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Treating infections caused by carbapenemase-producing Enterobacterales (CPE): a pragmatic approach to antimicrobial stewardship on behalf of the UKCPA Pharmacy Infection Network (PIN)

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The emergence of carbapenemase-producing Enterobacterales (CPE) as a major cause of invasive infection both within the UK and internationally poses a very real concern for all providers of healthcare. The burden of morbidity and mortality associated with CPE infections is well described. The need for early, targeted, effective and safe antimicrobial therapy remains key for the management of these infected patients yet reliable antimicrobial treatment options remain scarce. In the absence of a universal treatment for these CPE invasive infections, individual treatment options tailored to susceptibilities and severity of infection are required. This working group from within the UK Clinical Pharmacy Association (UKCPA) Pharmacy Infection Network has developed evidence-based treatment recommendations to support infection specialists in managing these complex infections. A systematic review of peer-reviewed research was performed and analysed. We report consensus recommendations for the management of CPE-associated infections. The national expert panel makes therapeutic recommendations regarding the pharmacokinetic and pharmacodynamic properties of the drugs and pharmacokinetic targets, dosing, dosage adjustment and monitoring of parameters for novel and established antimicrobial therapies with CPE activity. This manuscript provides the infection specialist with pragmatic and evidence-based options for the management of CPE infections.

1. Introduction

This guidance has been prepared by a working group of specialist antimicrobial and infectious diseases pharmacists within the UK Clinical Pharmacy Association (UKCPA) specialist group, Pharmacy Infection Network (PIN). The guidance advises on the safe and effective antimicrobial treatment of carbapenemase-producing Enterobacterales (CPE) infections. There are accompanying recommendations for the appropriate infection prevention and control precautions advised for CPE in addition to treatment advice provided by the Working Party of the British Society for Antimicrobial Chemotherapy (BSAC), the Healthcare Infection Society (HIS) and the British Infection Association (BIA) to advise on the treatment of infections caused by MDR Gram-negative bacteria.[1,2]

1.1. What is the scope of this manuscript?

We examine the background information and available published literature and then (i) propose a series of treatment principles, (ii) review the place in therapy of antimicrobial treatments that may be effective for treatment of CPE infections and (iii) advise on dose optimization to maximize treatment response. These recommendations should be interpreted based on available susceptibilities and read in conjunction with the BSAC/HIS/BIA guidance on treatment of infections caused by MDR Gram-negative bacteria.

These recommendations advise on the treatment for Enterobacterales with acquired carbapenemases, specifically NDM, VIM, IMP, KPC and OXA-48 [as defined by UK Standards for Microbiology Investigations: Detection of bacteria with carbapenem-hydrolysing β-lactamases (carbapenemases)].[1]

These recommendations *do not* include advice on the management of MDR non-Enterobacterales pathogens or carbapenem-resistant Enterobacterales with non-carbapenemase resistance mechanisms. *Acinetobacter* and *Pseudomonas* spp. may host several mechanisms conferring resistance to carbapenems, including carbapenemases (class D and class B), porin loss (e.g. reduced expression or polymorphism) and multidrug efflux pumps. An attempt has been made to include information relating to these organisms where possible. Pathogens with intrinsic carbapenem resistance are outside the scope of this review.

These recommendations *do not* include specific information relating to dosing and treatment options for CPE infections in neonates and children.

These recommendations do include information on the use of unlicensed treatments, dosing and methods of administration that have been reported in the literature or theoretically have potential to maximize therapeutic effect. It is the responsibility of healthcare organizations to review the suitability of these options on an individual-patient basis. Clinicians and patients must be made aware of the unlicensed status when using doses outside of the UK marketing authorization. This review has sought to include all therapies with a UK license or promising therapies undergoing Phase III studies or awaiting UK licensing.

1.2. What is the evidence for these recommendations?

A systematic review was performed of peer-reviewed research using the searches shown in section 2.1. Experts from the working group were used to appraise the literature and provide consensus recommendations in the absence of clear evidence-based recommendations.

1.3. How frequently are the recommendations reviewed and updated?

These recommendations will be reviewed and updated every 5 years, as warranted by the emerging literature or by the availability of new therapies.

1.4. Defining CPE infections

Carbapenemases are enzymes that hydrolyse carbapenem antibiotics, conferring resistance. They are produced by a small but growing number of Enterobacterales strains. The presence of a carbapenemase does not always result in high-level resistance to carbapenems *in vitro*. There are different types of carbapenemase, of which KPC, OXA-48, NDM and VIM enzymes are currently the most commonly identified within the UK. Carbapenemases include enzymes from β-lactamase classes A, B and D (Ambler classification). The main classes of acquired carbapenemases are listed in Table 1.

1.5. Aim

The primary aim of the review was to assess the current available evidence for the treatment options of CPE infections. Secondary aims included: (i) analysing the optimum administration of β-lactams for treatment of invasive CPE infections; (ii) providing optimum dosing parameters for antimicrobial therapies; and (iii) reviewing the role of single and combination therapy for the treatment of CPE infection.

