections caused by MDR GNB with low mortality at higher-than-previous, but well-controlled dosage.

Evidence level: 3

The role of loading doses of colistin, monitoring of serum levels and optimal combination therapy are inadequately researched.

Evidence level: 4

Use of aerosolized colistin dry powder has recently been accepted by NICE in cystic fibrosis.

Evidence level: 3

Use of aerosolized colistin dry powder in ventilator-associated pneumonia as an addition to intravenous chemotherapy appears useful.

Evidence level: 3

The dose-relationship of colistin nephrotoxicity and the rarer neurotoxicity and encephalopathy, require investigation.

Evidence level: 4

Recommendations

- Reserve intravenous polymyxins for infections due to susceptible multi-resistant strains and preferably used in combination with other agents.

  Grading: Conditional recommendation for

- Give careful consideration to use of higher dosage regimens in critically ill patients

  Grading: Conditional recommendation for

- Closely monitor renal function especially in the elderly, those receiving high intravenous doses for prolonged periods and those on concomitant nephrotoxic agents e.g. aminoglycosides.

  Grading: Strong recommendation for

- Reconsider use of polymyxins in selective digestive decontamination regimens as these agents are now important last therapeutic options against carbapenemase-producing Enterobacteriaceae and are more threatened by resistance than previously appreciated.

  Grading: Good practice point.

- Need research on optimal rapid and practical methods of susceptibility testing outside intrinsically resistant groups such as Proteeae and *Serratia spp.*

Grading: Recommendations for research

- Aerosolised colistin dry powder should be used in cystic fibrosis according to NICE guidelines, Use in combination in ventilator-associated pneumonia may be considered pending further trials without methodological flaws.

  Grading: Conditional recommendation for

7.14 Fluoroquinolones

Fluoroquinones suppress susceptible Enterobacteriaceae in the intestinal flora and also select for quinolone-resistant MDR GNB [250] [131]. Such suppression has been used in neutropaenic patients alone or with colistin [269]. The continued efficacy of this combination in suppression and non-selection of resistance to either agent needs re-establishing with the increasing recognition of colistin resistance which may well emerge alongside existing quinolone-resistance. Prophylaxis with quinolones alone in neutropenia against susceptible bacteraemia seems effective even when quinolone-resistance levels in the treated population reach a high level. Trials of withdrawing prophylaxis have been reported and show problematic increases in Gram-negative bacteraemia (See 6.5.)

Fluoroquinolones (intravenous and oral) may be suitable for complicated urinary tract infections due to ESBL-producing Enterobacteriaceae if there is no resistance *in vitro*: however most ESBL-producing strains in the UK are resistant to fluoroquinolones including ciprofloxacin and levofloxacin. Furthermore quinolone resistance without ESBL production is now frequent, particularly in the multiple resistant if not MDR E. coli ST131 [89]. Newer quinolones in development are unlikely to provide substantial additional benefits over ciprofloxacin for infections due to Gram-negative pathogens. Three observational clinical studies have assessed the relative merits of quinolones and carbapenems for serious infections due to ESBL-producing organisms [181, 325, 326]. Two of

these found that carbapenems were superior to quinolones, although most strains were quinolone susceptible, whereas one study found equivalent effectiveness.

Fluoroquinolones have been used to treat infections caused by *S. maltophilia*; however resistance is not uncommon so combination with one or more of: trimethoprim/sulfamethoxazole, ceftazidime, or tigecycline has been proposed [327]. These combinations have not been shown to offer any advantages over trimethoprim/sulfamethoxazole alone. A wide range of resistance mechanisms exist: high-level resistance almost always involves mutations in the genes encoding subunits of the target-enzymes, DNA gyrase and topoisomerase 1V (*gyrA* and *p*arC respectively), but reduced susceptibility can arise from plasmid-acquired genes e.g. *aac (6')-1b-cr, oqxAB, qnrA,* etc. or via up-regulation of outer-membrane efflux pumps and porin loss [328].

Evidence

Quinolones are effective in treatment of complicated urinary tract infection caused by susceptible ESBL- producing Gram-negative bacteria, but resistance is common limiting their usefulness.

Evidence level: 2+

Recommendations

- Could use orally to treat UTI caused by MDR GNB that are susceptible

  Grading: Conditional recommendation for

7.15 Tigecycline and eravacycline

Tigecycline is a semisynthetic glycylglycine derivative of minocycline and like other tetracyclines is bacteriostatic. [329]. The main determinant of acquired plasmid-mediated,

resistance to older tetracyclines in Gram-negative bacteria, namely active efflux by *Tet* pumps is overcome by steric hindrance by a large substituent group. Tigecycline has *in vitro* activity against most Enterobacteriaceae except Proteeae i.e. *Proteus spp.*, *Providencia spp*. and *Morganella morganii.* MICs for *A. baumannii* (including many carbapenem resistant strains) and *S. maltophilia* are low (mostly 0.25-2mg./L) but, there are no break points or convincing efficacy studies. In common with other tetracyclines, tigecycline lacks useful activity against *P. aeruginosa.* . Tigecycline is vulnerable to the chromosomal resistance–nodulation–cell division (RND) multidrug efflux pumps, including *MexXY–OprM* of *P. aeruginosa*, and the AcrAB pump found in *Proteus mirabilis* which explains the intrinsic resistance of these species [330, 331]. Upregulation of analogous RND pumps in other Enterobacteriaceae and *A. baumannii*.

Whilst tigecycline resistant isolates of Enterobacteriaceae have been described from treatment naïve patients, another potential problem is the development of resistance during treatment of infections with Enterobacteriaceae and *Acinetobacter spp.* by the mutational up-regulation of *RND* pumps,, but the frequency is unclear particularly when used in combination [332-336]. Use of tigecycline is an independent predictor of emergence of tigecycline resistance when treating multi-resistant *K. pneumoniae* infection [337]. Further studies are required, possibly including different dosing regimens and in combination with other agents. Tigecycline has a potential to favour superinfections by *P. aeruginosa*, Proteeae [338] and sometimes *Klebsiella spp*. [339] [337]; again, these aspects require further investigation.

Subject to the earlier caveat about the lack of breakpoints, tigecycline has *in vitro* activity against *S. maltophilia*, and susceptibility rates of >87% have been reported [340]. However there is little clinical experience with the drug in treating infections caused by this organism.

Intravenous tigecycline is licensed for the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections [341, 342]. However, the US FDA issued a warning describing an increased mortality risk with its use when compared with other drugs[343, 344]. The highest risk was in patients treated for ventilator-associated pneumonia, which was not a licensed indication. However even in FDA approved uses there was a higher risk of death among patients given tigecycline compared with those given other antibacterial drugs [345, 346]. There are no RCTs comparing tigecycline with polymyxins, fosfomycin, sulbactam and other antibiotics against infections due to MDR GNB, alone or in combinations [347]. Several meta-analyses examine the efficacy and safety of tigecycline in general (not just against MDR GNB) and these reported conflicting findings. One very recent analysis reviews the earlier studies and includes a number of new trials. Clinical success rates were lower than comparator for hospital-acquired pneumonia and diabetic foot infection, with increased gastrointestinal adverse events and higher all-cause mortality probably due to reduced efficacy [348].

Further work on tigecycline is needed, as its efficacy in ventilator associated pneumonia might be improved using higher doses (i.e. 200 mg initial and then 100 mg twice daily): an increase in adverse events was not seen with this regimen[349] . Tigecycline in combination with other antibiotics (e.g. carbapenems and polymyxins) is a potentially valuable approach for infections caused by carbapenemase-producing *Klebsiella spp.*, as shown by [350] .In this retrospective cohort study largely of infections due to strains with KPC-3 carbapenemase 9/19 patients survived on tigecycline monotherapy, 0/11 on colistin monotherapy and 16/23 with tigecycline and colistin combinations. Two comparisons of monotherapy and combination therapy for infections with carbapenemase-producing *Klebsiella spp*. give further survival data on monotherapy: survival was respectively 71/116 for tigecycline and 70/132 for colistin [316] and 16/27 for tigecycline and 12/22 for colistin [351].

Whilst the *in vitro* data supports use of tigecycline in respiratory infection there is poor correlation between the laboratory results and clinical outcome [334, 352, 353].

Eravacycline is a novel intravenous fluorocycline with a similar spectrum to tigecycline. It showed non-inferiority to ertapenem in a Phase 3 trial of complicated intra-abdominal infection but failed to show non-inferiority to levofloxacin in an iv/oral switch Phase 3 trial of complicated UTI [354-356].

Evidence

The role of tigecycline remains uncertain in the treatment of infections due to MDR GNB.

Evidence level: 1-

Recommendations

- Could use tigecycline in combination in the treatment of multi-resistant soft tissue and intra-abdominal infections

  Grading: Conditional recommendation for

- Use alone in hospital-acquired respiratory infections is unlicensed and not advised with licensed dosing as outcomes are not clearly satisfactory in Acinetobacter and MDR GNB infections.

  Grading: Conditional recommendation against

- Use in combinations in hospital-acquired respiratory infections: precise combinations depend on the antibiotic-susceptibility of the MDR GNB causing the infection.

Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

- Use higher-than licensed dosing such as 100mg twice daily for infections due to MDR GNB in critical care

  Grading: Conditional recommendation for.

- Investigate if higher dosing counters the unexpectedly high mortality seen even in infections due to strains apparently susceptible *in vitro*.

  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

7.16 Fosfomycin

Fosfomycin, a strongly hydrophilic phosphonic acid (unrelated to aminoglycoside or macrolide antibiotics), inhibits the addition of phosphoenol-pyruvate to N-acetyl-glucosamine in synthesis of the bacterial cell wall. Fosfomycin MICs of *E. coli* vary from 1-4mg/L : those for *Klebsiella spp*. are higher at 2-64mg/L EUCAST breakpoints for both formulations are S <32mg/L, R >32mg/L *Morganella morganii* and *Bacteroides spp.* are inherently resistant and activity against *P. aeruginosa* is controversial, particularly in combination, although MICs=>128mg/L. The drug is otherwise very broad in its spectrum. Fosfomycin was active against 72% of Enterobacteriaceae resistant to carbapenems in a German study [357]. *In vitro* testing with discs required the addition of Glucose 6 phosphate to the disc. In this study there were 22% major discrepancies between agar dilution in medium containing glucose-6 phosphate and disc or E-test testing and it is not clear if glucose-6- phosphate was present in discs and E-tests, an area for quality control development. There are similarly no published details on the reliability of automated susceptibility testing methods.

Fosfomycin trometamol is used as an oral treatment for patients with uncomplicated lower UTI due to fosfomycin-susceptible organisms resistant to first line agents. At the conventional dosage of 3g on a single occasion this oral formulation gives an adequate urinary concentration for 2 days (see 9.3.). An earlier oral product was a calcium salt only 30-40% of which was absorbed: this gave peak plasma levels of 7 to 9mg/L 4 hours after a 3g dose. The trometamol salt which replaced this is better absorbed (60% bioavailable) reaching peak plasma levels of 32mg/L 2 hours after a 3g dose.).

Experience with IV fosfomycin disodium (not a trometamol, formulation) is limited in the UK where it has only recently been introduced specifically for treatment of infection with multi-resistant bacteria. It has been more widely used elsewhere in Europe. The intravenous sodium salt reaches levels of 25mg/L after a 1G dose. A very early single open comparison of 38 patients with acute pyelonephritis showed that 7 days of intravenous fosfomycin 2g six hourly achieved only a 44% response rate [358]; the authors therefore concluded the drug had no role in pyelonephritis: the oral trometamol salt has never been examined for pyelonephritis. Intravenous dosage with MDR GNB is now usually at 24g/day in 3 divided doses but dosage reduction is needed in renal impairment as the drug is exclusively renally excreted, unchanged. The formulation has a high sodium load and the most frequently encountered side effect is hypokalaemia (26% patients) [359]. Fosfomycin exhibits excellent penetration into tissue after an intravenous dose as it is a small (138 Da), molecule with negligible protein binding; it also has a long serum half-life of between 4 – 8 hours [360].

A prospective salvage study of 11 ICU patients with serious infections caused by carbapenem-resistant *K. pneumoniae* reported an all-cause mortality of 2/11, although analysis of the claimed successes is complicated because 6 patients were also treated

with colistin and 3 with gentamicin [361]. A larger outcome study of 48 patients (mainly VAP) infected with KPC-producing *K. pneumoniae* and to a lesser extent, VIM-producing *P. aeruginosa* reported clinical success when fosfomycin was used mainly in combination with colistin or tigecycline in 54.2% patients and 28-day all-cause mortality of 37.5% [362]. Of 15 patients with colistin-, tigecycline- aminoglycoside- and carbapenem- resistant KPC-producing Klebsiella infection (one with an additional carbapenem-resistant P. aeruginosa) 9 responded to fosfomycin combinations and in 8 microbiological eradiation was achieved.

The use of intravenous fosfomycin has been reviewed extensively. Clinical cure was described in 1242 of 1529 (81.2%) of patients overall (for both Gram-positive and -negative pathogens) [363]. Most of the Gram-negative infections in this series were due to *P. aeruginosa,* (which most would regard as resistant), but also included infections due to *Enterobacter spp.*, *Klebsiella spp.*, *E. coli, Proteus spp.* and *S. typhi*. Most patients also received concomitant antibiotics, so again interpretation is difficult. A wide variety of infections were treated and fosfomycin was well tolerated. Despite *in vitro* resistance to fosfomycin, most patients with infections caused by *P. aeruginosa* improved although this may reflect concomitant antibiotics.

Further detailed studies of the parenteral form used alone in single indications (such as urinary tract infection, and ventilator-associated pneumonia are required to establish its relative efficacy and usefulness for specific MDR GNB. Similarly in combination therapy comparisons of specific combinations are required.

Evidence

Further details and regimens for the oral formulation are given in 9.6.3.

The parenteral formulation may be a valuable treatment alternative for infections due to MDR GNB including carbapenemase- and MBL- producing strains. However, further detailed comparative trial experience is necessary to determine its optimal use.

Evidence level: 3

Recommendations

- Consider parenteral fosfomycin, probably in combination, as part of salvage treatment for susceptible MDR GNB: clear indications for use are not yet established.

  Grading: Conditional recommendation for.

- Need comparative clinical trials to establish optimal indications for, and optimal use of, parenteral fosfomycin, a potential drug of last resort against MDR GNB.

  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials.

7.17 Trimethoprim/sulfamethoxazole

Trimethoprim/sulfamethoxazole (available as intravenous and oral formulations) has *in vitro* activity against *Stenotrophomonas maltophilia*[340] and some less frequently encountered non-fermenting Gram-negative bacilli (e.g. *Achromobacter spp., Alcaligenes spp., Burkholderia spp., Chryseobacterium spp.* and *Elizabethkingia spp.*)[364]. These species have inherent resistance to most other antibiotics and often produce MBLs. *Stenotrophomonas sp.* typically have similar percentage susceptibility at the CLSI breakpoint to sulphonamides alone and trimethoprim/sulfamethoxazole but are resistant to trimethoprim alone. The combination has greater in-vitro potency than either trimethoprim or sulfamethoxazole. A similar comment applies to *Achromobacter*

spp. and with few exceptions to *Alcaligenes spp*. *Chryseobacterium spp.* and *Elizabethkingia spp*[364].. These genera are susceptible to trimethoprim and more strains of these genera and *Burkholderia spp.* are more susceptible to trimethoprim/ sulfamethoxazole than either component alone[364] . The clinical use of sulphonamides alone against non-fermenters has not been explored and the combination of trimethoprim/sulfamethoxazole is usually used in *S. maltophilia* infections and for simplicity, against those due to these other unusual species. Problems occur with disc susceptibility testing of *S. maltophilia* and there are few data on the performance of automated susceptibility systems. Trailing endpoints are frequent and results vary with, the temperature of incubation and the susceptibility testing medium used. Occasional resistance to trimethoprim/sulfamethoxazole is not well understood in these non-fermenters but resistance to trimethoprim-sulfamethoxazole caused via the *sulI* gene has been described repeatedly in *S. maltophilia*[365]. A recent systematic review suggested that some strains of *Acinetobacter spp.* are susceptible to trimethoprim-sulfamethoxazole and that use against this genus can be guided by *in vitro* testing[366]. However over half the UK strains of *A. baumannii* show high level resistance [364].

Evidence

Trimethoprim/sulfamethoxazole has wide *in vitro* activity against *S, maltophilia, Achromobacter spp., Alcaligenes spp., Burkholderia spp., Chryeobacterium spp. and Elizabethkingia spp.*

Evidence level: 3

Susceptibility testing methods for these organisms are not well established but some *S. maltophilia* have resistance to trimethoprim and sulfamethoxazole, Carbapenem resistance is inherent to most of these species.

Evidence level: 3

Recommendations

- Use in treatment of infections due to susceptible *S. maltophilia* and consider in infections due to *Achromobacter spp., Alcaligenes spp., Burkholderia spp., Chryeobacterium spp. and Elizabethkingia spp.*

  Grading: Conditional recommendation for

7.18 Intravenous combination therapy for infections due to carbapenemase-producers

Although results of RCTs will be available , most of the current evidence for advantage of combination therapy for carbapenem-resistant infections derives from observational studies and reports mainly focus on severely-ill patients or those where the pathogen has reduced sensitivity to colistin [367]. An international working group report recommended combination including a carbapenem as optimal treatment but only in settings where NDM carbapenemases are infrequent [368]. However, retrospective studies are liable to bias in that investigators have no control over antibiotic use.

Different studies and reviews of combination therapy have reached contradictory conclusions. One systematic review identified that evidence for combination treatment was poor quality and inherently biased, being based on small observational studies with heterogeneity of i) antibiotic choice and activity against responsible pathogens, ii) antibiotic dosage and iii) severity of illness [369]. These authors concluded that any benefit in outcome between monotherapy with colistin and combination of colistin with other agents (aminoglycoside, tigecycline, carbapenem or rifampicin) was uncertain. There were methodological problems in the studies reviewed. Another systematic review [370] which lacked quality assessments likewise found only observational studies with marked heterogeneity, and suggested no proven benefit in terms of mortality between

combination treatment and monotherapy except for three more homogenous studies exclusively of bacteraemias due to KPC-producing *Klebsiella spp.* in critically ill patients which are worth detailed consideration [350, 371, 372].

First[350],in a 3-centre retrospective cohort study found 16/23 patients survived with tigecycline and colistin combinations and 12/14 with colistin-tigecycline-carbapenem combinations compared with 11/22 with colistin monotherapy and 10/19 with tigecycline monotherapy. Secondly, Qureshi et al (2012)[371] in a 2-centre retrospective cohort study showed that 3/7 receiving polymyxin monotherapy, 1/5 receiving tigecycline monotherapy, 2/4 receiving carbapenem monotherapy and 2/3 other antibiotics as monotherapy survived 28 days compared with 5/6 receiving colistin combinations and 6/6 receiving tigecycline combinations.. Thirdly, Zarkotou et al (2011)[372] noted 3/7 survivals with colistin, 3/5 with tigecycline and 0/1 on carbapenem, all as monotherapy, compared with 9/9 receiving combined tigecycline and colistin, 3/3 receiving tigecycline and carbapenems and 8/8 among those treated with other combinations . Two studies of bacteraemias involving VIM-1-producers considered in this review produced even less interpretable results. A third systematic review of polymyxin treatment found mortality at 30 days was lower in patients given combination treatment [373]. A 2017 systematic review and meta-analysis favours combination use of polymyxins [374].

Given this background, conclusions from further individual on-RCT studies must be interpreted with caution, but some support combination treatment. A larger retrospective cohort study of 661 infections caused by KPC-carbapenemase-producing strains of *K. pneumoniae* reported improved survival in patients treated with two or more active drugs versus those given monotherapy [316] . Mortality at 14 days in bacteraemias with an unknown or non-urinary source was 52.8% with monotherapy and 34.1% with combination treatment. A similar result with 49.1% and 24.8%

mortality respectively was seen with lower respiratory tract infection. There was no significant difference in bacteraemias from a known urinary source. Overall death rates on monotherapy were 62/132 (47%) with colistin, 45/116(39%) with tigecycline, and28/70 (40%) with gentamicin. With two drug therapy mortality was 38/134 (28%) and with three drug therapy 67/217 (31%). Only the use of meropenem in a combination produced a statistically significant improvement to 54/205 (26%). Use of meropenem was associated with lower mortality only if the MIC ≤8 mg/L as was the case for 37% of the isolates. Colistin resistance was significantly associated with increased mortality. Overall combinations including tigecycline, colistin and meropenem were associated with the lowest mortality (12.5% OR 0.11 95%CI 0.02-0.69). Epidemiologically overall colistin, tigecycline and gentamicin resistance rates were 11%, 9% and 6% in 2010 but by 2014 were 21%, 27% and 25%.

A further review including some previously reviewed studies, suggested superiority of combination- over mono-therapy with mortality rates of 27.4% vs. 38.7% respectively. Again carbapenem-containing regimens had the lowest mortality (18.8%)and this was associated with isolates that were not resistant by the EUCAST breakpoint [375]. Similar findings were reported in a retrospective observational study of 205 bacteraemias caused by carbapenemase-producing *K. pneumoniae* [351]. Combination therapy was associated with a lower mortality rate of 27% compared with 44% for monotherapy - 11/27 with tigecycline, 10/22 with colistin, and 7/12 with carbapenems. The difference in mortality was most marked in the more severe cases. Furthermore, mortality with a carbapenem-containing combination was 19.3% (6/31) compared to 30.6% (22/72) without a carbapenem (5/16 in those treated with tigecycline and colistin alone). Mortality on carbapenem-containing regimens in this study was lower only if the carbapenem MIC was <=8mg/L The authors comment that 40% of isolates with MICs by Etest <=8 were found resistant by automated machines. These studies suggest i) that

KPC-carbapenemase –producing *Klebsiella spp.* commonly appear meropenem susceptible *in vitro* and ii) that treatment combinations containing conventionally-dosed carbapenems are advisable in such cases with lower MICs.

Much higher doses of meropenem by continuous infusion can also be used (See 7.1.). This extends the MIC range of strains that can be treated. Continuous infusion therapy of meropenem with doses up to 13.2G daily with levels optimised by therapeutic drug monitoring when used in combinations (mainly with colistin and tigecycline), were associated with 73% clinical cures in patients with KPC-producing *K. pneumoniae* with MIC >16<64 mg/L [376]. These are better outcomes in treatment of more-resistant KPC-producing Klebsiella than apparent in earlier studies of these more resistant KPC-producing Klebsiella. Direct comparisons have not been made including comparison with high-dose continuous infusion meropemen alone. The application of this approach to other carbapenem-resistant isolates with MICs within the attainable range has not been assessed.

Anecdotal reports suggest double carbapenem combinations of ertapenem plus either meropenem or doripenem can be effective as last resort treatment for infections due to *K. pneumoniae* producing KPC carbapenemase but not those with NDM enzymes. This is perhaps because ertapenem binds tightly to the KPC enzyme, acting as an inhibitory substrate and thereby protects the meropenem or doripenem [377, 378].

In cases where the *Klebsiella spp.* strain was resistant to colistin and carbapenems, the use of gentamicin in combination with various agents was independently associated with reduced mortality in a retrospective cohort study [379] . However this was in the epidemiological context of a clonal *K. pneumoniae* ST512 (CC258) lineage with a KPC enzyme. This lineage commonly has the AAC (6')-1b enzyme; which confers resistance to amikacin but largely spares gentamicin; it is unlikely to be true for isolates with NDM

carbapenemases, which mostly have Arm A or Rmt ribosomal methyltransferases, conferring high level resistance to all standard aminoglycosides, including gentamicin and plazomicin. Plazomicin might have a future role with non-NDM-producing, gentamicin-resistant strains.

Evidence for efficacy of tigecycline in combination largely derives from observational studies but microbiological cure rates with monotherapy are lower than clinical cure rates and mortality rates are high. Pooled results from 5 observational studies suggested a clinical response rate of 77% (567/733) for all patients and 81% (329/408) for tigecycline monotherapy in the treatment of complicated intra-abdominal infection [380]. Another review of five observational studies of uncomplicated soft tissue and intra-abdominal infection with tigecycline similarly found monotherapy was effective [381]. These studies contain no data on response by resistances present and studies were with the licensed dose of 50mg twice daily.

In an open label RCT of treatment of ventilator-associated or hospital-acquired pneumonia caused by multidrug-resistant *Acinetobacter spp.* addition of rifampicin to colistin did not affect 30-day mortality or length of hospital stay, but was associated with a higher rate of microbiological eradication [382]. A retrospective observational study of 251 blood-stream infections treated with colistin or, colistin-sulbactam, colistin-carbapenem or another colistin combination reached the similar conclusion that mortality was not affected but microbiological eradication was higher with combination treatment [383]. Another observational study of 101 patients with MDR Acinetobacter infections did not show any improvement in mortality rates for combination therapy (e.g. colistin plus tigecycline or carbapenem plus tigecycline) over a single agent (usually colistin) but the group size in this study was small [384].

In the case of multidrug-resistant Pseudomonas infections a prospective cohort study showed no outcome advantage in combination versus monotherapy [385]. Combination therapy with aminoglycosides did not reduce the development of resistance [386]. Fosfomycin in combination with tigecycline or colistin was effective in 54% of 48 patients with infections with MDR GNB, some of which had Pseudomonas infection [362].

The recent introduction of ceftazidime/avibactam and the possibilities of using this in treatment may change the need to use combination treatment for some KPC or ceftazidime-resistant OXA-48 carbapenemase-producing strains.

Evidence

Two of four systematic reviews do not show a benefit of combination therapy over monotherapy.

Evidence level 2++

In infections with KPC-carbapenemase producing *Klebsiella spp.,* combination therapy including meropenem is associated with lower mortality than colistin monotherapy if the meropenem MIC is <8mg/L but this was not the case with strains with higher MICs unless continuous infusion therapy with higher than licensed doses was used (See 7.1). Combinations with other agents such as tigecycline or an aminoglycosides to which carbapenemase-producing strains are susceptible also seem advantageous but only the expected results of a new RCT will resolve this.

Evidence Level 3

Paul et al (2014)[369] detail the hazards of bias in favour of combination therapy that arise without an RCT. Data from a subset with bacteraemia with *Klebsiella spp.* Producing KPC-carbapenemases in the second systematic review performed by Falagas et al

(2014)a[370] suggests that in treatment of carbapenem-resistant Enterobacteriaceae infection, colistin used in combination with other agents is associated with a lower mortality than colistin alone and this is also a finding in the review of Ni et al (2015)[373].

Evidence level: 1+

The evidence that tigecycline combinations, including other antibiotics active against Enterobacteriaceae, are more effective than tigecycline alone in intra-abdominal infections is poor

Evidence level: 1-

Ertapenem in combination with meropenem may be effective as salvage therapy for infections with KPC-carbapenemase-producers but the evidence is very weak.

Evidence level: 3

In treatment of multidrug resistant Acinetobacter respiratory infections, addition of rifampicin to colistin does not affect 30 day mortality.

Evidence level: 1+

Recommendations

- Use colistin with meropenem to treat susceptible KPC-producing *Klebsiella* infection if the meropenem MIC is <=8mg/L and consider higher meropenem dose by continuous infusion if the MIC is >8 and =<32mg/L

  Grading: Conditional recommendation for

- Consider colistin with aminoglycosides or tigecycline in infections with strains producing other carbapenemases or KPC strains which are susceptible to these agents but resistant to meropenem

Grading: Conditional recommendation for

- Consider if ceftazidime/avibactam should be used with a carbapenem or colistin to treat infections with KPC3-producers based on latest evidence at the time of use.

  Grading: recommendation for research and possibly conditional

  recommendation for use restricted to trials.

8 Oral agents for secondary/tertiary care treatment

8.1 Mecillinam and Pivmecillinam

Pivmecillinam (the oral form of mecillinam) can be considered alone as oral therapy for lower UTI caused by AmpC producing Enterobacteriaceae. The antibiotic is not active against carbapenemase producers. It has been suggested as active against ESBL-producing *E. coli*. Patients with infections with such strains referred from the community for intravenous treatment with carbapenems might be considered for oral follow-on therapy with pivmecillinam alone for UTI because of mecillinam's apparent activity *in vitro*. However, additional measures are desirable and this oral treatment is dealt with under community use. (See 9.4 for more detail). Patients should be carefully monitored both clinically and microbiologically if pivmecillinam is prescribed alone in hospital for infections involving ESBL-producers as treatment failure is a risk.

8.2 Cefixime and oral cephalosporins

Cefixime is an oral third-generation cephalosporin, which has been used as an oral switch for patients with pyelonephritis. Among uropathogenic Enterobacteriaceae, it is not active alone against ESBL-producing *E. coli* because of their multiple resistances including quinolones [387] but is useful if ESBL-producing organisms or CPE are not present. Cefixime could be used in combination with co-amoxiclav against ESBL-

producing Enterobacteriaceae as supported by *in vitro* data [388]. Data from transconjugant *E. coli* further suggests cefixime plus clavulanate is effective against strains producing CTX-M-15 enzyme which has higher cefixime MICs than strains producing CTX-M-9 enzyme [389]. Other oral cephalosporins including cefdinir, ceftibuten, and cefpodoxime also showed synergy with clavulanate whereas sulbactam was less effective as a potentiator. Cefixime, with or without clavulanate, was not active against AmpC-producing organisms nor would it be expected to be active against CPE. Consequently cefixime-co-amoxiclav combinations should not be used against cephalosporin-resistant organisms without tests to distinguish AmpC and ESBL production. No clinical trials of cefixime together with clavulanate or amoxicillin/clavulanate against ESBL-producing *E. coli* have been published. Cefixime is detectable in faeces after administration. Other cephalosporins e.g. cephalexin which are fully absorbed, are not detectable in faeces and less frequently provoke *C. difficile* may be better partners for clavulanate, although in vitro data to support this combination are lacking [105]. Synergy *in vitro* between cephalosporins and mecillinam because of their different target penicillin-binding proteins is likely and synergy of cephalexin with fosfomycin (earlier known as alafosfalin or fosfonomycin), another cell-wall active antibiotic is also recorded [390].

Evidence

Cefixime with clavulanate, which is not available commercially, *in vitro*, has reliable activity against ESBL-producing *E. coli* and *Klebsiella spp.* (not *Enterobacter spp.* where AmpC will cause resistance). Cefixime is not useful alone against MDR GNB and no clinical studies with oral cephalosporins and clavulanate or amoxicillin/clavulanate have been published.

Evidence level: 3

Recommendations

- Do not use cefixime or other oral cephalosporins alone for treating infections caused by ESBL-, AmpC- or Carbapenemase producing Enterobacteriaceae.

  Grading: Conditional recommendation against

- Oral cephalosporins need clinical trials with clavulanate (alone or with amoxicillin) against ESBL-producing *E. coli* UTI.

  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

8.3 What are the recommended antibiotics for community care, including care homes?

Most MDR GNB infections encountered in the community involve the urinary tract. As described earlier, ESBL-producing Enterobacteriaceae are a significant and growing problem, whereas there are few community infections in the UK involving CPE. There are no published randomized controlled trials of antibiotic treatment of UTIs due to ESBL-producing organisms in the community or care homes. Recommendations must rely on observational studies of ESBL-producing GNB, or randomized controlled trials of effectiveness of antibiotics against UTIs caused by GNB lacking ESBLs.

8.4 What are the risk factors for patients with UTIs caused by MDR GNB in the UK?

In order to help the assessment of patients we review risk factors for MDR GNB and suitable oral agents for acute uncomplicated and complicated UTI. Prospective and retrospective epidemiological studies identified several risk factors for carriage of ESBL-producing *E. coli* [99, 136, 184, 391-393 394].[395] Patients are at increased risk if they have:

- recurrent UTI

- persistent urinary symptoms after an initial antibiotic,
- over 7 days hospital admission in the last 6 months,
- residence in a care home
- recent travel and especially healthcare in a country with increased antimicrobial resistance. Details of countries where prevalence is currently high are given in 8.5.
- previously known UTI (within a year) caused by bacteria resistant to amoxicillin-clavulanate, cephalosporins or quinolone or recent treatment with these agents [396].

There is no UK data validating an Italian scoring system devised and tested in 2009 for carriage of ESBL-producing bacteria on admission to hospital or incorporating information on travel, overseas healthcare in the previous 2 years or migration. The Italian scoring system identifies risk based on hospitalisation within the previous 12 months OR 5.69 (95% CI 2.94-10.99), transfer from another healthcare facility OR 5.61 (95% CI 1.65-19.08), Charlson comorbidity score >4 OR3.80 (95% CI 1.90-7.59), B-lactam or fluoroquinolone prescription within the previous 3 months OR 3.68 (95%CI 1.96-6,91, recent urinary catheterization OR 3.52 (95%CI 1.96-6.91) and age >70 years OR 3.20 (95%CI 1.79-5.70)[99] . This model of risk factors has been re-assessed in the US to see if it can be used to realistically restrict the need for carbapenem treatment to an identifiable high risk subgroup [397]. In the US evaluation, risk factors for community-onset clinical infection involving MDR GNB diagnosed within 48 h. of admission were: hospitalization OR 2.63 (95%CI 1.323-5.41), inter-hospital transfer OR5.30 (95%CI 2.67-10.71), urinary catheterization OR 6.89(95%CI 3.62-13.38), B-lactam or quinolone prescription OR 3.47 (95% CI 1.91-6.41) and additionally immunosuppression in the

preceding 3 months 2.34 (95% CI 1.14-4.8). Age over 70 was not a risk factor but age was not examined as a continuous variable. In this model, the sensitivity and specificity were >=94% and <=65% for scores of 3 or below and <=58% and >=95% for scores of 8 or above. Urinary catheterization was also a risk factor in a Spanish study [398]. A further paired US retrospective case-control studies compared infections with CTX-M ESBL producing *E. coli* infections with *E. coli* lacking CTX-M enzymes to uninfected controls; carbapenemase-producers were excluded. Patients with infections with CTX-M-producers were more likely to be male, have dementia or dependency, have higher Charlson median scores, receive H2 antagonists, and have exposure to health-care settings [393]. Recent antibiotics did not differ between the two groups except that trimethoprim/sulfamethoxazole use was commoner in the non CTX-M-producing group. Exposure to immunosuppressives was also commoner in the CTX-M group. A similar 75-77% of strains were present within 48 h. of admission. When patients with strains producing CTX-M-ESBLs were compared to controls, the former had a higher incidence of comorbidity (Charlson score =>5),and were more often resident in nursing homes with greater exposure to healthcare and more indwelling urinary catheters. They were more likely to be receiving H_2 antagonists or proton pump inhibitors and to have exposure to oxyimino cephalosporins within the last 3 months.

Evidence

Quoted rates of resistance in the community are biased to an unknown extent by infection occurring shortly after hospital discharge, care home cross-infection, an excess of treatment failures represented in the samples tested and an unknown proportion of patients with risk factors and recent antibiotic use.

Evidence level: 2-

UK surveillance suggests MDR GNB remain uncommon in community UTIs with few carbapenemase producers.

Evidence level: 3

Empirical antibiotic choice for lower urinary tract infection can be guided by the presence of established risk factors for a multi-resistant organism.

Evidence level: 2+

Predictive models have been established in Italy and the USA for ESBL-producing E. coli infections and colonisation on admission to hospital but these have not been validated in the UK nor do they consider travel-, migration-, or household-associated risks.

Evidence level: 2+

Recommendations

- In younger women with acute uncomplicated UTI, only consider MDR GNB in choosing empirical treatment if there are risk factors or recent foreign travel to countries where such strains are highly prevalent.

  Grading: Strong recommendation for

- If the defined risk factors for MDR GNB are present avoid cephalosporins, quinolones, trimethoprim and co-amoxiclav in treatment of lower UTIs unless the pathogens are confirmed to be susceptible.

  Grading: Strong recommendation against

- Building on previous work, predictive scoring should be developed in the UK for the presence of ESBL-producing E. coli in primary care and on admission to

hospital to restrict the need to prescribe carbapenems and other antimicrobial agents generally active against ESBL-producing organisms.

Grading: Strong recommendation for.

9 Which oral antibiotics are preferred for use in treating uncomplicated UTIs due to MDR GNB in the community?

9.1 Trimethoprim

Due to increasing resistance trimethoprim is no longer the suggested first-line empirical therapy for post menopausal women and older men in Public Health England guidance and nitrofurantoin is advised instead. In Wales trimethoprim remained until 2016 the suggested first-line empirical therapy for uncomplicated UTI in the community except for the elderly and for patients who have received antibiotics in the preceding 3 months.

Following advice to decrease trimethoprim use, an 86% reduction in trimethoprim use was seen in a Swedish region (hospitals and community) from 2004-2006 with a compensatory increase in nitrofurantoin, pivmecillinam and ciprofloxacin use. This programme resulted in no overall change in trimethoprim resistance. Before the intervention trimethoprim resistance was more prevalent in *E. coli* phylogroups A, B1 and D than in phylogroup B2 strains, although rates were high in ST131 which belongs to phylogroup B2.There was a marked change after the intervention in the distribution of resistance between phylogroups and associated sequence types with an increase in the trimethoprim resistance in phylogroup B2 (including ST131) and a decrease in trimethoprim resistance in phylogroup A and B1 strains (which seldom cause extraintestinal infection) and to a lesser extent in phylogroup D. Trimethoprim resistance was associated with a change in prevalence of *dfrA1.* Resistance to other antibiotics, including those substituted for trimethoprim increased in phylogroup A and B1 strains. [118], Amongst 273 urine isolates of E. coli collected in 2006 versus the same

number collected in 2004, strains of ST69 (which includes the former clonal group A), ST12 and unusual strains became more prevalent increasing respectively from 4.8 to 8.1%, from 2.6 to 4.8% and from 42 to 51%. By contrast strains of ST131, ST127, and ST80 declined in prevalence from 4.8 to 2.2%, 8.1 to 3.7% and 5.1% to 1.1%. There were statistically significant increases in trimethoprim resistance rates in the strains of ST131 and ST127. This would suggest that in types ST131 and ST 127 susceptible strains were eliminated by the antibiotics substituted for trimethoprim (quinolones, pivmecillinam and nitrofurantoin) but because of resistance linkage trimethoprim resistance increased in these sequence types. Information is lacking on ST80. The increase in strains ST69 and ST12 suggests they may have been selected by the antibiotics substituted for trimethoprim but it is not clear which antibiotics would have this effect as these STs are usually only resistant to ampicillin and in the case of ST69 trimethoprim. In a structured survey of extraintestinal strains from US veterans in 2011 quinolone-resistant ST 131 accounted for 78% of quinolone resistant strains which comprised 29% of reported strains overall. It accounted for 56% of trimethoprim resistant strains and 52% of quinolone and trimethoprim resistant strains [399]. This suggests that quinolones have the potential to select against trimethoprim susceptible ST131 strains, decreasing in the Swedish intervention study the overall prevalence at that time but potentially selecting for later increased prevalence of the ST 131. Thus, because of resistance linkage, community-wide change in use of a single antibiotic may unpredictably change the epidemiology and the prevalence of antibiotic resistance in more pathogenic phylogroups. It cannot be assumed that risk factors for multi-resistance, or the likelihood of success with an antibiotic in reinfection or recurrent infection will stay the same after abandonment of trimethoprim as a first line agent. This aspect of change needs urgent study.

Trimethoprim-resistant strains are much more frequently resistant to amoxicillin than trimethoprim-susceptible strains and this is a feature of ST69. Trimethoprim resistance rates in ESBL-producing *E. coli* in 2010 in the West Midlands were between 86% and 92% depending on whether the strain was not, or was, ST131. Ciprofloxacin resistance is also usual in these strains [93]. Trimethoprim consequently is a poor choice for patients with treatment failures on amoxicillin with, or without, clavulanate, cephalosporins or quinolones who require an urgent prescription before samples can be tested for antibiotic susceptibilities.

More generally, trimethoprim should not be used as empirical treatment for UTI if there are risk factors for an antibiotic resistant bacterium unless i) susceptibility has been confirmed in the previous month ii) there are no new risk factors for resistance, and iii) there have been no treatment failure with trimethoprim. In the absence of resistance, trimethoprim attains excellent bacteriological cure, two-weeks after completion of treatment, 94% of women using a 3-day course achieved bacteriological cure compared with 97% of those using a 10-day course (n =135) [400].

Evidence:

Trimethoprim use has not been explored as a risk factor for MDR GNB infection but resistance is common generally and very common in ESBL-producing bacteria. Trimethoprim is no longer recommended as a first line antibiotic choice for post menopausal women and older men with UTI and has little place in treatment of infection due to MDR GNB. ..

Evidence level: 3

3 day courses are almost as effective as longer courses in bacteriological cure of susceptible infections.

Evidence level: 1+

Recommendations:

- Do not use trimethoprim in treating MDR GNB or treatment failures with other agents unless *in vitro*-susceptibility has been demonstrated.

