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Proposed changes to management of lower respiratory tract infections in response to the *Clostridium difficile* epidemic

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Clostridium difficile infection (CDI) remains a major healthcare problem associated with antibiotic use in hospitals. Recent years have seen a dramatic increase in the incidence of CDI in the UK and internationally. Lower respiratory tract infections (LRTIs) are the leading indication for antibiotic prescription in hospitals and are therefore a critical battleground in the fight against inappropriate antibiotic use and healthcare-associated infections. This article reviews the evidence for interventions to reduce CDI in hospitalized patients with LRTIs. Reducing prescriptions of cephalosporins and fluoroquinolones in favour of penicillin-based regimens and increased use of tetracyclines have been proposed. Expanding outpatient management of LRTIs and reducing length of hospital stay will limit patient exposure to the healthcare environment in which *C. difficile* is most easily acquired. Intravenous (iv) broad-spectrum antibiotics are often prescribed when narrower spectrum, oral antimicrobials would be equally effective and, in a proportion of patients, antibiotic therapy is used unnecessarily. Shorter antibiotic regimes may be as effective as prolonged therapy and reduce antibiotic-related complications. Early switch from iv to oral therapy allows simpler antibiotic regimens and facilitates early discharge from hospital. Simple improvements in the management of LRTIs have the potential to reduce the incidence of healthcare-associated infections.

Keywords: pneumonia, antibiotics, severity assessment, resistance, guidelines

Introduction

The 2009 update of the British Thoracic Society (BTS) community-acquired pneumonia (CAP) guidelines has recently been published.[1] Publication takes place against a backdrop of an unprecedented epidemic of hospital-acquired infections.[2] The increasing incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infections (CDIs) has attracted the concern of physicians, politicians, journalists and the public.[2]

The inappropriate, excessive or unnecessary use of antibiotic therapy is among the leading causes of the spread of resistant, hospital-acquired organisms.[3] If we are to target inappropriate usage of antibiotics, focusing on their usage in respiratory tract infections (RTIs) is a logical starting point as they are the most common infectious diseases requiring hospitalization in Western countries.[4,5] Many countries have seen an increase in broad-spectrum antibiotic use in CAP,[6] including the UK.[7] Broad-spectrum antibiotics are strongly associated with CDI, and as such the *C. difficile* epidemic cannot be addressed without addressing antibiotic prescribing for RTIs.

In this review we discuss the role of antibiotic prescribing and management practices in RTIs that may have contributed to the rise of *C. difficile*, and discuss proposed changes to management that aim to control the epidemic.

Literature sources

The current review was based on a search of PubMed for articles using major MeSH terms '*Clostridium difficile*', 'pneumonia' and 'respiratory tract infection' between 1970 and September 2009. Separate searches of PubMed were performed using the above search terms in combination with text terms 'cephalosporins', 'macrolides', 'co-amoxiclav', 'penicillin', 'tetracyclines', 'severity', 'biomarkers' and 'intravenous antibiotics'. The literature search was supplemented by reviewing relevant national guidelines, reference lists and the authors' personal files.

The extent of the problem

C. difficile is a Gram-positive, anaerobic, spore-forming bacillus that infects the large bowel.[2] CDI is most frequently acquired within healthcare facilities, although community-acquired infection is increasingly recognized.[8] It is strongly associated with the use of broad-spectrum antibiotic therapy.[9] Manifestations range from trivial diarrhoea to life-threatening pseudo-membranous colitis.[10]

It has been estimated that an average district general hospital in the UK will incur costs of £400000 and >200 additional bed days annually due to CDI.[11] Cases of CDI have risen

dramatically over the last 20 years.[2,12] Recent UK Department of Health statistics reported 10 846 cases of CDI in the National Health Service (NHS) from April to June 2008, with 80% of these cases reported in patients over the age of 65 years. Over 50 000 cases of CDI were reported in England in 2007 and CDI was cited in >4000 death certificates.[2] This contrasts with <5000 cases in England in 1993 when the first BTS CAP guidelines were introduced, and ~20 000 cases in the year 2000. In our own hospitals in Tayside, UK, ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) discharges citing *C. difficile* have risen dramatically since 1998 (Figure 1). This pattern is similar to that reported by many UK NHS institutions.[2] Although these trends may be partly explained by increased awareness and increased testing for the disease, it is widely accepted that the incidence is rising. CDI in UK hospitals has been described as an epidemic.