Table 1. Common β-lactamase classes A, B and D (Ambler classification) identified in Enterobacterales

β-lactamase class variant(s)	β-lactamase class variant(s)
Class A (serine)	KPC, GES
Class B (zinc) MBLs	NDM, VIM, IMP
Class D (serine)	OXA-48

2. Methodology

2.1 Evidence appraisal

A literature review was conducted to identify CPE-related treatment options and data included were identified by searches of MEDLINE, Embase and references from relevant original articles. Secondary and tertiary literature was also reviewed, including manufacturers' product datasheets on individual therapies. Search terms and main heading descriptors (Medical Subject Headings) 'carbapenemase producing Enterobacterales', 'antimicrobial therapy', 'antibiotic treatment' and 'treatment' were included. Search criteria were broad and intended to capture all CPE treatment options. Prospective and retrospective articles in English that reported original research on clinical patients or patient outcomes of CPE infections in acute care were included. Studies focusing predominantly on non-Enterobacterales pathogens were excluded. All articles were screened by one author (S.H.) and screened independently by two authors (S.H. plus a second author) for each subject area. A flow chart of the systematic review process is given in Figure S2 (available as Supplementary data at *JAC-AMR* Online).

All recommendations and dosing advice were based on expert opinion and agreed upon within the working group. All three senior authors (S.H., M.G. and J.S.) had to agree unanimously for a recommendation to be included.

3. Recommendations for management of CPE infections

The content of the manuscript has been derived from current best peer-reviewed publications and expert opinion and support existing BSAC/HIS/BIA guidance on treatment of infections caused by MDR Gram-negative bacteria. General recommendations for prescribers are outlined in Table 2. Specific antimicrobial dosing advice is outlined in the drug monographs (Appendix S1).

3.1. General management of CPE infection

For the treatment of CPE infection, the following good practice principles of infection management are advised.

(i) Antimicrobial therapy should be discussed with the local infection specialist team (including microbiology and/or infectious diseases clinicians and the antimicrobial or anti-infective pharmacists) to agree a safe and effective tailored treatment option for the patient.
(ii) Antimicrobial therapy should be initiated and administered promptly and without any unnecessary delay in patients with systemic evidence of CPE infection.
(iii) Antimicrobial therapy should be guided by recent or previous culture and susceptibility results. These may vary between strains, including samples obtained from a single patient during a single infection.
(iv) Antimicrobial therapies should only be started in response to symptoms of infection. Colonization with CPE does not always correlate with active or invasive infection. Screening

Table 2. Summary of recommendations for prescribers managing patients with CPE infection

Topic	Recommendation	Strength
Treatment of invasive CPE infections	For non-severe presentation of urinary source infection, including BSI secondary to UTI, consider use of monotherapy with a susceptible therapy with demonstrated efficacy for UTI/BSI (e.g. β-lactam/β-lactamase inhibitor). For severe infection, including all non-UTIs, consider use a minimum of two antibiotics to which the organism is susceptible. There is insufficient evidence to conclude which combinations are most effective. For UTIs with no systemic involvement, consider treatment with a single agent that is known to concentrate in the urine and to which the isolate is susceptible.	expert opinion
Dosing of antimicrobials	For IV β-lactams requiring multiple daily dosing, consider administering as an extended or continuous infusion to optimize $T_{>MIC}$ if: (i) the MIC is high (intermediate or low-level resistance); or (ii) for critical care patients with augmented renal function; or (iii) infections in deep tissue, e.g. respiratory tract infection.	expert opinion
Antimicrobial-specific advice in CPE infection		
aminoglycosides	Where phenotypic susceptibilities are available, aminoglycosides can be used as part of combination therapy to treat CPE infections. Aminoglycoside antibiotics should be considered for treatment of UTIs where susceptibilities allow.	expert opinion
β-lactam/β-lactamase inhibitor therapy	Novel β-lactam/β-lactamase inhibitor combination therapies may be considered for monotherapy or in combination therapy for treatment of invasive CPE infections where susceptibilities known. Meropenem/vaborbactam is recommended for treatment of invasive infections caused by KPC-producing resistant Enterobacterales. Ceftazidime/avibactam is recommended for treatment of invasive infections caused by KPC- and OXA-48-producing resistant Enterobacterales. Isolates with KPC-3 resistance profile should be treated with caution with ceftazidime/avibactam, as outlined by BSAC Expert Committee. Aztreonam in combination with avibactam (as ceftazidime/avibactam or aztreonam/avibactam) may be considered as salvage treatment option for MBL-producing Enterobacterales where other licensed therapies are unavailable.	expert opinion
carbapenems	Carbapenems may be used in combination with other agents, including a second carbapenem. Outcomes are likely to be improved if the organism appears susceptible on *in vitro* testing (meropenem MIC $\leq$8 mg/L) or is close to the breakpoint. High-dose meropenem and/or extended administration therapy should be considered for organisms with an MIC of 4–8 mg/L. There are insufficient data available to recommend the routine use of dual carbapenem therapy to overcome CPE resistance mechanisms.	expert opinion
cefiderocol	Cefiderocol-based therapy may be considered for combination therapy for invasive CPE infections including Class B Ambler-expressing pathogens (NDM, IMP and VIM resistance mechanisms).	expert opinion
ceftazidime	Ceftazidime, and other third/fourth-generation cephalosporins, can be considered for the treatment of OXA-48-producing CPE organisms where co-produced ESBLs or AmpC enzymes are absent and where phenotypic susceptibilities are available. Ceftazidime is the preferred third-generation cephalosporin as lower MIC values are generally found for Enterobacterales.	expert opinion
ciprofloxacin	Ciprofloxacin may be considered as part of combination therapy where isolates have demonstrated *in vitro* susceptibility.	expert opinion
colistin	Colistin is not recommended as monotherapy for systemic infections. Colistin therapeutic drug monitoring is recommended for all patients treated with parenteral treatment to minimize risk of toxicity.	expert opinion
co-trimoxazole	When susceptibilities are known, co-trimoxazole may have a limited role in the treatment of less severe CPE infections, especially UTIs.	