  Grading: Strong recommendation against

- Do not use trimethoprim to treat lower UTIs as a first line agent if ≥ 50 years old. Only consider use if there are no risk factors for resistance, or confirmed, *in vitro* susceptibility

  Grading: Conditional recommendation against

9.2 Nitrofurantoin

Nitrofurantoin is widely used for acute uncomplicated UTI in the community, and is now the recommended first line treatment in England. It attains only low concentrations in renal tissue and the blood stream and should not be used if pyelonephritis or bacteraemia is suspected: treatment may fail if used for ascending infection [401]. Nitrofurantoin resistance is inherent in *Proteus spp.*, *Morganella morganii*, *Providencia spp.* and *Serratia spp.* and the drug may not be effective in the alkaline urine produced by urease-producing bacteria such as these and possibly *Staph saprophyticus,* which is apparently susceptible *in vitro* but also produces large amounts of urease. Nitrofurantoin resistance is very common in CPE [120].

In early studies nitrofurantoin had a minimal effect on rectal flora and a recent metagenomics study supports this [402, 403]. Resistant strains of *E. coli* and increased numbers of Proteeae may be detected in the faecal flora [404, 405] but UTIs breaking through prophylaxis in recurrent infection are usually due to strains that remain

susceptible unlike the situation with trimethoprim [404, 405]. Recurrent UTIs after nitrofurantoin treatment of ESBL-producing *E. coli* may reflect relapse or recurrent infection arising from persistent carriage in the gastrointestinal flora: these possibilities cannot easily be distinguished. Frequent recurrence of UTI due to ESBL strains may justify using an alternative antibiotic regimen such as fosfomycin, or amoxicillin-clavulanate with pivmecillinam, with a greater theoretical chance of changing the gastrointestinal flora, which may act as the source for reinfection.

If a patient has a reduced glomerular filtration rate, urinary concentrations of nitrofurantoin may be too low to be effective. eGFR frequently declines with age, on average by between 6 and 9ml/min/1.73m^2 per decade. Around half of women over 75 years and men over 85 years have an eGFR under 60mL/min/1.73m^2 which used to be the lower limit for use of nitrofurantoin [401]. In a cohort study of lower UTI in 21,317 women treated with nitrofurantoin and 7926 treated with trimethoprim, there was no greater risk of nitrofurantoin treatment failure in patients with creatinine clearance of 30-50ml/min; however the risk of pulmonary adverse events was significantly increased with creatinine clearance <50ml/min (HR 4.1, 95% of CI.31-13.09) [406]. In 2014, and in the context of increasing antibiotic resistance to trimethoprim the UK, the Medicine and Healthcare Regulatory Agency reviewed the evidence for use of nitrofurantoin in reduced renal function[407]. They concluded on evidence [401, 406] that the eGFR below which nitrofurantoin should not be used could be lowered to 45 ml/min/1.73m^2. . The MHRA further stated that a short course (3 to 7 days) may be used with caution in patients with an eGFR of 30 to 44 ml/min/1.73m^2; but only advocates prescribing in such patients for lower UTIs with suspected or proven multidrug resistant pathogens when the benefits of nitrofurantoin are considered to outweigh the risks of side effects. Long term or repeated courses of nitrofurantoin are associated with severe pulmonary fibrosis [408]. Nevertheless 219 courses of prophylaxis

for one year for recurrent UTI in normal patients were not associated with a single case so this unwanted effect may be rare under controlled conditions where the drug is very effective [405] . Nitrofurantoin is poorly tolerated by some patients, but the modified release form has fewer side effects [409]. When used in this formulation an open RCT over 20 years ago (n = 538) found that nitrofurantoin had equivalent clinical cure rates to trimethoprim/sulfamethoxazole and trimethoprim (both given for 7 days) in a group of patients with acute uncomplicated lower UTI[409]. The rate of gastrointestinal adverse effects was similar between groups (7-8%). At this time the rates of nitrofurantoin resistance across all pathogens isolated was 3.9% whereas the rate of trimethoprim resistance was 12.5%. Trimethoprim- but not nitrofurantoin-resistance is now far commoner.

A recent review and meta-analysis suggested nitrofurantoin had a similar clinical cure rate to comparators but with a 5- rather than 3-day course for nitrofurantoin apparently producing better cure rates [410]. However 5 day and 3 day courses have not been directly compared in adequate numbers and Public Health England has not recommended 5 day courses. We consider in MDR GNB UTI that course lengths should be those that produce the best rates of bacteriological cure. There is no convincing evidence that shorter courses are equivalent to longer courses specifically in MDR GNB infections nor that the risk of serious unwanted effects is increased with longer courses . Whether such longer course lengths should be used more generally for nitrofurantoin is therefore unresolved. Unwanted effects in the systematic review were mainly gastrointestinal and no pulmonary events were reported although this may reflect short follow up periods [410]. There are no specific studies of nitrofurantoin in UTI caused by ESBL-producing organisms, but UTIs that are susceptible to nitrofurantoin have a similar response rate irrespective of ESBL-production. However ESBL-producing members of the *E coli* ST131 clone which are common in the UK and elsewhere often

have urinary virulence factors that are associated with recurrence, infection of the upper urinary tract and bacteraemia [411] and when infection reaches the upper tract nitrofurantoin is ineffective. Nitrofurantoin resistance has appeared in this sequence type (See 6.3.4). Further comparative studies in UTIs due to ESBL-producing *E. coli* are needed.

Evidence:

Nitrofurantoin is effective in lower, uncomplicated UTI and resistance rates remains low in *E. coli* although new plasmid-mediated mechanisms of resistance are now described. Mechanisms of acquired resistance in the UK, including in travellers, have not been recently studied. Resistance is intrinsic in *Proteus spp.* and *Serratia spp..*

Evidence level: 1+

There is usually no change in faecal Enterobacteriaceae during or immediately after use. Breakthrough infection, when the drug is used prophylactically, remains susceptible unlike with trimethoprim.

Evidence level: 3

Nitrofurantoin's activity is reduced in alkaline urine.

Evidence level: 4

Use of nitrofurantoin in moderate renal impairment, as seen with increasing age, has been controversial, but unrestricted use down to an eGFR of >45mL/min may be acceptable.

Evidence level: 1+

Use in moderate renal impairment or in long term/repeated courses may be associated, albeit rarely with serious pulmonary unwanted effects.

Evidence level: 3

Five-day not 3-day courses are recommended for susceptible ESBL-producing E. coli.

Evidence level: 1+

Recommendations:

- Could use nitrofurantoin for 5 days to treat uncomplicated, lower urinary tract infections with nitrofurantoin-susceptible *MDR E. coli* (not Proteeae or *P. aeruginosa*).

  Grading: Strong recommendation for

- Do not use repeatedly if there is moderate renal impairment, or in long-term courses, as these are associated with rare unwanted pulmonary effects.

  Grading: Conditional recommendation against

- Use alternative agents if there are repeated recurrences with MDR GNB but do not anticipate the emergence of resistance in *E. coli* infections on a single recurrence as selection for resistant strains in the urine or faecal flora is rare.

  Grading: Conditional recommendation for

- Need comparative studies of nitrofurantoin and other active antimicrobials in patients with ESBL-producing *E. coli* and *Klebsiella spp.*

  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials.

9.3 Fosfomycin trometamol

Fosfomycin has not been widely used in the UK, where the oral form was available between Feb 1994 and 1996 was thereafter withdrawn and not marketed for nearly two decades until 2013. Its use elsewhere in Europe has been associated with clinical success in lower UTIs. Fosfomycin suppresses Enterobacteriaceae in the faecal flora of 60% of patients by day 3 after a single dose but this rapidly drops to 30% at days 10 to 14: in contrast, nitrofurantoin does not suppress these organisms [403].

Oral fosfomycin should be administered while fasting or 2 or 3 hours before meals, as food can slow its absorption, leading to lower concentrations in the urine [412]. Oral fosfomycin is licensed solely for the treatment of uncomplicated cystitis. A single oral dose of 3 grams results in a plasma C_{max} of 22-32 mg/L and a urine maximum concentration (U_{max}) of 1053-445mg/L[413] The urinary concentration remains inhibitory for *E. coli* for at least 48 hours. In elderly patients with a mean GFR of 40mL/min concentrations after 24 hours exceeded those reported for healthy young subjects but there was considerable variation in excretion rates [414].

Treatment with a 3g. single dose of fosfomycin trometamol was associated with clinical success rates (defined as the resolution of symptoms after treatment) between 77.8% and 94.2% in four observational studies (some complicated and some receiving >1 dose) of treatment of lower UTI due to multi-resistant bacteria [415]. Oral fosfomycin trometamol has been used successfully for prophylaxis of pyelonephritis in patients with asymptomatic bacteriuria (ASB) in pregnancy, and there are reports of its use, sometimes in combination, in chronic prostatitis. The use and kinetics of fosfomycin has recently been extensively reviewed following its re-introduction to Canada [413].

Evidence

Fosfomycin is effective and well tolerated in treatment of UTI but the oral drug has only been studied in lower UTI.

Evidence level: 2++

Plasmid- and chromosomally-mediated resistance has emerged in populations where fosfomycin is widely used.

Evidence level: 2-

Recommendations

- Use in the treatment of lower UTI due to MDR Enterobacteriaceae. Oral formulation available. Useful for infections with ESBL-producers or carbapenemase producers .. No trials of oral formulation for upper UTI.

  Grading: Strong recommendation for

- Carry out ongoing local and national surveillance of use and resistance because of previous emergence of bacterial resistance in populations and the drug's potential as an important parenteral agent.

  Grading: Strong recommendation for

9.4 Mecillinam and Pivmecillinam

Pivmecillinam is an oral inactive ester and prodrug that is converted to microbiologically active mecillinam, penicillin, after intestinal absorption. Mecillinam has *in vitro* activity against most Enterobacteriaceae (including those with copious AmpC and some with ESBLs), but innate resistance occurs in *Proteus spp., Morganella morganii, Providencia spp.,* some *Serratia spp.*, and most non-fermenters including

Acinetobacter spp. and P. aeruginosa. Mecillinam has no activity against enterococci or *S. saprophyticus*.

Some TEM and SHV ESBLs confer clear resistance[416] [389] and an inoculum effect on testing is common for other ESBL producers [417]. In one study of ESBL-producing *E. coli* the MIC_{50} by agar dilution was 1mg/L with an inoculum of 10^4 cfu/spot but the MIC_{90} was 4mg/L [418]. Experiments with *E. coli* transconjugants showed that mecillinam MICs rose to 8mg/L when CTX-M-15 or -3 were present but only to 0.25-0.5mg/L with CTX-M-9 or -14. Combination with clavulanate reduced all mecillinam MICs for ESBL producers (except SHV-4) to <=4mg/L at high inocula and <=2mg/L with usual light inocula[389]. In another study of combination with clavulanate [418] 47/48 ESBL producers, were susceptible to mecillinam. Most of these produced CTX-M-3 (found in N. Ireland) not the commoner CTX-M-15 enzymes usual in England, Wales, and Scotland. There was no difference between the MICs for transconjugants producing CTX-M-3 and -15 in the earlier study. Synergy with clavulanate was detected in 40 - 60.4% of ESBL-producing isolates depending on the method of assessment. When a high inoculum was used, there was a marked inoculum effect raising the MIC of mecillinam alone but not mecillinam plus clavulanate. This study needs to be repeated with *E. coli* ST131 strains producing CTX-M-15 enzyme and also often OXA-1 which is not inhibited by clavulanate but said to have little activity against mecillinam

Mutants resistant to mecillinam by non-ESBL mechanisms can readily be obtained by laboratory selection. These show mutations in many different cellular functions [68]. However, a recent study of mecillinam-resistant clinical isolates found them all to have mutations leading to inactivation of the *cysB* gene. Reduced cysteine biosynthesis results in accumulation of the transcriptional regulator guanosine 3'-diphosphate 5'-diphosphate (ppGpp) so that the mecillinam targeted PBP2 becomes non-essential [419]. Addition of cysteine to the growth medium *in vitro* reversed the resistance to

mecillinam for such mutants raising possible issues with regard to current *in vitro* testing media.

Mecillinam is inactive against Enterobacteriaceae with KPC enzymes but some published data suggest *in vitro* activity against isolates with OXA-48-like enzymes [68, 389] and even some with NDM-1 enzymes, as reflected in an MIC_{50} of 4mg/L for NDM carbapenemase-producing *E. coli* [420] although this low value is disputed by others (D,M. Livermore, unpublished data).

Pivmecillinam at 200mg three time dailyonly produces sustained inhibition in Monte Carlo simulations if the mecillinam MIC is <= to 0.25mg/l suggesting a higher dose or lower EUCAST breakpoint may be required respectively to produce and predict clinical response [421].

Pivmecillinam is used mainly for lower urinary tract infection, where it has similar short-term symptomatic efficacy to amoxicillin and trimethoprim/sulfamethoxazole if organisms are susceptible [422, 423] and also to norfloxacin in 3- or 7- day regimens [424]. Seven-day pivmecillinam regimens are associated with more frequent clinical success than 3-day regimens [425]. Pivmecillinam prophylaxis in children with vesicoureteric reflux markedly reduced faecal *E. coli* and urinary breakthrough with *E. coli;* unlike nitrofurantoin, breakthrough infection with enterococci was common, reflecting different *in vitro* resistance [426]. Urinary concentrations are very high [427].

Clinical trials of pivmecillinam against ESBL-producing Enterobacteriaceae are limited to case series. In one small trial pivmecillinam was used alone with 30/39 patients receiving 400mg three times daily and 9/39 receiving 200mg three times daily. Dosage did not affect clearly the cure rates regardless of whether the UTI was complicated. Twenty eight patients were noted to have calculi, prostatic hypertrophy or urinary catheters (i.e. complicated UTI) and 6 of these were bacteriological failures. Two other

bacteriological failures were seen among the remaining 11 patient. Bacteriological cure was attained in 31/39 (79% overall), but five relapsed; clinical cure was attained in 16/19 patients but the rest were lost to follow-up [428]. There is no theoretical, trial or practise evidence to support a regimen with a loading dose of 400mg followed by 200mg three times dailywhich has been recommended in the UK as a compromise[429]. A population-based Norwegian study of pivmecillinam treatment of community-acquired UTIs examined the impact of MICs and ESBL-production in *E. coli*: it is not clear this was restricted to uncomplicated lower UTIs for which, alone, pivmecillinam is licensed [430]. A total of 343 patients were included, of whom 158 (46%) were treated with pivmecillinam. Eighty-one patients had infections caused by ESBL producing *E. coli*, and 41 (51%) received pivmecillinam as the primary treatment usually at a dose of 200mg three times dailyfor at least 7 days. Mecillinam MICs were higher for ESBL-producers than non-producers : 68% of strains had CTX-M Group 1 enzymes (including CTX-M-15) and 28% had Group 9 enzymes (including CTX-M-9 and -14. Treatment failure was (atypically) defined as a new antibiotic prescription appropriate for UTI within two weeks of the initial therapy or failure to clinically improve. Clinical treatment failure with pivmecillinam was observed in 18 (44%) of patients infected by ESBL-producing strains and in 16 (14%) of patients with ESBL non-producing strains Mecillinam MICs for isolates from treatment failures (n=34, 18 ESBLs) averaged 2mg/L (range 1-4mg/L) compared with MICs of <1mg/L for all isolates from treatment successes (n=124, 23 ESBLs). Treatment failures occurred in 50% of cases with mecillinam MICs of 2mg/L rising to 63% at MICs of 4mg/L This compares with a EUCAST breakpoint of S=<8mg/L, R>8mgL for mecillinam, again suggesting inadequate levels or too high a breakpoint. Multivariate analysis showed that ESBL status (odds ratio (OR) 3.2, 95% confidence interval (CI) 1.3-7.8, p = 0.009) and increased MIC of mecillinam (OR 2.0 for each doubling value of MIC, CI 1.4-3.0, p<0.001) were associated with pivmecillinam

treatment failure. Treatment failure rates above 25% were associated with mecillinam MICs >=2mg/L for ESBL-producers and >4mg/L for isolates lacking ESBL. From the transconjugant study cited earlier it is likely that UK CTX-M-15 producing isolates will be in this more resistant category and will respond poorly if pivmecillinam is used alone. This study must be seen also in the context of the earlier studies on the doses necessary to achieve adequate urinary concentrations.

There has been controversy over whether studies should be repeated with higher doses such as 400mg three times daily but a more effective action to improve cure rates may be combined use of a 200mg three times dailyregimen together with amoxicillin/clavulanate at 375mg three times daily We recommend this combination if oral pivmecillinam follow-on therapy is prescribed following hospital or OPAT iv treatment for UTI involving an ESBL-producer. Co-administration of amoxicillin/clavulanate may not only provide efficacy via inhibition of ESBL but also 10- to 100- fold bactericidal synergy by combining amoxicillin's action on PBP1 and 3 and mecillinam's action on PBP2 [431].

Future use of co-amoxiclav, rather than clavulanate without amoxicillin, in combination with mecillinam is partly supported by a high quality double-blind multicentre RCT of mecillinam and ampicillin-congeners without clavulanate in pyelonephritis in 1995 – in the era before CTX-M enzymesEquivalent results to cefotaxime/cefadroxil were achieved with an oral switch from parenteral mecillinam (no longer available) and ampicillin to pivmecillinam (at 400 mg three times daily) plus an oral ampicillin prodrug,suggesting that synergy of amoxicillin and pivmecillinam potentially would be clinically useful in follow-on therapy for pyelonephritis. In modern circumstances, including against ESBL-producers, this efficacy might be restored by protecting both mecillinam and amoxicillin by using them with clavulanate. A clinical success rates of 93% for pivmecillinam as against 53% with pivampicillin in a study in 1986 of

pyelonephritis suggests the drug has activity in the upper urinary tract [432]. However, it is important to note that clinical trials of the combination of amoxicillin/clavulanate with pivmecillinam have never been undertaken in pyelonephritis, and pivmecillinam has no license for pyelonephritis.

Further clinical comparative studies with outcome data are urgently required for pivmecillinam, with and without clavulanate (probably administered as amoxicillin/clavulanate), for both complicated (including upper urinary tract) and lower urinary tract infection against ESBL producers. Amoxicillin/clavulanate unlike clavulanate alone is available and licensed for upper UTI. These trials would determine pivmecillinam's role and its potential to reduce the need for hospitalisation or OPAT admissions to administer iv agents active against ESBL-producers.

Pivmecillinam is claimed to have a minimal effect on the intestinal and vaginal flora of the host with little selection for resistant bacteria, vaginal Candida or *C. difficile* [433]. However, the earlier study of [426][CD7] suggests it markedly reduces faecal *E. coli* at least in children . In an *in vitro* human gut model, it did not elicit *C. difficile* germination, proliferation or toxin production; suggesting that superinfection with this pathogen should be rare if the drug is used alone [434]. Clinical studies with pivmecillinam-amoxicillin/clavulanate regimens should include studies on persistence of ESBL-producing *E. coli* gut colonisation and new infections with *C. difficile.*

Overall there are uncertainties about how pivmecillinam should best be used in the modern era. The drug has very valuable potential and these uncertainties need resolution by large clinical trials which are now urgent. Selection for resistant strains (such as SHV-producers) in the interim would be unfortunate and for this reason we await further substantive trials and action and do not include its use alone in our general recommendations.

Evidence:

Pivmecillinam is a prodrug for mecillinam and is the sole oral β-lactam (excluding tebipenem and faropenem which are available only in Asia) with some activity against ESBL- and AmpC-producing organisms. It has a European license, and is widely and effectively used for lower UTI in some countries. Parenteral mecillinam has been manufactured in the past but is now unavailable.

Evidence level: 2++

Pivmecillinam has no published clinical trials against CPE and *in vitro* activity appears poor or non-existent.

Evidence level: 4

Urinary levels following doses of 200mg three times daily are inadequate to inhibit some ESBL-producing MDR GNB including some with CTX-M-15 considered susceptible by the current EUCAST breakpoint (S=<8mg/L).

Evidence level: 3

Failure rates with 200mg three times daily pivmecillinam used alone against lower UTIs due to ESBL-producing *E. coli* are too high to recommend regular use in such infections. A higher dose - 400mg three times daily - has been proposed but there is no convincing evidence to show it is more effective Comparative studies with fosfomycin have not been reported but there are no suggestions of such ESBL-related failures in existing fosfomycin studies in the absence of resistance.

Evidence level: 3

There are inadequate trial data to support the use of pivmecillinam in *Klebsiella* infection especially where the strain responsible produces ESBLs

Evidence level: 4

In vitro evidence and early trials of combination with ampicillin or pivampicillin suggest that a useful measure to increase efficacy would be combination with amoxicillin as well as clavulanate (See below).

Evidence level: 2+

In vitro studies suggest that clavulanate (available clinically only as amoxicillin/clavulanate) would protect mecillinam from destruction by ESBLs and lower its MICs for Enterobacteriaceae. If pivmecillinam is prescribed as follow-on to OPAT or in-patient treatment, use of the combination is recommended.

Evidence level: 3

Clinical trials of pivmecillinam alone versus pivmecillinam with amoxicillin/clavulanate in lower UTI would be in the public interest. These should be sized to give information on efficacy against ESBL-producing bacteria and should include studies on the bowel-flora and associated recurrence rates and C. difficile. If results of combination treatment are satisfactory consideration should be given to trials in upper UTI including economic assessment against OPAT treatment. Comparative trials with nitrofurantoin or fosfomycin trometamol for MDR GNB lower UTI are also required.

Evidence level: 4

Recommendations

- Consideration should be given to reducing the mecillinam EUCAST breakpoint for classification of susceptibility

  Grading: Conditional recommendation for

- Treat lower UTI due to ESBL-negative *E. coli* with pivmecillinam at 200mg three times daily: do not use for infections caused by Proteeae*, Klebsiella* or *Pseudomonas*. Some ESBL-producing *E. coli* respond, but efficacy is poor against CTX-M-15 enzyme producers: dosing at 400mg three times daily may be no more effective. Consider combination of the 200mg dose with 375mg amoxicillin/clavulanate for follow on to parenteral therapy for such infections in hospital or OPAT.

  Grading: Conditional recommendation for

- Requires clinical comparative trials in UTI in the public interest in i) alone or together with amoxicillin/clavulanate for UTI involving ESBL-producing organisms including particularly those producing CTX-M-15 enzymes ii) in uncomplicated lower UTI generally compared with fosfomycin trometamol and nitrofurantoin as the relative advantages of these drugs have not been directly compared by industry over the least 10 years as MDR GNB have become more problematic.

  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

10 Managing urinary tract infection

10.1 Diagnosis and the need for treatment or prophylaxis

Because UTIs are the major group of infections due to antibiotic-resistant Gram negative infections in primary care, we have chosen to make specific recommendations about their diagnosis and about specific antibiotic stewardship.

Good practice in differentiating urinary infections from other infections and asymptomatic bacteriuria is vital to reduce the unnecessary use of antibiotics. When

clinical variables were examined in a validation study[435], of a previously derived predictive dipstick rule--based on having nitrite or both leucocytes and blood, [436][RE8] the positive predictive value for urinary infection was 82% for women with all three of cloudy urine, dysuria, and nocturia. The negative predictive value for urinary infection was 67% when none of these three features was [436]present[RE9]. When individual clinical features were considered alone, cloudy urine or dysuria was predictive of UTI, but nocturia or smelly urine was not[RE10] [435], which brings into question its value in the assessment above of the combination of cloudy urine, dysuria and nocturia. In women aged 17-70 years with uncomplicated UTI, the negative predictive value when nitrite, leucocytes, and blood are ALL negative was 76% [435][RE11]. The positive predictive value for having nitrite alone or nitrite together with either blood or leucocytes was 92% [435]. A systematic review of diagnostic studies found that the presence of vaginal discharge or vaginal irritation reduced the probability of urinary infection to 20-30% [437].

Several different studies have shown the prevalence of asymptomatic bacteriuria is about 6% in men and 16% of women aged over 65 years [438] and is higher in older age groups and in the institutionalized elderly. In a cohort study, 1173 elderly female residents without catheters in care homes were followed for 9 years with urine cultures every six months[439] No relationship was found between ever having had asymptomatic bacteriuria and death after adjusting for covariates (hazard ratio, 1.10; CI, 0.78 to 1.55). The death rate in the group who never had asymptomatic bacteriuria was similar to those who had bacteriuria but either received no treatment or were treated *(P* > 0.2) [439]. The lack of benefit in treating asymptomatic bacteriuria was confirmed in another smaller study: neither mortality nor the frequency of symptomatic episodes was reduced, but for every three women with asymptomatic bacteriuria in a care home given antibiotics (the type was not specified in this study), one experienced adverse effects (such as rash or GI symptoms) [440]. Cumulatively, 3-6% of people acquire

bacteriuria per day of urinary catheterisation even with best practice for insertion and care of the catheter, and therefore many older people with long term catheters have bacteriuria [441, 442]. Intermittent catheterisation is associated with a lower incidence of asymptomatic bacteriuria than long-term catheterisation [443]. Catheterised patients should only receive antibiotic treatment when they are systemically symptomatic to reduce the risk of colonisation by antibiotic resistant bacteria [441, 442]. Differentiating urinary tract infection from asymptomatic bacteriuria can be particularly challenging in elderly patients with dementia as they cannot always describe their symptoms. A positive urine culture or dipstick test will not differentiate between UTI and ASB [439]. Patients with asymptomatic bacteriuria may have white blood cells in the urine just as in true infection. In older patients including those with dementia, diagnosis should be based on a full clinical assessment, including vital signs.

A Canadian randomized controlled trial of a diagnostic and treatment algorithm for UTI implemented in care homes, using a multifaceted approach, reduced antibiotics for urinary indications by 31%, compared to control care homes, with no increase in hospital admissions or mortality [444]. Patients were considered for antibiotic treatment based primarily on presence of fever greater than 37.9˚C or 1.5˚C increase above baseline on at least two occasions over last 12 hours and one or more signs of UTI[444] The full algorithm used is shown in Figure 5. [RE12]Fewer courses of antibiotics for suspected urinary tract infections per 1000 resident days were prescribed in the intervention nursing homes than in control care homes (1.17 *versus* 1.59 courses per 1000 resident days). Antimicrobials for suspected UTI represented 28.4% of all courses of drugs prescribed in the intervention nursing homes compared with 38.6% prescribed in the control care homes (weighted mean difference – 9.6%, – 16.9% to –2.4%). No significant difference was found in admissions to hospital or mortality between the study arms.

In recurrent UTI, deciding whether to give prophylaxis is a balance between the benefits of reducing symptomatic relapse and pyelonephritis versus side effects and the risks of selecting antibiotic resistance. Guidance is based on a systematic review of 19 trials. Nightly prophylaxis in non-pregnant women with recurrent urinary infection showed that prophylaxis reduced the relative risk of having one microbiological recurrence by five- fold (0.21) (95% CI 0.13 to 0.34), giving number needed to treat of 1.85 over 6–12 months[445] However, adverse effects occurred, particularly following nitrofurantoin, and 30% of women did not adhere to treatment. Any benefit was lost as soon as the prophylaxis stopped. Post-coital antibiotics were equally effective to nightly prophylaxis [445, 446]. Previous studies before the rise in resistance showed the same effect with postcoital single-dose cephalexin when used for recurrent urinary infection in pregnancy [447][RE13]. If recurrence is not too frequent it may be better to provide the patient with standby nitrofurantoin, to take as soon as symptoms occur; this approach was shown to result in less use of antibiotics and intuitively should result in less antibiotic resistance. Studies with cephalexin before the rise of ESBLs showed a slight increase in use wth post coital cephalexin offset considerably by antibiotics used in treatment of UTI recurrences[RE14] [448]. The offset needs to be taken into account in individual patients if standby nitrofurantoin is used. Prophylaxis, if used, can usually be stopped after a year without a resumption of the recurrences [405] and there are now European guidelines that this review should be made at 6 months [449]. The increase in trimethoprim resistance makes prophylaxis with this drug less suitable than it was and prolonged nitrofurantoin is associated with an increased risk of unwanted pulmonary damage, although this is rare. Patients on prophylaxis for >6months should be reviewed. If the patient wishes to continue with a prophylactic regimen, consideration should be given in advance as to which antibiotic would be appropriately substituted for trimethoprim, nitrofurantoin or indeed ciprofloxacin (which can also be used in

prophylaxis), if resistance develops or a breakthrough infection occurs. Persisting with an agent where breakthrough with a resistant strain has occurred will be ineffective. Cranberry juice prophylaxis is less effective in preventing breakthrough infection but cotrimoxazole generates more multiple resistance in breakthrough strains[RE15] [450]. Prophylaxis with beta-lactam antibiotics commonly selects for resistant Enterobacteriaceae in the faecal flora and is not recommended[RE16] [451]. There are relevant studies of prophylaxis after symptomatic UTI in infants which show similar problems with emergence of resistance on continuous prophylactic antibiotics, including resistance to cephalosporins due to ESBL-production [452][RE17]

NICE notes that prophylactic antibiotics given at catheter change or insertion do not reduce infections in those with neurological conditions and recommends that they should not be used [453]: such use for any indication contributes to pressure on emergence of resistance and should be avoided. .. NICE recommends that clinicians should consider antibiotic prophylaxis at change of catheter for patients who:

i) have a history of symptomatic urinary tract infection after catheter change or

ii) experience trauma during catheterisation (frank haematuria after catheterisation or two or more attempts of catheterisation). Placement of an incontinence implant is also an indication for short term prophylaxis but the recent insertion of an orthopaedic implant is not.

Evidence

Specific symptoms and signs hitherto accepted as characteristic of urinary infection have different predictive values.

Evidence level: 1+

In women with uncomplicated urinary infection the highest positive predictive value for strip testing was for having nitrite alone or nitrite with either positive leucocyte esterase or blood.

Evidence level 1+

There is no patient benefit in treating asymptomatic bacteriuria

Evidence level: 1+

Using an algorithm based on fever and at least one sign of urinary infection reduces the number of antibiotic prescriptions in nursing homes

Evidence level: 3

Treatment or prophylaxis with antibiotics in catheterised patients increases colonisation by antibiotic -resistant strains.

Evidence level: 1+

Prophylactic antibiotics given short-term at catheter change or insertion do not reduce infections but are indicated with specific criteria of i) traumatic catherisation, ii) previous severe symptomatic infection on catheter change, or iii) to cover placement of a urinary continence implant.

Evidence level: 4.

In recurrent UTI, antibiotic prophylaxis is very effective whether given daily (Evidence level 1++) or post coitally (Evidence level 1+) but an alternative is to consider pre-prescribed standby antibiotics to take at the onset of symptoms.

Evidence level 4.

If prophylaxis is used and effective it should be usually restricted to six-months prescription,

Evidence level 3

Previous resistances, or breakthrough of resistant isolates on prophylaxis should preclude use of an agent and consideration should be given to unwanted effects with long courses and what antibiotic would be chosen for breakthroughs.

Evidence level 4

Recommendations

- Always consider the positive and negative predictive value of specific symptoms before sending urine for culture or starting antibiotics for a UTI. Use dipstick tests, if no catheter is present, to confirm the diagnosis, before prescribing especially when symptoms are mild or not localized.

  Grading: Strong recommendation for

- For an elderly patient, do NOT send urine for culture or start empirical antibiotics unless there are specific symptoms or signs of UTI and none elsewhere. Use the algorithm in Figure 5 to decide whether to do this in elderly patients especially in those with dementia

  Grading: Conditional recommendation for

- Do not prescribe antibiotics in asymptomatic bacteriuria (ASB) in the elderly with, or without, an indwelling catheter.

  Grading: Strong recommendation for

- Avoid antibiotic prophylaxis for urinary catheter insertion or changes unless there is previous history of symptomatic UTI with the procedure, insertion of incontinence implant, or trauma at catheterization.

  Grading: Conditional recommendation for

- To reduce recurrent UTI, consider firstly, the option of pre-prescribed standby antibiotics to take when symptoms begin, rather than daily or post-coital antibiotic prophylaxis.

  Grading: Conditional recommendation for

- Where prophylaxis is used successfully for recurrent infection in adults limit use to six months.

  Grading: conditional recommendation for

10.2 Choosing a suitable antibiotic

Choosing an antibiotic to which a uropathogen is susceptible, is important as UTI symptoms resolve more slowly when an inappropriate antibiotic is given [454][CD18]. All patients should be given advice on when to seek further medical advice, i.e. if their symptoms worsen (even if, after taking antibiotics, on the same day) or do not improve after several days. Treating patients with infections due to MDR GNB in the community is a challenge as oral antimicrobial treatment is preferred. ESBL-producing bacteria are generally resistant to trimethoprim, ciprofloxacin, amoxicillin and cephalosporins; susceptibility to amoxicillin/clavulanate is variable and interpretation by the laboratory is affected by different breakpoints used formerly by BSAC, and currently by EUCAST, or CLSI.

Local community antibiotic guidance should be informed by national and local surveillance data. An algorithm on choices based on the individual agents discussed is given in Figure 4.[RE19] Choosing between fosfomycin, pivmecillinam and nitrofurantoin is difficult as there are no direct comparisons of these three antibiotics in infections due to ESBL-producing organisms. High failure rates with pivmecillinam may be due to the precise ESBL present and not using the drug in combination with amoxicillin/clavulanate, or possibly inadequate dosage: optimal ways to use the drug

now in the UK have not been proven. In urinary infections due to non-ESBL-producing organisms nitrofurantoin for 3, or5 days (or 7 days ,which is not significantly different from the results of a 5 day course) [410] and a single dose of fosfomycin have similar efficacy [455, 456].

In a systematic review of the length of antibiotic treatment for acute uncomplicated urinary infection before the rise in prevalence of ESBL-producing Enterobacteriaceae, therapy for 3 days, delivered in the case of fosfomycin trometamol by a single 3g dose, was similarly effective to prolonged therapy in achieving symptomatic cure for cystitis[RE20]. However, in this systematic review, bacteriological failure rates in the subgroup of trials where the same antibiotic was used in both short and long treatment arms of the trial, were higher (RR 1.37, 95% CI 1.07 to 1.74, P = 0.01). After a single dose of fosfomycin high concentrations are usually maintained in the urine for 2 days. This is usually curative in uncomplicated UTI in women, but for infection due to confirmed ESBL-producers, or in males, a second dose on the third day has been suggested to promote bacteriological cure [457][CD21]. On the same basis 5 not 3 days nitrofurantoin would be recommended for confirmed ESBL-producing bacteria and 7 days for pivmecillinam regimens. Although frequently used as an end-point in regulatory trials, it is uncertain if bacteriological cure immediately after treatment is of any long term clinical or bacteriological significance in patients with UTIs involving MDR GNB but the precautionary principle of adequate elimination of infections with MDR GNB would suggest regimens for best bacteriological cure should be followed in such cases. Eight studies in the systematic review included pivmecillinam at various doses and durations. An analysis of E. coli strains from persistent or relapsed infection after pivmecillinam showed an increased frequency of phylogenetic group B2 (which includes ST131) and showed that when matched by virulence factors 7 days treatment was preferable to 3 days therapy because it was less likely to be followed by persistence

or relapse [458][RE22]. Studies of urinary infection with strains producing the CTX-M-15-ESBL suggest that pivmecillinam alone at 200mg three times daily is inadequate treatment. *In vitro* studies suggesting use with amoxicillin/clavulanate have not been followed by clinical trials.

Based on evidence collected before the spread of ESBL-producing strains nitrofurantoin (100mg twice daily) should be given for 3 or 5, not 7, days for fully susceptible strains. No trials of nitrofurantoin 100mg twice daily with ESBL-producing strains have been published although the antibiotic is widely used. Efficacy, relapse/recurrence rates or incidence of spread to the upper urinary tract or blood stream are all uncertain and no studies have been published on the emergence of resistance during or after treatment or in relapses. MDR *Klebsiella spp.*, but not *E. coli*, are commonly resistant to nitrofurantoin but the mechanisms for resistance in the UK have not been investigated recently.

Evidence

Local community antibiotic guidance on empirical treatment of urinary infection should be informed by national and local surveillance data.

Evidence level: 4

In lower uncomplicated UTI where risk factors for MDR GNB are present these four treatment options can be used rather than trimethoprim:

Fosfomycin trometamol

Evidence level: 2+

nitrofurantoin (unless patients eGFR is less than 45 ml/min/1.73m$^{2)}$.

Evidence level: 2+

Pivmecillinam but in vitro and clinical data suggest this is less successful than a0 and b) for ESBL-producing bacteria likely to be present in the UK.

Evidence level: 3

Another other relevant antibiotic if the causative organism is confirmed as susceptible.

Evidence level: 4

Recommendations

- Inspect up-to-date national and local antibiotic surveillance when compiling local antibiotic guidelines on treatment of UTI.

  Grading: Strong recommendation for

- If there are risk factors for MDR GNB or previous presence of MDR GNB and the patient is symptomatic, send a urine specimen for culture and susceptibility testing

  Grading: Strong recommendation for

- Always inform the patient or their carer(s) on what to look out for and how to re-consult if symptoms worsen or do not improve as community-onset *E. coli* bacteraemias of urinary origin are increasing

  Grading: Strong recommendation for

- Use fosfomycin, or nitrofurantoin or as third-line choice pivmecillinam, guided where possible i) by susceptibility testing and ii) by this guideline's recommendation on choice, combinations, dosing and duration, for uncomplicated lower urinary tract infection where MDR GNB are suspected.

Grading: Strong recommendation for

- Use nitrofurantoin for 5 days with MDR GNB. Alternatively use fosfomycin trometamol 3g orally as single dose, and repeat on third day only if MDR GNB are confirmed to improve bacteriological cure. Pivmecillinam at 200mg three times daily for 7 days may be a third line choice but consider combination use with amoxicillin/clavulanate. Clinical trial results on pivmecillinam for MDR GNB in the UK are urgently required. .

  Grading: Conditional recommendation for

10.3 Treatment of pyelonephritis and complicated UTI caused by MDR Gram-negative bacteria

Whenever resistant pathogens are anticipated, it is essential to send a urine specimen for culture and susceptibility testing before empirical treatment and such specimens will be useful in this condition even if resistant pathogens are not anticipated. As nitrofurantoin, pivmecillinam and oral fosfomycin are currently considered inappropriate in suspected or confirmed pyelonephritis, intravenous ertapenem (unlicensed in Europe for this indication) should be given in an Outpatient Parenteral Antibiotic Therapy setting to treat patients with pyelonephritis confirmed or suspected to be caused by ESBL-producing pathogens that are resistant to trimethoprim and quinolones [163, 164]. If the patient requires admission to hospital meropenem or, depending on costs and local policy, ceftolozane/tazobactam or temocillin should be given for infection due to ESBL-producing strains. Piperacillin/tazobactam may be considered if the isolate has been shown to be susceptible. Amikacin might be considered but activity may be impaired if AAC (6')-1b-cr is produced. In practise strains with this enzyme may be reported as either susceptible or resistant and the enzyme cannot easily be detected: no trials of amikacin use against such strains have

been reported. Measuring amikacin levels promptly and adjusting doses is less likely to be easily supportable than use of gentamicin but the latter is unsuitable for infection with ESBL-producers unless susceptibility is known.

Ceftazidime/avibactam or non-B-lactam agents in combination perhaps with meropenem should be considered for infections with CPE- See Figure 4. Temocillin may have a place for more susceptible strains with KPC-carbapenemases but this has not been established by trials: it does not have a role against strains with MBLs or OXA-48 like carbapenemases. Such factors and choices are important when empirically treating pyelonephritis caused by probable or confirmed MDR GNB as this may be complicated by bacteraemia [94].

If a patient with pyelonephritis due to ESBL-producing bacteria has penicillin or cephalosporin-hypersensitivity, there are two alternative strategies. Firstly meropenem can be given despite a risk of cross-allergenicity that is now thought to be largely hypothetical. In this case caution must be exercised with appropriate drugs ready to treat any severe acute reaction. This seems to be safe [154] . Alternatively urgent susceptibility tests by automated methods should be performed. Depending on any previous results for the patient's isolates, intravenous gentamicin or amikacin (which has more auditory than vestibular toxicity but a lower resistance rate than gentamicin) may initially be used until a less toxic antibiotic can be identified from the concurrent susceptibility testing. Trimethoprim, ciprofloxacin or co-amoxiclav can be used in pyelonephritis if the pathogen is known to be susceptible (or a susceptible organism has been isolated in the preceding month with a satisfactory therapeutic response). A retrospective cohort study of community onset acute pyelonephritis due to ESBL-producing *E. coli* compared 85 patients receiving carbapenems with 67 receiving other agents to which the infecting bacterium was susceptible *in vitro*. There was no difference in rates of clinical or microbiological failure [459]. A randomized double-blind

controlled trial showed that 7 days of ciprofloxacin 500 mg twice daily was as effective as 14 days trimethoprim/sulfamethoxazole against susceptible organisms. However trimethoprim and quinolone resistance are now common and therefore none of these agents remain suitable for empirical use in pyelonephritis [460]. The substitution of OPAT therapy for oral antibiotic use in early pyelonephritis has not been costed in its effects on services.

Evidence

Pending antibiotic susceptibility testing, patients at increased risk of MDR GNB and suspected of pyelonephritis or complicated UTIs (i.e. indwelling catheter, recent urinary instrumentation, renal stones, prostatic obstruction, diabetes, immunosuppression, pregnancy, functional or anatomical urological abnormality [437] can be treated empirically with:

a) outpatient intravenous therapy with ertapenem.