When discussing the causes of these increases, hospital cleaning receives much of the media attention and is a key part of the overall strategy to reduce hospital-acquired CDI.[13] Hand washing is critical to preventing the spread of infection within hospitals once it is established, and there is evidence of poor hand washing practice among medical, nursing and support staff that may have contributed to the spread of CDI.[14,15] Good infection control procedures are essential, including isolation of cases and barrier nursing.[16,17] An increasingly virulent *C. difficile* strain, known as ribotype 027, has been described.[18] This novel strain produces increased quantities of *C. difficile* toxins A and B along with an additional binary toxin. Disease associated with this strain is reported to be more severe and more difficult to treat. Other medical factors such as increasing prescriptions for gastric acid suppressant drugs have played a role.[19] There is, however, broad agreement that antibiotic therapy is one of the primary drivers of CDI in hospitals.[20] Respiratory infections are the leading indication for antibiotic prescribing in UK hospitals, and therefore potentially a major driver of CDI and other healthcare-associated infections.[21,22]

How does CAP management contribute to CDI?

In the UK, 80% of antibiotic prescribing takes place in primary care, and 80% of these prescriptions are for lower RTI (LRTI).[21]
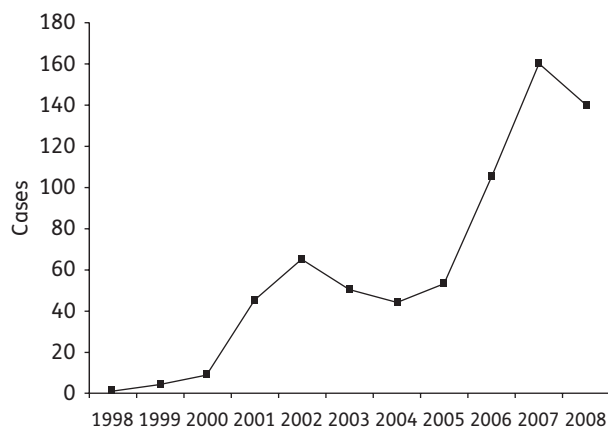
The majority of these prescriptions broadly follow the national recommendations for treatment of CAP although chest radiograph confirmation is not sought in most cases and many will represent cases of viral infections or upper RTIs. In the secondary care environment, CAP is the most common cause of severe sepsis and accounts for 6% of all intensive care unit (ICU) admissions in the UK.[23] Hospital admissions for infectious disease and particularly CAP have been rising in recent years and the average age of the UK population is also rising.[7] This has the effect of increasing antibiotic prescribing in hospitals, particularly to elderly patients, thereby significantly increasing the number of patients at risk of developing CDI.

Regrettably, there are no studies, in the UK or internationally, that specifically address the issue of CDI as a complication of CAP therapy. Most studies have examined antibiotic use in hospitals without considering the diagnosis for which they were prescribed. It is notable, however, that of the four classes of antibiotic most strongly implicated in the CDI epidemic (second- and third-generation cephalosporins, 'respiratory quinolones', macrolides and clindamycin) all except clindamycin are, or have been, most frequently prescribed for respiratory infections.

Antibiotics save lives in CAP.[24] Prior to the widespread introduction of antibiotics in the 1950s, patient mortality in CAP was >50%; however, this figure has now fallen to ~10%. There are currently no therapies other than antibiotics that have been proven to reduce mortality in CAP and no new therapies have been licensed for CAP since antibiotics were introduced. Despite the efficacy of antibiotics in CAP, the number of deaths attributable to CAP greatly exceeds those attributable to CDI. For example, in Scotland, *C. difficile* was recorded on 2088 death certificates between 2001 and 2007, whereas pneumonia was directly responsible for 17 534 deaths over the same period.[25] The mortality rate for hospitalized patients with CAP is 5.7%–14% based on UK studies,[1] while in the UK CDI has been associated with a 28 day mortality of 11%–23%.[26]