Continued

Table 2. *Continued*

Topic	Recommendation	Strength
fosfomycin	Fosfomycin IV is recommended to be used in combination with other active agents when used for systemic therapy, due to its vulnerability to acquired resistance.	expert opinion
plazomicin	Plazomicin IV may be considered as part of combination therapy where isolates have demonstrated *in vitro* susceptibility. Therapeutic drug monitoring is advised in patients with concurrent renal dysfunction or requiring prolonged therapy (>72 h) to exclude accumulation and toxicity.	expert opinion
rifampicin	The use of rifampicin for non-*Acinetobacter* spp. is not recommended due to the lack of *in vivo* study data supporting its use.	expert opinion
tigecycline	Tigecycline may be considered as part of combination therapy where isolates have demonstrated *in vitro* susceptibility. Tigecycline is not recommended for UTIs due to inadequate urinary tigecycline concentrations required for therapeutic activity. A high-dose tigecycline regimen (100 mg IV q12h) should be considered when treating pathogens with high MIC (0.5–2 mg/L) and/or in the treatment of respiratory infections.	expert opinion
temocillin	Temocillin may be considered in combination with other active agents for KPC-producing organisms where susceptibilities are known. High-dose temocillin (6 g/day) is recommended for the treatment of invasive KPC infections of non-urinary source. The use of monotherapy temocillin (4 g/day) for the treatment of uncomplicated UTI with KPC organisms should be considered where susceptibilities are known.	expert opinion

may identify colonized patients though rectal swab or stool sample to inform local infection prevention and control practice.

(v) Ongoing antimicrobial therapy should be reviewed daily to confirm effectiveness. Regular review of treatment is advised to assess the need for continued treatment and review the potential for de-escalation or IV-to-oral switch where appropriate.

(vi) Antimicrobial dosing should be tailored to the individual patient and adapted to current renal and hepatic function, body weight and suspected site of infection. Monitoring for potential toxicities and adverse effects is recommended for all patients on systemic antimicrobial therapy.

All antimicrobial treatment recommendations within this guidance are based on the assumption of confirmed susceptible isolates.

3.2. Use of combination versus monotherapy antimicrobials for CPE infections

The use of combination therapy, defined as treatment with two or more antimicrobials active against the CPE, has been much debated over the last decade. (Note: β-lactam/β-lactamase inhibitor therapies are described as a single therapy in this analysis.) The main argument made for combination therapy is the potential for synergy or additive effect of combination therapy to prevent selection of resistant pathogens and/or improve treatment outcomes.

Prior to the introduction of the novel β-lactam/β-lactamase inhibitor therapies to clinical practice, analysis of invasive KPC infections ($n = 105$) identified that significantly more treatment failures were seen with monotherapy (49% versus 25%; $P = 0.01$) from non-urinary sources.[3] Also, higher rates of treatment failure with monotherapy for respiratory tract infections were observed (67% versus 29%; $P = 0.03$). A 2014 systematic review of antibiotic treatment of infections caused by CPE[4] found that the majority of studies did not show statistically significant differences in mortality or treatment failures between combination therapy and monotherapy. However, three studies reviewed, including a total of 194 patients with bacteraemia, demonstrated a significantly lower mortality with combination therapy, colistin/polymyxin B or tigecycline combined with a carbapenem. More recent (2018) analysis of colistin monotherapy versus colistin plus meropenem failed to demonstrate a survival benefit with combination therapy.[5] This work was done predominantly with *Acinetobacter baumannii*. In the subgroup of CPE pathogens there was a non-significant trend to favour combination therapy; the subgroup was underpowered to demonstrate any clear benefit.

Some interpretation of these works is required. Firstly, the use of tigecycline as monotherapy for any bloodstream infection (BSI) is not routinely advised due to its inadequate serum levels. Tigecycline should only be used for BSI in combination with another agent; the addition of an aminoglycoside is commonly used in practice. Secondly, many of the pathogens reported in these retrospective studies were non-Enterobacterales, notably *A. baumannii*. The resistance mechanisms may differ with these organisms and the clinical presentation and source of infection may differ from Enterobacterales. And finally, the time to effective therapy differs greatly in these retrospective studies but remains possibly the greatest predictor of treatment outcomes. Early targeted therapy is imperative for the optimum management of these patients. Many of the retrospective studies analysed

randomized patients late in therapy or after 'failed' initial treatments; these may impair treatment outcomes and make direct study comparison challenging.

There are emerging data to identify the patient groups where monotherapy may be considered. The INCREMENT study highlights that combination therapy only results in improved survival among patients with a high probability of death as defined by their INCREMENT-CPE mortality score (an adapted Pitt bacteraemia score) (see Figure S1).[6] Patients with urinary or biliary tree infections and reduced acuity of infection on presentation may be safely trialled on single directed therapy (if available).