Evidence level: 2+

b) admission for i) intravenous meropenem, temocillin, or ceftolozane/tazobactam if infected by ESBL-producing *E. coli* or *Klebsiella spp.*, ii) intravenous fosfomycin and colistin with or without meropenem, or ceftazidime/avibactam therapy if infected by a susceptible carbapenemase-producer.

Evidence level: 1+

If hypersensitive to penicillin treat with meropenem with caution or gentamicin (if no past evidence of resistance) or amikacin

Evidence level: 4

c. Trimethoprim, ciprofloxacin or co-amoxiclav if urine testing shows an organism that was susceptible in the preceding month and there has been no history of clinical failure.

Evidence level: 1+

Recommendations

- In pyelonephritis always collect a urine sample before treatment. MDR GNB are unlikely to respond to oral treatment so consider risk factors for an MDR isolate including travel. Use an active oral agent only if the patient is well enough and if known to have had ciprofloxacin-, trimethoprim-, or co-amoxiclav-susceptible MDR GNB in last month.

  Grading: Conditional recommendation for

- If the patient has pyelonephritis and risk factors for MDR GNB, start, if hospitalisation not required, empirical intravenous therapy with ertapenem if OPAT therapy available. This will treat ESBL and Amp-C producing Enterobacteriaceae. If the patient needs hospitalisation, or OPAT is not available, admit for meropenem, temocillin or ceftolozane/tazobactam if no evidence of CPE organism. If the patient is penicillin-hypersensitive then the hospital may use amikacin or meropenem, or if only susceptible isolates in the past, gentamicin. If carbapenem-resistant bacteria are, or have been, present, base treatment on susceptibility testing of recent or current isolates.

  Grading: Strong recommendation for

10.4 What is the threshold level of resistance for changing the choice of empirical treatment for urinary tract infections?

Most patients with UTI are treated empirically, particularly in a first episode of lower UTI. Failure of empirical therapy particularly in complicated UTI (e.g., pyelonephritis) is a common source of Gram-negative bacteraemia where increased 30-day mortality is associated with ineffective empirical therapy [256, 461] though maybe only in patients with sepsis syndrome. The probability of ineffective empirical therapy would be predicted to increase as the proportion of ESBL-producing, or carbapenem-resistant, bacteria rise. Older narrower spectrum antibiotics may be recommended for empirical use in order to slow the emergence of resistance. One group of authors asserts that the right of future patients to come to less harm outweighs the right of the present patient to share in decisions on antibiotic treatment [462] but this is a view many do not share. There is no agreement within the Working Party on the threshold resistance rate to an antibiotic that would justify substitution of other agents, nor on the degree to which routine laboratory testing of submitted samples overestimates the "true" resistance rate [463]. Rates of 20% have been suggested as justifying a change of empirical treatment in UTI. Confounders are i) that resistance rates are affected by duplicates within the series including when infection control sampling is intensive [464],ii) a bias towards performing culture and susceptibility only for difficult/unresponsive cases iii) by sequential testing second-line agents only for resistant strains according to local laboratory policy [117] and iv) differences in breakpoints between laboratories. These sources of variation may justify central susceptibility testing of all UTI from sentinel groups of GPs in regions for national surveillance purposes or requirements for national notification and annual updating of method changes and assessment of their effects [465]. Local and regional and variations exist in resistance rates for ESBLs as demonstrated by regional and national surveys. Quinolone resistance rates in *E. coli* are below 20% in most reported susceptibility surveys but resistance in bacteraemia is associated with increased

mortality and with the ST 131 group of strains which have an unrivalled ability to acquire other resistances. The risk of selection for resistance with a switch from trimethoprim leads us not to recommend their widespread use.

When the probability of bacteraemia associated arising from UTI rises, a lower threshold for altering normal treatment to cover a resistant strain is needed owing to the greater risk to the individual patient. A threshold of <5% resistance may be appropriate for higher risk situations.

Evidence

There are no accurate current figures on the prevalence of antibiotic resistance in UTI. Routine clinical data are subject to sample bias. These probably lead to overestimated resistance.

Evidence level: 2-

A threshold of 20% true resistance has been suggested as an indication to change "first line" empirical treatment of lower UTI. A lower threshold of, perhaps, 5% is appropriate when the risk of the patient becoming bacteraemic is increased. The Working Party consider that, in the absence of accurate national resistance surveillance these, or similar thresholds, presently can only be applied at a local laboratory level with i) careful de-duplication ii) precisely understood testing policies and iii) consistent local methodology.

Evidence level: 4

Recommendations

- Locally assess the true rate of resistance and determine from this when changes to guideline recommendations for empirical therapy in UTI are necessary

including recommendations where the risk of antibiotic-resistant bacteraemia is high.

Grading: Conditional recommendation for

- Personalise empirical chemotherapy for each patient by considering current features of bacteraemia, risk factors for antibiotic resistance and past susceptibility testing including the presence of MDR GNB in the patient or unit.

Grading: Conditional recommendation for

11 What effect does good antibiotic stewardship have on rates of MDR GNB?

11.1 The impact of good antibiotic stewardship in secondary/tertiary care facilities

The evidence base and practice of antibiotic stewardship in the UK has been recently promulgated in the Public Health England "Guidelines for Antimicrobial Prescribing and Stewardship Competencies" [466] and the guidance from NICE (National Institute for Health and are excellence) Guideline 15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use [467]. This report will focus on aspects of stewardship that pertain to MDR GNB: more general aspects can be found also in the above sources. A Cochrane systematic review showed that interventions to reduce excessive antibiotic prescribing to hospital inpatients might reduce antimicrobial resistance and that interventions to increase effective prescribing can improve clinical outcome [468]. Of the 89 studies cited to 2009 (reporting 95 interventions), 56 were interrupted time series (ITS), 25 were RCTs, 5 were controlled before-after studies (CBAs) and three were controlled clinical trials (CCTs). The reporting of outcomes was very variable (only 13/25 RCTs reported on mortality and only 5 on readmissions) complicating comparative assessment of studies. Interventions that enhanced the quality of prescribing in patients (defined softly as prescribing in accordance with

guidelines) with any infection had no effect on mortality whereas interventions to increase compliance with evidence-based guidelines in community-acquired pneumonia, usually due to Gram-positive *Streptococcus pneumoniae,* was associated with reduced mortality. Reducing prescribing for all indications, determined as excessive by reference to evidence-based guidelines, was associated with increased re-admission but not with increased mortality or length of stay. Restrictive and persuasive interventions were associated with improved prescribing outcomes based on median outcome effect (proportion of subjects with an improvement or change in antibiotic selection, dose, route or duration versus control). Multifaceted interventions were common but not necessarily more effective than simple interactions. Most (80/95, 84%) of the interventions targeted the antibiotic prescribed (choice of antibiotic, timing of first dose and route of administration). The remaining 15/95 interventions aimed to change exposure of patients to antibiotics by targeting the decision to treat or the duration of treatment. Only nine studies reported the effect of interventions on colonization or infection with antibiotic-resistant Gram-negative bacteria. Seven of these were ITSs, with a median effect size of 47% [469-474].

Although most studies reported >25% reduction in colonisation/infection with resistant Gram-negative bacteria, the confidence intervals were wide and in two studies the effects were not statistically significant [471, 475] and one crossover study of cycling empirical gentamicin, ceftazidime, and piperacillin/tazobactam showed an unintended increase of 39% in colonization with GNB resistant to any of the target drugs [476]. One cluster CCT in neonatal units, showed, as intended, a reduction from baseline in colonization/infection of 68% by cefotaxime-resistant organisms, predominantly *E. cloacae*, when the initial empirical treatment was penicillin and tobramycin rather than ampicillin-cefotaxime [477]. This study, the only one of the nine to report on mortality, showed a small increase in mortality when penicillin and tobramycin was substituted

for cefotaxime ampicillin in matched neonatal units. A 2017 update of this Cochrane review [478] concluded that there was still no statistically significant evidence that antibiotic stewardship reduced multiple antibiotic resistance although the impact on *C. difficile* is undoubted. Additionally this updated unwanted effects from stewardship interventions including an aminoglycoside substitution producing acute kidney [282]injury[RE23] (See 7.12) and studies where there was consequent delay in instituting antibiotics. Furthermore some studies reported a disruption of interaction between physicians and infection specialists as guidelines were used more frequently. Nevertheless an editorial on this review called for stewardship to be adopted in every health care institution[479]. One must now consider the homogeneity and quality of local hospital guidelines given guideline compliance is being used as a criterion of good stewardship.

In the 2013 Cochrane review[468], 11 studies of attempts to reduce excessive prescribing, reported data on mortality with no significant overall effect seen (and this continued to be the case in the 2017 revision[RE24]). Interestingly one of the interrupted time-series studies examined the impact of a switch from penicillin and gentamicin to penicillin and amikacin in a neonatal unit with gentamicin-resistant *E. cloacae* infections and showed a reduction in gentamicin-resistant *E. cloacae* but an increase is *E. aerogenes* and enterococci [474].

Kaki *et al.* produced another systematic review of antibiotic stewardship programmes, limited to the critical care unit [480]. These included three RCTs, three ITSs, and 18 uncontrolled before-and-after studies. Introduction of various antibiotic stewardship interventions led to 11% to 38% reductions in antimicrobial defined daily doses/1000 patient-days (except in a single study that found an increase of 6%), and lower total antimicrobial costs. Stewardship programmes led to shorter average duration of antibiotic therapy, less inappropriate use and fewer antibiotic-related adverse events.

They also found some reductions in antimicrobial resistance rates extending beyond six months.

A meta-analysis of 52 ITS was used to compare restrictive versus persuasive interventions [468]. Restrictive interventions had significantly greater impact on prescribing outcomes at one month (32%), 95% CI 2-61%, P=0.03) and on microbial outcomes at 6 months (53%, 95% CI 31-75%, P=0.001) but there were no significant differences at 12 or 24 months. Clinical outcome data were limited with 11 studies reporting on all-cause mortality but with no defined time-boundary - 4 studies showed increased mortality, 7 found decreased mortality giving a non-significant overall effect(0.92 95%CI 0.81-1.06 P=0.25).

In the USA, the Department of Veterans Affairs recently commissioned a systematic review of antimicrobial stewardship programmes (ASP) [481, 482][RE25]. The key findings have been published and the reader is referred to these publications for details [483, 484][RE26]. To avoid duplication, the VA systematic review only included papers meeting their eligibility criteria but not included in the 2013 Cochrane review. The review reported mixed results for clinical/microbial outcomes and overall improvement in prescribing. Because (i) few studies of different interventions reported each outcome, (ii) of inconsistency across studies and (iii) medium/high risk of bias, the strength of evidence for all clinical outcomes was low: no single antimicrobial stewardship programme was found to be superior but amongst studies since 2000 the greatest body of evidence of effectiveness was for decreasing inappropriate or increasing appropriate antibiotic use. Effects were seen across all species of Gram-negative bacteria and broad-spectrum antimicrobials.

There are individual studies of high quality. Introduction of a stewardship programme in one US hospital reduced the use of broad spectrum agents, and was associated with a

reduction in hospital-acquired infections caused by MDR GNB from 37% to 8% over 6 years [485]. Similarly resistance in *P. aeruginosa* declined when state guidelines on stewardship were implemented using a computerized programme in an Australian ICU [486]. In another study in Israel, a carbapenem-restriction policy was used as part of a successful infection control strategy also including emergency department flagging of colonized or infected patients, building an isolation facility, eradication of clusters, environmental and personnel hand cultures, with rectal screening of 8376 patients. This was effective in controlling an outbreak of carbapenem-resistant *Klebsiella pneumoniae*. Although there was a significant reduction in meropenem use, prescription of colistin rose [487]. Restriction of use of some antibiotics may need, or lead to, use of a diversity of other agents and even introduction of newly available antibiotics or appropriate use of older agents. These aspects also need to be subject to stewardship with appropriate actions in responsible bodies within hospitals and reporting to users. This can be complex and time-consuming. Some effective interventions are simple, for example, a high-quality study compared 8- and 15-day antibiotic treatment of ventilator-associated pneumonia (n=401) and did not find any difference in mortality or unfavourable outcome. Patients who received 8 day treatment had significantly less emergence of MDR pathogens (42% versus 62% p=0.04) but had a higher recurrence rate if they initially had non-fermenting organisms as pathogen (40.6% versus 25.4% risk difference 15.2% (CI 3.9%-26.6%)[488].

Early rapid and automated diagnostic tests for organisms and their antibiotic susceptibilities together with promptly administered and appropriate antibiotics is likely to improve prognosis and all UK laboratories should have access to this technology in a cost-effective manner. New methods with much faster results than systems such as VITEK2 and Phoenix are under development. As a performance measure, overall time to activate treatment appropriate to the bacterial susceptibility

can and should be assessed and repeatedly audited against what could best be achieved with modern methods. Objectively-countable disseminated infections, such as bacteraemia, may reflect failed initial diagnosis or treatment and are associated with a poor outcome if septic shock develops. As such, bacteraemias are suitable for outcome audits.

The deployment of antibiotic stewardship programmes is variable, as shown by a survey of 660 hospitals in 67 countries [489]. This study included the first data from sites in Asia, Africa and South America, many with considerable problems with MDR GNB. There is an urgent need for the adoption of an international antibiotic stewardship timetable.

Evidence

Up-to-date local resistance and outcome surveillance data are needed to inform guidelines on empirical antibiotic advice and must be persuasive to medical and nursing staff, to all prescribers and to pharmacists advising on guidelines.

Evidence level: 4

Interventions intended to decrease prescribing that is excessive (by reference to guidelines) for specific antibiotics have been associated with reductions in both colonisation and infections caused by carbapenem, aminoglycoside or cephalosporin-resistant bacteria but this is not a consistent finding across all stewardship initiatives

Evidence level: 2++

Restrictive rather than persuasive prescribing interventions cause a significant short-term change in prescribing and there is scanty evidence that they may contribute to reductions in the prevalence of resistant GNB. Persuasive prescribing interventions should also be used and are as effective over a 1- to 2- year period

Evidence level: 2++

Clinical outcome data on infections that is linked to antibiotic prescribing should be collected as well as data on resistance and prescriptions of antimicrobials to ensure stewardship approaches do not degrade outcomes, and ensure high and consistent standards between hospitals.

Evidence level: 2++

Audit and feedback should be used to reduce antimicrobial use in hospitals. Local and national advice on which antibiotics to prescribe are a useful standard against which to conduct audit and to explore clinical and microbiological outcomes

Evidence level: 4

Recommendations

- Provide an on-going antimicrobial stewardship programme in all care settings, based on resistance rates, with audit of compliance with guidelines, surveillance of outcomes, and active feedback.

  Grading: Strong recommendation for

- Use restrictive prescribing policies to acutely reduce the incidence of infection, or colonization, with MDR GNB; thereafter, maintain persuasive and restrictive approaches and monitor that gains persist.

  Grading: Strong recommendation for

- Identify through horizon scanning, and make available, new antimicrobials that may be required to treat MDR GNB. Monitor their use through formulary/drug and therapeutics committees.

  Grading: Conditional recommendation for

11.2 The national monitoring of good antibiotic stewardship in secondary/tertiary care facilities

Antibiotic therapy differs from other treatment in man in being directed against diverse and frequently unknown organisms and in exercising selection for resistant organisms, these change the potential target for drug action and may then cause infection either in the same or other patients. Treatment options for infections due to MDR GNB are restricted and failure to deploy appropriate treatment in these infections may be associated with a poor outcome whereas excessive use of a single agent in a hospital or unit is more likely to select for superinfection caused by resistant organisms. The clinical governance of antibiotic policies therefore is a balance between treatment of the individual and management of the community's antibiotic armamentarium.

Antibiotic use and the prevalence of MDR GNB are now widely monitored in communities and hospitals but (i) monitoring use does not indicate whether use was appropriate, and (ii) monitoring the accumulative prevalence of resistant strains is no guide to the incidence rate of new cases caused by MDR GNB. Root cause analysis of individual cases is burdensome and very complex if it is intended to relate to outcome. It also runs the risk of bias with regard to outcome unless the proportions of resistant or susceptible organisms that are examined match the overall population. It does not produce reliable statistically comparable data between institutions to support good practice. Nevertheless, such comparisons were used with MRSA bacteraemia and *C. difficile* in the past in the UK but these are acute events unlike chronic prevalence of antibiotic resistant strains.

Clinical trials early in a product's availability offer guidance on efficacy against susceptible organisms and with some agents, an indication of potential for selection for resistance. However, antibiotic efficacy is not usually sustained as resistance emerges,

and unlike other classes of drug, early clinical trials become less relevant with the passage of time. Anticipating when empirical therapy should include coverage against MDR GNB is difficult but is a key part of local guidelines. Recommendations that i) limit use of broad spectrum drugs such as carbapenems, or ii) which reserve particular agents for patients with MDR GNB present in infections that have a potential high mortality, need also to consider the potential hazard of poor clinical outcomes..

Despite assistance from other professions, deployment of infection and microbiology specialists into surveillance and away from patient care is frequent, and mundane tasks in surveillance employing specialists should be reduced to a minimum, without compromising excessively data quality. Routine national reporting systems on bacteraemia in the UK should be routinely linked to public health date of death data held nationally for each person by the Office for National Statistics as has been described in one study restricted to E. coli bacteraemia [102]. Such linked information should be fed back annually to, and within, individual hospitals and summarized findings provided to hospitals to enable comparisons of performance. Incidence and mortality rates in bacteraemia at the local level would provide key assurance on the prevention of systemic infections and the quality of outcomes. If these data on outcome were provided by patient, it would provide a focus to examine and attempt to reduce, the increasing incidence of bacteraemias and their associated mortality. Further these data would ensure locally that overall and specific audit could be made of the antibiotic resistance in organisms and the antibiotics actually deployed to treat serious infections that they caused. Added to existing data, such audit and source information could nationally and locally identify locations where there is high mortality either in primary or secondary/tertiary care enabling appropriate investigation and action to be locally taken. A crucial foundation has already been organized in England and Scotland via mandatory reporting of bacteraemia data for *E. coli* which specifically includes, *inter*

alia, data on community or hospital onset, and nursing home residency entered locally by laboratories. In England laboratories voluntarily and automatically (via computer links) submit antibiotic susceptibility data for 82% (54,301/66,512 over 2 years) of cases of *E. coli* bacteraemia reported by the mandatory programme, which does not, itself capture susceptibility data. This could be built upon to deliver local and nationally useful data on outcome by antibiotic resistance [94]. Furthermore, this process should be expanded to capture mortality information on other important bacteraemias e.g. *Klebsiella spp.* where prevalence is increasing and resistance is a major global threat or indeed to all bacteraemias. Reduction in the absolute number of associated deaths from bacteraemia may well involve changes other than in chemotherapy provided audit suggests chemotherapy is actively employed and appropriate. This requires multidisciplinary joint engagement and clinical management expertise in the community quite as much as in hospital to avoid sepsis and improve its management. A decrease in prevalence of bacteraemia and multi-drug-resistance within such infections is one aspect of this. Quantitative reduction in the number of deaths, and not changes in the comparative position of hospitals and communities in their respective peer groups should be the focus.

Bacteraemias should be, assigned reliably as being of community, wider healthcare or hospital onset so that responsibility can be assigned and accepted for performance by relevant commissioning groups, public health services and hospitals. Whilst the date of sampling of bacteraemia can be recorded, patients may become colonized by the causative bacterium much earlier and the exact timing of acquisition usually cannot be proven from existing laboratory records. IT coordination and shared responsibility across the health economy is needed to access the last date of discharge from hospital, which may be a practical proxy for date of colonization in cases of apparent community acquisition that are actually hospital-acquired. Where care does not involve transfer to a

tertiary centre and the patient is not being admitted to multiple hospitals in a conurbation, such information should already be available in many localities but non-automated extraction is time consuming. It is important for securing improvement that the bacteria isolated from bacteraemias can be related to likely acquisition in hospital, wider healthcare or community and not simply to onset in hospital or community and that responsibility for resistant strains falls accurately on hospitals or community commissioners of healthcare. Targeting reductions in MDR GNB in potentially life-threatening infection is problematic because of variations between community populations in ethnic origin associated apparently with antibiotic resistance such as ESBL-production [4, 137].[RE27] For this reason a simple process of commissioned reduction in resistance may be unachievable in some communities and their associated hospitals.

Residence in a nursing home is a marker of healthcare acquisition, not general community acquisition, and nursing-home patients should be separately and reliably categorized. Dates of hospital discharge of patients admitted from nursing homes may be relevant to intervention if the patient has moved between the nursing home and hospital recently – say within the last 2 years.

Tertiary and international referral in some hospitals(including referrals from armed forces deployed overseas [490])[RE28] even if the hospitals are not formally categorized as specialist hospitals may also skew their resistance profile towards multiple resistance [491, 492][RE29] so it is important to keep a balance between recognizing that this may be a reason for high resistance rates and ensuring that such resistant strains should be, as they always have been, a target for effective infection control. Again for this reason targeting antibiotic resistance reduction appropriately within a national context, may be more straightforward if it is directed at a local level.

Dates of collection of blood cultures, as recorded in laboratory computer systems, may be distorted by entry of default dates of registration on Monday mornings after submission of samples from Friday night on wards. There is no information on the frequency of this problem but it is time-consuming to retrospectively correct or prospectively avoid. An interval of <3 days since admission, is recommended for defining 'community onset' as more practical than the 48 hour limit suggested internationally and probably without important consequence, if permitted. This should be investigated if the mandatory programme is expanded as recommended. Laboratory data should not be reported multiple times and should utilize as little manual entry as possible and hospital trusts should ensure the automated transfer of data from laboratory systems to monitoring bodies. Information transfer should be frequent. However in the presence of good infection control and absence of an ongoing MDR GNB outbreak, annual batch processing of mortality linkage and annual central audit should be adequate in most hospitals for governance monitoring of hospitals and this would be adequate to support changes to infection management including antibiotic policy (which are seldom made more frequently). Not only good performance in reducing antibiotic use but also in better-than- average performance in bacteraemia reduction and better outcomes in bacteraemia (including that which is antibiotic resistant) should be rewarded.

Such laboratory-based extended surveillance of all bacteraemias would address (i) the diversity of organisms and, at a local level, the match to antibiotics prescribed (which itself could be centrally reported, if pharmacy systems and laboratory systems are linked by patient/NHS number and then ordered by concatenated patient/NHS number and reversed Julian date) ii) the usual, but not invariable, progression in antibiotic resistance rates. (iii) the need for organisations to make changes to prescribing policy with document control, feedback to clinicians and corporate responsibility of CCGs and

hospitals for infection management. To address bacterial species- and resistance-specific aspects in any locality, analysis (including trend analysis) of data cumulated over 5 years may be needed to avoid problems with small numbers of some pathogens. Individual hospitals need more local as well as the existing national data to systematically analyse, explain and address unsatisfactory outcomes. The already striking increase in incidence of E. coli bacteraemia often in patients being admitted from the community will probably increase further, with better ascertainment of sepsis. Commissioning attention needs to be paid to the appropriateness of prior chemotherapy (i.e. for UTIs in the community) to attempt to reduce such rising incidence and associated mortality. Owing to the rise of MDR GNB, central monitoring of, and action on, informatics is required in all hospitals. Collation of information is required to explain clinical and resistance outcomes by patients and to plan action in hospital and community onset cases. Early Warning Scores, which are required for such analysis, are frequently now available on computerised systems to monitor vital signs. Separate patient-based prescribing systems record the date of prescription and antibiotics given. Laboratory data systems record (i) the date of collection of the first positive blood culture for an organism-episode from a patient, and (ii) the organism and its antimicrobial susceptibilities. These data sets should be linked electronically along with, from hospital patient administration systems, the admission date, the date of last hospital discharge and place of residence (i.e. home or residential care). Early Warning Scores of 6 or more within 3 days of the bacteraemia indicate a poorer prognosis in bacteraemia but this data is continuously collected and may be difficult to link as single values. The most difficult area to address is usually the unequivocal assessment of outcome. Mortality is associated with poor functional state and co-morbidities, which may link to age and have been assessed automatically from computerized discharge records of diagnoses (ICD or Diagnosis-related group codes) in the US [493][RE30] and

France [RE31][494]. Defining mortality at a point less than 30 days after bacteraemia could tighten linkages to resistance and inappropriate prescribing, and should be studied. Acute renal injury is also a useful outcome measure as is subsequent development of *C. difficile* infection within 28 days. Sometimes these linkages can be made expediently without linking systems by exporting data and linking it in data bases or spreadsheets but the mechanics of this should not be dependent directly and solely on infection specialists, although they must advise on what should be done.

Quality and commissioning organisations should ensure hospitals are collecting and analysing all such data to explain and improve their results in the treatment of serious infections uch as bacteraemias not just those with MDR GNB. Particular scrutiny of year-on-year improvement in outcome of bacteraemia and reduction in prevalence according to onset in hospital or the community is needed both in CCGs and hospitals. Application of enhanced definitions of place of likely acquisition together with the working party's definitions of multi-resistance as applied to hospitals and the community and within the context of the local communities population make-up, may explain the reasons for, and sometimes enable multi-facetted action on, problematic multiple resistance as a whole health economy approach. . Hospital-, community-healthcare and community-onset bacteraemia therefore require separate analysis.

Evidence

Key components of an effective antimicrobial stewardship programme are consistent effort and audit of outcome by specialists with full communication and support from electronic prescribing/laboratory and clinical records. Computerised systems can and should be integrated. Also required are full accountability of responsible organisations for occurrence of serious infections, and the outcomes of treating them. Accurate

information is required on serious infections with MDR GNB but must not be assessed in isolation.

Evidence level: 2+

Hospital or community antibiotic use (by DDDs, or perhaps better in the context of resistance selection, number of patients exposed to each agent), should be reviewed locally together with antibiotic resistance data. These data sets are available from pharmacy and microbiology systems respectively. Audit on compliance with local guidelines can be undertaken, but this provides no assurance on clinical outcome in severe infections: these require comparison with performance of other similar institutions and analysis to ensure the quality of care.

Evidence level: 2++

Extended surveillance of bacteraemia with appropriate record linkage both centrally and in the hospital would provide clinical outcome assurance in the most severe infections and also a means of comparing improvement in hospitals and communities. Further this would lead to a sharp focus on improvements to antibiotic guidance, usage and infection control

Evidence level: 2+

Recommendations

- Ensure production of local guidelines for empirical and definitive antibiotic use, regularly updated for community-, wider healthcare-, and hospital- onset infections, and audit compliance with these.

  Grading: Conditional recommendation for

- Integrate hospital IT to deliver annually linked data for each bacteraemia, including patient demographics, whether the bacteraemias onset was in the community, wider healthcare or hospital, antibiotic resistances of isolates, antibiotics prescribed, and maximum early warning score or occurrence of septic shock, and, if possible, defined time-limited (not admission-limited) mortality. Use these integrated data to review the adequacy of treatment of infection in communities and hospitals

  Grading: Good practice recommendation

- Central public health departments or the Chief Medical Officers should receive bacteraemia data from the jurisdictions of trusts and CCGs or equivalent primary care organisations.. Annually, either peripherally or centrally they should ensure computerized record linkage to give dates of death to be added to, organism, specific antibiotic resistance and pattern, date of collection, nursing home residency, optionally local records on last hospital discharge before bacteraemia. This data should be made available, for open interrogation and downloading, with rolling cumulative data within the health service. They should ensure information findings on mortality rate are categorized by locality (separately for hospitals and for community with associated separate wider healthcare data)..

  Grading: Strong recommendation for

- Make publicly available tabulated incidence and outcome data for bacteraemia giving hospital onset data by region and hospital, and for community and wider healthcare outcome data by CCG or equivalent primary care organisation. Correlate this data with similar analysed and tabulated annual data on total antibiotic use and organism and antibiotic resistance in clinical infections

Grading: Good practice recommendation

- Continuously monitor bacteraemia outcomes and antibiotic resistance by organism and devise improvement programmes to both, locally and appropriately within health economies.

  Grading: Good practice recommendation

- Consider central production of unbiased national or regional data on true resistance rates in community-onset localized or systemic infections to guide national community antibiotic recommendations.

  Grading: Strong recommendation for

11.3 Antibiotic stewardship in the community and care homes to reduce MDR Gram-negative infections

Several RCTs in the UK communities have shown that multifaceted interventions that included i) general practice staff education and ii) education of the patient through improving communication during the doctor-patient consultation have improved prescribing [495, 496]. There have also been several Cochrane reviews that included studies in hospitals, but which should be transferable to the community and care homes, aiming to improve antibiotic prescribing. In one Cochrane review, restrictive interventions (selective reporting of laboratory susceptibilities, formulary restriction, and antibiotic policy change strategies) had a greater effect in the short term in reducing use of broad spectrum antibiotics than persuasive interventions (distribution of educational materials; educational meetings; local consensus processes; educational outreach visits; local opinion leaders; reminders provided verbally, on paper or on computer; audit and feedback). However both were equally effective in controlling antibiotic use and antimicrobial resistance after 6 months [468]. In a separate Cochrane review, printed

educational materials alone had an effect on the practice of healthcare professionals and patient health outcomes [497]. Based on seven RCTs and 54 outcomes, the median absolute risk difference in categorical practice outcomes was 0.02 when printed educational materials were compared to no intervention (range from 0 to +0.11) [497]. Other Cochrane reviews show multifaceted interventions are more effective. Moreover, interventions that are based on cognitive theories and consider personal attitudes, subjective norms and perceived behavioural controls (confidence and other barriers) are more likely to be successful, e.g., posters raise awareness and change subjective norms but are ineffective when used alone.

In an audit and feedback process, an individual's professional practice or performance is measured and then compared to professional standards or targets. The results of this comparison are then fed back to the individual. In general practices this will probably be via the medicine manager, local GP prescribing champions or in collaboration with local microbiologists. The aim is to encourage the individual to follow professional standards [498]. A Cochrane review considered 82 comparisons from 49 studies of any health care interventions in which audit and feedback was core and evaluated effects on professional practice. [498].There was a median 4.3% increase in healthcare professionals' compliance with desired practice (interquartile range (IQR) 0.5% to 16%) when i) baseline performance was low, ii) the source was a supervisor or colleague iii) it was provided more than once, iv) it was delivered in both verbal and written formats, and v) when it included both explicit targets and an action plan. In addition, the effect size varied based on the clinical behaviour targeted by the intervention [498]. An RCT evaluating a multifaceted intervention in English general practice aimed at improving antibiotic prescribing included feedback of practice level data on antibiotic prescribing and resistance: this led to a 4.2% fall in total antibiotic use [495]. In some parts of the UK, audit with action plans, and intense infection control measures, have been associated

with falls in quinolones and cephalosporin use and resistance [4, 499]. Incentives attached to action plans can be very effective but, without personal attitude changes, the change may reverse when the incentive is reduced [500]. Any audit indicators need to be well monitored, as implementation of an effective multiple-intervention strategy achieved no reduction of antibiotic prescription rates when deployed at a larger scale in general practice: the authors attributed the failure to a less tight monitoring of the intervention and audit [501]. It is necessary to demonstrate by further study, that such interventions can be effective at practice or hospital unit/hospital level.

Relevant outcomes, which should be monitored, include mortality from systemic infections such as bacteraemia, hospital admission, emergency room attendance, requirement for outpatient parenteral antibiotic therapy, re-consultation in person or by telephone, time-limited re-prescription of antibiotics and microbiological and clinical persistence of infection.

Evidence

Restrictive and persuasive interventions are equally effective in controlling antibiotic use and antimicrobial resistance and a multi-faceted approach is most effective

Evidence level: 1+

Audit and feedback interventions result in an increase in healthcare professionals' compliance with desired practice

Evidence level; 1++

Local and national surveillance data are needed to determine appropriate empirical antibiotic guidelines.

Evidence level: 3

Collection and analysis of outcome data is important in assessment of measures needed to improve the management of infection and to reduce the increase in antibiotic use and resistance.

Evidence level 2+

Recommendations

- Use persuasive and restrictive interventions to reduce the total antibiotic consumption, particularly broad-spectrum antibiotics in the, community and care homes.

  Grading: Strong recommendation for

- Provide and use active feedback of monitoring to prescribers, and nursing staff ensuring optimization of clinical, microbiological, and antimicrobial prescribing outcomes. Use audit and feedback to reduce inappropriate antimicrobial use in the community and wider healthcare.

  Grading: Strong recommendation for

- Review outcome data linked to antibiotic prescribing to improve quality of care in the community and care homes.

  Grading: Conditional recommendation for

12 Conclusions

The selection of antibiotics for the treatment of infections caused by Gram-negative bacteria (GNB) has always been difficult. Following the introduction of the first antibiotics with activity against GNB such as tetracycline, chloramphenicol and streptomycin, introduced in the late 1940's, resistance in *E. coli* causing urinary tract infection was observed at rates of 5-10% as early as 1953 [502]. Subsequently it emerged that Enterobacteriaceae can exchange and re-assort antibiotic resistance genes with great ease via plasmids, transposons, integrons and other mobile, or potentially mobile, genetic elements. This meant that resistances to antimicrobials no longer being used

were easily and stably maintained as the relevant resistance genes commonly become linked to, and compromise, antibiotics that remain in use. These linked resistances became transferable to a wider and more versatile range of strains.

As each class of new agent was introduced so resistance negated its reliable empirical use for the treatment of serious sepsis and also undermined any future reliance on the older agents. This is exemplified in the UK by the rise of plasmid mediated TEM beta-lactamase conferring resistance to ampicillin in the 1960's, aminoglycoside modifying enzymes conferring gentamicin resistance in the 1970's, extended spectrum TEM and SHV beta-lactamases conferring cephalosporin resistance in the 1980's and beginning in the 1990s CTX-M ESBLs, DNA gyrase mutations, and dihydrofolate reductases conferring resistance to third generation cephalosporins, fluoroquinolones and trimethoprim, respectively . We are now facing a similar process with carbapenems and polymyxins.

The bacterial ability to maintain older resistances may undermine any benefit from the introduction of more resolute antibiotic stewardship. Over-reliance on stewardship as the sole strategy for reducing MDR GNB may not be productive although reductions in antibiotic use if they are substantial enough to reduce selection in the human microflora for resistant strains are welcome. Use of a diversity of agents focused to proven bacterial infection may be more important than restricting [478] entirely the use of certain antibiotics and classes. Empirical prescribing based on generic clinical diagnoses will also need to be safely reduced.

Because of widely differing usage of antibiotics active against GNB in both medicine and agriculture in different parts of the globe since the 1980's we have created widely differing rates of occurrence of MDR GNB in these different locations and in some cases between food animals and man. Furthermore the increasing recognition of restricted

extraintestinal pathogens in different species suggests that animal husbandry quality and control of these strains may be variable. Higher rates of MDR GNB pose therapeutic problems for those countries. In addition over the last decade the movement of people, goods and food has resulted in countries such as the UK meeting unpredictable and alarming appearances of MDR GNB by importation [49]. Imported food-producing animals from overseas founder stock, and foodstuffs, need to be free of important antibiotic resistance in Gram negative bacilli to just as great an extent as returned travellers for biosecurity and as a foundation for enhanced antimicrobial stewardship.

In order to produce relevant guidelines for the empirical treatment of infections caused by MDR GNB an understanding of the local epidemiology and susceptibility patterns is essential. The unpredictability of horizontal gene transfer and nosocomial spread may necessitate specific guidelines being produced for individual hospitals/communities. The present guideline has attempted to assess the relative clinical efficacy of different agents. We have found very few good quality clinical trials to support treatment regimens, particularly for licensed older agents, formerly little-used, that have been re-introduced into regular use. Finding much more rapidly a mechanism to address this deficit in trials is an important overarching research objective as the existing pattern of industry-sponsored initial regulatory trials fails to address the need.

It is self-evident that selection of antibiotic treatment based on susceptibility testing is the optimum strategy for treating infections caused by MDR GNB. The initiative to develop and deploy molecular and rapid phenotypic susceptibility testing methods will help refine antibiotic usage. Any additional expense must be funded within the healthcare system for these to be introduced. Risk factor, rule-based prescribing for MDR GNB is unlikely to be sufficiently predictive alone for the reasons outlined above but risk-assessment of travel, household spread, and screening on admission to hospitals needs urgent improvement. However we have attempted to present an

evidence base and suggestions to support the development of local prescribing policies and possibly for the future application of such technologies and overall improvement in outcomes.

Over-reliance on empirical piperacillin/tazobactam, and for treatment failure meropenem, has and will drive selection for resistance to these agents, and UK health policy is attempting to contain this upsurge in usage. For patients presenting with serious sepsis convincingly caused by GNB and in the absence of prior exposure to healthcare in countries/hospitals with endemic carbapenemase producing Enterobacteriaceae, carbapenems remain the best empirical therapy with early and embedded shift to alternative definitive treatment. The overall prevalence of resistance in E. coli alone to piperacillin-tazobactam or gentamicin (approximately 10%) is the basis for this superiority of carbapenems although factors such as aminoglycoside toxicity and C.difficile risk must be considered. Combinations of these agents or cephalosporins without B-lactamase inhibitors increase antibiotic use and are unlikely to produce adequate activity against ESBLs because of resistance linkage. Algorithms for predicting accurately presence of ESBLs need urgent validation in the UK health service so piperacillin/tazobactam or gentamicin can be safely used to provide Gram-negative cover in their absence, and cephalosporin-BLI combinations in their presence thus diversify antibiotic use in serious infections within a stewardship framework. Use of piperacillin/tazobactam or existing licensed aminoglycosides as empirical therapy where ESBL-producing strains are prevalent such as after overseas travel or hospitalisation, in communities where such travel has been frequent, and hospital or nursing home exposure is unwise. Historical evidence suggests these agents continue to be appropriate for sepsis if these risk factors are not implicated.

In England, use of the Commissioning for Quality and Innovation (CQUIN) payments framework (or public health control of institutions and community healthcare) needs

to be sensitive to the requirement to have safe effective antibiotics to use in sepsis caused by non-MDR GNB which remain the majority of GNB causing serious infections in UK hospitals. The role and utility of the latest generation of BL/BLI combinations is yet to fully emerge. The early reports of emergence of resistance to ceftazidime-avibactam in KPC-3-producing carbapenem resistant Enterobacteriaceae is extremely ominous [503]. Nevertheless, at the moment new BL/BLIs and fosfomycin offer the only immediate new help to treat the latest MDR GNB particularly for carbapenemase producers and ESBL-producing GNB. Further development of BLI combinations for oral use is an urgent need in primary care.

Initiatives are being put in place to address the paucity of new agents but they will take time to give results which are by no means inevitable. A greater emphasis in communities should be given to the better use of existing treatments for effective treatment of complicated and upper UTI with prevention of bacteraemia and in hospitals to an auditable improved outcome in well-defined groups of patients with life-threatening Gram-negative infections such as bacteraemia. This effort should match the attention given to reducing inappropriate use of wide-spectrum agents for less important infections and should ensure that reductions in antibiotic use are appropriate and do not adversely affect patients. Computerised support to spare infection professional time is necessary locally for surveillance of bacteraemia to focus attention on improvements in performance in life-threatening infection.

Greater research and deployment efforts in the area of very rapid diagnostics to guide immediate prescribing are needed. In the healthcare environment stopping spread of infection with MDR GNBs is of paramount importance and such infection control measures have been dealt with comprehensively in another working-party publication[3].

The greatest long-term threat arises from the fundamental epidemiology of GNB, with their large faecal reservoirs in both humans and food animals leading to dissemination into the environment [21]. This leads to unpredictable acquisition by individuals with high rates of commensal carriage and subsequent infection. Not only antibiotic control in man but parallel control of use of the same agents in food animals is important. This is exemplified by use of colistin, mequindox and fosfomycin [504] in food animals in China and other parts of the world, and consequent emergence of plasmid-mediated colistin, nitrofurantoin and fosfomycin resistance mediated by MCR-1 and *fosA* as discussed previously (See 6.3.4. The close association of NDM MBL with connections with the Indian sub-continent is likely to change with the demonstration of this carbapenemase in poultry, farm workers, flies and wild birds in Shandong, China. [289]. Practical measures to contain human importations of carbapenemases but also assessment and potentially prevention of any spread in foodstuffs are urgent at this early stage. Variations in the prevalence of MDR GNB in different localities and cultural backgrounds even within the UK need to be further explored and considered in empirical therapy. Separate effects of migration, travel, household cross- colonization/infection and food consumption need to be rapidly studied to make risk assessments practical and effective.

Internationally, public health hygiene measures to reduce faecal oral transmission such as clean water initiatives and sewerage and irrigation systems to prevent transmission are of major importance. Food stuffs including imports should be regulated for the presence of GNB resistant to third-generation cephalosporins, quinolones and possibly in the future carbapenems. Failure to address these under-recognised threats will undo our ability to treat infections caused by MDR GNB. If we do not control human and agricultural use of antibiotics and the spread of MDR GNB from faeces back into humans and food animals as a consistent multi-faceted, global-scale, public-health programme, we will suffer greatly.

13 Further Research and development

Without consideration of the research needed for new compounds and formulations in the antibiotic pipeline, there are numerous areas which require research with a 5 year horizon for completion.