Some of the ways in which management practices in LRTIs may contribute to CDI are summarized in Figure 2. It should be emphasized that while this review has focused on *C. difficile*, these practices may also contribute to other healthcare-associated and antibiotic-resistant infections such as MRSA and extended-spectrum β-lactamase-producing *Escherichia coli*.
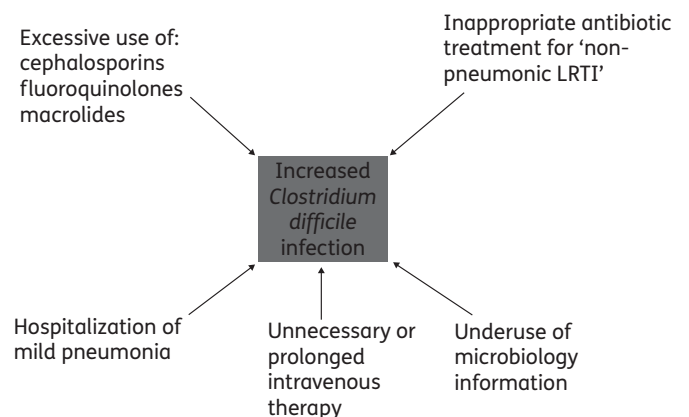
Figure 1. ICD-10 discharges reporting *C. difficile* as a diagnosis in NHS Tayside 1998–2008.

Figure 2. Management practices in CAP that may contribute to increasing CDI.

The role of national guidelines

The first BTS guidelines for the management of CAP in adults were published in 1993.[27] In the absence of a robust evidence base on the aetiology or management of CAP in the UK at that time, consensus guidelines, based largely on expert opinion, were produced. The guidelines were widely criticized: second- and third-generation cephalosporins were recommended for severe CAP; the severity scoring system classified the majority of elderly patients in the severe category, regardless of physiological embarrassment; and the guidelines did not clearly differentiate between CAP and non-pneumonic respiratory illness. These factors were accused of contributing to the CDI epidemic, owing to excessive use of high-risk antibiotics, to at-risk patients, with little indication.[28–33]

After the publication of the first BTS guidelines in 1993, antibiotic consumption data, along with reports from various hospitals, demonstrated a progressive increase in the use of cephalosporins and macrolide antibiotics.[28,30–33] At this time the extent of the *C. difficile* epidemic became clear; many hospital Trusts rejected the BTS recommendations. In the 1999 BTS survey, nearly 20% of respiratory units reported concern over CDI, and although 65% reported the use of the combination of cephalosporin and macrolide antibiotics for severe CAP, as suggested by the guidelines, other regimens such as co-amoxiclav and benzylpenicillin-based regimens were also reported.[34] The survey demonstrated, however, that there was significant misunderstanding of the guidelines, with nearly a quarter of respondents recommending β-lactam/macrolide dual therapy for non-severe CAP and some even recommending cephalosporins for mild CAP.

Misinterpretation of the guidelines, rather than the guideline recommendations themselves, may have influenced much of the subsequent problem. Nevertheless, significant changes were made when the guidelines were reviewed in 2001.[31] By 2009, CDI rates in England had increased by 400%.[2]

Risk factors for CDI in CAP patients

The antibiotics most strongly associated with the development of *C. difficile* diarrhoea include clindamycin and third-generation cephalosporins.[2,8,9,11] More recently fluoroquinolones, carbapenems and prolonged courses of aminopenicillins have been implicated.[2,35,36]

CDI disproportionately affects elderly patients, and up to 90% of patients presenting to hospital with CAP are over the age of 65 years.[37] Many have other risk factors for development of CDI (Table 1).

Cephalosporins

The antimicrobial spectrum of cephalosporin antibiotics is wide; in addition to coverage of *Streptococcus pneumoniae*, cephalosporins provide coverage of methicillin-susceptible *S. aureus* and a spectrum of Gram-negative organisms.