The new β-lactamase inhibitor therapies (combinations of avibactam, vaborbactam or relebactam with a Gram-negative agent) with activity against CPE are associated with non-inferior treatment outcomes to standard of care. The randomized, prospective, open-label, comparative study that compared meropenem/vaborbactam with best available antibiotic treatment for complex CPE infections reported non-inferior clinical cure and 28 day mortality rates.[7] Observational study of ceftazidime/avibactam for CPE compared with colistin is clouded by the use of additional anti-CPE therapies, therefore the suitability of monotherapy is assumed but cannot be safely confirmed. The RESTORE-IMI 1 publication reports non-inferior clinical outcomes with imipenem/cilastatin/relebactam versus imipenem/cilastatin plus colistin but is predominantly tested against carbapenem-resistant *Pseudomonas*. Whilst excellent clinical cure rates and trend to improved mortality are demonstrated, the applicability of these imipenem/cilastatin/relebactam results to non-*Pseudomonas* organisms remains unclear.

There are currently no data to inform whether combination therapy prevents or promotes emergence of resistance in this setting.

Recommendations

- For non-severe presentation of urinary source infection, including BSI secondary to urinary tract infections (UTIs), consider use of monotherapy with a susceptible therapy with demonstrated efficacy for UTI/BSI (e.g. β-lactam/β-lactamase inhibitor).
- For severe infection, including respiratory tract infections, consider use of a minimum of two antibiotics to which the organism is susceptible. There is insufficient evidence to conclude which combinations are most effective.

3.3. Treatment of CPE UTIs

For renally excreted antimicrobials, accumulation of therapeutic drug in the urinary tract may achieve the desired therapeutic concentrations to overcome low-level resistance. The high therapeutic concentration within the urinary tract may therefore be sufficient for monotherapy treatment in uncomplicated urinary infections. The review by Lee and Burgess[3] found an 81% success rate (9/11) in patients treated for UTIs, with 8 of these cases treated with monotherapy.

Aminoglycoside therapy resulted in a significantly higher rate of microbiological clearance of carbapenem-resistant *Klebsiella pneumoniae* in the urine compared with polymyxin B or tigecycline in one study.[8] There was no difference in failure rates between aminoglycoside monotherapy and combination therapy (0/6 and 4/24, respectively; $P = 0.6$) in the study by Lee and Burgess[3] mentioned above. Patients successfully treated with monotherapy included those with BSIs ($n = 3$) and UTIs ($n = 2$).

Enterobacterales with carbapenemase resistance mechanisms may retain phenotypic susceptibility to co-trimoxazole. When susceptibilities are known, co-trimoxazole may have a limited role in the treatment of less severe CPE infections, especially UTIs. Surveillance data from the CRACKLE registry demonstrates susceptibility rates of less than 30% for tested CPE isolates.[9,10]

Tigecycline has inadequate therapeutic levels in the urinary system for effective therapeutic use. Whilst some case studies have reported success with tigecycline in UTI, there is insufficient evidence to recommend the use of tigecycline for the management of UTI.

Recommendations

- For UTIs with no systemic involvement, consider treating with a single agent that is known to concentrate in the urine and to which the isolate is susceptible.
- Aminoglycoside antibiotics should be considered for treatment of UTIs where susceptibilities allow.
- Tigecycline is not recommended for treatment of UTIs due to suboptimal drug levels within the urinary system.

3.4. Optimizing administration of antimicrobials

Pharmacokinetic/pharmacodynamic principles should be used to optimize (improve efficacy and minimize toxicity) antimicrobial utilization when possible. This is due to increasing antimicrobial resistance and limited availability of novel antimicrobial agents. Consider administering antimicrobials with short half-lives that exhibit time-dependent antimicrobial activity (e.g. β-lactam agents) by prolonged infusion as this dosing strategy results in an increased likelihood of optimal antimicrobial activity. Extended infusions, defined as a drug administered over 3–4 h, or continuous infusions, defined as a drug administered over 24 h, of β-lactams will increase the time above the MIC ($T_{>MIC}$).[11] The true benefit of extended infusion/continuous infusion administration of β-lactams is expected with high-MIC pathogens [intermediate (or susceptible, increased exposure) or low-level resistance]. Patients infected with low-MIC pathogens and/or not critically unwell are not likely to benefit from β-lactams being administered by extended infusion/continuous infusion. Infection in difficult-to-penetrate tissue (e.g. respiratory) may benefit more from administration by extended infusion/continuous infusion.[12] The BLING III study is a prospective, randomized controlled trial that aims to address this hypothesis in critical care patients requiring anti-pseudomonal β-lactams.[13]

Recommendations

- For IV β-lactams requiring multiple daily dosing, consider administering as an extended or continuous infusion to optimize $T_{>MIC}$ if:
  (i) the MIC is high (intermediate or low-level resistance); or
  (ii) for critical care patients with augmented renal function; or
  (iii) infections in deep tissue, e.g. respiratory tract infection.

3.5. Role of carbapenems in CPE infections

Several studies have demonstrated that combination therapy involving a carbapenem is effective. In a review of 105 cases of KPC infection, treatment failure was higher with carbapenem monotherapy compared with carbapenem-based combination therapy (60% versus 26%).[3] In an Italian multicentre study of 447 patients with KPC-producing *K. pneumoniae*, combination therapy with tigecycline, colistin and meropenem (2 g meropenem q8h infused over an extended period of 3 h) was associated with lower mortality (OR 0.52; 95% CI 0.35–0.77).[14] Combinations that included meropenem were associated with significantly higher survival rates when the KPC-producing *K. pneumoniae* isolate had a meropenem MIC of ≤8 mg/L. How this translates to other non-KPC-producing CPE resistance mechanisms is less clear.