- Diagnostic tests and or serum markers should be formally and comprehensively assessed for safety and efficacy as aids in deciding when to start and stop antimicrobial treatment, particularly in critically ill patients and those with haematological malignancies.

- Develop and introduce new cheap, rapid, and preferably bedside, diagnostic tests for important multiple antibiotic resistant organisms in urine and blood.

- Undertake RCT studies of antimicrobial agents (both new and old) in the treatment of Gram-negative infection in areas where multi-resistance is likely e.g. admissions unit, critical care and urology in hospitals and in treatment of infections due to ESBL-producing bacteria in the community. Identified research areas in this guideline include

    a. Use of continuous infusion meropenem at dose determined by nomogram if infection with KPC-carbapenemase –producing Klebsiella with MIC of >8<64mg/L.

    b. Use of temocillin for non-urinary infections with trials to establish their optimal dosage

    c. Use of temocillin alone, or in combination, in UTIs caused by Enterobacteriaceae with KPC-enzyme.

d. Use of ceftazidime/avibactam alone when non-MBL carbapenemase-producing organisms cause infection in comparison with alternatives, including combination therapy.

e. Use of ceftolozane/tazobactam in *P. aeruginosa* infections in cystic fibrosis

f. *In vitro* and *in vivo* research to identify the usefulness of aztreonam in combination with avibactam for infections due to Enterobacteriaceae with MBLs and other carbapenemases.

g. Research into the role of loading doses of colistin, monitoring of serum levels and optimal combination therapy.

h. Research into use of polymyxin-containing and non-containing selective digestive decontamination regimens and the prevalence of newly identified polymyxin resistance mechanisms

i. Optimal rapid and practical methods of colistin susceptibility testing outside intrinsically resistant species such as Proteeae and Serratia *spp*.

j. Higher dosing studies with tigecycline to investigate if the unexpectedly high mortality in infections with strains that are apparently susceptible *in vitro*, can be reduced

k. Optimal use of high dose tigecycline in combinations in hospital-acquired respiratory infections

l. Specific system-based and resistance-mechanism-based indications for use of parenteral fosfomycin, in infections due to MDR GNB.

m. Cefixime (or other oral cephalosporin) with clavulanate (alone or with amoxicillin) against ESBL-producing *E. coli* UTI.

n. Nitrofurantoin versus fosfomycin trometamol versus pivmecillinam (with or without amoxicillin/clavulanate) in patients with ESBL-producing *E. coli* and *Klebsiella spp.*

o. Use of meropenem, or temocillin or ceftolozane/tazobactam in community onset pyelonephritis where hospitalisation is required and where MDR GNB excluding CPE are, or are likely to be, present. These studies should include assessment of meropenem or aminoglycosides if the patient describes penicillin-hypersensitivity.

- Undertake surveillance in both the hospital and community populations, and households of newly detected colonised individuals, for incidence of known mechanisms of resistance and the emergence of novel resistance mechanisms to currently used antimicrobials. Link this surveillance to travel, prior hospitalisation as in-patient, or residential healthcare.

- Develop new models of licensing and funding of antimicrobials for treating MDR GNB infections. Develop non-microbial therapies for MRGNB (e.g. phage, antibacterial peptides, etc.)

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16 Transparency declarations

The BSAC, BIA and HIS commissioned the authors to undertake the Working Party Report. All authors but not the members of the patient advisory panel are, or have been, members of one or more of these societies. In addition:

PH: Consultancy: BioMerieux, Becton-Dickinson, Eumedica, Merck, Novartis, MagusCommunications, Pfizer, Wyeth; director of ModusMedica (medical education company); Funded research: Astra-Zeneca, Merck, Novartis, and Pfizer.

REW: family shareholdings in Astra Zeneca, Bayer, GSK, Johnson & Johnson, Merck, Pfizer and Roche amounting to approx. 15% of portfolio value.

CM: Travel expenses Merieux Diagnostics

DML: Advisory Boards or ad-hoc consultancy Accelerate, Achaogen, Adenium, Allecra, AstraZeneca, Auspherix, Basilea, BioVersys, Centauri, Discuva, Meiji, Merck, Pfizer, Roche, Shionogi, Tetraphase, VenatoRx, Wockhardt, Zealand, Paid lectures – AstraZeneca, Beckman-Coulter, Cardiome, Merck and Nordic. Relevant shareholdings in– Dechra, GSK, Merck, Perkin Elmer, Pfizer amounting to <10% of portfolio. Contract research: Achaogen, Allecra, AstraZeneca, Melinta, Meiji, Merck, Roche, Wockhardt.

DAE: Received funding to attend conferences from MSD, Eumedica, Gilead and Astellas.

APRW: Consultant on Drug Safety Monitoring Boards for Roche and Genentech. Advisory Panel for 3M.

All other authors no conflicts declared.

1

2 **Table 1. Summary of recommendations for stakeholders including prescribers**

Organisation	Recommendation	Strength
Central public health authorities	Central public health departments or the Chief Medical Officers should receive bacteraemia data from the jurisdictions of trusts and CCGs or equivalent primary care organisations bacteraemia data in their localities. Annually, either peripherally or centrally they should ensure computerized record linkage to give dates of death. They should ensure information is categorized by locality (separately for hospitals and for community with associated separate wider healthcare data), date of onset or acquisition, organism, specific antibiotic resistance and pattern, the mortality rate, This data should be made available, for open interrogation, with rolling cumulative data within the health service.	Strong for
	Make publicly available tabulated incidence and outcome data for bacteraemia giving hospital onset data by region and hospital, and for community and wider healthcare onset data by CCG or equivalent primary care organisations. Correlate this data with similar analysed and tabulated annual data on total antibiotic use and organisms and antibiotic resistance in clinical infections.	Good practise
	Consider central production of unbiased national or regional data on true resistance rates in community-onset localized or systemic infections to guide national community antibiotic recommendations.	Strong for
Commissioning and quality organisations	Continuously monitor bacteraemia outcomes and antibiotic resistance by organism and devise improvement programmes to both, locally and appropriately within health economies.	Good practise
	Provide and use active feedback of monitoring to prescribers, and nursing staff ensuring optimization of clinical, microbiological, and antimicrobial prescribing outcomes. Use audit and feedback to reduce inappropriate antimicrobial use in the community and wider healthcare.	Conditional for

	Use persuasive and restrictive interventions to reduce the total antibiotic consumption, particularly broad-spectrum antibiotics in the, community and care home setting.	Strong
	Ensure production of local guidelines for empirical and definitive antibiotic use, regularly updated for community-, wider healthcare-, and hospital- onset infections and audit compliance with these.	Conditional for
Hospital and primary care: general	Provide an on-going antimicrobial stewardship programme in all care settings, based on resistance rates, with audit of compliance with guidelines, surveillance of outcome, and active feedback	Strong
	Identify through horizon scanning, and make available, and make available new antimicrobials that may be required to treat MDR GNB. Monitor use through formulary/drug and therapeutics committees.	Conditional for
	Use restrictive prescribing policies to acutely reduce the incidence of infection or colonisation with MDR GNB; thereafter, maintain persuasive and restrictive approaches and monitor that gains persist.	Strong for
	Integrate hospital IT to deliver annually linked data for each bacteraemia, including patient demographics, whether the bacteraemias onset was in the community, wider healthcare or hospital, antibiotic resistances of isolate, antibiotics prescribed, and maximum early warning score or occurrence of septic shock, and if possible defined time-limited (not admission-limited) mortality. Use these integrated data to review the adequacy of treatment of infection in communities and hospitals	Good practise
Hospital & 1^0 care treatment of UTI	Inspect up-to-date national and local antibiotic surveillance when compiling local antibiotic guidelines on treatment of UTI. Follow local guidance on what antibiotics to prescribe,	Strong for
	For an elderly patient, do NOT send urine for culture or start empirical antibiotics unless there are specific symptoms or signs of UTI and none elsewhere. Use the algorithm in Figure 5 to decide whether to do this in elderly patients especially in those with dementia	Conditional for

	Do not prescribe antibiotics in asymptomatic bacteriuria (ASB) in the elderly with, or without, an indwelling catheter.	Strong for
	Always consider the positive and negative predictive value of specific symptoms before sending urine for culture or starting antibiotics for a UTI. Base decision on when to prescribe (whatever the age) primarily on symptoms. Use dipstick tests, if no catheter is present, to confirm the diagnosis, before prescribing especially when symptoms are mild or not localized.	Strong for
	If there are risk factors for MDR GNB or previous presence of MDR GNB and the patient is symptomatic, send a urine specimen for culture and susceptibility	Strong for
	Building on previous work, predictive scoring should be developed for the presence of ESBL-producing *E. coli* in primary care and on admission to hospital to restrict the need to prescribe carbapenems and other antimicrobial agents generally active against ESBLs	Strong for
	Need to quantify risks of infection with/ carriage of, extraintestinal pathogenic *E. coli* and of *Klebsiella sp.* resistant to all antibiotics and relate to time since travel to countries with high prevalence of MDR GNB and incorporate in risk assessments for clinical infection with MDR GNB in the community and on admission to hospital to guide therapy	Strong for
	If defined risk factors for MDR GNB are present avoid cephalosporins, quinolones, trimethoprim and co-amoxiclav in treatment of lower UTIs unless the pathogens are confirmed to be susceptible.	Strong for
	Personalise empirical chemotherapy for each patient by considering current features of bacteraemia, risk factors for antibiotic resistance and past susceptibility testing including the presence of MDR GNB in the patient, hospital unit, nursing home, or community.	Conditional for
	In pyelonephritis always collect a urine sample before treatment. MDR GNB are unlikely to respond to oral treatment so consider risk factors for MDR GNB including travel. Use an active oral agent only if patient is well enough and if known to have had ciprofloxacin-, trimethoprim-, or co-amoxiclav-susceptible MDR GNB in last month.	Conditional for

	If the patient has pyelonephritis and risk factors for MDR GNB, start, if hospitalisation not required, empirical intravenous therapy with ertapenem if OPAT therapy available. This will treat ESBL and Amp-C producing Enterobacteriaceae. If hospitalisation required for this or OPAT not available, admit for meropenem, temocillin or ceftolozane/tazobactam if no evidence of CPE organism. If the patient is penicillin-hypersensitive then the hospital may use amikacin or meropenem, or if only susceptible isolates in the past, gentamicin. If carbapenem-resistant bacteria are, or have been, present, base treatment on susceptibility testing of recent or current isolates.	Strong for
	Locally assess the true rate of resistance and determine from this when changes to guideline recommendations for empirical therapy for UTI in guidelines are necessary including recommendations where the risk of antibiotic-resistant bacteraemia is high.	Conditional for
Primary care prescriber for UTI	Always inform the patient or their carer(s) on what to look out for and how to reconsult if symptoms worsen or do not improve as community-onset *E. coli* bacteraemias of urinary origin are increasing	Strong for
	In younger women with acute uncomplicated UTI, only consider MDR GNB in choosing empirical treatment if there are risk factors See Section 9.3.1. or recent foreign travel to countries where such strains are highly prevalent.	Strong for
	Use fosfomycin, nitrofurantoin or pivmevillinam, guided where possible i) by susceptibility testing and ii) by this guideline's recommendation on choice, dosing and duration, for uncomplicated lower urinary tract infection where MDR GNB are suspected.	Strong for
	Use nitrofurantoin for 5 days with MDR GNB. Alternatively use fosfomycin trometamol 3g orally as single dose, and repeat on third day only if MDR GNB confirmed to improve bacteriological cure. Pivmecillinam alone at 200mg three times daily for 7 days may be a third line choice but consider combination use with amoxicillin/clavulanate depending on clinical trial results at the time.	Conditional for

	Review outcome data linked to antibiotic prescribing to improve quality of care in the community and care homes	Conditional for
	To reduce recurrent UTI, consider firstly, the option of pre-prescribed standby antibiotics to take when symptoms begin, rather than daily or post-coital antibiotic prophylaxis. Where prophylaxis is used successfully for recurrent infection in adults limit use to six months.	Conditional for
	Avoid antibiotic prophylaxis for urinary catheter insertion or changes unless there is previous history of symptomatic UTI with the procedure, insertion of incontinence implant, or trauma at catheterization.	Conditional for

Table 2 Summary recommendations for specific antibiotics

Amikacin	Modernise use of amikacin, which has improved activity, with development of validated nomograms. Ensure assays are readily available before repeat doses and consider, because of the risks of toxicity, the practicality of monitoring with audiograms.	Conditional for
Amoxicillin/clavulanate	Use for lower UTI due to known ESBL-producing bacteria only if current isolates, or if using empirically, recent isolates, are fully susceptible.	Conditional for
Ampicillin/sulbactam	Could use against some carbapenem-resistant apparently sulbactam-susceptible *A. baumannii* isolates, Caution needed in the UK because of a higher range of MICs. Absence of a breakpoint prevents categorisation as susceptible/resistant.	Conditional for
Aztreonam	Do not use aztreonam alone empirically if MDR GNB or Gram-positive or anaerobic pathogens are suspected	Strong against
	Do not use aztreonam for CTX-M ESBL- or AmpC- producing bacteria even if these appear susceptible *in vitro*	Strong against
	Use aztreonam for MBL- or OXA-48- producing strains if it is certain that they do not produce ESBLs or AmpC	Strong for
	Research usefulness of aztreonam in combination with avibactam for bacteria producing MBLs with ESBL/AmpC enzymes and for those with other carbapenemases.	Conditional for Research

Cefepime	Could use cefepime to treat infection caused by ESBL- or Amp-C-producing bacteria if susceptible to the EUCAST breakpoint of MIC =<1mg/L	Conditional for
	Do not use cefepime even at increased dose for isolates with i) MIC of 2-8 mg/l (CLSI "susceptible dose dependent") or ii) MIC 2-4mg/L (EUCAST intermediate, or iii) strains with stable derepression of AmpC or iv) strains that produce both AmpC and ESBLs.	Strong against
	Do not use cefepime to treat infection caused by carbapenemase-producing Enterobacteriaceae	Strong against
Cefixime and other oral cephalosporins	Do not used for treating infection caused by ESBL, AmpC and carbapenemase-producing Enterobacteriaceae	Conditional
Cefoxitin	Confirmation needed of its usefulness as a carbapenem-sparing agent for in-patients to empirically treat urinary infection or use definitively for infections caused by CTX-M-15-producing *E. coli*: its short serum half-life means it is unsuitable for OPAT and probably it has insufficient advantage to displace existing agents.	Research and trials
Ceftazidime	Use ceftazidime for susceptible infections with *P. aeruginosa* including quinolone- or some imipenem- resistant strains	Strong for
	Do not use ceftazidime to treat infections due to ESBL-or AmpC-producing Enterobacteriaceae or CPE (other than OXA-48 producers), even if *in vitro* tests suggest the isolate is susceptible	Conditional against
Ceftazidime/avibactam	Could use ceftazidime/avibactam as an alternative to carbepenems for infection with ESBL- and AmpC- producing Enterobacteriaceae but alternatives may be cheaper	Conditional for

	Evaluate further ceftazidime/avibactam use alone or in combination when non-MBL carbapenemase-producing organisms cause infection. KPC-3 producing Klebsiella are vulnerable to mutations in the enzyme causing resistance	Research and trials
	Consider if ceftazidime/avibactam should be used with a carbapenem or colistin to treat infections with KPC3-producers based on latest evidence at the time of use	Research and trials
	Do not use for treating infection with anaerobes or bacteria producing MBLs: these are resistant	Strong against
Ceftolozane/tazobactam	Use ceftolozane/tazobactam to treat susceptible infections with *P. aeruginosa* resistant to ceftazidime	Conditional for
	Conduct clinical trials in *P. aeruginosa* infections in cystic fibrosis	Research and trials
	Use ceftolozane- tazobactam as an alternative to carbapenems to treat urinary or intra-abdominal infection involving ESBL-producing *E. coli*. Caution may be needed when treating infections with ESBL-producing *Klebsiella spp.* owing to a higher resistance rate.	Conditional for
	Do not use for infections due to AmpC- or carbapenemase- producing Enterobacteriaceae or MBL/ESBL- producing *P. aeruginosa*.	Strong against
Ertapenem	Use ertapenem to treat serious infections with ESBL and AmpC-producing Enterobacteriaceae.	Strong for
	Apply antibiotic stewardship to use of all carbapenems to minimize the risk of developing resistance either by acquisition of carbapenemase-producing strains or by porin loss.	Strong for

	Preferred carbapenem for outpatient antibiotic treatment (OPAT) of susceptible infections in view of the once daily dosing regimen	Conditional for
Fluoroquinolones	Could use orally to treat UTI caused by MDR GNB that are susceptible	Conditional for
Fosfomycin	Use in the treatment of lower UTI due to MDR Enterobacteriaceae. Oral formulation available is useful for ESBL producers after repeated recurrence after nitrofurantoin and potentially for carbapenemase-producers	Conditional for
	Consider dosage and trials of oral formulation for upper UTI	Research and trials
	Consider parenteral fosfomycin, probably in combination, as part of salvage treatment for susceptible MDR GNB: clear indications for use are not yet established. Potential drug of last resort	Research and trials
	Need comparative clinical trials to establish optimal indications for, and optimal use of, oral and parenteral drug.	Research and trials
	Carry out ongoing local and national surveillance of use and resistance because of previous emergence of bacterial resistance in populations and the drug's potential as an important parenteral agent.	Strong for
Gentamicin	Could use gentamicin empirically in the UK if the likelihood of MDR GNB is low.	Conditional for
	Could use gentamicin as a carbapenem sparing agent for urinary, intra-abdominal and bacteraemic infections due to ESBL-producing *E. coli* when susceptibility is confirmed but do not use empirically if the risk of MDR GNB is raised	Conditional for
	Could use gentamicin in combinations for urinary, intra-abdominal and bacteraemic infections due to gentamicin-susceptible KPC-producing *Klebsiella*	Conditional for

	spp. if strain is resistant to colistin and meropenem (See Section 7.18).	
	Use once daily dosage of gentamicin or tobramycin if no renal impairment, followed by measurement of levels 6 to 14 hours post dose and adjust repeat dosage by reference to the appropriate 7mg/kg or 5mg/kg nomogram. Consider increased risks of toxicity if there is co-administration of nephrotoxic or ototoxic drugs	Strong for
Imipenem & Meropenem	Use meropenem or imipenem or ertapenem to treat serious infections with ESBL and AmpC-producing Enterobacteriaceae.	Strong for
	Apply antibiotic stewardship to use of all carbapenems to minimize the risk of developing resistance either by acquisition of carbapenemase-producing strains or, with ertapenem, by porin loss.	Strong for
	Do not use imipenem to treat susceptible Pseudomonas infections	Conditional for
	Introduce in the UK mandatory reporting of meropenem- or imipenem- resistant Enterobacteriaceae from all anatomical sites and specimens.	Strong for
	Test all meropenem- or imipenem- resistant isolates of Enterobacteriaceae immediately for the precise level of resistance and for an indication of the responsible class of carbapenemase (e.g. MBL/KPC (or other serine)/OXA48-like). Submit to agreed reference laboratories to determine susceptibility to a wide range of potentially active agents including, as appropriate, colistin, ceftazidime/avibactam, temocillin, aminoglycosides, fosfomycin and tigecycline.	Strong for
	Consider use of continuous infusion meropenem in combination at dose determined by nomogram if infection with KPC-carbapenemase –producing Klebsiella with MIC of >8 & <64mg/L.	Research and trials

Nitrofurantoin	Could use nitrofurantoin for 5 days to treat uncomplicated, lower urinary tract infections with nitrofurantoin-susceptible MDR *E. coli* (not Proteeae or *P. aeruginosa*).	Strong for
	Do not use repeatedly if there is moderate renal impairment (eGFR<45mks/min/1.73m^2.), or in long-term courses, as these are associated with rare unwanted pulmonary effects.	Conditional against
	Use alternative agents if there are repeated recurrences with MDR GNB but do not anticipate the emergence of resistance in *E. coli* infections on a single recurrence as selection for resistant strains in the urine or faecal flora is rare	Conditional for
	Need comparative studies of nitrofurantoin and other active antimicrobials in patients with ESBL-producing *E. coli* and *Klebsiella spp*	Research and trials
Piperacillin/tazobactam	Use for infections with known ESBL-producing bacteria only if current isolates, or, if using empirically, isolates from the recent past, are fully susceptible by EUCAST criteria.	Conditional for
	Consider definitive use of piperacillin/tazobactam to treat infections caused by *P. aeruginosa* if susceptible by EUCAST criteria.	Conditional for
Pivmecillinam	Consideration should be given to reducing the mecillinam EUCAST breakpoint for classification of susceptibility	Conditional for
	Treat lower UTI due to ESBL-negative *E. coli* with pivmecillinam at 200mg three times daily: do not use for infections caused by Proteeae*, Klebsiella* or *Pseudomonas*.	Conditional for
	Some ESBL-producing E. coli respond, but efficacy is poor against CTX-M-15 & OXA-1 enzyme producers: dosing at 400mg three times daily may be no more effective. Consider combination of the lower dose with 375mg three times daily	Conditional for

	amoxicillin/clavulanate for follow on to parenteral therapy for such infections in hospital or OPAT.	
	Requires clinical comparative trials in the public interest i) alone or together with amoxicillin/clavulanate for UTIs due to ESBL-producing organisms including particularly those producing CTX-M-15 enzymes ii) in uncomplicated lower UTI generally against fosfomycin trometamol and nitrofurantoin as the relative advantages of these drugs have not been directly compared over the least 10 years as MDR GNB have become more problematic.	Trials and research
Polymyxins(including colistin)	Reserve intravenous colistin for infections due to polymyxin susceptible but multiresistant bacteria and preferably use in combination with other agents.	Conditional for
	Give careful consideration to use of higher dosage regimens in critically ill patients	Conditional for
	Use colistin with meropenem to treat susceptible KPC-producing *Klebsiella spp.* if the meropenem MIC is <=8mg/L and consider higher meropenem dose by continuous infusion if the MIC is >8 and =<32mg/L.	Conditional for
	Consider colistin with aminoglycosides or tigecycline in infections with strains producing KPC or other carbapenemases, which are susceptible to these but resistant to meropenem with MIC>32mg/L.	Conditional for
	Closely monitor renal function especially in the elderly, those receiving high intravenous doses for prolonged periods and those on concomitant nephrotoxic agents e.g. aminoglycosides	Strong for
	Reconsider use of polymyxins in selective digestive decontamination regimens as these agents are now important last therapeutic options .against carbapenemase-producing Enterobacteriaceae and are more threatened by resistance than	Good practise

	previously appreciated	
	Need research on optimal rapid and practical methods of susceptibility testing outside intrinsically resistant groups such as *Proteeae* and *Serratia spp.*	Research and trials
	Aerosolised colistin dry powder should be used in cystic fibrosis according to NICE guidelines Use in combination in ventilator-associated pneumonia may be considered pending further trials without methodological flaws.	Conditional for
Temocillin	Use alone for UTIs and associated bacteraemia caused by AmpC- or ESBL-producing Enterobacteriaceae.	Conditional for
	Continuous infusion or thrice-daily dosing may be desirable for systemic infections with ESBL- or Amp-C producing bacteria.	Research and trials
	Could use for UTIs with KPC-producing Enterobacteriaceae but not for OXA-48 or MBL-producers, on basis of published in-vitro data.	Research and trials
Tigecycline	Could use tigecycline in combination in the treatment of multiresistant soft tissue and intra-abdominal infections	Conditional for
	Use alone in hospital-acquired respiratory infections is unlicensed and not advised as outcomes with current dosing are not clearly satisfactory in Acinetobacter and MDR GNB infections.	Conditional against
	Use in combinations in hospital-acquired respiratory infections: precise combinations depend on the antibiotic-susceptibility of the MDR GNB causing the infection.	Research and trials
	Use higher-than licensed dosing such as 100mg twice daily for infections due to MDR GNB in critical care	Conditional for

	Investigate if higher dosing counters the unexpectedly high mortality seen even in infections due to strains apparently susceptible *in vitro*.	Research and trials[23]
Tobramycin	Avoid tobramycin for MDR Enterobacteriaceae because of risk of resistance due to AAC (6')1 and AAC (6')-1b-cr	Conditional against
	Use tobramycin in preference to other aminoglycosides for susceptible Pseudomonas infection	Conditional for
	Use once daily dosage of tobramycin if no renal impairment followed by measurement of levels 6 to 14 hours post dose and adjust repeat dosage by reference to nomogram.	Strong for
Trimethoprim	Do not use trimethoprim in treating MDR GNB or treatment failures with other agents unless *in vitro*-susceptibility has been demonstrated.	Strong against
	Do not use trimethoprim to treat lower UTIs as a first line agent. Only consider use if there are norisk factors for resistance, or confirmed, *in vitro* susceptibility	Conditional against
Trimethoprim/sulfamethoxazole	Use in treatment of infections due to susceptible *S. maltophilia* and consider in infections due to *Achromobacter spp., Alcaligenes spp., Burkholderi spp., Chryeobacterium spp. and Elizabethkingia spp.*	Conditional for

24 **Table 3 Levels of evidence for intervention studies** [1]

1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1 +	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews or RCTs with a high risk of bias*
2++	High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal. Interrupted time series with a control group: (i) there is a clearly defined point in time when the intervention occurred; and (ii) at least three data points before and three data points after the intervention
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal OR Controlled before–after studies with two or more intervention and control sites
2-	Case–control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal. Interrupted time series without a parallel control group: (i) There is a clearly defined point in time when the intervention occurred; and (ii) at least three data points before and three data points after the intervention. Controlled before–after studies with one intervention and one control site
3	Non-analytic studies (e.g. uncontrolled before–after studies, case reports, case series)
4	Expert opinion. Legislation

25 *Studies with an evidence level of '1-'and '2-'should not be used as a basis for making a

recommendation.

RCT randomised controlled trial.

Table 4 Grading of Recommendations [11] .

	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain.	Recommendation for research *and possibly* conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

31 **Table 5 Stability of various β-lactam antibiotics and different inhibitor activities against important β-lactamases found in MDR GNB**

	Enterobacteriaceae								***Acinetobacter***		***Burkholderia***	***Pseudomonas***
Inhibitor	**AmpC**	**TEM ESBL**	**SHV-ESBL**	**CTX-M ESBL**	**OXA-1**	**OXA-48**	**KPC**	**IMP/VIM/NDM**	**native**	**OXA-23/24/58**	**native**	**native**
clavulanate	Not inhibited	Inhibited	Inhibited	Inhibited	Weak inhibition	Not inhibited	Not inhibited	Not inhibited		Not inhibited		
sulbactam	Not inhibited	Inhibited	Inhibited	Inhibited	Weak inhibition	Not inhibited	Not inhibited	Not inhibited		Not inhibited		
tazobactam	Not inhibited+	Inhibited	Inhibited	Inhibited	Weak inhibition	Not inhibited	Not inhibited	Not inhibited		Not inhibited		
avibactam	Inhibited	Inhibited	Inhibited	Inhibited	?	Inhibited	Inhibited[X]	Not inhibited		Not inhibited		
B-lactam												
temocillin	Stable	Stable	Stable	Stable	Stable	Labile	Moderately stable	Labile	Inherently inactive	Inherently inactive	Inherently inactive	Inherently inactive
piperacillin	Labile*	Labile	Labile	Labile	Labile	Labile	Labile	Labile	Acquired R near universal	Labile	Variable	Active
ceftazidime	Labile*	Labile	Labile	Labile	Stable	Stable	Labile	Labile	Acquired R near universal	Labile	Variable	Active
meropenem/imipenem	Stable	Stable	Stable	Stable	Stable	Labile	Labile	Labile	Active	Labile	Variable	Active
ertapenem	Moderately stable*	Stable	Stable	Stable	Stable	Labile	Labile	Labile	Inherently inactive	Inherently inactive	Inherently inactive	Inherently inactive
aztreonam	Labile*	Labile	Labile	Labile	Stable	Labile	Labile	Stable	Inherently inactive	Inherently inactive	Inherently inactive	Active
mecillinam	Stable	Moderately stable	Labile	Moderately stable	Stable	Labile	Labile	Labile	Inherently inactive	Inherently inactive	Inherently inactive	Inherently inactive

+ except Morganella morganii

*May appear active if AmpC is inducible, as induce weakly

[X] Inhibition not reliable with KPC3

Table 6 Studies of the efficacy of Colistin

Study	No of patients	Conditions treated	Pathogens	Duration (mean)	Outcome
Levin 1999[305]	59	VAP 33%; UTI 20%; BSI 15%; CNS 8%	*A. baumannii* 65%; *P. aeruginosa* 35%	12 days	58% success overall. Worst in pneumonia group (25%)
Garnacho-Montero *et al.* 2003[304]	21	VAP 100%	*A. baumannii* 100%	14 days	57% success
Linden *et al.* 2003[306]	23	VAP 78%; BSI 35%; Intra-abdominal 26%	*P. aeruginosa* 100%	17 days	61% favourable
Markou *et al.* 2003[307]	24	VAP 63%; Catheter related 12%; Meningitis 4%	*A. baumannii* 24%; *P. aeruginosa* 76%	13.5 days	73% success
Michalopoulos *et al.* 2005[308]	43	VAP 73%; BSI 33%	*A. baumannii* 19%; *P. aeruginosa* 81%	18.6 days	69% clinical cure
Reina *et al.* 2005[309]	55	VAP 53%; UTI 18%; BSI 16%	*A. baumannii* 65%; *P. aeruginosa* 35%	13 days	15% cure on day 6 of treatment
Koomanachaie et al 2007[505]	78	VAP 58%; BSI 10%	*A. baumannii* 91%; *P. aeruginosa* 9%	12 days	81% clinical response

VAP ventilator associated pneumonia

UTI urinary tract infection#BSI bloodstream infection

CNS central nervous system

Figure 1 Flow chart of systematic review

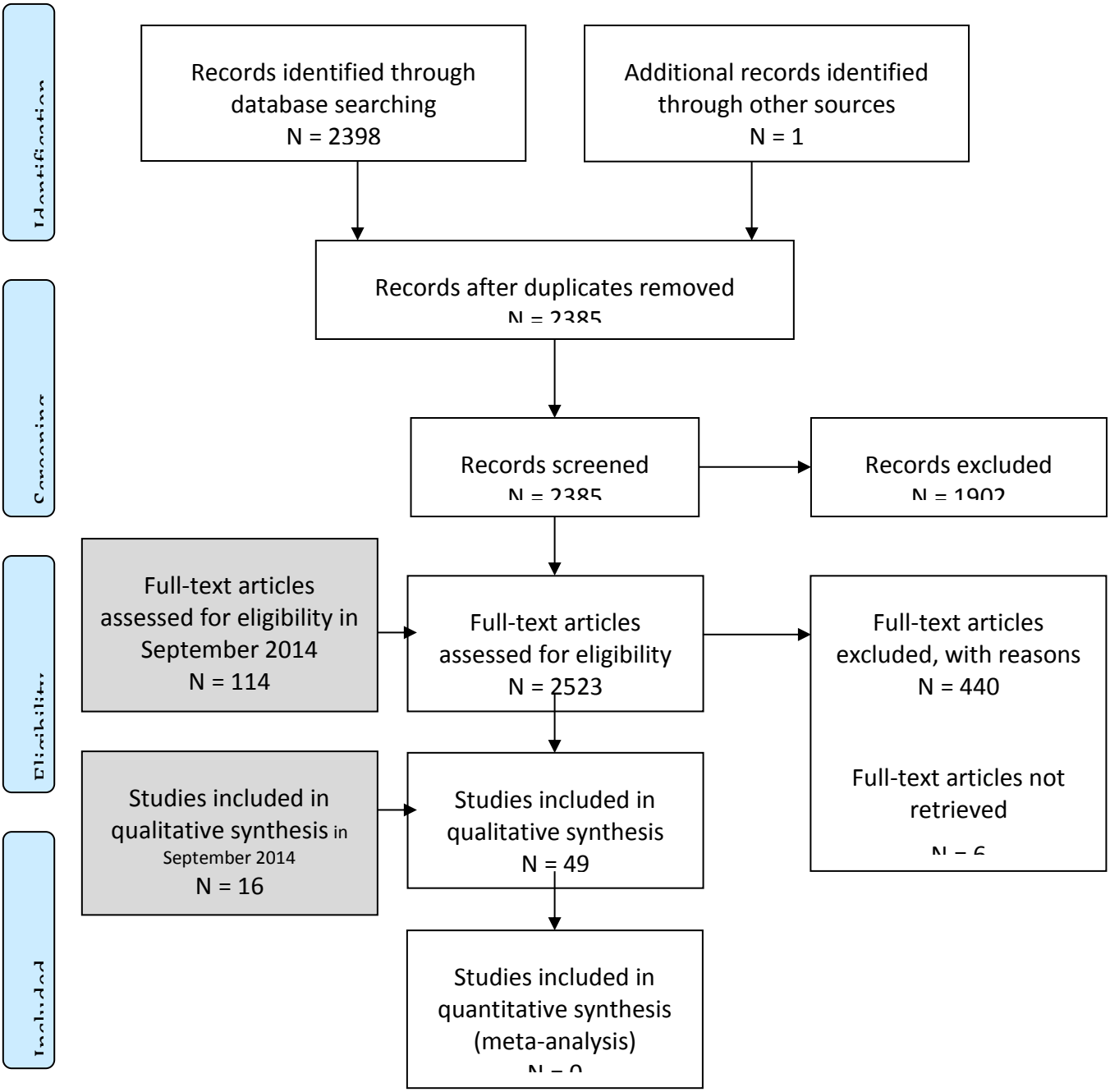


Figure 2 – Carbapenemase-producing Enterobacteriaceae submitted to and confirmed by PHE-AMRHAI-Colindale from Laboratories in England.

Courtesy of Dr Katie Hopkins, Public Health England

In a national context, a regional non PHE centre in an area of KPC endemicity became active in 2014 and did not submit or report isolates

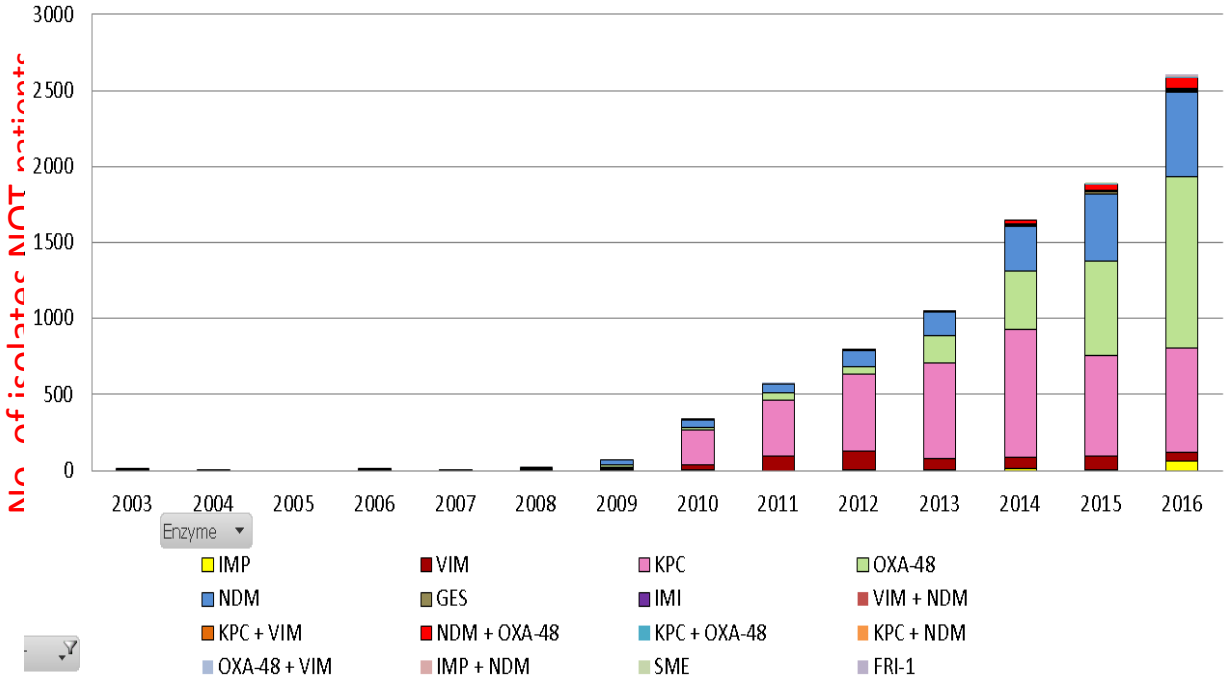
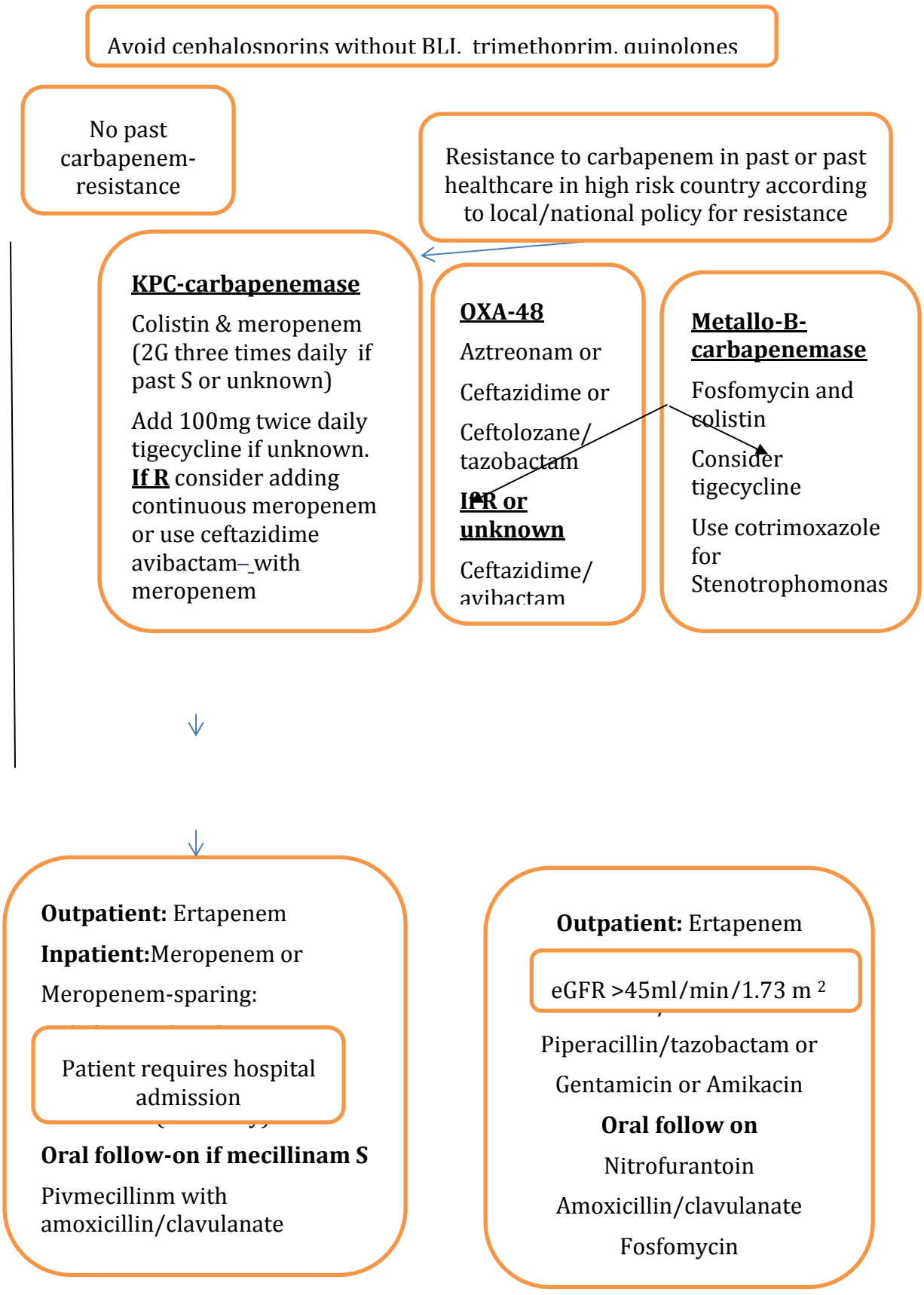


Figure 3 Suggested algorithm for the treatment of MDR Gram negative bacteria admitted to UK hospitals

Figure 4 Suggested algorithm for the treatment of UTI in the UK community likely to be due to MDR GNB.