Since the 1993 BTS CAP guidelines, cephalosporins have been the most frequently used antibiotics for patients with severe CAP in the UK.[34] The administration of second- and third-generation cephalosporins, particularly to elderly patients, is strongly associated with the development of *C. difficile* diarrhoea.[28] This

Table 1. Risk factors for development of CDI

CDI risk factor
Age >65 years[38]
Co-morbidities
Severity of presenting illness[9,39]
Admission from nursing home
Malignancy (particularly haematological malignancy)[40,41]
Prolonged hospitalization[39,42]
Gastric acid suppressant medications[19,42,43]
Immunosuppression[42]
Intensive care unit admission
Nasogastric intubation[44]
Inflammatory bowel disease[44]
Gastrointestinal and transplant surgery

association was recognized as early as the 1970s, but the scale of the problem was not recognized until the mid-1990s.[20] Since then, efforts have been made to reduce cephalosporin prescribing.

There is evidence of reduction in CDI following restriction of use of cephalosporins and clindamycin. These interventions result in significant immediate reductions in the incidence of CDI, but a less impressive long-term reduction. A recent systematic review pooled the results of these antibiotic restriction interventions and reported an immediate reduction of ~90 cases of CDI per year, but with a sustained decrease of only 12 cases per year.[36] Many of these studies report interventions in the context of outbreaks. The natural history following an outbreak is for there to be a decline in cases over time, a concept known as regression to the mean, and as such the significance of the intervention is not straightforward to interpret. Another systematic review has described the majority of these studies as poor quality and having major methodological limitations.[46]

Fluoroquinolones

Two 'respiratory quinolones' are licensed for use in the UK; moxifloxacin and levofloxacin. Neither is recommended as a first-line agent, but they have been considered as second-line alternatives since the 2001 BTS guidelines.[31] These agents are active against all the major bacterial pathogens causing CAP including *S. pneumoniae*, *Legionella pneumophila* and other 'atypical' organisms. Resistance to fluoroquinolones is extremely low in the UK; <1% of pneumococcal isolates are resistant to levofloxacin.[47] Their broad spectrum of action makes fluoroquinolones an attractive option for CAP. There is, however, minimal evidence that they are more effective than narrower spectrum agents. A recent meta-analysis, focusing primarily on fluoroquinolones, showed no survival benefit when comparing regimens covering atypical pathogens with narrower spectrum regimens.[48]

Fluoroquinolone use was encouraged in the 2001 BTS guidelines as these agents were, at that time, associated with a low risk of CDI. Reports, however, suggest fluoroquinolones are emerging as a major cause of CDI, and are particularly associated with the epidemic and hypervirulent 027 ribotype.[18,35] Fluoroquinolones, particularly moxifloxacin, have been shown to induce *C. difficile* growth and toxin production in an animal model of

CDI.[49] A study following an outbreak in Quebec, Canada, found fluoroquinolones were the antibiotic most strongly associated with CDI; adjusted hazard ratio (AHR) of 3.44 [95% confidence interval (CI) 2.65–4.47]. In contrast, cephalosporins carried less than half the risk [the AHR in this study was 1.56 (95% CI 1.15–2.39)].[39]

Macrolides

Macrolides are reported to reduce mortality in severe pneumonia. This evidence is based almost entirely on observational, uncontrolled studies with a large potential for bias by indication. There is, nevertheless, a large body of such evidence from different populations and different healthcare systems.[50–60] BTS guidelines recommend the use of macrolide antibiotics for moderate and severe pneumonia only; however, there is widespread use of macrolide antibiotics in mild pneumonia despite this.

Macrolides, such as clarithromycin, have some activity against enteric anaerobes and so promote the overgrowth of C. difficile.[61] Determining the impact of macrolide therapy on CDI in clinical practice is difficult because guideline-based practice is to use macrolide antibiotics in combination with cephalosporins or aminopenicillin/β-lactamase inhibitor combinations, not as monotherapy. The study by Impallomeni et al.[28] found an odds ratio (OR) for the development of CDI of 2.8 for erythromycin therapy, whereas MacGowan et al.[62] found an association between macrolide use in the 7 days prior to onset of CDI. There are no studies reporting the effect of restriction of macrolide therapy on CDI or other hospital-acquired infections.