There have been some published data reviewing the use of dual carbapenems for CPE infections. Ertapenem, usually in combination with meropenem, has been used to treat infections with KPC-producing pathogens. Ertapenem exploits its higher carbapenemase affinity to act as a suicide substrate thus leading meropenem to exert its antimicrobial activity. The clinical efficacy of this dual therapy is unclear and with the recent introduction of novel β-lactamase inhibitors, the clinical need for it is also unclear.[15]

The role of carbapenem-based treatment for CPE infection is less clear since the introduction of novel β-lactamase inhibitors with CPE activity. Whilst no direct head-to-head studies exist, the combination of a β-lactam with a new β-lactamase inhibitor, where susceptibilities are known, are expected to be more efficacious (e.g. meropenem/vaborbactam for KPC CPE and ceftazidime/avibactam for OXA-48 CPE infections) and should be used in preference to carbapenems.

Recommendations

- Carbapenems should not be used in preference to novel β-lactam/β-lactamase inhibitors for treatment of invasive CPE infections.
- Carbapenems may be used in combination with other agents, including a second carbapenem. Outcomes are likely to be improved if the organism appears susceptible on *in vitro* testing (meropenem MIC ≤8 mg/L) or is close to the breakpoint. High-dose meropenem and/or extended administration therapy should be considered for organisms with an MIC of 4–8 mg/L.[14,16]
- There are insufficient data available to recommend the routine use of dual carbapenem therapy to overcome CPE resistance mechanisms.

3.6. Role of colistin in CPE infections

In a review of 105 cases of KPC infection, polymyxin monotherapy was associated with higher rates of treatment failure compared with polymyxin-based combination therapy [24/49 (49%) versus 14/56 (25%); $P = 0.01$).[3] That review did not give details of the doses of polymyxin used. More recent analysis of colistin monotherapy (versus colistin plus meropenem) failed to demonstrate a survival benefit with combination therapy. This was predominantly infections with *A. baumannii* as the pathogen and in the subgroup of Enterobacterales pathogens there was a non-significant trend to favour combination therapy. However this subgroup was underpowered to demonstrate non-inferiority in Enterobacterales therefore the previous recommendations remain.[5]

Recommendations

- Where colistin is prescribed for the treatment of an invasive CPE infection, it should be used in combination with one or more other agents.
- Colistin therapeutic drug monitoring is recommended for all patients treated with parenteral treatment to minimize risk of toxicity.

3.7. Role of fosfomycin in CPE infections

Within the UK, the manufacturers advise that fosfomycin should be used only when conventional therapy is considered inappropriate and in combination for severe invasive infections. It has been demonstrated that resistance to IV fosfomycin can develop rapidly when it is used for monotherapy.[17] An *in vitro* study investigating the synergistic effect and impact on development of resistance of fosfomycin with colistin, meropenem or gentamicin found that all combinations showed improved bactericidal activity compared with fosfomycin alone and prevented the development of resistance in the majority of fosfomycin-susceptible isolates.[18] In a small case series of critical care patients with carbapenem-resistant *K. pneumoniae*, IV fosfomycin (4 g every 6 h, adjusted for renal impairment) was administered as combination therapy with colistin ($n = 6$), gentamicin ($n = 3$) and piperacillin/tazobactam ($n = 1$).[8] All-cause mortality was 18.1% but no patient developed a relapse of infection.

Recommendations

- Fosfomycin is recommended to be used in combination with other active agents when used for systemic therapy, due to its vulnerability to acquired resistance.

3.8. Role of temocillin in CPE infections

Temocillin is not active against most CPE but remains effective against KPC-producing Enterobacterales in *in vitro* studies. Retrospective analysis of KPC bacteraemia cases (with MIC ≤8 mg/L) treated with temocillin showed acceptable clinical outcomes.[19] Temocillin was predominantly used in combination therapy (with amikacin, tigecycline or fosfomycin). Monotherapy with temocillin has been trialled for urinary-sourced BSI with KPC identified (S. Hughes, Chelsea & Westminster NHS Trust, unpublished data).

New EUCAST breakpoints were published in 2020; the lower breakpoint for susceptibility has been reduced to 0.001 mg/L to accommodate WT species. All WT species will be covered in the intermediate or 'susceptible, increased exposure' group (MIC <16 mg/L) with high-exposure temocillin (6 g/day).[20] High urinary concentrations may permit the continued use of temocillin 2 g q12h for UTIs but higher doses (2 g q8h) are likely to be required for non-urinary infections.

Recommendations

- Temocillin may be considered in combination with other active agents for KPC organisms where susceptibilities are known.
- The highest licensed dose of temocillin (6 g/day) is recommended when treating invasive CPE infections of non-urinary source.
- The use of monotherapy temocillin (4 g/day) for the treatment of uncomplicated UTI with KPC-producing organisms should be considered where susceptibilities are known.

3.9. Role of tigecycline in CPE infections

Tigecycline is licensed for use in complicated skin and soft tissue infections (cSSTIs) and complicated intra-abdominal infections (cIAIs). Tigecycline's efficacy in respiratory, urinary and CNS infections is limited and the FDA highlights concerns about increased mortality in off-licensed indications, particularly hospital-acquired and ventilator-associated pneumonia.[21] The reasons for these findings are unknown, but poorer efficacy and safety than the study comparators cannot be ruled out.