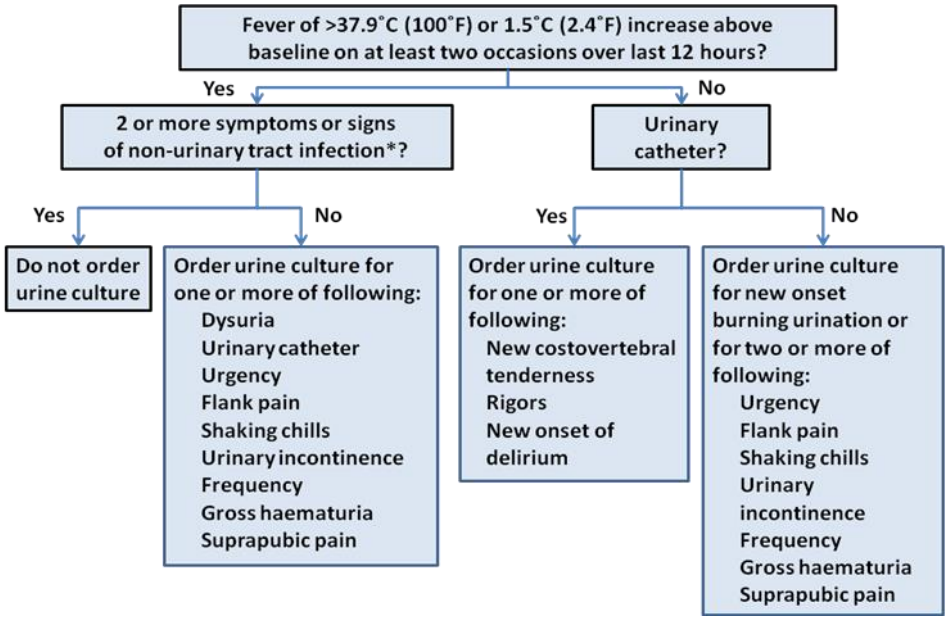
[1]Not nitrofurantoin if pyelonephritis or eGFR <45ml/min. or Age <50 years

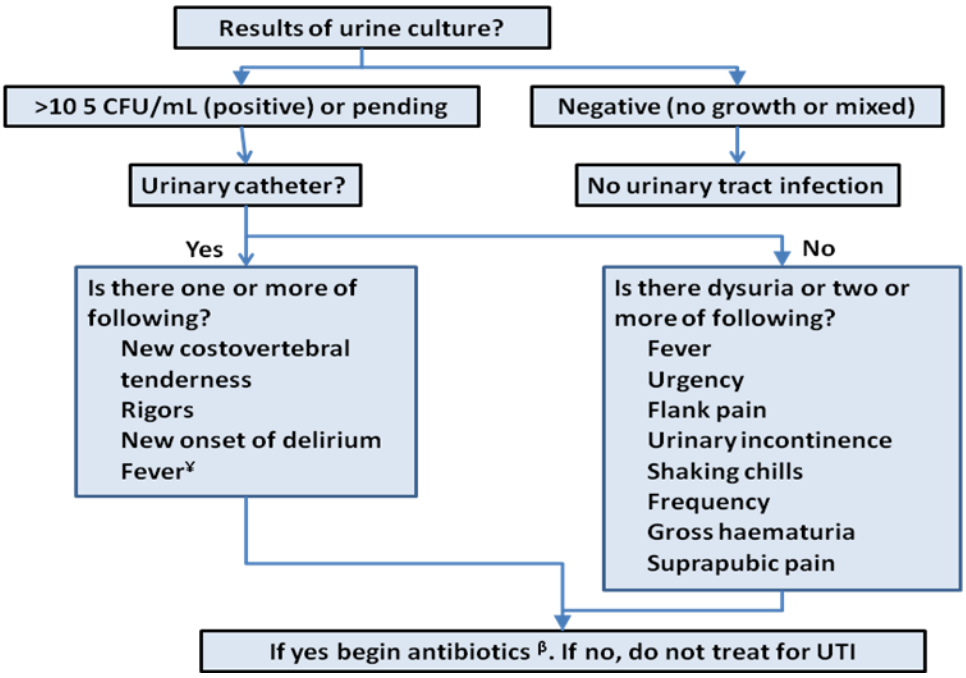
[2]Caution re prolonged/frequently repeated courses

[3] Not fosfomycin if pyelonephritis

[4] Unlike co-amoxiclav, 1st gen cephalosporins, fosfomycin, and pivmecillinam ciprofloxacin is generally active against *Proteus vulgaris, Morganella and Providencia.*

Figure 5: Diagnostic algorithm for ordering urine cultures and starting antibiotics if positive for nursing home residents in the intervention arm in the Loeb trial. (Loeb 2005)[CD32] [444]





*Respiratory symptoms include increased shortness of breath, increased cough, increased sputum production, new pleuritic chest pain. Gastrointestinal symptoms include nausea or vomiting, new abdominal pain, new onset of diarrhoea. Skin and soft tissue symptoms include new redness, warmth, swelling, purulent drainage.

¥ >37.9˚C (100˚F) or 1.5˚C (2.4˚F) above baseline on two occasions over last 12 hours

B Stop antibiotics if urine culture is negative or no pyuria is present

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[HoEFT33]

Appendix 1 – Glossary

AmpC β--lactamases: clinically important cephalosporinases encoded by the chromosomes of many Enterobacteriaceae or (less often) by plasmids. High-level expression confers resistance to penicillins (except temocillin), cephalosporins (except cefepime), aztreonam and penicillin- β-lactamase inhibitor combinations.

Antimicrobial: A substance that kills or inhibits the growth of microorganisms. This includes antibiotics and totally synthetic compounds.

Bacteraemia: The presence of micro-organisms in the blood stream

β-lactamases: Enzymes produced by some bacteria that confer resistance to β-lactam antibiotics such as penicillins and cephalosporins, by breaking down the central structure of the antibiotic.

Carbapenemases: These are β-lactamases that inactivate carbapenems such as meropenem; most also attack and confer resistance to penicillins and cephalosporins

CBA – (Controlled before and after study) is a more limited assessment than interrupted time series because it does not contain an initial pre-study period to examine underlying trends not a post-study period to assess the sustainability of trend, A cross-over study design may exclude bias due to sequential change,

CCG: Clinical Commissioning Group. This is a locality based authority in England responsible for primary care services and placing financial contracts with local hospitals for specific services

CQUIN: NHS England Commissioning for Quality and Innovation payments framework, to encourage care providers to share and continually improve how care is delivered and to achieve transparency and overall improvement in healthcare.

Cluster randomized controlled clinical trial. This is a trial where groups of individuals rather than individuals are randomized to treatment. This complex study design may reduce the chances of one patient's treatment having an effect on detection of effects in a patient randomized to a different treatment in the dame environment.

Colonization: Situation whereby microorganisms establish themselves in a particular environment, such as a body surface, without producing disease

Community-acquired: infection that is acquired outside of hospitals.

Community-onset or community-associated: usually defined as infection or colonization detected in an outpatient or within 48 hours of hospital admission. Recommended to permit extension to 72hours

CCT – (Controlled clinical trial) A ckinical trial where there is a comparative arm that is not randomized.

ESBL (extended-spectrum β-lactamase): β-Lactamases that attack cephalosporins with an oxyimino side chain, for example, cefotaxime, ceftriaxone, ceftazidime, ceftolozane as well as the oxyimino-monobactam aztreonam. Unlike AmpC β-lactamases (q.v.) they are inhibited by clavulanic acid and tazobactam and unlike carbapenemases (q.v.) they do not attack carbapenems. Avibactam inhibitis them and AmpC β-lactamases.

Healthcare – associated (acquired) : infection or colonization detected in an in-patient more than 48 hours after hospital admission or in a resident of a nursing (or residential) home.Recommended to permit extension to 72hours

Hospital-onset or Hospital–associated (-acquired): infection or colonization detected in an inpatient more than 48 hours after hospital admission. Recommended to permit extension to 72 hours.

IMP carbapenemase (of MBL class) prevalent particularly in Asia and Australia sometimes in association with a second carbapenemase (*bla*$_{KPC)}$ gene

Infection: Invasion by and multiplication of pathogenic microorganisms in the body, producing tissue injury and disease, requiring treatment.

ITS – (Interrupted time series). A series of sequential cases where an intervention is made in the middle of the study as in before and after studies but additional time periods before and after the two comparative periods are included to give information omn prior trends and sustainability. studied. There may be further interventions in the series similarly studied.

KPC *Klebsiella pneumoniae* carbapenemase-producing bacteria are drug-resistant Gram negative bacilli which spread rapidly and cause significant morbidity and mortality. They are the most prevalent carbapenemase producers encoded by the *bla*$_{KPC}$ gene, which can be found in other Gram negative species.

MBL (Metallo β-lactamase) producing Gram negative bacteria use a Zn^{2+} ion in expressing resistance to carbapenems and other B-lactams

MDR GNB –(Multi-drug resistant Gram-negative bacteria) are defined as bacteria resistant to at least three different antibiotic classes or susceptible to only one or two classes.

NDM New Delhi metallo β-lactamase is a carbapenemase located on a mobile genetic element *bla*$_{\text{NDM-1}}$ and is found on plasmids of various sizes. It is found in various species making outbreaks more difficult to identify.

OXA-48 carbapenemases hydrolyze penicillins at a high level but carbapenems at a low level sparing broad spectrum cephalosporins and are no susceptible to β-lactamase inhibitors. Recogniition in the laboratory can be difficult. The gene *bla*$_{\text{OXA-48}}$ is carried on a transposon and can be in a plasmid or chromosome.

Outbreak: at least two similar (i.e. not distinct) cases related in time and place

Porins: These are proteins that span the outer membrane of Gram-negative bacteria and mycobacteria forming pores that allow the entry of small water-soluble molecules, including antibiotics.

RCT (randomised controlled trial). Trials where patient allocation to the control and test arms of the study are allocated at random. They can be open label where treating physicians know which arm a patient has been allocated to or blinded where this is not the case. The latter is less likely to be subject to bias.

VIM MBL is a carbapenemase predominantly found in *Pseudomonas aeruginosa* but

found in Enterobacteriaceae as well. The genes *bla*$_{\text{VIM}}$ are located on mobile integrons .

.**Appendix 2 Remit scope and related NICE guidelines**

Joint BSAC/HIS/BIA Working Party on Multi-resistant Gram-negative bacteria

2.1.Guideline title

Treatment of MDR Gram-negative bacteria – report from a Joint Working Party

Short title: Treatment of Multi-Drug-Resistant Gram negative bacteria

2.2.Clinical need for the guideline

Epidemiology

There are a rising number of MDR Gram-negative infections across community and hospital care and the dual problems of finding an appropriate antibiotic and preventing spread.

APRHAI has recently produced brief guidelines on infection control and treatment options for these infections.

There is significant interest attracted by the May 2010 BSAC conference examining the dearth of new antibiotics effective against Gram-negative bacteria.

The Department of Health's recognised that whilst control of MRSA and C difficile has been relatively successful, Gram-negative infections have continued to increase.

Consequent to this is the surveillance subcommittee of APRHAI recommendation that E. coli bacteraemia be included in mandatory surveillance.

Current practice

Members of BSAC and HIS, with the knowledge of the Councils of each, have been discussing the issues surrounding the recent increase in infections with multi-resistant Gram-negative bacteria in UK hospitals.

Following discussions and consideration of the forthcoming APRHAI report we now believe it an appropriate time to set up a Joint Working Party to look at making authoritative recommendations both for treatment and prevention of transmission of these infections.

2.3.The remit

To examine and make recommendations both for treatment and prevention of transmission of multi-drug-resistant (MDR) Gram-negative infections, resulting in the publication of guidelines on:

- current epidemiology and infection control issues; and
- therapeutic issues and antibiotic guidance for treating infections caused by MDR Gram-negative bacteria.

For the purposes of this Working Party, the remit will mainly include infections in critical and non-critical care patients in secondary care. However, the same general principles would apply in community settings, particularly in areas where inappropriate treatment is encouraging selection. Consideration will be given to laboratory testing and susceptibility testing, although only screening and confirmatory tests available in a general microbiology laboratory. The use of antibiotic combinations in the therapy of infections will be considered, both parenteral and oral agents.

2.4. The Guideline

The guideline development process is described on the NICE website and reproduced in Appendix 3. The Working Party will follow the SIGN process when developing guidance including the hosting of a national stakeholder meeting as part of the national stakeholder consultation process.

..... 2.5. The Scope

Defines what the guideline will and will not examine and what the guideline developers will consider. The scope is based on the referral from the three Societies and is the final scope.

2.5.1. Population Groups that will be covered

a) Adults

Particular consideration given to patients of 65 years and older, and people at high risk of acquiring multi-resistant bacteria such as those requiring care in hospital settings

b) Children over 1 month old

2.5.2. Key clinical issues that will be covered

a) Antimicrobial treatment of MDR Gram-negative infections

b) Antimicrobial stewardship

c) Epidemiology

d) Surveillance

e) Infection prevention: standards, hand and environmental hygiene, organizational structures

Clinical situations that will not be covered include:

Cystic fibrosis

Community outbreaks

2.5.3. Infections that will be covered

Those caused by the following organisms

Escherichia coli, Klebsiella spp. including Klebsiella pneumoniae, Enterobacter spp., Pseudomonas aeruginosa, Acinetobacter spp., Proteus spp., Serratia spp., Citrobacter freundii, Morganella morgani

Sexually transmitted infections, Helicobacter ssp. Salmonella ssp. and some anaerobes are Gram-negative and are increasingly resistant, but were excluded because relevant public health control actions are substantially different or they have not been researched.

2.5.4. Antibiotics that will be considered

Standard antibiotics currently in use such as most cephalosporins, coamoxiclav, piperacillin/tazobactam quinolones, temocillin (pivmecillinam is the oral formulation of mecillinam

Old antibiotics that have been re-introduced: such as aminoglycosides (including gentamicin and amikacin), colistin, fosfomycin, nitrofurantoin

Recently developed antibiotics: tigecycline, cefepime, new B-lactam-B-lactamase inhibitor combinations and carbapenems or those new agents at preliminary stages of testing .

2.5.5. Healthcare settings

All settings in which NHS care is received

..... 2.6. Main outcomes

Outputs will be the production of guidelines, which will be approved via a process of national consultation. The intention is to inform and guide practice but also to highlight areas where more research is needed. The following will be produced and published as indicated:

Current epidemiology and infection control issues – Journal of Hospital Infection

Therapeutic issues and antibiotic guidance for treating infections caused by multi-resistant Gram-negatives – Journal of Antimicrobial Chemotherapy

In addition, it is expected that each Journal will carry a leading article or review article on the guidance that is published by the joint societies.

..... 2.7. Recommendations for practice

Treatment

Surveillance

Screening

Prevention of transmission

Cleaning and environment

..... 2.8. Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions.

Failure to implement the recommendations would result in greater costs in terms of life expectancy or quality. Screening and isolation will result in significant cost pressures where this is not currently practised, but these costs are set against reduced transmission and fewer cases needing antibiotic treatment. Prolonged isolation can have adverse effects on a patient's psychological health, so may have additional unexpected costs.

..... 2.9. Patient Representation And Equality

Patient representatives are invited to all meetings and involved in the writing and drafting of the guidelines. As part of these discussions potential impacts on equality of groups sharing protected characteristics are considered and incorporated into the guidelines. Health inequalities associated with socioeconomic factors and with

inequities in access for groups to healthcare and social care are considered and opportunities identified to improve health.

..... 2.10. Status

2.10.1 Scope

This is the final scope.

2.10.2 Timing

The development of the guideline recommendation began in July 2011.

Appendix 3 Guideline development process

3.1. Guidance document

Scottish Intercollegiate Guidelines Network. *SIGN 50: a guideline developer's handbook.* Revised edition. Edinburgh: Healthcare Improvement Scotland; 2014. Available at: http://www.sign.ac.uk [last accessed April 2017].

3.2. Related NICE guidance

National Institute for Health and Care Excellence. Infection: prevention and control of healthcare-associated infections in primary and community care. NICE Clinical Guideline 139. London: NICE; 2012. Last updated: February 2017. Available at: http://www.nice.org.uk/guidance/cg139 [last accessed April 2017].

National Institute for Health and Care Excellence. .Antimicrobial stewardship: prescribing antibiotics. London: NICE; Published date: January 2015 Last updated: January 2017. Available at: https://www.nice.org.uk/advice/ktt9/chapter/evidence-context [last accessed July 2017]

National Institute for Health and Care Excellence. .Urinary Tract Infection in Adults. London: NICE; Quality standard [QS90] Published date: June 2015. Available at: https://www.nice.org.uk/guidance/qs90/chapter/introduction

NICE approved guideline: Wilson AP, Livermore DM, Otter JA, et al. Prevention and control of multi-drug-resistant Gram-negative bacteria: recommendations from a Joint Working Party. *J Hosp Infect* 2016; 92 Suppl 1: S1-S44. Available at : http://www.journalofhospitalinfection.com/article/S0195-6701(15)00314-X/pdf

3.3. Process followed

The subject was identified by the Scientific Development Committee of the Healthcare Infection Society in February 2011 and approved by HIS in May 2011. The BSAC Council agreed a similar proposal at the same time. BIA Council agreed to join in September 2011. The members were chosen to reflect the range of stakeholders and not limited to members of the three Societies. The questions were decided at the first meeting of the

Group in November 2011 from issues presented to the members and patient representatives by staff and patients in the preceding months. Each was debated by the Group before adoption. Enhance Reviews was paid for the serach and data extraction. Working Party members were not paid except for travel expenses.

3.4. Conflict of Interests

Conflicts of interest were registered at the outset and renewed during the process. They are stated in the Transparency declaration of the Report. In the event of a potential conflict being identified, the Working Party agreed that the member should not contribute to the section affected With one exception, no interests were declared that required any actions and this related to the infection control paper produced by the working party.

3.5.PICO:

Patients: All patient groups were included. The guideline is careful not to make recommendations which may prejudice clinical care based on gender, age, ethnicity or socio-economic status.

Interventions: interventions were identified in the literature to generate intervention specific recommendations

Comparisons: comparisons between intervention and standard management were used;

Outcomes were objective referring to length of hospital stay, mortality, rate of acquisition or infection.

3.6. Systematic Review Questions: Infection Control

1. What is the definition of Multidrug Resistant Gram-negative bacilli?
2. What Gram-negative bacilli cause infection control problems?
3. What are the relative contributions of community and hospital acquisition?
4. What is the evidence for reservoir and spread of mulitresistant Gram-negatives in Care Homes and secondary care?
5. What is the role of agricultural use of sewage and antibiotic treatment in veterinary practice in spreading ESBL?
6. What insights has national *E. coli* bacteraemia surveillance provided?
7. What is the role for screening in patients and staff?
8. What organisms should screening include?
9. Who, how and when to screen patients for Multidrug Resistant Gram-negative bacilli?

10. What can be done concerning patients unable to consent to a rectal swab?
11. How frequently does screening need to be performed?
12. Is there evidence for effective interventions on positive patients i.e. can carriage be cleared?
13. Selective decontamination: Why is it not used? Is there a role?
14. When should the environment be sampled?
15. What is the evidence that respiratory equipment contributes to transmission?
16. What national surveillance is performed and how should it be developed?
17. What is the evidence that sensor taps contribute to transmission?
18. Is there any cleaning method more effective than others at removing the Multidrug Resistant Gram-negative bacilli from the environment?
19. What is the evidence that infection control precautions prevent transmission?
20. Are standard infection control measures sufficient to stop transmission?
21. What are the minimum standards to stop spread in public areas, primary care or care homes?
22. Is there evidence for high/low risk areas within a healthcare facility?
23. Are there any organisational structures within a healthcare facility that play a role in the successful control of multi-resistant Gram-negative bacilli?
24. How should we undertake local screening, why is it important and how should it be interpreted?
25. At what point should passive surveillance switch to active surveillance i.e. screening?
26. What is the role of isolation in the care home/hospital settings?

Is there evidence of differences between organisms in respect of transmission, morbidity and mortality:

3.7. Antimicrobial Chemotherapy -Systematic Review Questions

1. What is the clinical importance of carbapenemases versus AmpC and CTX-M strains?
2. What impact have returning travellers made on UK epidemiology?
3. What is the global epidemiology of MDR-GNR?
4. How do Multidrug Resistant Enterobacteriaceae differ from the non-fermenters in terms of their prevalence and associated resistance genes?

5. What is the efficacy of carbapenems, mecillinam, temocillin, fosfomycin and colistin against specific pathogens?
6. What are the recommended antibiotics for community/secondary/tertiary care?
7. What is the threshold level of resistance for changing choice of empirical treatment for urinary infection?

Appendix 4 Systematic Review

4.1. Databases and Search terms Used 23/5/14[i]

4.1.1. Databases

The Cochrane Library; MEDLINE; EMBASE; CINAHL

MeSH Terms See 4.2.

Free text terms. See 4.2.

Search Date: Medline 1946-2014; Embase 1980-2012; CINAHL (1984-2012)

Search Results (Figure 1)

Total number of articles located after duplicates removed = 2523

Sift 1 Criteria

Abstract screening: Systematic review, primary research, infection relates to MDR Gram-negative infection, informs one or more review question

Articles Retrieved

Total number of studies selected = 597

Sift 2 Criteria

Full text confirms that the article is primary research (randomised controlled trial, non-randomised controlled trials, controlled before and after studies, interrupted time series, case control study, case series, prospective cohort, systematic review; informs one or more of the review questions.

Articles selected for appraisal (10 full text publications could not be retrieved)

Total number of studies selected = 49

Critical appraisal

Articles presenting primary research or a systematic review and meeting the sift criteria were critically appraised by two reviewers using SIGN and EPOC criteria. Consensus was achieved through discussion

Accepted and Rejected Evidence

No meta analyses were available

Accepted after critical appraisal 49

Rejected after critical appraisal 0

4.2. Search

4.2.1. CINAHL (January 1984-December 2012)

#	Query	Results
S83	**S48 AND S82**	**275**
S82	S55 OR S56 OR S81	515,966
S81	S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80	471,263
S80	TI ((time points n3 over) or (time points n3 multiple) or (time points n3 three) or (time points n3 four) or (time points n3 five) or (time points n3 six) or (time points n3 seven) or (time points n3 eight) or (time points n3 nine) or (time points n3 ten) or (time points n3 eleven) or (time points n3 twelve) or (time points n3 month*) or (time points n3 hour*) or (time points n3 day*) or (time points n3 'more than')) or AB ((time points n3 over) or (time points n3 multiple) or (time points n3 three) or (time points n3 four) or (time points n3 five) or (time points n3 six) or (time points n3 seven) or (time points n3 eight) or (time points n3 nine) or (time points n3 ten) or (time points n3 eleven) or (time points n3 twelve) or (time points n3 month*) or (time points n3 hour*) or (time points n3 day*) or (time points n3 'more than'))	1,527
S78	TI (multicentre or multicenter or multi-centre or multi-center) or AB random*	101,899
S77	TI random* OR controlled	94,669
S76	TI (trial or (study n3 aim) or 'our study') or AB ((study n3 aim) or 'our study')	87,121
S75	TI (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop)) or AB (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop))	283
S74	TI (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*) or AB (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*)	1,290

#	Query	Results
S73	(intervention n6 clinician*) or (intervention n6 community) or (intervention n6 complex) or (intervention n6 design*) or (intervention n6 doctor*) or (intervention n6 educational) or (intervention n6 family doctor*) or (intervention n6 family physician*) or (intervention n6 family practitioner*) or (intervention n6 financial) or (intervention n6 GP) or (intervention n6 general practice*) Or (intervention n6 hospital*) or (intervention n6 impact*) Or (intervention n6 improv*) or (intervention n6 individualize*) Or (intervention n6 individualise*) or (intervention n6 individualizing) or (intervention n6 individualising) or (intervention n6 interdisciplin*) or (intervention n6 multicomponent) or (intervention n6 multi-component) or (intervention n6 multidisciplin*) or (intervention n6 multi-disciplin*) or (intervention n6 multifacet*) or (intervention n6 multi-facet*) or (intervention n6 multimodal*) or (intervention n6 multi-modal*) or (intervention n6 personalize*) or(intervention n6 personalise*) or (intervention n6 personalizing) or (intervention n6 personalising) or (intervention n6 pharmaci*) or (intervention n6 pharmacist*) or (intervention n6 pharmacy) or (intervention n6 physician*) or (intervention n6 practitioner*) Or (intervention n6 prescrib*) or (intervention n6 prescription*) or (intervention n6 primary care) or (intervention n6 professional*) or (intervention* n6 provider*) or (intervention* n6 regulatory) or (intervention n6 regulatory) or (intervention n6 tailor*) or (intervention n6 target*) or (intervention n6 team*) or (intervention n6 usual care)	23,198
S72	TI (collaborativ* or collaboration* or tailored or personalised or personalized) or AB (collaborativ* or collaboration* or tailored or personalised or personalized)	38,021
S71	TI pilot	13,958
S70	(MH 'Pilot Studies')	36,433
S69	AB 'before-and-after'	17,437
S68	AB time series	1,670
S67	TI time series	359
S66	AB (before* n10 during or before n10 after) or AU (before* n10 during or before n10 after)	32,982
S65	TI ((time point*) or (period* n4 interrupted) or (period* n4 multiple) or (period* n4 time) or (period* n4 various) or (period* n4 varying) or (period* n4 week*) or (period* n4 month*) or (period* n4 year*)) or AB ((time point*) or (period* n4 interrupted) or (period* n4 multiple) or (period* n4 time) or (period* n4 various) or (period* n4 varying) or (period* n4 week*) or (period* n4 month*) or (period* n4 year*))	51,050

#	Query	Results
S64	TI ((quasi-experiment* or quasiexperiment* or quasi-random* or quasirandom* or quasi control* or quasicontrol* or quasi* W3 method* or quasi* W3 study or quasi* W3 studies or quasi* W3 trial or quasi* W3 design* or experimental W3 method* or experimental W3 study or experimental W3 studies or experimental W3 trial or experimental W3 design*)) or AB ((quasi-experiment* or quasiexperiment* or quasi-random* or quasirandom* or quasi control* or quasicontrol* or quasi* W3 method* or quasi* W3 study or quasi* W3 studies or quasi* W3 trial or quasi* W3 design* or experimental W3 method* or experimental W3 study or experimental W3 studies or experimental W3 trial or experimental W3 design*))	12,758
S63	TI pre w7 post or AB pre w7 post	9,367
S62	MH 'Multiple Time Series' or MH 'Time Series'	1,312
S61	TI ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies) or AB ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies)	11,680
S60	MH Experimental Studies or Community Trials or Community Trials or Pretest-Posttest Design + or Quasi-Experimental Studies + Pilot Studies or Policy Studies + Multicenter Studies	34,567
S59	TI (pre-test* or pretest* or posttest* or post-test*) or AB (pre-test* or pretest* or posttest* or 'post test*) OR TI (preimplement*' or pre-implement*) or AB (pre-implement* or preimplement*)	6,868
S58	TI (intervention* or multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*) or AB (intervention* or multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*)	151,748
S57	(MH 'Quasi-Experimental Studies')	5,747

#	Query	Results
S56	(TI (systematic* n3 review*)) or (AB (systematic* n3 review*)) or (TI (systematic* n3 bibliographic*)) or (AB (systematic* n3 bibliographic*)) or (TI (systematic* n3 literature)) or (AB (systematic* n3 literature)) or (TI (systematic* n3 review*)) or (AB (systematic* n3 review*)) or (TI (comprehensive* n3 literature)) or (AB (comprehensive* n3 literature)) or (TI (comprehensive* n3 bibliographic*)) or (AB (comprehensive* n3 bibliographic*)) or (JN 'Cochrane Database of Systematic Reviews') or (TI (information n2 synthesis)) or (TI (data n2 synthesis)) or (AB (information n2 synthesis)) or (AB (data n2 synthesis)) or (TI (data n2 extract*)) or (AB (data n2 extract*)) or (TI (medline or pubmed or psyclit or cinahl or (psycinfo not 'psycinfo database') or 'web of science' or scopus or embase)) or (AB (medline or pubmed or psyclit or cinahl or (psycinfo not 'psycinfo database') or 'web of science' or scopus or embase)) or (MH 'Systematic Review') or (MH 'Meta Analysis') or (TI (meta-analy* or metaanaly*)) or (AB (meta-analy* or metaanaly*))	59,817
S55	S49 OR S50 OR S51 OR S52 OR S53 OR S54	158,596
S54	TI ('control* N1 clinical' or 'control* N1 group*' or 'control* N1 trial*' or 'control* N1 study' or 'control* N1 studies' or 'control* N1 design*' or 'control* N1 method*') or AB ('control* N1 clinical' or 'control* N1 group*' or 'control* N1 trial*' or 'control* N1 study' or 'control* N1 studies' or 'control* N1 design*' or 'control* N1 method*')	1
S53	TI controlled or AB controlled	68,638
S52	TI random* or AB random*	117,418
S51	TI ('clinical study' or 'clinical studies') or AB ('clinical study' or 'clinical studies')	7,969
S50	(MM 'Clinical Trials+')	10,670
S49	TI ((multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*)) or AB ((multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*))	8,917
S48	S18 AND S21 AND S47	917
S47	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46	16,726

#	Query	Results
S46	TI ((belcomycin or colicort or colimycin* or colisitin or colisticin or Colistin or colistine or colomycin or (coly n1 mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin n1 E) or totazina)) OR AB ((belcomycin or colicort or colimycin* or colisitin or colisticin or Colistin or colistine or colomycin or (coly n1 mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin n1 E) or totazina))	171
S45	(MH 'Colistin')	134
S44	TI (((amdinocillin n1 pivoxil) or (FL n1 '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro n1 '109071') or (ro10 n1 '9071') or ro109071)) OR AB (((amdinocillin n1 pivoxil) or (FL n1 '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro n1 '109071') or (ro10 n1 '9071') or ro109071))	13
S43	TI (((Cephalosporanic n1 Acid*) or Cephalosporin* or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin)) OR AB (((Cephalosporanic n1 Acid*) or Cephalosporin* or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin))	1,569
S42	TI ((Axepim* or bmy 28142 or bmy28142 or BMY-28142 or Cefepim* or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfrom or maxipime or Quadrocef)) OR AB ((Axepim* or bmy 28142 or bmy28142 or BMY-28142 or Cefepim* or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfrom or maxipime or Quadrocef))	171
S41	(MH 'Cephalosporins+')	2,105

#	Query	Results
S40	TI ((berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin* or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin* or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin* or macrofuran or macrofurin or micofurantin* or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro n1 macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin* or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium n1 furagin) or ralodantin or trocurine or urantin or (uro n1 tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin)) OR AB ((berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin* or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin* or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin* or macrofuran or macrofurin or micofurantin* or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro n1 macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin* or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium n1 furagin) or ralodantin or trocurine or urantin or (uro n1 tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin))	325
S39	TI (((az n1 threonam) or azactam or azenam or azthreonam or aztreonam or (corus n1 '1020') or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam)) OR AB (((az n1 threonam) or azactam or azenam or azthreonam or aztreonam or (corus n1 '1020') or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam))	96
S38	(MH 'Aztreonam')	54
S37	TI ((fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or 'mk 0955' or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin)) OR AB ((fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or 'mk 0955' or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin))	57

#	Query	Results
S36	TI ((akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin* or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid)) OR AB ((akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin* or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid))	342
S35	(MH 'Amikacin')	140

#	Query	Results
S34	TI ((adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam* or epigent or (frieso n1 gent) or garabiotic or garalone or garamicin* or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame* or gentamicin* or gentamina or gentamycin* or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin* or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina)) OR AB ((adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam* or epigent or (frieso n1 gent) or garabiotic or garalone or garamicin* or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame* or gentamicin* or gentamina or gentamycin* or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin* or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina))	993
S33	(MH 'Gentamicins')	808

#	Query	Results
S32	TI ((Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin)) OR AB ((Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin))	1,269
S31	(MH 'Aminoglycosides+')	6,215
S30	TI (((chinolone n1 derivative) or fluoroquinolones or (haloquinolone n1 derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones)) OR AB (((chinolone n1 derivative) or fluoroquinolones or (haloquinolone n1 derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones))	834
S29	(MH 'Quinolines+') OR (MH 'Antiinfective Agents, Quinolone+')	4,842
S28	TI ((tigecycline or (tbg n1 mino) or tygacil or gar 936 or gar936 or (tert n1 butylglycinamido*))) OR AB ((tigecycline or (tbg n1 mino) or tygacil or gar 936 or gar936 or (tert n1 butylglycinamido*)))	208
S27	TI (((brl n1 '17421') or brl17421 or (thiophenemalonamic n1 acid) or negaban or temocillin or temopen)) OR AB (((brl n1 '17421') or brl17421 or (thiophenemalonamic n1 acid) or negaban or temocillin or temopen))	10

#	Query	Results
S26	TI ((aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox n1 clav) or amox-clav or (amoxi n1 plus) or (amoxNear/3clavulan*) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or amoxxlin or (amoxycillin-clavulanic n1 acid) or ancla or (auclatin n1 duo) or augamox or augmaxcil or augmentan or augmentin* or augmex or augpen or (augucillin n1 duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl n1 '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin n1 duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl n1 duo*) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin n1 plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox n1 duo) or clavumox or (co n1 amoxiclav) or (co n1 amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon n1 duo) or (croanan n1 duo) or curam or danoclav or (darzitil n1 plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina n1 plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox n1 cl) or vestaclav or viaclav or vulamox or xiclav or (zami n1 '8503'))) OR AB ((aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox n1 clav) or amox-clav or (amoxi n1 plus) or (amoxNear/3clavulan*) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or amoxxlin or (amoxycillin-clavulanic n1 acid) or ancla or (auclatin n1 duo) or augamox or augmaxcil or augmentan or augmentin* or augmex or augpen or (augucillin n1 duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl n1 '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin n1 duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl n1 duo*) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin n1 plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox n1 duo) or clavumox or (co n1 amoxiclav) or (co n1 amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon n1 duo) or (croanan n1 duo) or curam or danoclav or (darzitil n1 plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina n1 plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox n1 cl) or vestaclav or viaclav or vulamox or xiclav or (zami n1 '8503')))	805

#	Query	Results
S25	TI ((cl 307579 or cl298741 or cl307579 or tazabactam or tazobac* or tazocel or tazocillin* or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn)) OR AB ((cl 307579 or cl298741 or cl307579 or tazabactam or tazobac* or tazocel or tazocillin* or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn))	247
S24	TI ((acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin* or pipcil or pipera hameln or piperacil or piperacillin* or piperacin or pipera-hameln or pipercillin or piperilline or pipraci* or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin)) OR AB ((acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin* or pipcil or pipera hameln or piperacil or piperacillin* or piperacin or pipera-hameln or pipercillin or piperilline or pipraci* or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin))	296
S23	TI ((Carbapenem* or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin*)) OR AB ((Carbapenem* or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin*))	974
S22	(MH 'Carbapenems+')	559
S21	S19 OR S20	14,473
S20	(MH 'Drug Resistance, Microbial+')	14,182
S19	TI ((multiresistant or (multi n1 resistan*))) OR AB ((multiresistant or (multi n1 resistan*)))	604
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	7,706

#	Query	Results
S17	TI (((bacillus n1 morgan*) or (bacterium n1 morgana) or (morganella n1 morgagni*) or (morganella n1 morganii) or (proteus n1 morgagni) or (proteus n1 morgana*) or (salmonella n1 morgana))) OR AB (((bacillus n1 morgan*) or (bacterium n1 morgana) or (morganella n1 morgagni*) or (morganella n1 morganii) or (proteus n1 morgagni) or (proteus n1 morgana*) or (salmonella n1 morgana)))	20
S16	TI (((Citrobacter n1 freundii) or (bacterium n1 freundii) or (Escherichia n1 freundii))) OR AB (((Citrobacter n1 freundii) or (bacterium n1 freundii) or (Escherichia n1 freundii)))	32
S15	(MH 'Citrobacter')	40
S14	TI Serratia OR AB Serratia	238
S13	(MH 'Serratia') OR (MH 'Serratia Infections')	174
S12	TI Proteus OR AB Proteus	257
S11	(MH 'Proteus') OR (MH 'Proteus Infections')	118
S10	TI ((Acinetobacter or mima or mimae or herellea or acinetobacterium)) OR AB ((Acinetobacter or mima or mimae or herellea or acinetobacterium))	889
S9	(MH 'Acinetobacter Infections')	581
S8	TI 'p. aeruginosa' OR AB 'p. aeruginosa'	610
S7	TI (((bacillus n1 pyocyaneus) or (bacterium n1 (aeruginosum or pyocyaneum)) or (blue n1 apus) or (Pseudomonas n1 (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus)))) OR AB (((bacillus n1 pyocyaneus) or (bacterium n1 (aeruginosum or pyocyaneum)) or (blue n1 apus) or (Pseudomonas n1 (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))))	1,855
S6	TI ((enterobacter or aerobacter)) OR AB ((enterobacter or aerobacter))	370
S5	TI (('k. pneumoniae' or 'b. friedlander')) OR AB (('k. pneumoniae' or 'b. friedlander'))	200

#	Query	Results
S4	TI ((klebsiella or Calymmatobacterium or (aerobacter n1 aerogenes) or ((bacillus or bacterium) n1 pneumonia) or ((friedlaender or Friedlander) n1 bacillus) or (Hyalococcus n1 pneumonia) or Pneumobacillus)) OR AB ((klebsiella or Calymmatobacterium or (aerobacter n1 aerogenes) or ((bacillus or bacterium) n1 pneumonia) or ((friedlaender or Friedlander) n1 bacillus) or (Hyalococcus n1 pneumonia) or Pneumobacillus))	1,039
S3	(MH 'Klebsiella') OR (MH 'Klebsiella Infections')	835
S2	TI ((Eaggec or (escherichia n1 coli) or (e n1 coli) or (alkalescens-dispar n1 group) or (bacillus n1 escherichii) or (Coli n1 bacillus) or (Coli n1 bacterium) or colibacillus or (colon n1 bacillus))) OR AB ((Eaggec or (escherichia n1 coli) or (e n1 coli) or (alkalescens-dispar n1 group) or (bacillus n1 escherichii) or (Coli n1 bacillus) or (Coli n1 bacterium) or colibacillus or (colon n1 bacillus)))	2,914
S1	(MH 'Escherichia Coli') OR (MH 'Escherichia Coli Infections')	2,983

4.2.2. Cochrane Library (Issue 11, 2012)

ID Search

#1 MeSH descriptor: [Escherichia coli] explode all trees

#2 (Eaggec or (escherichia near/1 coli) or (e near/1 coli) or (alkalescens-dispar near/1 group) or (bacillus near/1 escherichii) or (Coli near/1 bacillus) or (Coli near/1 bacterium) or colibacillus or (colon near/1 bacillus)):ti,ab,kw (Word variations have been searched)

#3 MeSH descriptor: [Klebsiella] explode all trees

#4 (klebsiella or Calymmatobacterium or (aerobacter near/1 aerogenes) or ((bacillus or bacterium) near/1 pneumonia) or ((friedlaender or Friedlander) near/1 bacillus) or (Hyalococcus near/1 pneumonia) or Pneumobacillus):ti,ab,kw (Word variations have been searched)

#5 k. pneumoniae or b. friedlander:ti,ab,kw (Word variations have been searched)

#6 MeSH descriptor: [Enterobacter] explode all trees

#7 (enterobacter or aerobacter):ti,ab,kw (Word variations have been searched)

#8 MeSH descriptor: [Pseudomonas aeruginosa] explode all trees

#9 ((bacillus near/1 pyocyaneus) or (bacterium near/1 (aeruginosum or pyocyaneum)) or (blue near/1 apus) or (Pseudomonas near/1 (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))):ti,ab,kw (Word variations have been searched)

#10 p. aeruginosa:ti,ab,kw (Word variations have been searched)

#11 MeSH descriptor: [Acinetobacter] explode all trees

#12 (Acinetobacter or mima or mimae or herellea or acinetobacterium):ti,ab,kw (Word variations have been searched)

#13 MeSH descriptor: [Proteus] explode all trees

#14 Proteus:ti,ab,kw (Word variations have been searched)

#15 MeSH descriptor: [Serratia] explode all trees

#16 Serratia:ti,ab,kw (Word variations have been searched)

#17 MeSH descriptor: [Citrobacter freundii] explode all trees

#18 ((Citrobacter near/1 freundii) or (bacterium near/1 freundii) or (Escherichia near/1 freundii)):ti,ab,kw (Word variations have been searched)

#19 MeSH descriptor: [Morganella morganii] explode all trees

#20 ((bacillus near/1 morgan$) or (bacterium near/1 morgana) or (morganella near/1 morgagni$) or (morganella near/1 morganii) or (proteus near/1 morgagni) or (proteus near/1 morgana$) or (salmonella near/1 morgana)):ti,ab,kw (Word variations have been searched)

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#22 (multiresistant or (multi near/1 resistan$)):ti,ab,kw (Word variations have been searched)

#23 MeSH descriptor: [Drug Resistance, Multiple] explode all trees

#24 #22 or #23

#25 MeSH descriptor: [Colistin] explode all trees

#26 (belcomycin or colicort or colimycin$ or colisitin or colisticin or Colistin or colistine or colomycin or (coly near/1 mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin near/1 E) or totazina):ti,ab,kw (Word variations have been searched)

#27 MeSH descriptor: [Carbapenems] explode all trees

#28 (Carbapenem$ or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin$):ti,ab,kw (Word variations have been searched)

#29 MeSH descriptor: [Piperacillin] explode all trees

#30 (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin$ or pipcil or pipera hameln or piperacil or piperacillin$ or piperacin or pipera-hameln or pipercillin or piperilline or pipraci$ or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin):ti,ab,kw (Word variations have been searched)