Aminopenicillin/β-lactamase inhibitors (co-amoxiclav)

Since 2001 the BTS guidelines have recommended co-amoxiclav as first-line therapy for severe CAP.[31] Co-amoxiclav has a broad spectrum of antimicrobial activity, notably against S. pneumoniae, Haemophilus influenzae and S. aureus, in addition to possessing some anaerobic activity. It is this activity against enteric anaerobic bacteria that makes it an agent likely to induce C. difficile; indeed co-amoxiclav treatment can promote C. difficile proliferation in healthy volunteers.[63] Co-amoxiclav was the second most likely class of antibiotic to induce CDI in the early meta-analysis by Bignardi (OR 22.1, 95% CI 6.5–75.4).[9] This study took place before the use of fluoroquinolones increased and the epidemic 027 strain was described.

Depending on local strain epidemiology, co-amoxiclav may be less likely to induce CDI compared with cephalosporins or fluoroquinolones. Nevertheless, a number of UK hospitals have encountered problems with co-amoxiclav predisposing to CDI and this, in part, explains the increasing use of benzylpenicillin-based regimens as first-line therapy for severe CAP.[64]

Fowler et al.[65] reported a reduction in CDI rates in a time-series analysis in which co-amoxiclav and cephalosporin prescribing were restricted in favour of antibiotics less associated with CDI. The study, however, did not report pneumonia-specific mortality and used a combination treatment of benzylpenicillin and trimethoprim, which is not a well-recognized therapy option in CAP treatment.

Narrow-spectrum penicillins and tetracyclines

Narrow-spectrum penicillins and tetracyclines are widely regarded as the lowest risk agents for inducing CDI. Oral penicillin monotherapy has been used in Scandinavian countries for many years for mild pneumonia. The Scandinavian countries have a long-standing history of restrained antibiotic use and consequently have low rates of antimicrobial resistance and a low frequency of hospital-acquired infections.[66] Cephalosporins are the most widely recommended agents worldwide, even in Scandinavian countries.[67]

Tetracyclines are recommended by the 2009 BTS guidelines as an alternative therapy for mild pneumonia in penicillin-allergic patients.[1] Previous recommendations to use macrolides as alternative therapy have been questioned in light of increasing macrolide resistance among S. pneumoniae. UK pneumococcal resistance to erythromycin has increased to 14.6% of blood culture isolates and 12% of respiratory isolates. Comparatively, tetracycline resistance is 4% and 7.6%, respectively.[68] Doxycycline is licensed for use in the UK for treatment of mild CAP. Its spectrum of action covers the majority of respiratory bacterial pathogens including Mycoplasma pneumoniae, Chlamydophila pneumoniae and L. pneumophila in addition to S. pneumoniae. Although the evidence base for doxycycline in pneumonia is weak, with an absence of randomized controlled trials, it has been used in Scandinavian countries for many years with success. Tetracyclines may represent an important part of the strategy to reduce CDI. A previous systematic review has shown that compared with third-generation cephalosporins (OR 36.2, 95% CI 19.0–68.9) and fluoroquinolones (OR 8, 95% CI 4.5–14.3), tetracyclines were the least likely antibiotics to cause CDI (OR 1.3, 95% CI 0.1–19.6).[9]

In summary, reduced use of cephalosporins and fluoroquinolones, judicious use of macrolides and increased use of penicillin-based regimens and tetracyclines for mild CAP is likely to result in a reduced incidence of CDI.

Severity assessment tools and antibiotic prescribing

In the UK, initial antibiotic prescribing is often done by junior doctors. Studies have found that junior doctors in the UK have poor knowledge of the UK CAP guidelines.[69,70]

Severity assessment tools have been derived to guide initial management of patients with CAP.[71,72] These are based on the risk of 30 day mortality, but have been recommended to guide antibiotic choice in the BTS guidelines.[1,72] These provide objective means of choosing which patients require broad-spectrum antibiotic therapy and, in theory, may therefore reduce unnecessary treatment. They may be particularly useful for doctors with less experience of managing CAP. Many scoring systems have been derived, but the most widely used in the UK is the CURB65 score, the components of which are shown in Figure 3.[1,72] This score has been independently validated in >13 000 patients in 10 countries.[72–79] The BTS recommends outpatient treatment for patients in the lowest risk CURB65 classes (0 and 1).