The EMA Committee for Medicinal Products for Human Use (CHMP) has recommended that tigecycline should only be used within its licensed indications as a pooled analysis of clinical studies showed an increased mortality associated with tigecycline versus comparator agents. A similar communication from the FDA noted that the greatest increase in risk of mortality in the tigecycline arm was seen in ventilator-associated pneumonia (19.1% versus 12.3%); this may be related to the lack of pseudomonal coverage with tigecycline-based therapy.[22]

Combination therapy is advised for tigecycline-based therapies for invasive CPE infection; the bacteriostatic nature of tigecycline plus its high volume of distribution may result in suboptimal bacteraemia clearance when used alone. High-dose therapy (200 mg loading dose and 100 mg q12h) is often advised for respiratory infection or for high-MIC pathogens. A meta-analysis by Wang *et al.*[23] (2017) identified monotherapy to be associated with increased mortality against combination therapy [OR of 2.73 (95% CI 1.53–4.87) in six studies with a total of 250 patients]. This was replicated by the work of Ni *et al.*[24] (2016), which also identified superior ICU mortality outcomes for high-dose tigecycline regimens when compared with standard dose schedules [OR 12.48 (95% CI 2.06–75.43; P = 0.006)]. In addition, the authors found triple therapy with tigecycline-based therapy may be superior to that of dual therapy, with lower mortality rates identified on meta-analysis [OR 2.18 (95% CI 1.03–4.63; $P = 0.04$)].

The new fully synthetic tetracycline, eravacycline, may play a role in the treatment of MDR infections including CPE. Eravacycline has similar activity to tigecycline against Enterobacterales but with lower MICs (2-fold lower on average) and has a reported lower gastrointestinal intolerance profile. Eravacycline is unaffected by *tet*(M), *tet*(K) and *tet*(B), but MICs are elevated in the presence of *tet*(A) and *tet*(X). *In vitro* data show promise for CPE infections but a lack of clinical outcomes data precludes current recommendation of eravacycline for treatment of CPE invasive infections where other established therapies are available.

Recommendations

- Where tigecycline is prescribed for the treatment of an invasive CPE infection, it should be used in combination with one or more other agents with anti-CPE activity.
- A high-dose tigecycline regimen (100 mg IV q12h) should be considered when treating pathogens with high MIC (0.5–2 mg/L) and/or in the treatment of respiratory infections.

3.10. Novel β-lactamase inhibitors in CPE infection

The majority of comparison studies of combination and monotherapy for CPE infections occurred before the introduction of novel β-lactam/β-lactamase inhibitor therapies to practice. These new therapies provide a valuable addition to the armamentarium of anti-CPE therapies.

3.10.1. Ceftazidime/avibactam

Ceftazidime/avibactam therapy for CPE infection has been well described in clinical practice but data are limited to non-randomized controlled trials and registry-based analysis. These descriptive analyses show promise for ceftazidime/avibactam use in invasive CPE infections, particularly those with OXA-48-mediated resistant pathogens. The BSAC/HIS/BIA Working Party on Gram-negative resistant pathogens advises some caution with ceftazidime/avibactam use in KPC-producing resistant organisms due to concerns about reduced clinical efficacy and selection of resistant organisms (KPC-3).[2]

In vitro activity of ceftazidime/avibactam is well reported but clinical data on the efficacy in severe infections caused by CPE are still lacking. As of April 2020, only one prospective, observational study had been published. Through the CRACKLE observational study, a total of 38 and 99 patients treated for CPE infection with ceftazidime/avibactam and colistin were analysed.[25] Many patients had confirmed bacteraemia (46%) or respiratory infections (22%) and combination therapy was more commonly seen with colistin-based therapy (63% versus 94%). Ninety-seven percent of isolates were KPC-producing *K. pneumoniae*. In-hospital mortality at 30 days was 8% (3/38) and 33% (33/99) in the ceftazidime/avibactam and colistin groups, respectively.[25]

In retrospective case studies, ceftazidime/avibactam has been reported with mixed results. Results from haematology patients with invasive KPC infection showed similar outcomes with monotherapy and combination therapy [33% (9/27) and 30% (10/33), respectively] and similar outcomes to case series of salvage therapy ceftazidime/avibactam in patients treated with a compassionate use programme.[26,27] The retrospective case series by Shields *et al.*[28] demonstrated clinical success, defined as no microbiological growth of CPE following ≥7 days of ceftazidime/avibactam, for 59% (22/37) and 30 day survival for 76% (28/37). No difference was noted in clinical outcomes of monotherapy and combination therapy with ceftazidime/avibactam [58% (15/26) and 64% (7/11), respectively]. Development of ceftazidime/avibactam-resistant isolates was identified in 30% (3/10) of patients without microbiological cure, highlighting concerns about the development of resistance, particularly for KPC-3 isolates. No prospective randomized controlled studies are available to date to demonstrate the efficacy of ceftazidime/avibactam against best available therapy (BAT).

The benefit of avibactam in combination with ceftazidime for OXA-48-producing CPE with no co-located ESBL or AmpC resistance is unclear. Ceftazidime monotherapy may be considered if other resistant mechanisms are not found, as outlined by the BSAC/HIS/BIA Working Party guidance on treatment of infections caused by MDR Gram-negative bacteria.[2]

3.10.2. Meropenem/vaborbactam

A randomized, prospective, open-label, comparative study (TANGO-II) compared meropenem/vaborbactam (2 g/2 g IV over 3 h, q8h) with best available antibiotic treatment (polymyxin, carbapenem, aminoglycoside or tigecycline alone or in combination; or ceftazidime/avibactam alone) in adults with complex UTI (cUTI), cIAI, hospital-acquired pneumonia, ventilator-associated pneumonia or bacteraemia suspected or documented to be caused by carbapenemase-resistant Enterobacterales (CRE).[29] Due to small patient numbers (meropenem/vaborbactam arm, $n = 32$; best available antibiotic arm, $n = 15$) this trial was a descriptive study following on from TANGO-I and although no formal power or sample size calculations were performed, a modified ITT (mITT) analysis was undertaken.[30] No significant difference between meropenem/vaborbactam and best available antibiotic treatment was found in cure rate at the end of treatment (mITT 66% versus 33%; $P = 0.04$) and all-cause mortality at 28 days (mITT 15.6% versus 33.3%, 95% CI of difference −44.7% to 9.3%; $P = 0.20$). Higher rates of nephrotoxicity were noted in the comparator treatment arm where the use of well-known nephrotoxic agents such as colistin, polymyxin and/or aminoglycosides was prevalent (10 of 14 patients).