#31 (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac$ or tazocel or tazocillin$ or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn):ti,ab,kw (Word variations have been searched)

#32 MeSH descriptor: [Amoxicillin-Potassium Clavulanate Combination] explode all trees

#33 (aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox near/1 clav) or amox-clav or (amoxi near/1 plus) or (amoxNear/3clavulan$) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or amoxxlin or (amoxycillin-clavulanic near/1 acid) or ancla or (auclatin near/1 duo) or augamox or augmaxcil or augmentan or augmentin$ or augmex or augpen or (augucillin near/1 duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl near/1 '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin near/1 duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl near/1 duo$) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin near/1 plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox near/1 duo) or clavumox or (co near/1 amoxiclav) or (co near/1 amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon near/1 duo) or (croanan near/1 duo) or curam or danoclav or (darzitil near/1 plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina near/1 plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox near/1 cl) or vestaclav or viaclav or vulamox or xiclav or (zami near/1 '8503')):ti,ab,kw (Word variations have been searched)

#34 ((brl near/1 '17421') or brl17421 or (thiophenemalonamic near/1 acid) or negaban or temocillin or temopen):ti,ab,kw (Word variations have been searched)

#35 (tigecycline or (tbg near/1 mino) or tygacil or gar 936 or gar936 or (tert near/1 butylglycinamido$)):ti,ab,kw (Word variations have been searched)

#36 MeSH descriptor: [Quinolones] explode all trees

#37 ((chinolone near/1 derivative) or fluoroquinolones or (haloquinolone near/1 derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones):ti,ab,kw (Word variations have been searched)

#38 MeSH descriptor: [Aminoglycosides] explode all trees

#39 (Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin):ti,ab,kw (Word variations have been searched)

#40 MeSH descriptor: [Gentamicins] explode all trees

#41 (adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam$ or epigent or (frieso near/1 gent) or garabiotic or garalone or garamicin$ or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame$ or gentamicin$ or gentamina or gentamycin$ or gentamyl or gentamytrex or gentaplus or gentarad or

gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin$ or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina):ti,ab,kw (Word variations have been searched)

#42 MeSH descriptor: [Amikacin] explode all trees

#43 (akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin$ or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid):ti,ab,kw (Word variations have been searched)

#44 MeSH descriptor: [Fosfomycin] explode all trees

#45 (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or 'mk 0955' or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin):ti,ab,kw (Word variations have been searched)

#46 MeSH descriptor: [Aztreonam] explode all trees

#47 ((az near/1 threonam) or azactam or azenam or azthreonam or aztreonam or (corus near/1 '1020') or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam):ti,ab,kw (Word variations have been searched)

#48 MeSH descriptor: [Nitrofurantoin] explode all trees

#49 (berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin$ or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin$ or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin$ or macrofuran or macrofurin or micofurantin$ or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro near/1 macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin$ or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium near/1 furagin) or ralodantin or trocurine or urantin or (uro near/1 tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin):ti,ab,kw (Word variations have been searched)

#50 MeSH descriptor: [Cephalosporins] explode all trees

#51 ((Cephalosporanic near/1 Acid$) or Cephalosporin$ or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or

Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin):ti,ab,kw (Word variations have been searched)

#52 MeSH descriptor: [Amdinocillin Pivoxil] explode all trees

#53 ((amdinocillin near/1 pivoxil) or (FL near/1 '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro near/1 '109071') or (ro10 near/1 '9071') or ro109071):ti,ab,kw (Word variations have been searched)

#54 #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53

#55 #21 and #24 and #54 (21)

4.2.3. Embase (January 1980 to December 1012)

1 exp Escherichia coli/ (255846)

2 (Eaggec or (escherichia adj coli) or (e adj coli) or (alkalescens-dispar adj group) or (bacillus adj escherichii) or (Coli adj bacillus) or (Coli adj bacterium) or colibacillus or (colon adj bacillus)).ti,ab. (240749)

3 exp Klebsiella/ (30199)

4 (klebsiella or Calymmatobacterium or (aerobacter adj aerogenes) or ((bacillus or bacterium) adj pneumonia) or ((friedlaender or Friedlander) adj bacillus) or (Hyalococcus adj pneumonia) or Pneumobacillus).ti,ab. (22836)

5 ('k. pneumoniae' or 'b. friedlander').ti,ab. (5513)

6 exp Enterobacter/ (12784)

7 (enterobacter or aerobacter).ti,ab. (9700)

8 exp Pseudomonas aeruginosa/ (55073)

9 ((bacillus adj pyocyaneus) or (bacterium adj (aeruginosum or pyocyaneum)) or (blue adj apus) or (Pseudomonas adj (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))).ti,ab. (43474)

10 'p. aeruginosa'.ti,ab. (17572)

11 exp Acinetobacter/ (12028)

12 (Acinetobacter or mima or mimae or herellea or acinetobacterium).ti,ab. (10917)

13 exp Proteus/ (14447)

14 Proteus.ti,ab. (10461)

15 exp Serratia/ (9507)

16 Serratia.ti,ab. (7407)

17 exp Citrobacter freundii/ (1778)

18 ((Citrobacter adj freundii) or (bacterium adj freundii) or (Escherichia adj freundii)).ti,ab. (1675)

19 exp Morganella morganii/ (1134)

20 ((bacillus adj morgan$) or (bacterium adj morgana) or (morganella adj morgagni$) or (morganella adj morganii) or (proteus adj morgagni) or (proteus adj morgana$) or (salmonella adj morgana)).ti,ab. (804)

21 or/1-20 (396800)

22 (multiresistant or (multi adj resistan$)).ti,ab. (5599)

23 exp multidrug resistance/ (29629)

24 22 or 23 (33705)

25 exp Colistin/ (8049)

26 (belcomycin or colicort or colimycin$ or colisitin or colisticin or Colistin or colistine or colomycin or (coly adj mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin adj E) or totazina).ti,ab. (3104)

27 exp Carbapenems/ (4745)

28 (Carbapenem$ or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin$).ti,ab. (18086)

29 exp Piperacillin/ (14822)

30 (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin$ or pipcil or pipera hameln or piperacil or piperacillin$ or piperacin or pipera-hameln or pipercillin or piperilline or pipraci$ or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin).ti,ab. (6462)

31 exp Amoxicillin-Potassium Clavulanate Combination/ (23616)

32 (aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox adj clav) or amox-clav or (amoxi adj plus) or (amox adj3 clavulan$) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or amoxxlin or (amoxycillin-clavulanic adj acid) or ancla or (auclatin adj duo) or augamox or augmaxcil or augmentan or augmentin$ or augmex or augpen or (augucillin adj duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl adj '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin adj duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl adj duo$) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin adj plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox adj duo) or clavumox or (co adj amoxiclav) or (co adj amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon adj duo) or (croanan adj duo) or curam or danoclav or (darzitil adj plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina adj plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox adj cl) or vestaclav or viaclav or vulamox or xiclav or (zami adj '8503')).ti,ab. (11598)

33 exp Quinolones/ (101072)

34 ((chinolone adj derivative) or fluoroquinolones or (haloquinolone adj derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones).ti,ab. (15677)

35 exp Aminoglycosides/ (10599)

36 (Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin + or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin).ti,ab. (56708)

37 exp Gentamicins/ (70647)

38 (adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam$ or epigent or (frieso adj gent) or garabiotic or garalone or garamicin$ or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame$ or gentamicin$ or gentamina or gentamycin$ or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin$ or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina).ti,ab. (23700)

39 exp Amikacin/ (28644)

40 (akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin$ or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid).ti,ab. (9841)

41 exp Fosfomycin/ (5561)

42 (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or 'mk 0955' or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin).ti,ab. (2386)

43 exp Aztreonam/ (10567)

44 ((az adj threonam) or azactam or azenam or azthreonam or aztreonam or (corus adj '1020') or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam).ti,ab. (3245)

45 exp Nitrofurantoin/ (9724)

46 (berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin$ or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin$ or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin$ or macrofuran or macrofurin or micofurantin$ or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro adj macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin$ or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium adj furagin) or ralodantin or trocurine or urantin or (uro adj tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin).ti,ab. (3412)

47 exp Cephalosporins/ (150937)

48 (Axepim$ or bmy 28142 or bmy28142 or BMY-28142 or Cefepim$ or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfrom or maxipime or Quadrocef).ti,ab. (2995)

49 exp tazobactam/ (3045)

50 (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac$ or tazocel or tazocillin$ or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn).ti,ab. (3809)

51 exp temocillin/ (499)

52 ((brl adj '17421') or brl17421 or (thiophenemalonamic adj acid) or negaban or temocillin or temopen).ti,ab. (236)

53 exp tigecycline/ (3876)

54 (tigecycline or (tbg adj mino) or tygacil or gar 936 or gar936 or (tert adj butylglycinamido$)).ti,ab. (1970)

55 exp cefepime/ (9948)

56 ((Cephalosporanic adj Acid$) or Cephalosporin$ or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin).ti,ab. (45983)

57 exp pivmecillinam/ (685)

58 ((amdinocillin adj pivoxil) or (FL adj '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro adj '109071') or (ro10 adj '9071') or ro109071).ti,ab. (280)

59 or/25-58 (349366)

60 21 and 24 and 59 (4969)

61 (review or review,tutorial or review, academic).pt. (1901059)

62 (systematic$ adj5 review$).tw,sh. (70959)

63 (systematic$ adj5 overview$).tw,sh. (869)

64 (quantitativ$ adj5 review$).tw,sh. (15516)

65 (quantitativ$ adj5 overview$).tw,sh. (203)

66 (quantitativ$ adj5 synthesis$).tw,sh. (2716)
67 (methodologic$ adj5 review$).tw,sh. (3414)
68 (methodologic$ adj5 overview$).tw,sh. (238)
69 (integrative research review$ or research integration).tw. (94)
70 (meta-analys$ or meta analys$ or metaanalys$).tw,sh. (96394)
71 (meta synthesis or meta synthesis or metasynthesis).tw,sh. (238)
72 (meta-regression or meta regression or metaregression).tw,sh. (2242)
73 (synthes$ adj3 literature).tw. (1448)
74 (synthes$ adj3 evidence).tw. (3583)
75 integrative review.tw. (604)
76 data synthesis.tw. (8747)
77 (research synthesis or narrative synthesis).tw. (547)
78 (systematic study or systematic studies).tw. (7413)
79 systematic comparison$.tw. (1183)
80 comprehensive review$.tw. (6873)
81 critical review.tw. (11216)
82 quantitative review.tw. (488)
83 structured review.tw. (492)
84 realist review.tw. (34)
85 realist synthesis.tw. (12)
86 review.ti. (264011)
87 systematic$ literature review$.tw. (3464)
88 'systematic review'/ (55637)
89 'systematic review (topic)'/ (2885)
90 meta analysis/ (67746)
91 'meta analysis (topic)'/ (5552)
92 (synthes$ adj2 qualitative).tw. (428)
93 (systematic adj2 search$).tw. (7848)
94 systematic$ literature research$.tw. (102)
95 (review adj3 scientific literature).tw. (833)
96 (literature review adj2 side effect$).tw. (10)
97 (literature review adj2 adverse effect$).tw. (2)
98 (literature review adj2 adverse event$).tw. (6)
99 (evidence-based adj2 review).tw. (1915)
100 critical analysis.tw. (5559)

101 (review$ adj10 (papers or trials or trial data or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).tw. (248295)

102 review.ti. (264011)

103 metanaly$.tw. (316)

104 letter.pt. (800258)

105 editorial.pt. (417835)

106 104 or 105 (1218093)

107 or/61-103 (2212977)

108 107 not 106 (2200787)

109 (clin$ adj2 trial).mp. (968683)

110 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (190403)

111 (random$ adj5 (assign$ or allocat$)).mp. (101920)

112 randomi$.mp. (613392)

113 crossover.mp. (59181)

114 exp randomized-controlled-trial/ (334017)

115 exp double-blind-procedure/ (112280)

116 exp crossover-procedure/ (35737)

117 exp single-blind-procedure/ (16758)

118 exp randomization/ (60197)

119 or/109-118 (1282139)

120 intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab. (175033)

121 (hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw. (1363115)

122 demonstration project?.ti,ab. (2081)

123 (pre-post or 'pre test$' or pretest$ or posttest$ or 'post test$' or (pre adj5 post)).ti,ab. (78013)

124 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab. (673)

125 trial.ti. or ((study adj3 aim?) or 'our study').ab. (724065)

126 (before adj10 (after or during)).ti,ab. (394152)

127 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or 'more than')).ab. (10006)

128 pilot.ti. (43036)

129 (multicentre or multicenter or multi-centre or multi-center).ti. (34428)

130 random$.ti,ab. or controlled.ti. (819713)

131 review.ti. (264011)

132 *experimental design/ or *pilot study/ or quasi experimental study/ (5205)

133 ('quasi-experiment$' or quasiexperiment$ or 'quasi random$' or quasirandom$ or 'quasi control$' or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab. (105122)

134 or/120-133 (3341084)

135 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (18985259)

136 human/ or normal human/ or human cell/ (14037258)

137 135 and 136 (14004971)

138 135 not 137 (4980288)

139 ('time series' adj2 interrupt$).ti,ab. (922)

140 134 not (138 or 139) (2996658)

141 108 or 119 or 140 (5157863)

142 and 141 (1860)

4.2.4. Medline (January 1946 to December 2012)

1 exp Escherichia coli/ (224545)

2 (Eaggec or (escherichia adj coli) or (e adj coli) or (alkalescens-dispar adj group) or (bacillus adj escherichii) or (Coli adj bacillus) or (Coli adj bacterium) or colibacillus or (colon adj bacillus)).ti,ab. (226847)

3 exp Klebsiella/ (13720)

4 (klebsiella or Calymmatobacterium or (aerobacter adj aerogenes) or ((bacillus or bacterium) adj pneumonia) or ((friedlaender or Friedlander) adj bacillus) or (Hyalococcus adj pneumonia) or Pneumobacillus).ti,ab. (18345)

5 ('k. pneumoniae' or 'b. friedlander').ti,ab. (3902)

6 exp Enterobacter/ (5504)

7 (enterobacter or aerobacter).ti,ab. (8130)

8 exp Pseudomonas aeruginosa/ (30232)

9 ((bacillus adj pyocyaneus) or (bacterium adj (aeruginosum or pyocyaneum)) or (blue adj apus) or (Pseudomonas adj (aeruginosa or aureofaciens or pyoceaneus or pyocyanea or pyocyaneus))).ti,ab. (35984)

10 'p. aeruginosa'.ti,ab. (14103)

11 exp Acinetobacter/ (5262)

12 (Acinetobacter or mima or mimae or herellea or acinetobacterium).ti,ab. (8005)

13 exp Proteus/ (8091)

14 Proteus.ti,ab. (9496)

15 exp Serratia/ (5505)

16 Serratia.ti,ab. (6720)

17 exp Citrobacter freundii/ (438)

18 ((Citrobacter adj freundii) or (bacterium adj freundii) or (Escherichia adj freundii)).ti,ab. (1361)

19 exp Morganella morganii/ (133)

20 ((bacillus adj morgan$) or (bacterium adj morgana) or (morganella adj morgagni$) or (morganella adj morganii) or (proteus adj morgagni) or (proteus adj morgana$) or (salmonella adj morgana)).ti,ab. (601)

21 or/1-20 (360253)

22 (multiresistant or (multi adj resistan$)).ti,ab. (3949)

23 exp drug resistance, multiple/ (21763)

24 22 or 23 (24405)

25 exp Colistin/ (2107)

26 (belcomycin or colicort or colimycin$ or colisitin or colisticin or Colistin or colistine or colomycin or (coly adj mycin) or colymicin or colymycin or coly-mycin or multimycin or (Polymyxin adj E) or totazina).ti,ab. (2346)

27 exp Carbapenems/ (6668)

28 (Carbapenem$ or doripenem or ertapenem or Imipemide or Imipenem or Invanoz or Invanz or meropenem or Merrem or 'MK 0787' or MK0787 or MK-0787 or N Formimidoylthienamycin or N-Formimidoylthienamycin or Penem or Ronem or S 4661 or S-4661 or SM 7338 or SM-7338 or Thienamycin$).ti,ab. (11771)

29 exp Piperacillin/ (2035)

30 (acopex or avocin or cl 227,193 or Cl 227193 or cl 227193 or cl 227193 or cl227,193 or Cl227193 or cl227193 or cl227193 or Cl-227193 or cl-227193 or cypercil or hishiyaclorin or ivacin or pentcillin or pentocillin or picillin$ or pipcil or pipera hameln or piperacil or piperacillin$ or piperacin or pipera-hameln or pipercillin or piperilline or pipraci$ or pipraks or pipril or piprilin or pitamycin or t 1220 or t1220 or t-1220 or taiperacillin).ti,ab. (4319)

31 (cl 307579 or cl298741 or cl307579 or tazabactam or tazobac$ or tazocel or tazocillin$ or tazocin or tazomax or tazonam or tazopril or yp 14 or yp14 or ytr 830 or ytr 830h or ytr830 or ytr830h or zosyn).ti,ab. (2217)

32 exp Amoxicillin-Potassium Clavulanate Combination/ (1914)

33 (aclam or aktil or ambilan or amocla or amoclan or amoclav or amoksiklav or amolanic or amometin or (amox adj clav) or amox-clav or (amoxi adj plus) or (amox adj3 clavulan$) or amoxiclav or amoxiclav-bid or amoxiclav-teva or amoxsiklav or

amoxxlin or (amoxycillin-clavulanic adj acid) or ancla or (auclatin adj duo) or augamox or augmaxcil or augmentan or augmentin$ or augmex or augpen or (augucillin adj duo) or augurcin or ausclav or auspilic or bactiv or bactoclav or bioclavid or (brl adj '25000') or brl25000 or brl-25000 or cavumox or ciblor or (clacillin adj duo) or clamax or clamentin or clamobit or clamonex or clamovid or clamoxin or (clamoxyl adj duo$) or clarin-duo or clavamox or clavar or clavinex or clavodar or clavoxil or (clavoxilin adj plus) or clavubactin or clavudale or clavulanate-amoxicillin or clavulin or (clavulox adj duo) or clavumox or (co adj amoxiclav) or (co adj amoxyclav) or coamoxiclav or co-amoxiclav or coamoxyclav or (cramon adj duo) or (croanan adj duo) or curam or danoclav or (darzitil adj plus) or e-moxclav or enhancin or fleming or fugentin or (fullicilina adj plus) or gumentin or hibiotic or inciclav or klamonex or kmoxilin or lactamox or lansiclav or moxiclav or moxicle or moxyclav or natravox or nufaclav or palentin or quali-mentin or ranclav or spektramox or stacillin or suplentin or synermox or synulox or (velamox adj cl) or vestaclav or viaclav or vulamox or xiclav or (zami adj '8503')).ti,ab. (9184)

34 ((brl adj '17421') or brl17421 or (thiophenemalonamic adj acid) or negaban or temocillin or temopen).ti,ab. (179)

35 (tigecycline or (tbg adj mino) or tygacil or gar 936 or gar936 or (tert adj butylglycinamido$)).ab,ti. (1161)

36 exp Quinolones/ (33277)

37 ((chinolone adj derivative) or fluoroquinolones or (haloquinolone adj derivative) or ketoquinolines or oxoquinolines or quinolinones or quinolones).ti,ab. (11055)

38 exp Aminoglycosides/ (122582)

39 (Aminoglycosides or Anthracyclines or Aclarubicin or Daunorubicin or Plicamycin or Butirosin Sulfate or Sisomicin or Hygromycin B or Kanamycin or Dibekacin or Nebramycin + or Metrizamide or Neomycin or Framycetin or Paromomycin or Ribostamycin or Puromycin or Spectinomycin or Streptomycin or Dihydrostreptomycin Sulfate or Streptothricins or Streptozocin).ti,ab. (52288)

40 exp Gentamicins/ (16678)

41 (adelanin or alcomicin or apigent or apogen or apoten or azupel or bactiderm or biogaracin or bristagen or cidomycin or danigen or dermogen or dianfarma or dispagent or duragentam$ or epigent or (frieso adj gent) or garabiotic or garalone or garamicin$ or garamycin or garbilocin or gencin or gendril or genoptic or genrex or gensumycin or gentabiotic or gentabiox or gentac or gentacidin or gentacin or gentacor or gentacycol or gentacyl or gentafair or gentagram or gentak or gental or gentaline or gentalline or gentalol or gentalyn or gentamax or gentame$ or gentamicin$ or gentamina or gentamycin$ or gentamyl or gentamytrex or gentaplus or gentarad or gentasil or gentasol or gentasone or gentasporin or gentatrim or gentavet or genticin$ or genticyn or gentiderm or gentimycin or gentocin or gentogram or gentomycin or genum or geomycine or gevramycin or g-mycin or gmyticin or g-myticin or grammicin or hexamycin or jenamicin or konigen or lacromycin or lisagent or martigenta or migenta or miragenta or miramycin or nichogencin or nsc 82261 or nsc82261 or obogen or ocugenta or ocu-mycin or oftagen or ophtagram or opthagen or optigen or opti-genta or ottogenta or pyogenta or refobacin or ribomicin or rigaminol or rocy gen or rovixida or rupegen or sagestam or sch 9724 or sch9724 or sedanazin or servigenta or skinfect or sulmycin or tangyn or u-gencin or versigen or yectamicina).ti,ab. (19829)

42 exp Amikacin/ (3372)

43 (akacin or akicin or amicacina or amicasil or amicin or amiglymide v or amikacin$ or amikafur or amikalem or amikan or amikayect or amikin or amiklin or amikozit or amiktam or amitracin or amixin or amukin or apalin or bb k 8 or bb k8 or bbk 8 or bb-k 8 or bbk8 or bbk-8 or bb-k8 or biclin or biklin or biokacin or briclin or briklin or chemacin or cinmik or fabianol or gamikal or glukamin or kacinth-a or kanbine or kormakin or likacin or lukadin or miacin or mikasome or onikin or oprad or orlobin or pediakin or pierami or riklinak or savox or selaxa or selemycin or sulfate amikacin or tybikin or vs 107 or vs107 or yectamid).ti,ab. (7140)

44 exp Fosfomycin/ (1378)

45 (fosfocil or fosfocin or fosfocina or fosfomicin or fosfomycin or fosfonomycin or 'mk 0955' or mk 955 or mk0955 or mk955 or monuril or phosphomycin or phosphonomycin).ti,ab. (1779)

46 exp Aztreonam/ (1233)

47 ((az adj threonam) or azactam or azenam or azthreonam or aztreonam or (corus adj '1020') or dynabiotic or primbactam or SQ 26,776 or sq 26,776 or sq 26776 or SQ-26,776 or sq26776 or sq-26776 or urobactam).ti,ab. (2333)

48 exp Nitrofurantoin/ (2253)

49 (berkfurin or biofurin or chemiofuran or dantafur or f 30 or f30 or fua-med or furaben or furadantin$ or furadantoin or furadina or furadoine or furadonin or furadonine or furalan or furanpur or furantocompren or furantoin$ or furobactina or furofen or furophen or infurin or ituran or ivadantin or macrobid or macrodantin$ or macrofuran or macrofurin or micofurantin$ or mitrofuratoin or nephronex or nierofu or nifurantin or nifuryl or (nitro adj macro) or nitrofuracin or nitrofuradantoin or nitrofurantine or nitrofurantoin$ or nitrofurin or novofuran or nsc 2107 or nsc2107 or orafuran or parfuran or phenurin or (potassium adj furagin) or ralodantin or trocurine or urantin or (uro adj tablinen) or urodil or urodin or urofuran or urolong or urotablinen or uro-tablinen or urotoina or uvamin).ti,ab. (2721)

50 exp Cephalosporins/ (35352)

51 (Axepim$ or bmy 28142 or bmy28142 or BMY-28142 or Cefepim$ or cefepitax or ceficad or cepimax or forzyn beta or maxcef or maxfrom or maxipime or Quadrocef).ti,ab. (1916)

52 ((Cephalosporanic adj Acid$) or Cephalosporin$ or Cefamandole or Cefoperazone or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cefotaxime or Cephalothin or Cephapirin or Cephalexin or Cefaclor or Cefadroxil or Cephaloglycin or Cephradine or Cephaloridine or Ceftazidime or Cephamycins or Cefmetazole or Cefotetan or Cefoxitin).ti,ab. (35099)

53 exp Amdinocillin Pivoxil/ (199)

54 ((amdinocillin adj pivoxil) or (FL adj '1039') or FL1039 or fl1039 or FL-1039 or pivamdinocillin or Pivmecillinam or Selexid or coactabs or (ro adj '109071') or (ro10 adj '9071') or ro109071).ti,ab. (237)

55 or/25-54 (246506)

56 21 and 24 and 55 (3195)

57 exp clinical trial/ (706293)
58 exp randomized controlled trials/ (85563)
59 exp double-blind method/ (118498)
60 exp single-blind method/ (17086)
61 exp cross-over studies/ (30990)
62 randomized controlled trial.pt. (342334)
63 clinical trial.pt. (476450)
64 controlled clinical trial.pt. (85694)
65 (clinic$ adj2 trial).mp. (552367)
66 (random$ adj5 control$ adj5 trial$).mp. (443104)
67 (crossover or cross-over).mp. (59003)
68 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (162179)
69 randomi$.mp. (509202)
70 (random$ adj5 (assign$ or allocat$ or assort$ or reciev$)).mp. (150717)
71 or/57-70 (968331)
72 (review or review,tutorial or review, academic).pt. (1758734)
73 (systematic$ adj5 review$).tw,sh. (40365)
74 (systematic$ adj5 overview$).tw,sh. (663)
75 (quantitativ$ adj5 review$).tw,sh. (3684)
76 (quantitativ$ adj5 overview$).tw,sh. (153)
77 (quantitativ$ adj5 synthesis$).tw,sh. (1107)
78 (methodologic$ adj5 review$).tw,sh. (2696)
79 (methodologic$ adj5 overview$).tw,sh. (180)
80 (integrative research review$ or research integration).tw. (78)
81 meta-analysis as topic/ (12608)
82 (meta-analys$ or meta analys$ or metaanalys$).tw,sh. (62359)
83 (meta synthesis or meta synthesis or metasynthesis).tw,sh. (215)
84 (meta-regression or meta regression or metaregression).tw,sh. (1650)
85 meta-analysis.pt. (37918)
86 (synthes$ adj3 literature).tw. (1070)
87 (synthes$ adj3 evidence).tw. (2956)
88 integrative review.tw. (583)
89 data synthesis.tw. (6328)
90 (research synthesis or narrative synthesis).tw. (463)
91 (systematic study or systematic studies).tw. (5679)

92 systematic comparison$.tw. (953)

93 systematic comparison$.tw. (953)

94 evidence based review.tw. (965)

95 comprehensive review$.tw. (5290)

96 critical review.tw. (9227)

97 quantitative review.tw. (382)

98 structured review.tw. (376)

99 realist review.tw. (24)

100 realist synthesis.tw. (11)

101 review.ti. (212126)

102 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).tw. (80949)

103 metanaly$.tw. (137)

104 letter.pt. (766872)

105 editorial.pt. (310993)

106 comment.pt. (493546)

107 or/104-106 (1166749)

108 or/72-103 (1897061)

109 108 not 107 (1860495)

110 intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab. (128957)

111 (pre-intervention? or preintervention? or 'pre intervention?' or post-intervention? or postintervention? or 'post intervention?').ti,ab. (7451)

112 demonstration project?.ti,ab. (1742)

113 (pre-post or 'pre test$' or pretest$ or posttest$ or 'post test$' or (pre adj5 post)).ti,ab. (52427)

114 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab. (472)

115 trial.ti. or ((study adj3 aim?) or 'our study').ab. (500725)

116 (before adj10 (after or during)).ti,ab. (314768)

117 ('quasi-experiment$' or quasiexperiment$ or 'quasi random$' or quasirandom$ or 'quasi control$' or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw. (84783)

118 ('time series' adj2 interrupt$).ti,ab,hw. (744)

119 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or 'more than')).ab. (7043)

120 pilot.ti. (32084)

121 Pilot projects/ (74648)

122 (clinical trial or controlled clinical trial or multicenter study).pt. (595489)

123 (multicentre or multicenter or multi-centre or multi-center).ti. (24301)

124 random$.ti,ab. or controlled.ti. (624993)

125 (control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt. (342332)

126 'comment on'.cm. or review.ti,pt. or randomized controlled trial.pt. (2652864)

127 (rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti. (1254855)

128 exp animals/ not humans.sh. (3812817)

129 (or/110-126) not (or/127-128) (3811646)

130 71 or 109 or 129 (4107075)

131 and 130 (822)

4.3.Clinical Review Tables

4.3.1. Antibiotic stewardship

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Ben-David 2010 ITS **Setting** Tertiary (one hospital) Israel January 2006–December 2008	To assess the effect of an intensified intervention, that included active surveillance, on the incidence of infection with carbapenem-resistant *K. pneumoniae* **Participants** *N*=390 Age: not reported Male: not reported, female: not reported Inclusion criteria: data from medical records of all patients who acquired CRKP infection Exclusion criteria: not reported	**Bacteria**: *K. pneumoniae* **Resistant to**: carbapenems, cephalosporins, fluoroquinolones, trimethoprim-sulfamethoxazole **Mechanism of resistance**: not reported	**Intervention** 1. Enhanced national infection control programme: contact precautions were used for the care of all patients with CRKP colonization or infection; the prevalence of colonization or infection was reported daily, and this information was mailed to the hospital management and the national coordinator; and patients infected with CRKP had their names entered into a database so that they could be identified at hospital re-admission 2. Active surveillence programme: obtaining rectal culture samples from patients hospitalized in ICUs and in step-down units, at admission to the unit and once weekly until the patient was discharged **Length of pre-intervention**: 17 months prior **Length of post-intervention**: 19 months following	**Infection control** Before the intervention, the incidence of clinical infection with CRKP had increased 6.42-fold to 6.93 cases per 10,000 patient-days After an enhanced infection control and active surveillance programme was introduced, the incidence of clinical infection reduced to 1.8 cases per 10,000 patient-days (*P*<0.001). The slope significantly changed with the introduction of the intervention from 0.12 to -0.07 (*P*<0.001)	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable quality)**
Borer 2011 ITS	To devise a local strategy for eradication of a hospital-wide outbreak caused by CRKP	**Bacteria**: *K. pneumoniae*	**Intervention** 1. Emergency department flagging system	**Bacterial colonization and infection** During the intervention, the CRKP	**ITS** **Protection against secular**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Setting Tertiary (one hospital) Israel May 2006–May 2010	**Participants** *N*=803 Adolescents 13–18 years, adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+years Male: 410, female: 393 Inclusion criteria: data from medical records of patients with CRKP infection Exclusion criteria: not reported	**Resistant to**: carbapenems **Mechanism of resistance**: not reported	2. Building of a cohort space or ward 3. Intensive active surveillance in high-risk wards 4. Epidemiological investigations 5. Carbapenem-restriction policy **Length of pre-intervention**: 11 months prior **Length of post-intervention**: 36 months following	undetected ratio showed a significant increase from 55.7% for June–December 2007 to 71.2% in 2008, 78.9% in 2009 and 92.5% for February– May 2010 (*P*≤0.001). From May 2006 through April 2007 (pre-intervention), the CRKP-IN incidence density per 10,000 patient-days was 5.26. After the intervention programme was introduced, the incidence of clinical CRPK infection reduced to 2.91 cases per 10,000 patient-days (*P*<0.001) in 12/2007, 1.91 in 12/2008 and 1.28 in 12/2009. The slope changed significantly with the introduction of the intervention (*P*=0.004). **Antibiotic use** Meropenem use showed a statistically significant decrease from 2007 to 2010 (*P*≤0.001); colistin use increased significantly during the same period (*P*≤0.001)	**changes (high quality)** **Protection against detection bias (acceptable to low quality)**
Church 2011 ITS **Setting** Secondary (one hospital) USA	To assess the possible effects of varying usage of levofloxacin, gatifloxacin and moxifloxacin on *P. aeruginosa* susceptibility to piperacillin-tazobactam, cefepime and tobramycin **Participants** *N*: not reported Age: not reported	**Bacteria**: *P. aeruginosa* **Resistant to:** aminoglycosides (tobramycin), cephalosporins (cefepime), piperacillin/tazobactam **Mechanism of**	**Intervention** 1. Levofloxacin replaced with gatifloxacin in 2001 2. Gatifloxacin replaced with moxifloxacin in 2006 Ciprofloxacin available throughout study period **Length of pre-intervention**: 15	**Antibiotic resistance and susceptibility** No association between the susceptibility of *P. aeruginosa* isolates to tobramycin and formulary changes was noted. With cefepime, a significant change in susceptibility was detected after the introduction of gatifloxacin (*P*=0.0099) and moxifloxacin (*P*=0.0571). In the case	**ITS** Protection against secular changes (low quality) Protection against detection bias (low quality)

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
January 2000-December 2008	Male: not reported, female: not reported Inclusion criteria: data from clinical microbiology and pharmacy databases of the Medical University of South Carolina Medical Centre Exclusion criteria: not reported	**resistance**: not reported	months prior **Length of post-intervention 1**: 60 months **Length of post-intervention 2**: 30 months following	of piperacillin/tazobactam, a positive change in susceptibility over time was detected after introduction of moxifloxacin (*P*=0.0589). In each analysis, the effect of total fluoroquinolone usage was not significant	
Cohen 2011 ITS **Setting** Tertiary (one hospital) Israel March 2006–August 2010	To describe the implementation of an institution-wide, multiple-step intervention to curtail the epidemic spread of CRKP **Participants** *N*=33,570 Age: not reported Male: not reported, female: not reported Inclusion criteria: all patients affected by CRKP Exclusion criteria: not reported	**Bacteria**: *K. pneumoniae* **Resistant to**: carbapenems **Mechanism of resistance**: not reported	**Intervention** 1. Single-room isolation and contact precautions 2. Cohorting of patients and nursing staff, screening of patients in the same room as newly identified carriers of CRKP, and local protocol for continued cohorting of returning patients 3. Weekly active surveillance in the ICU 4. Active surveillance of patients on admission to the emergency department **Length of pre-intervention:** not reported **Length of post-intervention 1**: 14 months **Length of post-intervention 2**: 39 months **Length of post-intervention 3**:	**Bacterial colonization and infection** The incidence (total number of cases of in-hospital CRKP acquisition detected by clinical cultures) and weekly point prevalence were reported as the number of cases per 1000 hospital beds Incidence was found to change significantly after intervention 2 (06/2007) and 3 (10/2008). Prevalence was found to change significantly only in September 2009 (after intervention 4) In the emergency department, the mean rate of compliance with the active surveillance protocol (± SD) was 43% ± 10%	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable to low quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
			2 years **Length of post-intervention 4**: 15 months		
Dortch 2011 ITS **Setting** Tertiary (one TICU, one SICU) USA January 2001–December 2008	To examine the effect of the antibiotic stewardship programme on the incidence of resistant Gram-negative HAIs **Participants** SICU *N*=6044, TICU *N*=14,802 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 14,277, female: 6569 Inclusion criteria: all patients admitted to the SICU or TICU during the study period who contracted an HAI with microbiological confirmation of at least one Gram-negative pathogen, at least 18 years of age Exclusion criteria: not reported	**Bacteria**: *P. aeruginosa, Acinetobacter* spp. **Resistant to**: aminoglycosides, carbapenems, cephalosporins (third- and fourth-generation), fluoroquinolones **Mechanism of resistance**: not reported	**Intervention** 1. Antibiotic stewardship: April 2002, guidelines for prophylactic antibiotics were devised for select procedures 2. Antibiotic rotation: January 2005, institution-wide initiative for surgical prophylaxis based on the Surgical Care Improvement Project **Length of pre-intervention**: 15 months **Length of post-intervention 1**: 11 months **Length of post-intervention 2**: 16 months	**Antibiotic use** Both in the SICU and TICU and there was a significant decrease in the utilization of total broad-spectrum antibiotics (BLIC, carbapenems, fluoroquinolones, third- and fourth-generation cephalosporins) targeting Gram-negative pathogens over the observation period (*P*<0.001) **Infection** During the 8-year observation period, the proportion of healthcare-associated infections caused by MDR Gram-negative pathogens decreased from 37.4% (2001) to 8.5% (2008), whereas the proportion of healthcare-associated infections caused by pan-sensitive pathogens increased from 34.1% to 53.2%	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable to low quality)**
Lewis 2012 ITS **Setting** Tertiary (11 ICUs and immediate care units)	To examine the effect of restricting ciprofloxacin use on the resistance of nosocomial Gram-negative bacilli, including *P. aeruginosa*, to group 2 carbapenems in a hospital's ICUs and intermediate care units **Participants** *N:* not reported	**Bacteria**: *E. aerogenes, E. cloacae, P. aeruginosa, A. baumannii* **Resistant to**: carbapenems (imipenem, meropenem,	**Intervention** Restriction of ciprofloxacin: ciprofloxacin use was restricted hospital wide in July 2007; after this restriction, pre-approval by the on-call infectious diseases fellow was required for its use **Length of pre-intervention**: 42	**Antibiotic use** Following the restriction of ciprofloxacin, there was a significant decreasing trend (*P*=0.0027) in its use, from 87.09 DDD/1000 patient-days in 2004 to 8.04 DDD/1000 patient-days in 2010. Use of the group 2 carbapenems increased significantly (*P*=0.0134) from 11.96	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
USA January 2004–December 2010	Age: not reported Male: not reported, female: not reported Inclusion criteria: all clinical ICU and intermediate care unit specimens (blood, sterile fluid, sputum, urine, wounds and anaerobic specimens) with test results that were positive for *P. aeruginosa, E. aerogenes, E. cloacae, A. baumannii* and *S. maltophilia*. Only nosocomial cases, defined as involving patients who had a hospital length of stay exceeding two days Exclusion criteria: results of surveillance and environmental sample cultures.	doripenem), cephalosporins (cefepime), piperacillin/tazobactam, fluoroquinolones (ciprofloxacin) **Mechanism of resistance**: not reported	months **Length of post-intervention**: 42 months	DDD/1000 patient-days in 2004 to 28.19 DDD/1000 patient-days in 2010. Overall, there was a hospital-wide decrease of 18.4% (*P*<0.0001) in the use of antibacterials during the study time **Infection** There were no changes observed in the number of nosocomial *S. maltophilia* isolates per 10,000 patient-days following the restriction of ciprofloxacin **Antibiotic resistance** Over the seven-year time period, there was a decrease of 13.7% in the percentage of ciprofloxacin-resistant *P. aeruginosa* isolates that were collected, which equates to a decrease of 3.9% per year (*P*=0.0017). No significant changes was observed in the susceptibilities to the group II carbapenems of nosocomial Enterobacteriaceae or *A. baumannii* isolates	**(acceptable quality)**
Meyer 2009 ITS **Setting** Tertiary (one ICU) Germany	To test whether reduction of third-generation cephalosporin use has a sustainable positive impact on the high endemic prevalence of third generation cephalosporin-resistant *K. pneumoniae* and *E. coli* in an ICU **Participants** *N*=3758	**Bacteria**: *E. coli, K. pneumoniae, P. aeruginosa* **Resistant to**: cephalosporins (third-generation), piperacillin **Mechanism of**	**Intervention** 1. Education programmes for professionals and patients in July 2004 2. Education sessions on antibiotic guidelines were held in the departments of surgery and anaesthesiology	**Antibiotic use** Following the implementation of guidelines in a surgical ICU, a significant and sustainable decrease in the use of third-generation cephalosporins of -110.2 DDD/1000 patient-days (95% CI -140.0 to -80.4, R^2=0.468) was observed. There was a significant reduction in the use of	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
January 2002–December 2006	Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**resistance**: ESBL	3. Empiric standard therapy for peritonitis and other intra-abominal infections was switched from third-generation cephalosporins to piperacillin in combination with a beta-lactamase inhibitor. The duration of antibiotic therapy for open fractures was shortened to single-shot pre-operative prophylaxis **Length of pre-intervention**: 30 months **Length of post-intervention**: 30 months	ampicillins (-167.4 DDD/1000, 95% CI -223.8 to -110.9, R^2=0.378) and in the use of imidazoles (-94.5 DDD/1000, 95% CI -121.2 to -67.7, R^2=0.463) The use of aminoglycosides decreased steadily before and after the intervention (slope -1.4 DDD/1000 patient-days per month, 95% CI -1.8 to -1.0, R^2=0.430); piperacillin and piperacillin/tazobactam showed a significant increase in level of 64.4 DDD/1000 patient-days (95% CI 38.5–90.3) and continued to increase by 2.3 DDD/1000 patient-days (95% CI 1.0–3.6) per month after the intervention (R^2=0.745)	**(high quality)**
Meyer 2010 ITS **Setting** Tertiary (one ICU) Germany January 2002–December 2006	To evaluate the impact of a reduced duration of antibiotic prophylaxis for cerebrospinal shunts on total antibiotic use in the ICU and key resistant pathogens **Participants** *N*=11,887 Age: not reported Male: not reported, female: not reported Inclusion criteria: monthly data on antimicrobial use obtained from the computerized pharmacy database. Monthly resistance data collected	**Bacteria**: *E. coli, K. pneumoniae, P. aeruginosa* **Resistant to**: carbapenems (imipenem), cephalosporins (third-generation) **Mechanism of resistance**: not reported	**Intervention** Change in antibiotic prophylaxis: Revised recommendation of single-shot prophylaxis with cefuroxime for shunt catheters, beginning in January 2004 **Length of pre-intervention**: 24 months prior **Length of post-intervention**: 36 months following	**Antibiotic use** Following the implementation of a comprehensive teaching session on antibiotic prophylaxis in cerebrospinal shunts in a surgical ICU, pre-operative prophylaxis for shunt catheters was changed into single-shot prophylaxis, and total antibiotic use decreased (–147.3 DDD/1000 patient-days, *P*=0.052). This corresponded to a decrease of 15% in the use of cefuroxime. The reduction in total antibiotic consumption was sustainable and did not increase over the next 36	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	from the microbiology laboratory. Only samples taken in the ICU were considered Exclusion criteria: copy strains – defined as an isolate of the same species showing the same susceptibility pattern throughout a 1-month period in the same patient, no matter what the site of isolation			months.	
Yong 2010 ITS **Setting** Tertiary (one ICU) Australia January 2000–December 2006	To perform an evaluation of changes in antibiotic susceptibility patterns in common Gram-negative organisms isolated from an ICU to demonstrate whether an observed reduction in broad-spectrum antibiotic use alters the resistance patterns of local bacteria **Participants** *N*=13,295 Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**Bacteria**: *E. coli, Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa, Acinetobacter* spp. **Resistant to**: aminoglycosides, carbapenems (imipenem), cephalosporins (ceftazidime), fluoroquinolones (ciprofloxacin) **Mechanism of resistance**: not reported	**Intervention** National guidelines on antimicrobial prescribing; antibiotic stewardship via computerized decision support systems. In 2001, one system guiding antibiotic use outside the ICU – a web-based antimicrobial approval system for third-generation cephalosporins (cefotaxime and ceftriaxone). In 2002, targeting the ICU specifically – computerized decision support system for antibiotic prescribing **Length of pre-intervention**: 30 months **Length of post-intervention**: 54 months	**Antibiotic use** Following the implementation of national guidelines on antimicrobial prescribing and antibiotic stewardship, there was a significant reduction in the number of imipenem-resistant *E. coli* and *Klebsiella* spp. isolates observed in the ICU. A small but significant improvement in the number of imipenem-resistant *Acinetobacter* spp. isolates was also observed. For Enterobacteriaceae with potentially inducible beta-lactamases, no significant changes was observed in imipenem susceptibility, although gentamicin susceptibility increased at a rate of 2.1%/year (95% CI 0.7–3.4), and ciprofloxacin susceptibility increased at a rate of 0.9%/year (95% CI 0.1–1.7)	**ITS** **Protection against secular changes (high quality)** **Protection against detection bias (acceptable to low quality)**

	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				ICU antibiotic consumption The use of antibiotics to cover Gram-negative bacteria in the ICU, including third- and fourth-generation cephalosporins, carbapenems, extended-spectrum penicillins, aminoglycosides and fluoroquinolones remained stable during the study period	
Xue 2009 RCT **Setting** Tertiary (one ICU) China June 2007–December 2007	To determine the relation of carbapenem restriction with the incidence of MDR *A. baumannii* in VAP **Participants** *N*=26 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 15, female: 11 Inclusion criteria: Patients receiving mechanical ventilation for more than five days and diagnosed with VAP Exclusion criteria: not reported	**Bacteria**: *A. baumanniii* **Resistant to**: carbapenems **Mechanism of resistance**: ESBL	**Intervention** Carbapenem restriction policy limiting the use of third-generation carbapenems. Only used when severe sepsis and after consultation with a physician from the Department of Infectious Diseases. *N*=12 **Control group** Conventional treatment: no restrictions of carbapenem (doctors were able to prescribe if necessary). *N*=15 **Length of follow-up**: duration of treatment	**Mortality** Mortality rates did not differ significantly between the treatment groups (RR 0.78; 95% CI 0.29–2.12). **Antibiotic resistance** More patients in the conventional group developed a carbapenem-resistant strain of *A. baumannii*, although the difference was not statistically significant (RR 0.63; 95% CI 0.38–1.04)	**RCT** Low methodological quality (0) Small sample size

K. pneumoniae, Klebsiella pneumonia; P.aeruginosa, Pseudomonas aeruginosa; A. baumanniii, Acinetobacter baumanniii; E. coli, Escherichia coli; E. aerogenes; Enterobacter aerogenes; E. cloacae, Enterobacter cloacae; S. maltophilia, *Stenotrophomonas maltophilia*; CRKP, carbapenem-resistant *K. pneumoniae*; SICU, surgical intensive care unit; TICU, trauma intensive care unit; VAP, ventilator-associated pneumonia; MDR, multi-drug resistant; ESBL, extended-spectrum beta-lactamase; BLIC, beta-lactam/beta-lactamase inhibitor combinations; ITS, interrupted time series; RCT, randomized controlled trial; ICU, intensive care unit; FQ, fluoroquinolones; 3/4CEPH, third- and fourth-generation cephalosporins; HAI, healthcare-associated infection; CI, confidence interval; RR, risk ratio; DDD, defined daily dose; SD, standard deviation.