Severity scores have been successfully used to increase the number of patients treated on an outpatient basis.[80] This strategy has obvious advantages in terms of reducing potential
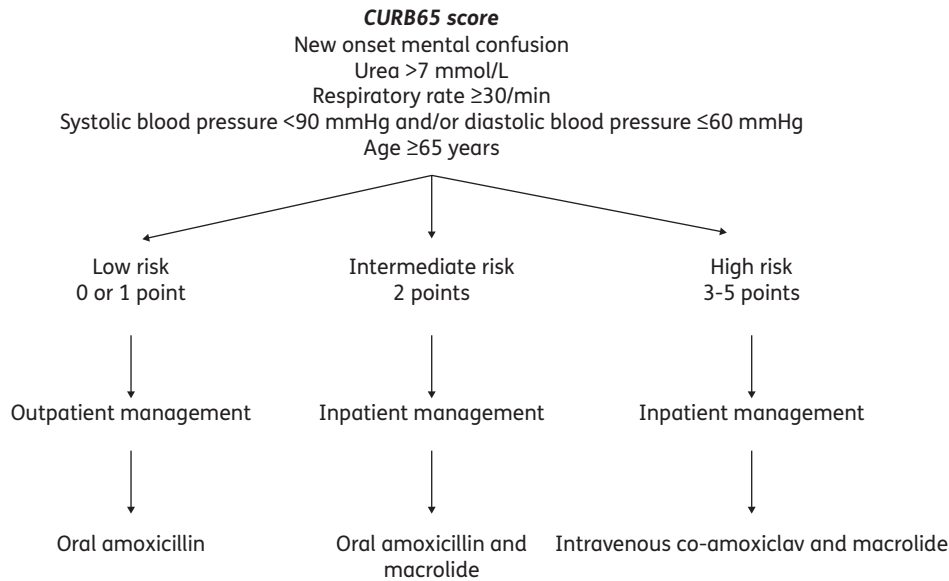
CURB65 score
New onset mental confusion
Urea >7 mmol/L
Respiratory rate ≥30/min
Systolic blood pressure <90 mmHg and/or diastolic blood pressure ≤60 mmHg
Age ≥65 years

Low risk 0 or 1 point	Intermediate risk 2 points	High risk 3-5 points
Outpatient management	Inpatient management	Inpatient management
Oral amoxicillin	Oral amoxicillin and macrolide	Intravenous co-amoxiclav and macrolide

Figure 3. BTS-recommended therapy for CAP. Adapted by permission from BMJ Publishing Group Limited from Lim et al.[1]

exposure to *C. difficile*. It is notable, however, that a large proportion of patients at low risk of death require admission to hospital.[81] This is particularly true in the elderly where admission may be required for social reasons and significant co-morbidity rather than the severity of pneumonia.[82] Studies relating to the impact of CURB65 in clinical practice are limited. At the time of writing no studies have reported CURB65-guided therapy being used to successfully increase the proportion of patients treated at home. Use of severity assessment tools to guide antibiotic therapy has not been studied, although the theoretical basis (that patients at low risk of death require narrower spectrum, oral antibiotic therapy) is sound.

In the future, biomarkers may be used to predict severity and to guide antibiotic therapy. The traditional biomarker, C-reactive protein (CRP), is widely available and correlates to some extent with severity of pneumonia.[83] It is not, however, sufficiently sensitive or specific to determine the requirement for antibiotic therapy.[84] Procalcitonin is a precursor of the hormone calcitonin and is raised substantially in bacterial infections. Procalcitonin has emerged as a potentially useful guide to antibiotic prescription in respiratory infections. In a randomized study in hospitalized patients with acute RTI, an admission procalcitonin measurement was used to determine whether patients should receive antibiotics. One arm of the study received procalcitonin-guided antibiotic therapy while the other received standard therapy. At the conclusion of the trial, there were 50% fewer antibiotic prescriptions in the procalcitonin group, with no major impact on outcome.[85,86]

The largest trial to date of procalcitonin-guided antibiotic therapy has recently been published.[87] This multicentre trial of 1359 patients with LRTIs found that procalcitonin guidance was associated with a mean reduction of 3 days in duration of antibiotic therapy with no increase in mortality or clinical failure. This reduction was associated with a significant reduction in antibiotic-related side effects.[87] Unfortunately, procalcitonin assays are currently not widely available in the UK and comparison with other severity indices, biomarkers (including CRP) and

independent validation of these findings is required before we can consider using biomarkers to limit antibiotic use in respiratory infections.