More recently, in a real-world, retrospective, non-comparative, multicentre observational study of meropenem/vaborbactam in 40 patients with CRE infections in the USA,[7] clinical success was achieved in 70% of patients. Failures were associated with high APACHE-II score, inactive empirical therapy (before meropenem/vaborbactam started) and single-agent empirical therapy. It is possible that respiratory infections and SSTIs were also more prone to treatment failure and recurrence.

Whilst promising trends to improvement with meropenem/vaborbactam are reported, the design of these studies means that firm conclusions cannot be made and the evidence supporting the use of meropenem/vaborbactam is still limited.[7,29–31]

3.10.3. Imipenem/cilastatin/relebactam (IMI/REL)

This triple combination therapy combines the well-established imipenem/cilastatin combination with the novel β-lactamase inhibitor, relebactam. Relebactam provides stability against some class A carbapenemases (e.g. KPC-2) thus protecting imipenem's activity.[32,33] Cilastatin is an enzyme with no antibacterial properties, which blocks renal metabolism of imipenem and thus maintains adequate urinary imipenem levels for therapeutic effect. This combination product was approved by the FDA and EMA in 2019 for treatment of cUTI and cIAI where limited alternative treatment alternatives exist. Whilst relebactam shares a similar structure to avibactam, the IMI/REL combination provides no additional OXA-48, MBL or GES activity to carbapenems alone. Relebactam provides potent inhibition of KPC enzymes *in vitro*. At present, it is unclear whether relebactam provides additional activity for KPC-3 enzymes resistant to avibactam.

The Phase III study compared the use of IMI/REL ($n = 31$) versus imipenem/cilastatin plus colistin ($n = 16$) for carbapenem-resistant pathogens (all isolates were IMI/REL- or colistin-susceptible *in vitro*).[32] Patients were treated for hospital-acquired pneumonia/ventilator-associated pneumonia, cUTI or cIAI for 5–21 days and the primary outcome, study-defined clinical cure, was similar in both groups (71% and 70% in IMI/REL and colistin groups, respectively). Mortality (28 day) and treatment-related adverse events were numerically lower in the IMI/REL group (10% versus 30% and 16% versus 31%, respectively). Treatment-emergent nephrotoxicity was lower with IMI/REL compared with the colistin group (10% versus 56%, respectively; $P = 0.002$). However, most infections were non-CPE related (77% infections due to *Pseudomonas*) and drawing conclusions on IMI/REL activity for treatment of Enterobacterales is challenging.

3.10.4. Aztreonam in combination with avibactam

A combination product is not currently on the market and is awaiting Phase III clinical trial completion. In the absence of a dedicated combination product, the off-label use of aztreonam prescribed in combination with ceftazidime/avibactam has been used to treat MBL infections. The rationale for this regimen is to combine ceftazidime/avibactam to stabilize aztreonam's activity against class B MBLs and particularly against any co-located ESBL/AmpC resistance mechanisms that may inhibit aztreonam alone. Whilst promising *in vitro* data exist for this combination, robust evidence-based practice is severely limited.[34] In patients with MBL infections with limited treatment options available, this combination therapy may be considered.

3.10.5. Ceftolozane/tazobactam

The ceftolozane/tazobactam combination provides no additional activity for CPE organisms. It may have a role in non-carbapenemase-producing organisms where other carbapenem resistance mechanisms are present (e.g. porin loss in *Pseudomonas* spp.).[2] This is outside the scope of this review and is not discussed in the monographs.

Recommendations

- Novel β-lactam/β-lactamase inhibitor combination therapies may be considered for monotherapy or in combination therapy for treatment of invasive CPE infections.
- Meropenem/vaborbactam is recommended for treatment of invasive infections caused by KPC-producing resistant Enterobacterales.
- Ceftazidime/avibactam is recommended for treatment of invasive infections caused by KPC- and OXA-48-producing resistant Enterobacterales. Isolates with a KPC-3 resistance profile should be treated with caution with ceftazidime/avibactam, as outlined by the BSAC Expert Committee.
- Aztreonam in combination with avibactam may be considered as a salvage treatment option for MBL-producing Enterobacterales where other licensed therapies are unavailable.