4.3.2. Other infection control measures

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Levin 2010 CBA **Setting** Tertiary (two ICUs) Israel Dates not reported	To analyse whether single patient rooms in the ICU decreased bacterial transmission between ICU patients **Participants** *N*=207 Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**Bacteria**: *Acinetobacter* spp., other Gram-negative bacteria **Resistant to**: carbapenems **Mechanism of resistance**: ESBL	**Intervention** ICU A converted to single patient rooms. Old ICU A *N*=64, new ICU A *N*=62 **Control group** ICU B remained open plan. Old ICU B *N*=44, new ICU B *N*=39 **Length of follow-up**: not reported	**Infection control** The single-room ICU A had a significantly lower ICU acquisition of resistant organisms when compared with ICU B during the same period [3/62 (5%) vs 7/39 (18%), respectively, *P*=0.043], which was confirmed using survival analysis (*P*=0.011). ICU B showed no changes over the study	**CBA** Low methodological quality (0)

ICU, intensive care unit; ESBL, extended-spectrum beta-lactamase; CBA, controlled before–after study.

4.3.3. Selective decontamination

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Agusti 2002 Quasi-randomized **Setting**	To determine the efficacy of SDD in patients with multi-drug-resistant *A. baumannii* intestinal colonization **Participants** *N*=54	**Bacteria**: *A. baumannii* **Resistant to**: aminoglycosides (tobramycine)	**Intervention** SDD: a combination of polymyxin E (colistin) (150 mg) and tobramycine (80 mg) administered in 20-mL liquid form x 4/day (orally or through	**Bacterial colonization** Rates of faecal, pharyngeal and axillary colonization did not significantly reduce during ICU stay in the control group (*P* value not reported). In the SDD group, the rate	**Quasi-randomized** Low methodological quality (0)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Tertiary (one ICU) Spain October 1998–June 1999	Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 16, female: 5 Inclusion criteria: Intervention group 1. All patients with *A. baumannii* fecal colonization 2. An expected ICU stay exceeding five days Control group 1. All patients admitted 1 October–30 Novembe 1998 with *A. baumannii* faecal colonization 2. At least one series of axillary-pharyngeal-rectal swab performed Exclusion criteria: not reported	**Mechanism of resistance**: not reported	nasogastric tube), and 0.5 g of gel containing 2% of colistin and tobramycine applied round the gum margins and oropharynx x 4/day. Duration of treatment from detection of *A. baumannii* to discharge from ICU. *N*=21 **Control group** No intervention. *N*=33 **Length of follow-up**: duration of treatment	of faecal and pharyngeal carriage was reduced significantly (*P*<0.001 and *P*=0.003, respectively), but not the rate of cutaneous carriage **Antibiotic resistance** MDR *A. baumannii* had not been detected at the time of faecal carriage in 21 of 33 (63.6%) of the control group and 11 of 21 (52.3%) of the SDD group. In the SDD group, all *A. baumannii* strains were tobramycin resistant and susceptible to colistin at the beginning of the study. No resistance to colistin developed during the study	Small sample size
Brun-Buisson 1989 Quasi-randomized **Setting** Tertiary (one ICU) France January 1987-May 1987	To study the efficacy of intestinal decontamination by oral non-absorbable antibiotic agents to control a nosocomial outbreak of intestinal colonization and infection with MDR Enterobacteriaceae, and to examine its effects on endemic nosocomial infection rates. **Participants** *N*=86 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: not reported, female: not reported	**Bacteria**: *Enterobacter* spp., *P. aeruginosa* **Resistant to**: aminoglycosides (amikacin), third-generation cephalosporins **Mechanism of resistance**: ESBL	**Intervention** SDD: a combination of polymyxin E (colistin), 50 mg; neomycin, 1 g; and nalidixic acid (quinolone), 1 g administered in liquid form x 4/day either orally or through a nasogastric tube, starting within 24 h of admission and continuing until discharge from the unit. *N*=36 **Control group** No prophylaxis. *N*=50 **Length of follow-up**: not reported	**Mortality** All-cause mortality and mortality from nosocomial infections did not differ significantly between patients receiving SDD or no prophylaxis **Clinical success/improvement** There was no significant difference between patients receiving SDD or no prophylaxis in: – the incidence of any nosocomial infection – the infections caused by Gram-negative bacteria – the number of nosocomial	**Quasi-randomized** Low methodological quality (0)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	Inclusion criteria: 1. Consecutive patients with unit stay exceeding two days 2. Severity score at admission >2 Exclusion criteria: 1. Severe neutropenia routinely receiving oral antibiotic prophylaxis			infections that needed antibiotic treatment There was no significant difference in the number of patients staying on ICU longer than seven or 15 days **Bacterial colonization** One SDD patient and 12 no prophylaxis patients were positive for MDR strains (RR 0.12; 95% CI 0.02–0.85). No new cases of MDR strains of Enterobacteriacae were detected during the first four months after the trial **Adverse events** Three no prophylaxis patients needed therapy for a septic episode caused by Enterobacteriacae; however, this was not significantly different from the intervention group	
Saidel-Odes 2012 RCT **Setting** Tertiary (one internal medicine ward) Israel November	To assess the effectiveness of SDD for eradicating CRKP oropharyngeal and gastrointestinal carriage **Participants** *N*=40 Middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 26, female: 14 Inclusion criteria: 1. Hospitalized patients with CRKP colonization with or without infection	**Bacteria**: *K. pneumoniae* **Resistant to**: carbapenems **Mechanism of resistance**: not reported	**Intervention** SDD: topical application in the oropharynx of colistin sulfomethate sodium 100,000 U per g and gentamicin sulfate 1.6 mg per g incorporated into the gel. Dose of 0.5 g x 4/day for seven days. Plus an oral solution of 80 mg of gentamicin and 1x10 U of polymyxin E (colistin), given orally or through a nasogastric tube X 4/day for seven days. *N*=20	**Mortality** The rate of mortality did not differ significantly between the SDD group and the placebo group. The causes of mortality were not reported. No adverse events were reported **Antibiotic susceptibility** CRKP isolates from patients in the SDD arm remained susceptible to gentamicin and polymyxin E throughout the study (MIC ≤2 mg/mL and ≤0.094 mg/mL, respectively)	**RCT** High methodological quality (++) Small sample size

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
2008–June 2010	2. >18 years of age 3. Available for a follow-up period (while hospitalized or as outpatients) of at least seven weeks Exclusion criteria: <18 years of age, pregnancy, lactation, a known allergy to one of the study drugs, renal failure with creatinine clearance less than 50 mL/min, treatment with intravenous gentamicin or intravenous, polymyxin E at the time of randomization		**Control group** Placebo: topical application in the oropharynx of the placebo gel, which was compounded from carboxymethyl cellulose. Dose of 0.5 g x 4/day for seven days. Plus two oral solutions, one containing sodium chloride 0.45% and the other containing pulverized sacarin, given orally or through a nasogastric tube X 4/day for seven days. *N*=20 **Length of follow-up**: six weeks	**Bacterial colonization** At the end of treatment, the number of participants in the SDD group that had a throat culture that was CRKP positive reduced from 30% to 0%, whereas in the placebo group, this reduced from 35% to 30% (*P*<0.0001)	

A. baumannii, Acinetobacter baumannii; K. pneumoniae, Klebsiella pneumoniae; MDR, multi-drug resistant; SDD, selective digestive decontamination; RR, risk ratio, CI, confidence interval; CRKP, carbapenem-resistant *K. pneumonia*; MIC, minimum inhibitory concentration; RCT, randomized controlled trial; ICU, intensive care unit.

4.3.4. Systematic reviews

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Falagas 2009[1] **Setting** International Search up to January 2009	To assess the clinical and microbiological effectiveness of fosfomycin in the treatment of MDR, XDR or PDR non-fermenting Gram-negative bacterial infections **Participants** *N*=33 Studies: 23 microbiological, one animal and three cohort studies and three case reports Inclusion criteria: microbiological, animal experimental or clinical data on the effect of fosfomycin against MDR non-fermenting Gram-negative pathogens such as *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas* spp. and *Burkholderia* spp. MDR, XDR or PDR non-fermenting Gram-negative bacilli or to Gram-negative bacilli with resistance to two or more classes of potentially effective antimicrobial agents Exclusion criteria: studies written in languages other than English, French, German, Italian or Spanish. Studies representing abstracts in	**Bacteria**: *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas* spp. and *Burkholderia* spp. See Table II in the paper for details of clinical studies	**Intervention** Fosfomycin **Control group** Combination of fosfomycin with other antimicrobial agents	**Microbiological**: a total of 1859 MDR non-fermenting Gram-negative isolates. Susceptibility rate to fosfomycin of MDR *P. aeruginosa* isolates was ≥90% and 50–90% in 7/19 and 4/19 relevant studies, respectively. 30.2% isolates of MDR *P. aeruginosa*, 3.5% MDR *A. baumannii* isolates were found to be susceptible to fosfomycin **Clinical**: 91% of the patients clinically improved (treatment of infections caused by MDR *P. aeruginosa*)	Low methodological quality (0) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	scientific conferences				
Falagas 2009[2] **Setting** Not reported Searches performed: 9 July 2008, 16 July 2008 and 11 September 2008	To evaluate the available clinical evidence regarding the effectiveness and safety of systemic colistin in children without cystic fibrosis **Participants** *N*=370 Studies: 10 case series and 15 case reports Inclusion criteria: studies with data regarding the use of intravenous, intrathecal, intramuscular or intraventricular colistin in paediatric patients for the treatment of infections caused by colistin-susceptible pathogens or for prophylaxis. All or the majority of patients involved in each individual study should not have cystic fibrosis Exclusion criteria: studies that focused on colistin use in paediatric patients with cystic fibrosis, or reporting the use of oral colistin or the use of colistin for topical treatment in paediatric patients. Abstracts in scientific conferences or studies published in languages other than English, Spanish, French, German, Italian or Greek	**Bacteria***: P. aeruginosa, A. baumannii, K. aerogenes, H. influenza, P. pyocyanin, P. aeruginosa, K. pneumoniae* and *A. aerogenes* See Table I in the paper for details of studies	**Intervention** Colistin for the treatment of infections (*N*=326) **Control group** Colistin for surgical prophylaxis or prophylaxis of infections in burns patients (*N*=44)	**Case series treatment:** 271 evaluable subjects Cure: 235/271 Improvement: 10/271 Deterioration: 6/271 Death: 20/271 Adverse effects (included in safety assessment *N*=311) 1. Nephrotoxicity: 33/311 had cylindruria or haematuria, 8/311 had a blood urea nitrogen elevation of >10% (in one child owing to an overdosage of colistin), 5/311 had renal tubular cells in the urine, 3/311 had proteinuria and 2/311 had a significant increase in serum creatinine levels during intravenous colistin treatment. Data regarding adverse events not provided for two children 2. Neurotoxicity: 0/311 3. Other: 8/311 **Case series prophylaxis:** Incidence of infection: 0/44 Death: 9/44 attributed to the underlying pathologies. No signs of colistin-related toxicity were found Adverse effects: 1. Tubular epithelial cells in urine, persistent for up to one week after withdrawal of colistin: 16/44	Acceptable methodological quality (+) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				2. Proteinuria, disappearing right after colistin withdrawal: 14/44 3. Oliguria during the initial stages of colistin treatment: 1/44 4. No adverse events: 13/44	
Falagas 2010[3] **Setting** International Searches up to January 2009	To the evidence on fosfomycin as a treatment option for infections caused by members of the family Enterobacteriaceae with advanced resistance to antimicrobial drugs, including producers of ESBL **Participants** *N*=119 Studies: 17 in-vitro microbiological studies, two prospective studies, one retrospective study and two case reports Inclusion criteria: studies on Enterobacteriaceae isolates with an advanced drug resistance (MDR, carbapenem resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases or metallo-β-lactamases) profile and their susceptibility to fosfomycin, and the clinical effectiveness of treatment with fosfomycin for infections with these pathogens Exclusion criteria: abstracts in scientific conferences or studies	**Bacteria***:* **Microbiological studies** *K. pneumoniae isolates, E. coli* **Clinical studies** *E. coli, S. typhimurium, S. typhi* See Table III in the paper for details of studies	**Intervention** Amoxicillin-clavulanate potassium **Control group** Fosfomycin–trometamol in two of the *E. coli* studies	**Microbiological success** 11 of the 17 studies reported that at least 90% of the isolates were susceptible to fosfomycin **Clinical efficacy** Measured in four studies. Two studies oral treatment for lower UTI with ESBL-producing *E. coli* (one prospective and one retrospective) resulted in the treatment group with clinical cure in 75 of the 80 (93.8%) patients included in these studies. Two case reports of infection due to MDR *Salmonella* spp. Reported treatment was effective with fosfomycin	Low methodological quality (0) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	published in languages other than English, Spanish, French, German, Italian or Greek				
Falagas 2012[4] **Setting** Not reported Searches from 2000 to 2010	To identify and evaluate the available data regarding the susceptibility of recent Gram-negative bacteria to isepamicin, including that of MDR strains of bacteria **Participants** *N*=512 Studies=11 microbiological, one RCT, one prospective study, one restrospective study Inclusion criteria: either a microbiological (in-vitro) study that evaluated the susceptibility of Gram-negative bacterial isolates (including MDR ones) to isepamicin or a clinical study that evaluated the use of isepamicin, given for the treatment of infections by the aforementioned pathogens or for prophylaxis for this type of infection. In addition, studies deemed relevant should have been published between 2000 and 2010 Exclusion criteria: studies that examined a sample of fewer than 10 isolates or patients, studies referring to synergistic or pharmacodynamic/	**Bacteria:** **Clinical studies** *S. epidermidis, E. coli, S. pneumoniae, P. aeruginosa* See Table II in the paper for details of studies	**Intervention** Isepamicin **Control group** Two clinical studies – amikacin one clinical study – isepamicin + levofloxacin for prophylaxis	**Microbiological:** isepamicin was more effective in four studies than amikacin, six studies reported as effective, one study both groups ineffective. In studies including MDR bacteria, 2/4 reported more effective than amikacin; 1/4 as effective as amikacin; 1/4 both isepamicin and amikacin ineffective **Clinical:** 1. Paediatric infection treatment studies: 100% clinical and bacteriological response for both the isepamicin and the amikacin arms. Definition of clinical response not stated (e.g. cure, improvement) 2. Prophylactic study: acute bacterial prostatitis 1.3%	Low methodological quality (0) This review was included because it is on the topic; however, the conclusions reached are not supported by the study design

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	pharmacokinetic parameters of isepamicin, studies that provided data regarding the susceptibility of isepamicin to micro-organisms other than Gram-negative bacteria or the susceptibility of other aminoglycosides only to Gram-negative bacteria. Abstracts in scientific conferences or studies published in languages other than English, Spanish, French, German or Italian				
Kaki 2011[5] **Setting** International Search January 1996 to December 2010	To evaluate the current state of evidence for antimicrobial stewardship interventions in the critical care unit **Participants** *N*=not available/not reported for all included studies Studies: three RCTs, three ITSs, and 18 uncontrolled before–after studies Inclusion criteria: application of any intervention; to improve antimicrobial utilization; and within an intensive care setting Exclusion criteria: if no intervention was applied, non-human or non-patient based, non-hospital based, or they did not involve intensive care patients. Additionally, antibiotic cycling. Conference abstracts	**Bacteria:** *P. aeruginosa,* *A. baumannii,* *E. coli,* *Klebsiella* spp., ESBL See Table I in the paper for details of studies.	**Intervention** Antimicrobial stewardship: 1. Antibiotic restriction/ pre-approval 2. Computer-assisted decision support 3. Infectious diseases consultant 4. Re-assessment on pre-specified date 5. Antibiotic de-escalation protocols 6. Antibiotic prophylaxis guideline 7. Antibiotic treatment guideline **Control group** Not reported, presumably no stewardship	Overall stewardship intervention: 1. Reductions in antimicrobial utilization (11–38% defined daily dose/1000 patient-days) 2. Lower total antimicrobial costs (US$ 5–10/ patient-day) 3. Shorter average duration of antibiotic therapy 4. Less inappropriate use 5. Fewer antibiotic adverse events. stewardship intervention beyond six months: 1. Reductions in antimicrobial resistance rates Antibiotic stewardship was not associated with increases in nosocomial infection rates, length of stay or mortality	High methodological quality (++)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Siempos 2007[6] **Setting** Not reported Search January 1950 to March 2006	To clarify whether carbapenems are more effective or safer than other broad-spectrum antibiotics for the empirical treatment of patients with HAP **Participants** *N*=2731 Studies: 12 RCTs Inclusion criteria: randomized controlled clinical trial; studied the role of carbapenems in comparison with other broad-spectrum antibiotics or a combination of antibiotics for the empirical treatment of patients with HAP; assessed the effectiveness, toxicity and mortality of both therapeutic regimens. Included both patients with HAP and patients with community-acquired pneumonia; however, only data regarding patients with HAP were extracted. Trials with both blind and unblind design were included, and only RCTs written in English, French and German Exclusion criteria: RCTs conducted primarily in neutropenic patients with solid organ tumours or haematological malignancies and trials that included fewer than 10	**Bacteria:** *P. aeruginosa* See Table I in the paper for details of studies	**Intervention** Carbapenems: 1. Imipenem/ cilastatin (eight studies) 2. Meropenem (four studies) **Control group** Imipenem/ cilastatin compared with: 1. Fluoroquinolones: levofloxacin, ciprofloxacin (three studies) 2. Other beta-lactams: piperacillin/tazobactam, aztreonam, cefepime, ceftazidime (five studies) Meropenem compared with: combination of a cephalosporin (ceftazidime, cefuroxime) with an aminoglycoside (amikacin, gentamicin, tobramycin)	1. All-cause mortality: lower mortality in the carbapenems group (OR 0.72, 95% CI 0.55–0.95) 2. Treatment success (clinical): no difference between groups (OR 1.08, 95% CI 0.91–1.29) 3. Treatment success (microbiological): no difference between groups (OR 1.04, 95% CI 0.72–1.50) 4. Adverse effects: no difference (0.81, 0.46–1.43) *P. aeruginosa* pneumonia subgroup: lower treatment success (OR 0.42, 95% CI 0.22–0.82) and lower eradication of *Pseudomonas* spp. strains (OR 0.50, 95% CI 0.24–0.89) in the carbamenems group. Late onset of HAP subgroup: no difference between groups (OR 1.34, 95% CI 0.91–1.97)	High methodological quality (++)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	patients with pneumonia who received a carbapenem. Experimental trials and trials focusing on pharmacokinetic and pharmacodynamics parameters. Finally, RCTs comparing the effectiveness and safety of two different carbapenems				

P. aeruginosa, Pseudomonas aeruginosa; A. baumannii, Acinetobacter baumannii; K. aerogenes, Klebsiella aerogenes; H. influenza, Haemophilus influenza; P. pyocyanin, Pseudomonas pyocyanin; K. pneumoniae, Klebsiella pneumoniae; A. aerogenes, Aerobacter aerogenes; E. coli; Escherichia coli; S. typhimurium, *Salmonella typhimurium*;*S.typhi, Salmonella typhi; S. pneumoniae, Streptococcus pneumoniae; S. epidermidis, Staphylococcus epidermidis;* MDR, multi-drug resistant; XDR, extensively drug resistant; PDR, pan-drug resistant; RCT, randomized controlled trial; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; OR, odds ratio; CI, confidence interval.

1. Falagas ME, Kastoris AC, Karageorgopoulos DE, Rafailidis PI. Fosfomycin for the treatment of infections caused by multidrug-resistant non-fermenting Gram-negative bacilli: a systematic review of microbiological, animal and clinical studies. *Int J Antimicrob Agents* 2009;**34**:111–120.

2. Falagas ME, Vouloumanou EK, Rafailidis PI. Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. *Int J Antimicrob Agents* 2009;**33**:503.e1–e13.

3. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis* 2010;**10**:43–50.

4. Falagas ME, Karageorgopoulos DE, Georgantzi GG, Sun C, Wang R, Rafailidis PI. Susceptibility of Gram-negative bacteria to isepamicin: a systematic review. *Expert Rev Anti-Infect Ther* 2012;**10**:207–218.

5. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. *J Antimicrob Chemother* 2011;**66**:1223–1230.

6. Siempos II, Vardakas KZ, Manta KG, Falagas ME. Carbapenems for the treatment of immunocompetent adult patients with nosocomial pneumonia. *Eur Respir J* 2007;**29**:548–560.

4.3.5. Treatment

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Betrosian 2007 RCT **Setting** Tertiary (1 ICU) Greece October 2004–February 2006	To evaluate the clinical efficacy and safety of high-dose regimen ampicillin sulbactam for the treatment of VAP from MDR *A. baumannii* **Participants** *N*=27 Age: not reported Male: 15, female: *N*=12 Inclusion criteria: all patients mechanically ventilated for more than 72 h with positive tracheal aspirates for *A. baumannii* Exclusion criteria: episodes of VAP in which *A. baumannii* was isolated in conjunction with another micro-organism	**Bacteria**: *A. baumannii* **Resistant to**: ampicillin/sulbactam and susceptible exclusively to colistin (polymyxin E) **Mechanism of resistance**: not reported	**Intervention** Ampicillin/sulbactam at a rate 2: 1 every 8 h. 24 g/12 g daily for seven to 10 days. *N*=13 **Control group** Ampicillin/sulbactam at a rate 2: 1 every 8 h. 18 g/9 g daily for seven to 10 days. *N*=14 **Length of follow-up**: one month	**Mortality** 14-day VAP mortality and 30-day all-cause mortality were not significantly different between treatment groups **Clinical success/improvement** The number of patients with clinical success and clinical failure was not significantly different between treatment groups **Bacterial colonization** The two treatment groups showed no difference in the eradication of *A. baumannii* isolates (bacteriological success), bacteriological failure or superinfection **Adverse events** There was no difference in the adverse effects experienced by participants	**RCT** Low methodological quality (0) Very small sample size
Betrosian 2008 RCT	To compare the clinical efficacy and safety of high-dose ampicillin/sulbactam vs colistin as monotherapy for the treatment of *Acinetobacter* spp. VAP	**Bacteria**: *A. baumannii* **Resistant to**: Aminoglycosides, carbapenems,	**Intervention** Colistin, intravenous 3 MIU every 8 h for eight to 10 days. *N*=15	**Mortality** 14-day VAP mortality and 28-day all-cause mortality were not significantly different between treatment groups	**RCT** Low methodological quality (0)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Setting Tertiary (2 ICUs) Greece Dates not reported	**Participants** *N*=28 Middle aged 46–64 years, aged 65–79 years Male: 14, female: 14 Inclusion criteria: ventilated patients for >72 h who developed MDR *A. baumannii* VAP Exclusion criteria: cases of VAP with mixed isolated micro-organisms, combination antibiotic therapy, allergy to beta-lactamase or penicillin, or previous enrolment in similar studies	cephalosporins, fluoroquinolones **Mechanism of resistance**: not reported	**Control group** Ampicillin/sulbactam, 9 g (at a rate 2:1) every 8 h for eight to 10 days, administered as follows: three vials (20 mL each) containing 3.0 g of ampicillin/sulbactam diluted in 200 mL of 5% dextrose provided within 1-h duration infusion. *N*=13 **Length of follow-up**: two-week- and one-month mortalities	**Clinical success/improvement** The number of patients with clinical success and clinical failure was not significantly different between treatment groups **Bacterial colonization** The two treatment groups showed no difference in the eradication of *A. baumannii* isolates (bacteriological success) or bacteriological failure (persistence of *A. baumannii* isolates (>104 CFU/mL) **Adverse events** There was no difference in the adverse effects experienced by participants	Small sample size
Chastre 2003 RCT **Setting** Tertiary (51 ICUs) France May 1999-June 2002	To compare the efficacy of eight days vs 15 days of antibiotic treatment of patients with microbiologically proven VAP **Participants** *N*=401 Middle aged 46–64 years, aged 65–79 years Male: 141, female: 46 Inclusion criteria: 1. >18 years of age 2. Clinical suspicion of VAP 3. Positive quantitative cultures of distal pulmonary secretion samples 4. Instigation within the 24 h	**Bacteria**: *E. coli, Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa, Acinetobacter* spp., *Proteus spp., Serratia spp., C. freundii, M. morgagnii* **Resistant to**: ticarcillin, methicillin **Mechanism of resistance**: ESBL	**Intervention** Antibiotics for eight days: specific antibiotics, doses and schedules are not reported. Antibiotics were selected by the treating physicians. As per protocol, the initial regimen should have preferably combined at least an aminoglycoside, or a fluoroquinolone and a broad-spectrum beta-lactam antimicribial agent. *N*=197 **Control group** Antibiotics for 15 days: specific	**Mortality** 28-day and 60-day all-cause mortality and in-hospital mortality did not significantly differ between the eight- and 15-day regimes **Clinical success/improvement** Risk differences (90% CIs) to develop an unfavourable outcome (defined as death, pulmonary infection recurrence, or prescription of a new antibiotic for any reason provided for ≥48 h) were not significantly different between the eight- and 15-day regimes for all patients (RR 2.6, 90% CI -5.6 to 10.7) and for those patients with	**RCT** High methodological quality (++)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
	following of appropriate empirical antibiotic therapy directed against the micro-organism/s responsible for the infection Exclusion criteria: 1. Pregnant 2. Enrolled in another trial 3. Little chance of survival 4. Neutropenia 5. Concomitant acquired immunodiffeciency syndrome 6. Immunosuppressants or long-term corticosteroid therapy 7. Concomitant extrapulmonary infection that required prolonged antimicrobial treatment 8. Attending physical declined full-life support. 9. Early-onset pneumonia (within the first five days of mechanical ventilation) and no antimicrobial therapy during the 15 days preceding infection.		antibiotics, doses and schedules are not reported. Antibiotics were selected by the treating physicians. As per protocol, the initial regimen should have preferably combined at least an aminoglycoside or a fluoroquinolone and a broad-spectrum beta-lactam antimicribial agent. *N*=204 **Length of follow-up**: three months	non-fermenting Gram-negative bacteria (RR 8.6, 90% CI -5.9 to 23.1) The rate of and time to (Kaplan-Meier method, log-rank test) pulmonary infection considered to be recurrence, relapses or superinfection was not significantly different between treatment regimes. **Antibiotic use** The number of antibiotic-free days was significantly less for all patients on the eight-day regime, but not for those patients with non-fermenting Gram-negative bacteria. No difference was found in the number of patients continuing to receive antibiotics after the end of the trial treatment regimen, or in the number of patients who received an additional course of antibiotics **Antibiotic resistance** For patients who developed recurrent pulmonary infections, those who had received the eight-day treatment of antibiotics had significantly less emergence of MDR pathogens compared with those who had received the 15-day treatment (42.1% vs 62.3% of recurrent infections, respectively; *P*=0.04)	

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Cox 1987 RCT **Setting** Secondary (two hospitals) USA March 1985–December 1985	To compare the efficacy of norfloxacin vs standard parenteral treatment of non-bacteraemic, hospital-acquired UTI **Participants** *N*=104 Age: not reported Male: not reported, female: not reported Inclusion criteria: 1. Hospitalized patients 2. >18 years of age 3. Documented UTI caused by an organism known or presumed susceptible to norfloxacin Exclusion criteria: 1. <18 years of age 2. Pregnant or not practising an effective means of birth control 3. A history of allergic diathesis or an allergy to nalidixic acid, oxolinic acid or norfloxacin 4. Functional renal abnormalities or unstable deteriorating renal function 5. Comatose or high probability of imminent death 6. Serious concurrent infection 7. Treated or recently completed treatment with antibiotics 8. History or visual disturbances, a psychiatric disorder or central nervous system disease	**Bacteria**: *E. coli, Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa, Serratia* spp., *C. freundii, M. morgagnii* **Resistant to**: not reported **Mechanism of resistance**: not reported	**Intervention** Norfloxacin 400 mg x2/day, minimum treatment seven days. *N*=52 (46 evaluable patients) **Control group** Aminoglycosides alone; aminoglycosides and meziocillin/ticarcillin; aminoglycosides and cephalosporin; aminoglycosides and vancomycin, cephalosporin, cefotaxime alone, administered in accordance with the manufacturers' guidelines. *N*=52 (48 evaluable patients) **Length of follow-up**: seven (SD two) days, optional four to six weeks	**Clinical success/improvement** No significant differences were found between norfloxacin and standard parenteral antibiotic treatment in the rate of participants that were clinically cured, showed clinical improvement or had treatment failure **Superinfection** Rates of superinfection and early re-infection also did not differ significantly between the norfloxacin and standard parenteral antibiotic treatment groups **Antibiotic resistance** No differences in the number of patients experiencing adverse events were found between those receiving norfloxacin and those receiving standard parenteral antibiotics	**RCT** Acceptable methodological quality (+)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
Giamarellou 1990 RCT **Setting** Tertiary (one ICU) Greece Dates not reported	To evaluate the efficacy of monotherapy with pefloxacin in secondary ICU pulmonary infections in comparison with imipenem **Participants** *N*=71 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 42, female: 29 Inclusion criteria: adult patients presenting serious bacterial infections of the respiratory tract Exclusion criteria: not reported	**Bacteria**: *E. coli, K. pneumoniae, Enterobacter* spp. (various Enterobacteriaceae), *P. aeruginosa, A. anitratus, P. mira, S. marcescens* **Resistant to**: aminoglycosides (gentamicine, tobramycin, netilmicin, amikacin), aztreonam, carbapenems (imipenem), cephalosporins (cefotaxime, ceftazidime, ceftriaxone), fluoroquinolones (ciprofloxacin) **Mechanism of resistance**: not reported	**Intervention** Pefloxacin intravenously 400 mg, every 8 h for 11.5 (SD 5.8) days. *N*=35 **Control group** Imipenem intravenously 1 g every 8 h for 12.9 (SD 6.2) days. *N*=36 **Length of follow-up**: duration of treatment	**Mortality** There were three deaths related to sepsis in the imipenem group and one in the pefloxacin group (although the sepsis was not related to the bronchopneumonia, but to an underlying abdominal infection). All-cause mortality was not reported **Clinical success/improvement** No differences were found in the number of patients cured, the number with superinfection that was cured, the number showing improvement and the number experiencing treatment failure. Bacterial eradication rates were significantly lower in the imipemem group [55.3% vs 82.9%, respectively (*P*<0.001)] **Antibiotic resistance** Resistance development among persisting strains was also significantly different (data not reported, *P*<0.05) **Adverse events** No systemic reactions or abnormal laboratory parameters were reported in either treatment group	**RCT** Acceptable methodological quality (+)
Huttner 2013	To investigate if intestinal carriage of ESBL-E can be eradicated	**Bacteria**: *Enterobacter* spp. (ESBL-E)	**Intervention** Colistin sulfate 50 mg (equivalent to 42 mg colistin	**Clinical success/improvement** The rate of eradication of ESBL-E was significantly different between	**RCT** High methodological

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
RCT **Setting** Secondary (all inpatient wards of a single hospital) Switzerland June 2009–June 2012	**Participants** *N*=58 Adolescents 13–18 years, adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 34, female: 24 Inclusion criteria: aged ≥18 years; ESLB-E-positive rectal swab Exclusion criteria: patients with active ESLB infection, patients treated with antibiotics active against ESLB-E, pregnancy/breastfeeding, contraindication to the use of study drugs, previous study enrolment and resistance of the colonizing ESLB-E strain to colistin (defined as MIC >2 mg/L	**Resistant to**: cefotaxime, cefotaxime/clavulanic acid, ceftazidime, ceftazidime/clavulanic acid, cefepime, cefepime/clavulanic acid **Mechanism of resistance**: ESBL	base or 1.26 million units 4x/day) and neomycin sulfate (250 mg equivalent to 178 mg neomycin base 4xday) for 10 days. In the presence of ESBL-E bacteriuria, the patients were also treated with nitrofurantoin (100 mg 3x/day) for five days. *N*=27 **Control group** Placebo. *N*=27 **Length of follow-up**: 28 (SD seven) days	treatment regimes during treatment (day 6; RR 0.40; 95% CI 0.23–0.70) or in the first day after treatment (RR 0.42; 95% CI 0.23–0.76), but did not differ in the end of follow-up **Treatment adherence** There was no significant difference between groups in the number of patients that adhered to treatment, measured by counting the number of pills on the boxes of study medication **Adverse events** No statistically significant difference was found between the treatment groups in the number of patients with at least one episode of liquid stool	quality (++)
Moskowitz 2011 RCT **Setting** Secondary (seven cystic fibrosis centres) USA February 2007–	To assess whether biofilm-growing bacteria susceptibility testing of *P. aeruginosa* correlates better with clinical outcomes in chronic cystic fibrosis airway infections, when compared with conventional antibiotic susceptibility testing **Participants** *N*=39 Adolescents 13–18 years, adults 19–45 years Male: 25, female: 14	**Bacteria**: *P. aeruginosa* **Resistant to**: aminoglycosides, fluoroquinolones **Mechanism of resistance**: not reported	**Intervention** Biofilm testing: bioflim regimens of two antibiotics were selected centrally using a published algorithm, which calculated for each bacterial morphotype the biofilm minimum inhibitory quotient of each drug, defined as achievable serum concentration divided by biofilm MIC. *N*=20 **Control group** Conventional testing: conventional regimens of two	**Antibiotic susceptibility** Participants were assigned to 12 different regimens. The most common regimens included meropenem (52%) and ciprofloxacin (49%). Azithromycin-containing regimens were used for only two participants (5%), both in the biofilm group. No participant received ceftazidime and tobramycin, a combination commonly used in cystic fibrosis clinical practice Of the agents tested, meropenem	**RCT** Acceptable methodological quality (+) Small sample size

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
October 2007	Inclusion criteria: diagnosis of cystic fibrosis, history of persistent *P. aeruginosa* airway infection, clinical stability at the time of screening, ≥14 years with at least one prior course of intravenous antibiotics Exclusion criteria: sputum culture negative for *P. aeruginosa*, sputum culture positive for *B. cepacia* complex species, hospitalization or treatment for an acute pulmonary exacerbation, treatment with oral or inhaled antipseudomonal antibiotics, or azithromycin or other macrolides, within 14 days prior to screening		antibiotics were selected centrally using a published algorithm, which calculated for each bacterial morphotype the conventional minimum inhibitory quotient of each drug defined as achievable serum concentration divided by conventional MIC. *N*=19 **Length of follow-up**: 14 days	was most active against biofilm-grown bacteria, but antibiotic regimens based on biofilm testing did not differ significantly from regimens based on conventional testing in terms of microbiological and clinical responses	
Rattanaumpawan 2010 RCT **Setting** Tertiary (one hospital) Thailand July 2006–September 2009	To determine whether nebulized CMS as adjunctive therapy of Gram-negative VAP was safe and beneficial **Participants** *N*=100 Middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: 64, female: 36 Inclusion criteria: hospitalized patients, ≥18 years of age, diagnosis of Gram-negative VAP Exclusion criteria: not reported	**Bacteria**: *E. coli* (ESBL +ve) and *E. coli* (ESBL -ve), *K. pneumoniae* (ESBL +ve) and *K. pneumoniae* (ESBL -ve), *E. cloacae, P. aeruginosa, A. baumannii* **Resistant to**: aminoglycosides, carbapenems, fluoroquinolones **Mechanism of resistance**: ESBL	**Intervention** Systemic antibiotic and nebulized CMS (parenteral) equivalent to 75 mg of colistin base reconstituted in 4 mL of NSS every 12 h via a nebulizer for 10 min. Continued until systemic antibiotic therapy of VAP was ended (decided by physician). *N*=51 **Control group** Systemic antibiotic(s) plus NSS equivalent to 75 mg of colistin base reconstituted in 4 mL of NSS every 12 h via a nebulizer for 10 min. Continued until systemic antibiotic therapy of VAP was ended. *N*=49	**Mortality** Rates of mortality due to VAP and all-cause mortality did not differ between the groups receiving intervention or control **Clinical success/improvement** Favourable microbiological outcome was significantly higher in the intervention group compared with the control group (RR 1.57, 95% CI 1.03–2.37),but no significant difference was observed on clinical outcomes The overall incidence of complications, bronchospasm and renal impairment did not differ between the two treatment groups	**RCT** Acceptable methodological quality (+)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
			Length of follow-up: 28 days		
Stenderup 1983 RCT **Setting** Community Denmark Dates not reported	To study the use of mecillinam as a prophylactic for travellers' diarrhoea **Participants** *N*=74 tourists Adults 19–45 years, middle aged 46–64 years, aged 65–79 years, elderly 80+ years Male: not reported, female: not reported Inclusion criteria: Danish tourists travelling to Egypt and the Far East Exclusion criteria: not reported	**Bacteria**: Enterotoxogeni *E. coli* **Resistant to**: mecillinam, tetracyline, sulfonamide, streptomycin, chloramphenicol, kanamycin, ampicillin, cephalosporin, carbenicillin **Mechanism of resistance**: not reported	**Intervention** Mecillincam, 200 g, 1x per day for 25 days. *N*=38 **Control group** Placebo. *N*=36 **Length of follow-up**: duration of treatment	**Antibiotic resistance** Only 8% of *E. coli* strains were resistant to three or more antibiotics in the pre-travel samples. Post-travel, after participants had received either mecillinam or placebo, approximately 50% or more of the *E. coli* was resistant to more than three antibiotics	**RCT** Low methodological quality (0)
Tannock 2011 RCT **Setting** Primary (14 long-term care facilities) New Zealand Dates not reported	To test the efficacy of probiotic strain *E. coli* Nissle 1917 in reducing the carriage of MDR *E. coli* **Participants** *N*=70 Age: not reported Male: not reported, female: not reported Inclusion criteria: not reported Exclusion criteria: not reported	**Bacteria**: *E. coli* **Resistant to**: fluoroquinolones (norfloxacin) **Mechanism of resistance**: ESBL	**Intervention** Probiotic: strain *E. coli* Nissle 1917, $5x10^9$-$5x10^{10}$ CFU one capsule twice daily for five weeks. *N*=36 **Control group** Placebo starch powder capsule. *N*=33 **Length of follow-up**: five weeks	**Clinical success/improvement** There was no significant difference between the probiotic and placebo groups in the number of people with faecal and urine samples becoming negative or remaining positive. **Antibiotic resistance** 103 norfloxacin-resistant *E. coli* isolates from 20 probiotic patients were tested for susceptibility. All isolates were resistant to norfloxacin (MIC >256 µg/mL) and ciprofloxacin. The majority of norfloxacin-resistant *E. coli* isolates were MDR. The combination of MDRs differed among strains. None of the isolates	**RCT** Acceptable methodological quality (+)

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment
				were ESBL producers.	
Wang 2009 RCT **Setting** Tertiary (one ICU) China March 2006–July 2006	To report the effectiveness of extended-infusion meropenem compared with conventional bolus dosing in the management of HAP due to MDR *A. baumannii* **Participants** *N*=30 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 19, female: 11 Inclusion criteria: HAP due to MDR *A. baumannii* Exclusion criteria: not reported	**Bacteria**: *A. baumanniii* **Resistant to**: carbapenems (meropenem) **Mechanism of resistance**: not reported	**Intervention** Extended intravenous meropenem infusion: 500 mg every 6 h over a 3-h infusion. *N*=15 **Control group** Conventional treatment: intravenous meropenem 1 g. every 8 h over a 1-h infusion. *N*=15 **Length of follow-up**: duration of treatment	**Clinical success/improvement** No significant differences were found between extended-infusion meropenem and conventional bolus dosing in the number of patients with treatment success at days 3, 5 and 7. The rates of relapse also did not significantly differ between the treatment groups **Antibiotic resistance** No patient developed a meropenem-resistant strain of *A. baumannii*, and the MIC_{90} for meropenem against *A. baumannii* remained at 2 μg/mL	**RCT** Acceptable methodological quality (+) Small sample size
Xue 2009 RCT **Setting** Tertiary (one ICU) China June 2007–December 2007	To determine the relation of carbapenem restriction with the incidence of MDR *A. baumannii* in VAP **Participants** *N*=26 Adults 19–45 years, middle aged 46–64 years, aged 65–79 years Male: 15, female: 11 Inclusion criteria: patients receiving mechanical ventilation for more than five days and diagnosed with VAP Exclusion criteria: not reported	**Bacteria**: *A. baumanniii* **Resistant to**: carbapenems **Mechanism of resistance**: ESBL	**Intervention** Carbapenem restriction policy limiting the use of third-generation carbapenems. Only used when severe sepsis and after consultation with a physician from the Department of Infectious Diseases. *N*=12 **Control group** Conventional treatment: no restrictions of carbapenem (doctors were able to prescribe if necessary). *N*=15 **Length of follow-up**: duration of treatment	**Mortality** The rates of mortality did not differ significantly between the treatment groups (RR 0.78; 95% CI 0.29–2.12). **Antibiotic resistance** More patients in the conventional group developed a carbapenem-resistant strain of *A. baumannii*, although the difference was not statistically significant (RR 0.63; 95% CI 0.38–1.04)	**RCT** Low methodological quality (0) Small sample size

Study details	Objective and participants	MDR Gram-negative bacteria	Intervention, control and follow-up	Results	Quality assessment

P. aeruginosa, Pseudomonas aeruginosa; E. coli, Escherichia coli; C. freundii, Citrobacter freundii; M. morgagnii, Morganella morgagnii; A. baumannii, Acinetobacter baumannii; A. anitratus, Acinetobacter anitratus; P. mira, Proteus mira; S.marcescens, Serratia marcescens; B. cepacia, Burkholderia cepacia; MDR, multi-drug resistant; VAP, ventilator-associated pneumonia; ESBL, extended-spectrum beta-lactamase; CMS, colistimethate sodium; RCT, randomized controlled trial; ICU, intensive care unit; UTI, urinary tract infection; HAP, hospital-acquired pneumonia; NSS, nebulized sterile normal saline; CFU, colony-forming unit; SD, standard deviation; RR, risk ratio; CI, confidence interval.