3.11. Novel siderophore cephalosporin therapy in CPE infection

The unpublished CREDIBLE-CR study compares use of cefiderocol largely as monotherapy (80%) in a randomized, open-label trial ($n = 118$) versus standard-of-care treatment for carbapenem-resistant Gram-negative bacterial BSI, hospital-acquired pneumonia and cUTI infections (data presented to FDA but not published in a peer-reviewed journal at time of review; M. Bassetti, M. Ariyasu, B. Binkowitz, T. D. Nagata, R. M. Echols, Y. Matsunaga, K. Toyoizumi, Y. Doi, unpublished data). A higher all-cause mortality rate was observed with cefiderocol treatment (versus BAT). The 28 day all-cause mortality was higher in patients treated with cefiderocol than in patients treated with BAT [25/101 (24.8%) versus 9/49 (18.4%), treatment difference 6.4%, 95% CI −8.6 to 19.2]. All-cause mortality remained higher in patients treated with cefiderocol than in patients treated with BAT through to Day 49 [34/101 (33.7%) versus 10/49 (20.4%), treatment difference 13.3%, 95% CI −2.5 to 26.9]. A high prevalence of *A. baumannii* infections (55%) was identified through this study and the applicability of these results to CPE remains uncertain. The EMA and FDA advise that cefiderocol should only be used when alternative therapies are not available.[35,36]

In a series of multinational surveillance studies, cefiderocol inhibited 97% of all carbapenem-non-susceptible Enterobacteriaceae, including 91.1% of ceftazidime/avibactam-resistant strains, at a concentration of $\leq$4 mg/L.[37] This novel therapy undoubtably has a role to play in the management of complex CPE infections, particularly those with difficult-to-treat MBLs. However, identifying optimum combination therapy remains a challenge.

Recommendations

- Novel siderophore cephalosporin-based therapy may be considered for combination therapy for invasive CPE infections including Ambler class B-expressing pathogens (NDM, IMP and VIM resistance mechanisms).

3.12. Aminoglycosides

3.12.1. Amikacin and gentamicin

Resistance to aminoglycosides varies depending on the resistance mechanism present. Gentamicin resistance mechanisms are frequently encountered with metallo-enzyme producers (>60%) and non-metallo-enzyme producers (~40%). Increased activity is seen with amikacin for CPE organisms, as reported in the ESPAUR 2017 report.[38] 16S rRNA methyltransferase enzymes (16S RMTases) are often co-located with CPE, notably NDM carbapenemase, and confer high-level resistance to all currently licensed aminoglycosides.

Where phenotypic susceptibilities exist, aminoglycosides can be used to treat CPE infections. The majority of case reports advise an aminoglycoside (often amikacin) in combination with another active antimicrobial for invasive CPE infection. The site of infection is likely to be the main determinant of suitability of an aminoglycoside-based treatment; tissue penetration in the lung, brain and bone and joint may be suboptimal for maximum bactericidal effects of aminoglycoside therapy.

3.12.2. Plazomicin

Plazomicin is a semi-synthetic aminoglycoside derived from sisomicin. Plazomicin evades almost all aminoglycoside-modifying enzymes but is inactive if 16S RMTases are present.

The CARE study (published only in correspondence at the time of review) directly compares plazomicin IV to colistin IV (both in combination with either tigecycline or meropenem) in patients with BSI or hospital-acquired or ventilator-associated bacterial pneumonia caused by suspected or confirmed CRE.[39] This multicentre, randomized, open-label trial reports a numerical lower mortality at follow-up and superior clinical cure with plazomicin-based therapy ($n = 18$ for plazomicin). Further studies are required to confirm the benefits of plazomicin for invasive infections.

Recommendations

- Where phenotypic susceptibilities are available, aminoglycosides (including plazomicin) can be used as part of combination therapy to treat CPE infections.
- Aminoglycoside antibiotics should be considered for treatment of UTIs where susceptibilities allow.

4. Drug dosing information

Optimizing dosing strategies to give the highest drug exposure according to pharmacokinetic and pharmacodynamic parameters is recommended. EUCAST breakpoint data and dosing strategies are adopted throughout these recommendations where available.

The antimicrobial monographs (see Appendix S1) provide information on how optimal dosing can be achieved. Please note that some recommendations reflect dosing strategies not covered by the product licence. For details of side effects and interactions please refer to the relevant Summary of Product Characteristics and the current BNF.

5. Limitations

Due to the lack of randomized controlled trials the recommendations in this guide are based on limited or low-quality evidence. However, it is intended as a pragmatic practical guide based on the best information available.

Meta-analyses show there is lack of consistency in outcome data. When well-conducted meta-analyses/review papers collating data on outcomes from individual studies were available these were used in preference.

Due to the heterogeneity and low patient numbers in the studies it is not possible to compare the outcomes of different combination therapies.

The majority of the studies report on KPC-producing *K. pneumoniae* as this is the most common CPE mechanism found within the USA where the majority of the literature is reported.

6. Conclusions

The management of infections associated with CPE remains a challenge for responsible clinicians and infection teams. Early identification and susceptibility testing are essential for the prompt initiation of effective antimicrobial treatment. As outlined by the

BSAC/HIS/BIA Working Party on Gram-negative resistant pathogens, the selection of antimicrobial treatment based on susceptibility testing is the optimum strategy for treating infections caused by CPE infection. Due to the array of resistance mechanisms and the prevalence of multiple classes within the UK, no universal treatment option is available and bespoke antimicrobial therapy is required for each infected patient. This guidance provides a summary of the most commonly used therapies for CPE infections and provides expert advice on options for optimizing therapy to maximize efficacy whilst minimizing toxicity.

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Author contributions

S.H., J.S. and M.G. designed the study methodology. S.H. and J.S. collated the available published literature. S.H. drafted the initial manuscript with all authors contributing significantly to revising it for submission. All authors (S.H., K.H., R.H., M.G. and J.S.) agreed on the final version for submission to the journal.

Supplementary data

Appendix S1 and Figures S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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