4.4. Systematic Review References

4.4.1.Antimicrobial Stewardship

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4.5. Excluded clinical studies

4.5.1.Case–control study

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Appendix 5: CPD material

1. Which of the following are appropriate monotherapy meropenem-sparing agents:

a) Temocillin

b) Cefixime

c) Ceftolozane/tazobactam

d) Fosfomycin

e) Ceftazidime/avibactam

Answer a, c, d, e

2. Which of the following are true:

a) Polymyxins do not require monitoring renal function in the elderly.

b) Fluoroquinolones can be used to treat urinary infection due to multidrug resistant Gram-negative bacteria

c) Oral pivmecillinam should be used alone in the treatment of upper urinary infection

d) Polymyxins should be given in combination with other agents if they are used in treating carbapenem-resistant Enterobacteriaceae.

e) Co-trimoxazole should be used in treatment of infections due to *Stenotrophomonas maltophilia*

Answer b, d, e

3. Which of the following are true:

a) In uncomplicated urinary infection due to a proven ESBL-producing organism, treatment is recommended for 3 days

b) If infection with MDR GNB is suspected, treat asymptomatic bacteriuria

c) Give antibiotic prophylaxis for urinary catheter insertion if previous history of symptomatic urinary infections associated with a catheter change or there is trauma during the catheter insertion

d) Daily antibiotic prophylaxis is preferable to standby antibiotics in recurrent urinary infection

e) Always send a urine specimen for culture if an antibiotic-resistant organism is suspected AND the patient is asymptomatic

Answer c,

4. Which of the following are true;

a) Ceftolozane-tazobactam is active against AmpC producing Enterobacteriaceae

b) Ceftazidime-avibactam is active against AmpC producing#

Enterobacteriaceae

c)KPC-producing *Klebsiella sp*. often produce aminoglycoside

methyltransferases conferring pan-aminoglycoside resistance

d) NDM-producing *E. coli* are usually mecillinam susceptible

e) Proteus sp. are usually resistant to fosfomycin

Answer b

Appendix 6: Consultation stakeholders

Antimicrobial Resistance and Hospital Acquired Infection

Advisory Committee (APRHAI)

British Medical Association

British Society of Antimicrobial Chemotherapy

British Infection Association

C. Diff Support

European Society of Clinical Microbiology and Infectious Diseases

Faculty of Intensive Care Medicine

Foundation Trust Network

Hand Hygiene Alliance

Healthcare Infection Society

Infection Prevention Society

Lee Spark Foundation

MRSA Action UK

NHS Confederation

NHS England

NHS Trust Development Authority

Patient's Association

Public Health England/ Wales/ Scotland/ Northern Ireland

Royal College of Pathologists

Royal College of General Practitioners

Royal College of Nursing

Royal College of Physicians

Royal College of Surgeons

Service User Research Forum Healthcare acquired Infections

UK Clinical Pharmacists Association

Unison

Appendix 7 Response from Stakeholders in consultation

Respondent	Address	Email	Date Rec/d
Conor Doherty	NHS GGC – paed infectious diseases	Conor.Doherty@ggc.scot.nhs.uk	23 May 2016
Ibai Los-Arcos	Infectious Diseases Division, Hospital Universitari Vall d'Hebron Avda. Vall d'Hebron, 119-129 08035 Barcelona. Spain	bai.losarcos@gmail.com	01 June 2016
Prof. Céline PULCINI	Nancy University Hospital, Nancy, France	celine.pulcini@univ-lorraine.fr	01 June 2016
Aaron Nagar	Microbiology Department, Antrim Area Hospital, 45 Bush Rd, Antrim, Northern Ireland, BT41 2RL	Aaron.Nagar@northerntrust.hscni.net	01 June 2016
Dr Paul Chadwick & Dr Alex Peel	Microbiology Department Salford Royal NHS Foundation Trust Stott Lane, Salford. M6 8HD	paul.chadwick@srft.nhs.uk; alex.peel@srft.nhs.uk	15 June 2016
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Egidia Miftode	Hospital of Infectious Diseases Iasi Str O Botez no 2, code 700274, Iasi Romania	emiftode@yahoo.co.uk	27 June 2016
Neil Woodford	Head, Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (AMRHAI) Public Health England 61 Colindale Avenue London, NW9 5EQ	Neil.Woodford@phe.gov.uk	27 June 2016

British Society for Antimicrobial Chemotherapy
Joint Working Party Paper on Multi resistant Gram-negative Infection: Treatment

Consultation deadline: Friday 17 June 2016

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Name	Conor Doherty	
Organisation Address & Postcode	NHS GGC – paed infectious diseases	

Email		Conor.doherty@ggc.scot.nhs.uk			
Phone number					
Conflict(s) of Interest		nil			
Document Indicate if you are referring to the **Full** version or the **Appendices**	**Page Number** **Number only** (do not write the word 'page/pg'). Alternatively write **'general'** if your comment relates to the whole document	**Line Number** **Number only** (do not write the word 'line'). See example in cell below	**Comments** **Please insert each comment on a separate row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**	**Changes:** **Mark as "Exclude" OR "Include" (and reason for change or no change)**	
EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP Response
			Generally a very useful document. My one concern is that there is no mention of children, infants, neonates. Paeds are increasingly faced particularly with multiresistant G-ve UTI's and the data here is all from all adult studies/perspectives. Unfortunately experience with quite a few of the alternative drugs discussed here is very scant and often appropriate doses/formulations are unknown/unavailable. 1) As a result carabpenem sparing strategies are particularly problematic due to lack of alternatives. I would suggest that the doc either declares itself as 'adult' guidance or discusses this		Specific mention made that does not cover neonates and mostly does not deal with paediatric dosage or paediatric-specific issues such prophylaxis of UTI

			2) Appropriate empirical treatment and prophylaxis strategies in the face of increasing trimethoprim resistance for paed UTI's is a major issue and not discussed		

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Name	Ibai Los-Arcos	
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Phone number		0034 93 274 6090			
Conflict(s) of Interest		None			
Document Indicate if you are referring to the **Full** version or the **Appendices**	**Page Number** Alternatively write **'general'** if your comment relates to the whole document	**Line Number** See example in cell below	**Comments** **Please insert each comment on a separate row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**	**Changes:** **Mark as "Exclude" OR "Include" (and reason for change or no change)**	**WP Response**
Full	61	1651	Mean prostatic fosfomycin levels in the uninflamed peripheral prostatic area after a 3 g dose of fosfomycin trometamol were higher than 4 µg/g in 70% of patients (Gardiner et al. 2014). In addition, fosfomycin-tromethamine monotherapy proved useful for the treatment of 2 cases of MDR Enterobacteriaceae prostatitis (Grayson et al. 2015) and also for the treatment of 53% of patients with difficult-to-treat chronic bacterial prostatitis, including 4/5 (80%) MDR Enterobacteriaceae (Los-Arcos et al. 2015). It could be an alternative agent for the treatment of MDR Enterobacteriaceae prostatitis, in isolates with fosfomycin MICs < 4 µg/ml.	Include	Reference to prostatitis included in fosfomycin section

References:

- Gardiner BJ, Mahony AA, Ellis A G, et al. Is fosfomycin a potential treatment alternative for multidrug-resistant gram-negative prostatitis? Clin Infect Dis 2014;58:e101–5.
- Grayson ML, Macesic N, Trevillyan J, et al. Fosfomycin for treatment of prostatitis: new tricks for old dogs. Clin Infect Dis 2015; 61:1141-3.
- Los-Arcos I, Pigrau C, Rodríguez-Pardo D, et al. Long-term fosfomycin-tromethamine oral therapy for difficult to treat chronic bacterial prostatitis. Antimicrob Agents Chemother 2015; 60: 1854-8.

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Name	Prof. Céline PULCINI	
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Phone number		
Conflict(s) of Interest	None	

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EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP Response
Full	general		Congratulations on your hard work! I miss a summary of the recommended dosing and durations of treatment for each antibiotic and I feel that a section on optimised PK/PD (prolonged infusions…) would be a plus		Dosing recommendations uness specifically otherwise referenced are as per product medicines license and outside scope of WP Report. Some information on prolonged infusion of meropenem now included but full section rather than illustration of benefit outside scope of WP

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Name	Aaron Nagar	
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Phone number	02894424113	
Conflict(s) of Interest	Speaker fee from Astellas	

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EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP Response
Full	40	1086	Change to "Ceftazidime –avibactam may be used as an alternative to carbapenems in exceptional circumstances i.e. infection with KPC producer"	Include: Though evidence is not there feel that Ceftazidime-avibactam should be reserved for infections for which there are limited options .i.e. KPC producers. Given targets to reduce carbapenem use, I fear ceftazidime-avibactam may be overused driving resistance to it.	Review is required to be evidence-based by NICE
Full	64	1743	Suggest changing the order of the oral agents i.e. nitrofurantoin, pivmecillinam and fosfomycin	Include: Feel this order is better as people tend to use the first agent in a guideline more. Feel that fosfomycin should be last as we may have to use the IV form more when CPE becomes more prevalent. It will not be useful if we drive resistance by PO fosfomycin overuse.	Order specified in new algorithm
Full	65	1754	Feel that the order of PO agents in the text	Include: Feel this order is	Order specified in

			should be changed to nitrofurantoin, pivmecillinam and fosfomycin	better as people tend to use the first agent in a guideline more i.e. feel that it indicates preference. Feel that fosfomycin should be last as we may have to use the IV form more when CPE becomes more prevalent. It will not be useful if we drive resistance by PO fosfomycin overuse.	algorithm
Full	65	1756	Feel that we should remove 7 days treatment for uncomplicated UTI due to an ESBL producer	Exclude: Feel that clinical staff over treat older patients with asymptomatic bacteriuria and are always looking for excuses to extend duration. I feel we should stick with shorter durations for symptomatic cure.	Comment is not evidence-based. WP specifically considered that bacteriologically optimum treatement required when MDR GNB being treated but not generally
Full	81	2179	Feel that we should discourage dipstick use in patients over 65 years of age as per SIGN guidance	Exclude: Find it very difficult to convince clinicians not to use urine dipstick to diagnose and treat asymptomatic bacteriuria as UTI.	Agree with specific point about asymptomatic bacteriuria and this has been added. Detailed technology review consideration of dipsticks in paper extended and changed

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Name	Dr Paul Chadwick, Clinical lead/consultant microbiologist Dr Alex Peel, Antimicrobial stewardship lead/consultant microbiologist	
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Phone number	01612065030	
Conflict(s) of Interest		

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Full	general		This guideline is welcomed as a resource to support treatment of MDR Gram negative infections and is supported by an extensive literature review. However, the recommendations in their current form appear as a fairly disjointed and inconsistent collection of statements. For example, the first recommendation starts with the role of temocillin vs Enterobacteria and Burkholderia and the second recommendation is for ampicillin-sulbactam vs Acinetobacter. This is not a logical or helpful sequence for presentation. Some of the recommendations appear as a surprise as they do not relate back to the preceding evidence or discussion. Care should be taken to ensure that this link is made and a justification provided for all recommendations Perhaps the functionality of the guideline could be improved with a more structured approach to the management of MDR Gram negatives? For example the role of each of the different classes of agents (recommended Y/N + comments) could be systematically presented as a table for each of the common		Very useful set of comments. 1. Antibiotics considered have been re-ordered to reflect important issues. 2. All recommendation checked for relationship to text and evidence 3. Too many mechanisms to consider all but additional table on mechanisms and activity added.

			resistance mechanisms, if necessary separated into different tables for the different organism groups (e.g. Enterobacteria, non-fermentors).		
Full	28	783	The conclusion that temocillin may be used as a carbapenem-sparing agent against Enterobacteria is (a reasonable) opinion of the authors but does not follow from the evidence presented. (The same opinion might also have be given for other classes of agent such as polymixins). Consideration should be given to simplifying and rephrasing the recommendation to 'temocillin can be used to treat infections due to Enterobacteria, including ESBL and AmpC producers'		Considered on a case by case basis
Full	30	830	The recommendation that 'Amoxicillin-clavulanate should not be used to treat infection with known ESBL-producing organism unless sensitivity known ' is generally not very helpful for a typical diagnostic laboratory where apparent co-amoxiclav susceptibility will be known either before or at the same time as ESBL production is confirmed. Alternatively, if the authors are suggesting that a patient with a history of ESBL positive UTI/infection should not be given co-amoxiclav until sensitivity for the current episode is confirmed, the recommendation should be clearly reworded		Detailed consideration given of this recommendation but given 6+% recurrence rate with ESBL infection previous susceptibility is an important factor in making this choice. Substantual cavaeats against use of coamoxiclav and piperacillin/tazobactam use in UK added both because of in vitro resistance and prevalence pf OXA-1 in UK isolates
Full	32	883	The following recommendation is not supported by any evidence linking clinical outcomes to sepsis severity criteria: 'Piperacillin-tazobactam can be considered for use in mild-moderate infections (i.e. not severe sepsis) due to ESBL-producing Enterobacteriaceae if supported by susceptibility results.' The evidence should be provided, the opinion justified, or the recommendation removed.		Recommendation changed to omit reference to severity of infection

Full	32	888	The following recommendation is not supported by any evidence. …'However combination with an aminoglycoside is advisable for severe infections.' The evidence should be provided, the opinion justified, or the recommendation removed.		Agree. Removed
Full	36	986	It is unclear why there needs to be a separate recommendation for ertapenem: 'Ertapenem is effective in treatment of infections with multi-resistant Enterobacteriaceae apart from carbapenemase producers' when this has apready been covered by the previous recommendation: ' Carbapenems should be used to treat serious ESBL-producing Gram-negative infections subject to antibiotic stewardship to minimize the risk of developing resistance'. Is there a reason why the general carbapenem recommendation is not extended to include AmpC resistance? For internal consistency within the document, we suggest merging these two recommendations as follow: 'carbapenems can be used to treat infections due to ESBL or AmpC producing Enterobacteria'.		Ertapenem has different properties and is now recommended for OPAT. AmpC issue now considered
Full	37	1010	The format of the following recommendation is internally inconsistent within the document: 'Although it retains good efficacy against infections with *Pseudomonas aeruginosa*, ceftazidime is not recommended for the treatment of other serious infections due to ESBL / AmpC producing Enterobacteriaceae, even if in vitro tests suggest the isolate is susceptible.' We suggest 1) separating the recommendations for treating Pseudomonas and Enterobacterial infections, 2) rephrasing the recommendation for Enterobacteria as follows: 'ceftazidime should NOT be used to		rephrased

			treat infections due to ESBL or AmpC producing Enterobacteria'		
Full	39	1074	Information relating to aztreonam-avibactam, while interesting, does not belong under a heading of ceftazidime-avibactam and is not directly relevant to the guideline – suggest remove		Separate aztreonam section added whoich houses the experimental combination aztreoname-avibactam
Full	40	1086	The format of the following recommendation is internally inconsistent within the document: 'With the exception of infections with metallo-β-lactamase strains, ceftazidime-avibactam, when available, should be used as alternative treatment to carbapenems'. We suggest rephrase this recommendation as follows: 'ceftazidime-avibactam can be used to treat infections due to Enterobacteria, including ESBL and AmpC producers'		Rewritten
Full	42	1140	The format of the following recommendation is internally inconsistent within the document (and implies that it should be used in preference to carbapenems): 'Ceftolozane-tazobactam should be used as alternative treatment to carbapenems in treating ESBL-producing Gram negative pathogens (but not carbapenemase producers). We suggest rephrase this recommendation as follows: 'ceftolozane-tazobactam can be used to treat infections due to Enterobacteria, including ESBL and AmpC producers'		Rewritten
Full	45	1231	There is potential overlap/duplication regarding combination therapy with this recommendation and the recommendation on page 56, line1518. Consider either removing 'and preferably used in combination with other agents' and adding a cross reference to the later section		Cross-references inserted where useful
Full	45	1234	The recommendation with regard to renal		To contaienm a;lready

			function is internally inconsistent within the document as side effects are not systematically considered for other agents. Many important unwanted effects occur for many different antimicrobials and relevant monitoring should be considered as a matter of course by the prescribing clinician (and this might include monitoring colistin levels also, which is not mentioned as a recommendation).		voluminous length Unwanted effects are highlighted where may be specifically over-looked.
Full	46	1266	The format of the following recommendation is internally inconsistent within the document: 'Fluoroquinolones can be used to treat urinary infection due to multidrug resistant Gram-negative bacteria based on susceptibility results.' We suggest rephrase this recommendation as follows: 'quinolones can be used to treat complicated urinary tract infections due to Gram negative bacteria'		Standardised
Full	51	1390	The format of the following recommendation is internally inconsistent within the document: 'Fosfomycin should be used in treatment of urinary infection due to multiresistant Gram-negative bacteria (oral administration only suitable for lower urinary infection)' We suggest rephrase as follows: 'Fosfomycin can be used to treat urinary tract infections due to Gram-negative bacteria (oral administration only suitable for lower urinary infection)'		Standardised
Full	52	1410	To improve internal consistency within the document, we suggest adding the following additional recommendation (which follows from the preceding evidence): 'aztreonam should NOT be used to treat infections due to ESBL or AmpC producing Enterobacteria'		Agreed
Full	65	1758	There is a recommendation to use 7 days		Debated at length within

			therapy for ESBL simple UTIs to improve bacteriological clearance. There is no mention of clinical outcomes evidence. Bacteriological clearance does not necessarily correlate well with clinical outcomes (e.g. high prevalence of asymptomatic bacteriuria in certain patient populations). This recommendation could lead to a large increase in ab use if implemented widely and it would need strong clinical evidence before doing so.		WP. Considered that best possible bacteriological clearance should be obtained with proven MDR GNB infection but caveat inserted about clinical relevance of bacteriological cure.
Full	66	1795	This recommendation: 'admission for intravenous aminoglycoside therapy' is potentially confusing as it appears to exclude an inpatient carbapenem option (presumably temocillin or other agents recommended above for Enterobacteria could also be considered). We suggest rephrase as 'admission for intravenous therapy with an aminoglycoside or carbapenem (? Or temocillin etc)		Whole section fo recommendations recast. Point accepted.
Full	General	General	Although the evidence base is weak in many areas, and the authors are to be commended for covering many topic areas, we feel the document does not read like it is focused on an infection specialist dealing with 'real world' problems e.g. a patient with KPC bacteraemia with MICs of x,y,z and renal failure and obesity etc – we note that the US has produced flowcharts previously (e.g. Medscape http://www.medscape.com/viewarticle/780065_9) see screenshot on following page, and more recent publications - clearly these may be based on minimal evidence but they do provide a start. We wonder whether consideration could be given by the WP to producing similar tools.		" simple flow-charts inserted but subject is too diverse to deal with all possible clinical situations

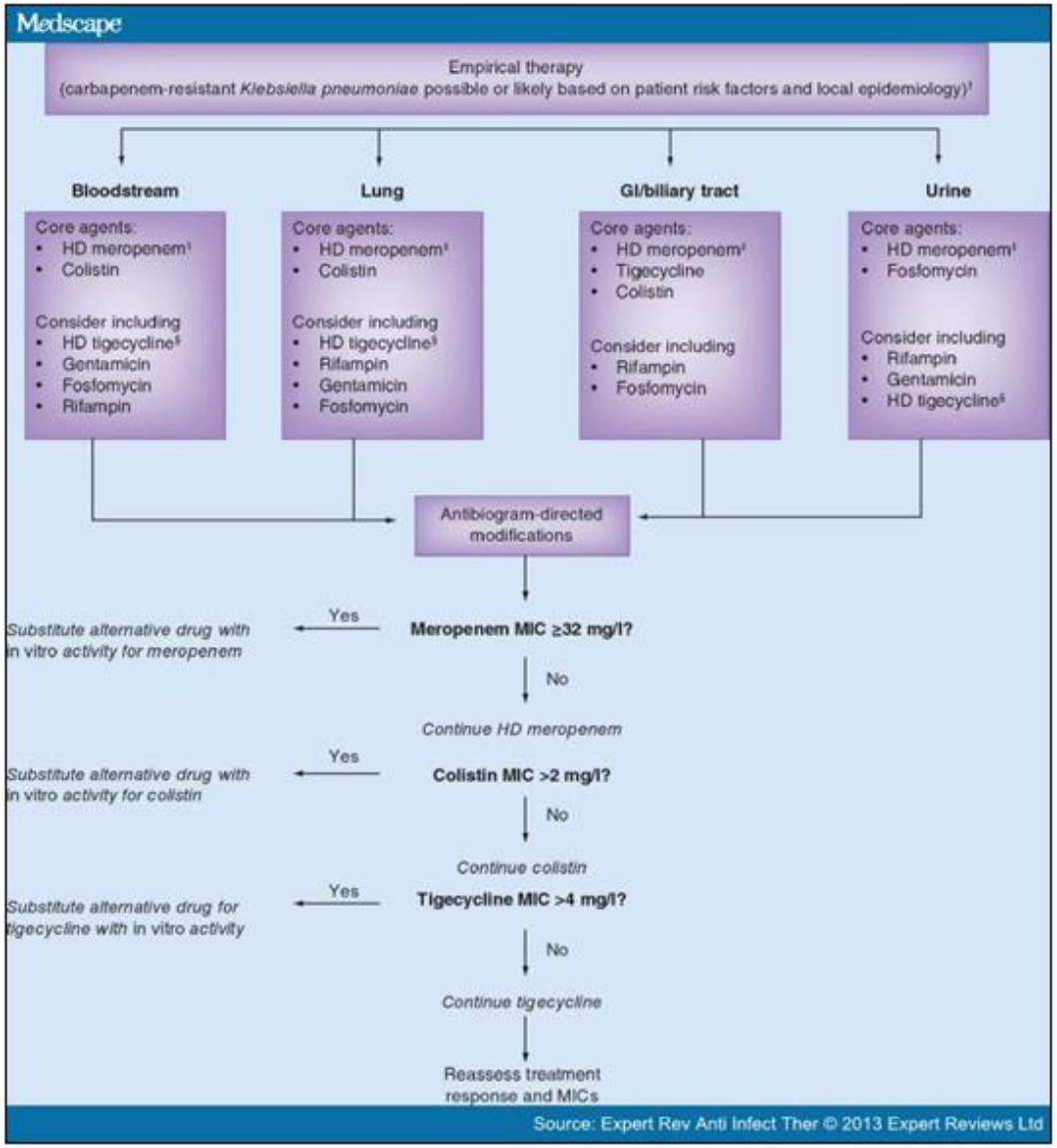

Figure 2.

Potential antibiotic combination therapy algorithm for the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections stratified to site of infection and antibiogram results. †Algorithm would be appropriate for institution where >50% of isolates exhibit carbapenem MICs in the treatable range with HD therapy (MIC <32 mg/ml). Specific drugs used for empirical therapy should be tailored the epidemiology of endemic carbapenem-resistant *Klebsiella pneumoniae* strains.‡HD meropenem (6 g daily, administered as prolonged infusion).§HD tigecycline (200 mg loading dose, 100 mg once a day), see text regarding the limitations and evidence supporting the use of HD regimens.HD: High-dose.

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Name	Rebecca Tilley	
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Conflict(s) of Interest	None	

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EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP Response
Full	15	423	Typo – "uin" instead of "in"	Exclude: correct the spelling	All typos dealt with
Full	38	1054	Typo – "Gram-egative" instead of "Gram-negative"	Exclude: correct the spelling	All typos dealt with
Full	52	1415	Typo – "mecillianam" instead of "mecillinam"	Exclude: correct the spelling	All typos dealt with
Full	74-75	2004-2009	All bacteraemias or just MRGN bacteraemias? This would require a standardised format to enable direct comparison but is also a very complex, multifactorial issue and would also need to capture sufficient clinical detail e.g. not all mortality is a result of inappropriate antibiotic prescribing; blood cultures often signal positive after the patient has died plus were there risk factors for MRGN identified during primary assessment? This also sounds a very labour intensive requirement. Please be aware that many microbiology consultants are already having to collate a lot of information as a mandatory requirement for bodies such as PHE without any additional resources being identified and would struggle to add more to the pile. Not all departments have junior doctors to assist	Exclude: needs modifying. Please specify whether all bacteraemias or not and give appropriate consideration to format and additional resources required, particularly if this were to become a mandatory requirement, to support business cases within local Trusts.	Accept point on consultant time and specifically added but priority of required action and information on Gram-negative bacteraemias is high. Extensive bacteraemia information added and advice taken from BIA.

			with this sort of responsibility.		
Full	82	2194	Would recommend that 1) the term “standby antibiotics” is explained and 2) that advice is given on how a clinician, bearing in mind this is often a GP, would decide which antibiotic would be appropriate as a “standby” option.	Exclude: Needs modification.	Clarified
Full	90	2246	There is a superscript β in the flowchart, but it does not appear to refer to anything	Exclude: Needs reviewing	Dealt with
Full	90	2252	There is a comment marked ¥, but this symbol does not appear in the flowchart.	Exclude: needs reviewing	Dealt with
Full	General		MRGNs are an increasing problem for us but we are not yet seeing many MRGN bacteraemias and CPEs remain very rare locally. The management of sepsis necessarily requires empirical broad-spectrum antibiotic treatment before we have positive microbiology but we are not yet at the stage where our local guidance advises empirical cover for MRGNs unless there are risk factors for this. We are concerned that the recent CQUIN – re: reduction in antibiotic consumption which is particularly targeting piperacillin-tazobactam and carbapenems seems to be at odds with the empirical management of sepsis and if our Trust has any hope of achieving this target (which incidentally uses historic baseline data from a time when MRGNs were far less prevalent) then we would need to be moving empirical therapy back to cephalosorins and quinolones for example. We are reluctant to do this from a C. difficile perspective and from driving resistance mechanisms yet further. We appreciate that this document is not directly related to the CQUIN and that we are venting our frustration but it would be helpful if BSAC could issue a position statement or guidance on this CQUIN and outline the best approach for microbiologists to a) do the right thing in terms of empirical therapy for the septic patient, particularly if there is a MRGN risk		We are also concerned about the potneital conflict between antibiotic-use reduction targets and potential mortality in bacteraemia which has similar 30 day mortality to C.difficile. Document extensively revised and your general points incorporated. Thank you

			plus b) reduce the risk of promoting antibiotic resistance plus c) meet contractual obligations. I know we are not the only Trust that is exasperated by the specifics within this DH requirement which seems to totally disregard all the improvements made in recent years with regard to C. difficile and antibiotic stewardship.		
Full	General		The document discusses using antibiotics such as temocillin, tigecycline, colisitin and fosfomycin. EUCAST does not provide guidance on interpretation of temocillin susceptibility either by disk or MIC. Tigecycline needs to be tested via MIC for anything other than E coli. Fosfomycin & colistin need to be tested by MIC. These requirements reduce the turnaround times for results. In addition, the turnaround times for CPE resistance mechanisms/additional sensitivities do not help support optimum patient management. Could PHE Colindale publish its testing methods/MIC interpretations to enable local testing rather than sending isolates to them? Is there a way to expedite EUCAST guidance on temocillin interpretations? Can BSAC offer recommendations to support local business cases for introducing technology that enables faster identification of e.g. CPEs in house as opposed to relying on reference laboratories?		In practice we now consider that molecular methodology is needed for colistin susceptibility testing and MICs for meropenem with MDR GNB and this has been added. To track the fast changing situation we have now recommended that i) mandatory reporting of carbapenem resistant isolates is introduced ii) isolates are dealt with expeditiously for patient benefit and iii) isolates referred where testing is beyond the scope of local laboratories.

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Conflict(s) of Interest	none	

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EXAMPLE: Full	16	45	Our comments are as follows ……	Exclude: Reason	WP response
Full	56	1515	Klebsiella pneumoniae carbapenemase-producing		Dealt with
full	47	1292	compared		Dealt with

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Conflict(s) of Interest		

Document Indicate if you are referring to the **Full** version or the **Appendices**	**Page Number** **Number only** (do not write the word 'page/pg'). Alternatively write **'general'** if your comment relates to the whole document	**Line Number** **Number only** (do not write the word 'line'). See example in cell below	**Comments** **Please insert each comment on a separate row.** **Please do not paste other tables into this table, as your comments could get lost – type directly into this table.**	**Changes:** **Mark as "Exclude" OR "Include" (and reason for change or no change)**	**WP Response**
Full	Many	Many	Group the urinary tract infection summaries and cephalosporin/antibiotic summaries	Include	Sections extensively re-ordered
Full	Many	Many	The referencing seems to be sporadic, with some areas very well referenced and others less so or not at all. A consistent approach throughout would be beneficial e.g. more references for UK statements in Pages 624-634	Include	Re-referenced and numerous references added
Full	Many	Many	Quite a lot of sections do not have an added line break following a new paragraph	Include	Line breaks removed for JAC
Full	Many	Many	After evidence and recommendations sometimes there are bullet points and other times not – consistency would be good	Include	Consistent approach adopted
Full	5	163	Infection also happens through bacteria gaining access to organs or bloodstream from internal sources e.g. gut translocation	Include	Evidence for translocation in absence of local infection is poor
Full	11	322	Extra space between 'tazobactam' and 'should'	Exclude	Typos dealt with
Full	13	370	Full stop required after 'resistance'	Include	Typos dealt with
Full	13	381	Extra space between 'of' and 'new'	Exclude	Typos dealt with
Full	13	388	Extra comma between 'the' and 'community'	Exclude	Typos dealt with
Full	14	404	Full stop required after 'incontinence'	Include	Typos dealt with
Full	15	423	Extra u in 'uin'	Exclude	Typos dealt with
Full	17	471	Extra space between 'treatment' and ','	Exclude	Typos dealt with
Full	17	483	Full stop required after '(Table 2)'	Include	Typos dealt with

Full	2	131	No Appendix 5 listed	Include	Appendices renumbered and referred to in text
Full	18	505	Extra comma required between 'required' and 'notably'	Include	Typos dealt with
Full	18	505	Extra comma between '.' and 'There'	Exclude	Typos dealt with
Full	23	643	Extra space required between '2009,' and 'and'	Include	Typos dealt with
Full	25	685	Et al should be italicised	Include	Typos dealt with
Full	25	694	Extra space between '5%' and ')'	Exclude	Typos dealt with
Full	26	702	Extra space between 'imported' and 'to'	Exclude	Typos dealt with
Full	26	733	Extra space required between 'compare,' and '('	Include	Typos dealt with
Full	30	817	Extra space between 'the' and 'study'	Exclude	Typos dealt with
Full	30	819	Extra space between 'MICs' and 'to'	Exclude	Typos dealt with
Full	32	879	Extra space between 'bactam' and 'is'	Exclude	Typos dealt with
Full	33	917	Extra full stop after 'ceftazidime' and'.'	Exclude	Typos dealt with
Full	35	960	Extra space between 'isolates' and 'of'	Exclude	Typos dealt with
Full	35	967	Extra comma between 'result' and '(Hyle)'	Exclude	Typos dealt with
Full	35	973	Extra space between 'did' and 'not'	Exclude	Typos dealt with
Full	37	1024	Extra space between 'responded' and '.'	Exclude	Typos dealt with
Full	38	1044	Extra space required between 'Eve' and 'in'	Include	Typos dealt with
Full	39	1066	Extra space between 'lactamases' and '(NDM'	Exclude	Typos dealt with
Full	39	1078	Extra space between 'trials' and ','	Exclude	Typos dealt with
Full	40	1097	Extra space between 'aeruginosa' and 'with'	Exclude	Typos dealt with
Full	42	1140	Extra space between 'bactam' and 'should'	Exclude	Typos dealt with
Full	43	1184	Extra space between 'period' and '(Huttner'	Exclude	Typos dealt with
Full	44	1211	Extra space required between 'toxicity' and '(Kelesidis'	Include	Typos dealt with
Full	46	1246	Extra space between 'quinolones' and ','	Exclude	Typos dealt with
Full	46	1255	Extra space between 'used' and 'to'	Exclude	Typos dealt with
Full	47	1276	Extra space between 'most' and 'Enterobacteriaceae'	Exclude	Typos dealt with
Full	48	1309	Extra space between 'Tumbarello' and '*et al*'	Exclude	Typos dealt with
Full	49	1345	Extra space between 'activity' and ':'	Exclude	Typos dealt with
Full	50	1370	Extra space between 'gentamicin' and '('	Exclude	Typos dealt with
Full	56	1518	Should 'except rifampicin' be included in the recommendation for combination therapy with colistin	Include	Considered but dealt with in text
Full	56-57	1539-1543	Is this truly accurate of UK practice. Internal	Include	Agree. Modified with

			work at St Thomas' Hospital several years ago highlighted much higher resistance rates than this.		additional references
Full	60	1624	Extra space between 'GI' and 'effects'	Exclude	Typos dealt with
Full	60	1630	Extra space between 'factors' and 'that'	Exclude	Typos dealt with
Full	56-63	N/A	Should there be a section on the use of sterilising agents or the use of NSAIDs in uncomplicated UTIs	Include	Probably not as emphasis is primarily on serious infection
Full	64	1738	Extra space between 'cure' and 'Brayfield'	Exclude	Typos dealt with
Full	67	1824	Extra space between 'or' and 'carbapenem'	Exclude	Typos dealt with
Full	67	1826	Extra space between 'situations' and ','	Exclude	Typos dealt with
Full	68	1852	Extra space between 'appropriate' and ','	Exclude	Typos dealt with
Full	68	1857	Extra space between 'institutions' and ','	Exclude	Typos dealt with
Full	69	1862	Extra space between 'and' and 'accounts'	Exclude	Typos dealt with
Full	70	1890	Extra space between 'One' and 'controlled'	Exclude	Typos dealt with
Full	70	1892	Extra space between 'most' and 'studies'	Exclude	Typos dealt with
Full	70	1898	Extra space between 'trials' and ','	Exclude	Typos dealt with
Full	71	1917	Extra space between 'few' and 'studies'	Exclude	Typos dealt with
Full	75	2011	Extra space between 'of' and 'new'	Exclude	Typos dealt with
Full	76	2053	Extra space between '%' and 'absolute'	Exclude	Typos dealt with
Full	78	2088	Extra space required between ')' and 'in'	Include	Typos dealt with
Full	78	2107	Extra space required between 'bacteriuria' , which also needs an I removed, and 'in'	Include/Exclude/Respell	Typos dealt with
Full	78	2110	Extra space between 'of' and 'colonisation'	Exclude	Typos dealt with
Full	80	2135	Extra space between 'resistance' and '.'	Exclude	Typos dealt with
Full	80	2147	Extra space between 'resistance' and '.'	Exclude	Typos dealt with
Full	80	2148	Extra space between 'on' and 'consensus'	Exclude	Typos dealt with
Full	80	2147	Full stop needed after 'i'	Include	Typos dealt with
Full	81	2167	Extra space between 'infection' and 'but'	Exclude	Typos dealt with
Full	81-83	N/A	Should there again be a section on the use of sterilising agents or the use of NSAIDs in uncomplicated UTIs	Include	See previous response
Full	84	2217	Extra space required between 'studies' and '(SIGN'	Include	Typos dealt with
Full	85	2224	Extra space required between 'grading' and '(SIGN', which is also superscripted unnecessarily	Include	Typos dealt with
Full	85	2225	Table sometimes has full stop and at other times does not	Include	Hopefully dealt with