In summary, validated severity markers have the potential to reduce inappropriate antibiotic use and to encourage outpatient management of CAP, with the likely result of reducing CDI.

Duration of antibiotic therapy

National guidelines recommend 7 days of antibiotic therapy for mild CAP, with 7–10 days therapy recommended for severe pneumonia.[1] Evidence from the UK is lacking, but an international audit recently showed variation in antibiotic duration from 3 to 28 days, variation that is not accounted for by the severity of pneumonia or patient response to treatment.[88]

Prolonged antibiotic therapy is associated with CDI and therefore shorter courses of antibiotic therapy may have a role in reducing *C. difficile* as well as other resistant organisms.[2,89] Evidence suggests that short-course regimens (≤7 days) are at least as effective as longer courses. For mild to moderate pneumonia, even shorter durations may be possible. In one study in the Netherlands, patients were randomized after 72 h of intravenous (iv) amoxicillin treatment either to a further 5 days of oral amoxicillin or to placebo. After 10 and 28 days of follow-up, there were no significant differences in clinical success between the group receiving 3 days of treatment and the group receiving 8 days of treatment.[90]

A recent meta-analysis of randomized controlled trials comparing short-course treatment (≤7 days) and longer treatment (>7 days) showed no significant differences in terms of clinical efficacy, bacterial eradication or mortality.[91]

Limiting the duration of antibiotic therapy to the minimum necessary to achieve clinical success is likely to reduce adverse effects and may be associated with a reduced incidence of *C. difficile*.

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Switching iv antibiotics to oral therapy

Many patients with CAP require initial treatment with iv antibiotics, due to severity, impaired swallowing or concerns about gastrointestinal absorption of drugs. Many patients, however, are treated with iv antibiotics where oral therapy would be adequate. In one audit in Dundee, 85%–90% of patients receiving iv antibiotics in hospital could have been managed with oral medication.[92] Oral therapy has several advantages, but in the context of CDI the main advantage is that it may facilitate early discharge from hospital, and therefore from the environment in which CDI is most easily acquired.

The UK Department of Health guidance has suggested a 48 h iv/5 day oral antibiotic approach with automatic stop dates.[2]

While this may be inappropriate for some cases of high-severity pneumonia, in principle this has many advantages. Early iv to oral switch may shorten length of stay in uncomplicated pneumonia and may also facilitate simplification of regimens, and reduce use of cephalosporins (because, in the UK, iv cephalosporins are usually switched to oral aminopenicillins).

In an open-label, controlled trial in the Netherlands, Oosterheert et al.[93] randomized 302 patients with severe pneumonia to either 7 days of iv antibiotics or 3 days of iv antibiotics followed by automatic switch to oral antibiotics at day 3 if clinically stable. After 28 days of follow-up the group with early iv to oral switch had an equivalent mortality rate (4% versus 6%) and a similar rate of clinical cure (83% versus 85%).[93]

Table 2. Clinical parameters suggesting safety of iv to oral switch in CAP

| BTS recommendations[1]	Clinical stability (Halms) criteria[94]
• resolution of fever for >24 h • pulse rate <100 beats/min • resolution of tachypnoea • clinically hydrated and taking oral fluids • resolution of hypotension • absence of hypoxia • improving white cell count • non-bacteraemic infection • no microbiological evidence of Legionella, staphylococcal or Gram-negative enteric bacilli infection • no concerns over gastrointestinal absorption	• temperature ≤37.8°C • respiratory rate ≤24 breaths/min • systolic blood pressure ≥90 mmHg • arterial oxygen saturation ≥90% • ability to maintain oral intake • normal mental status
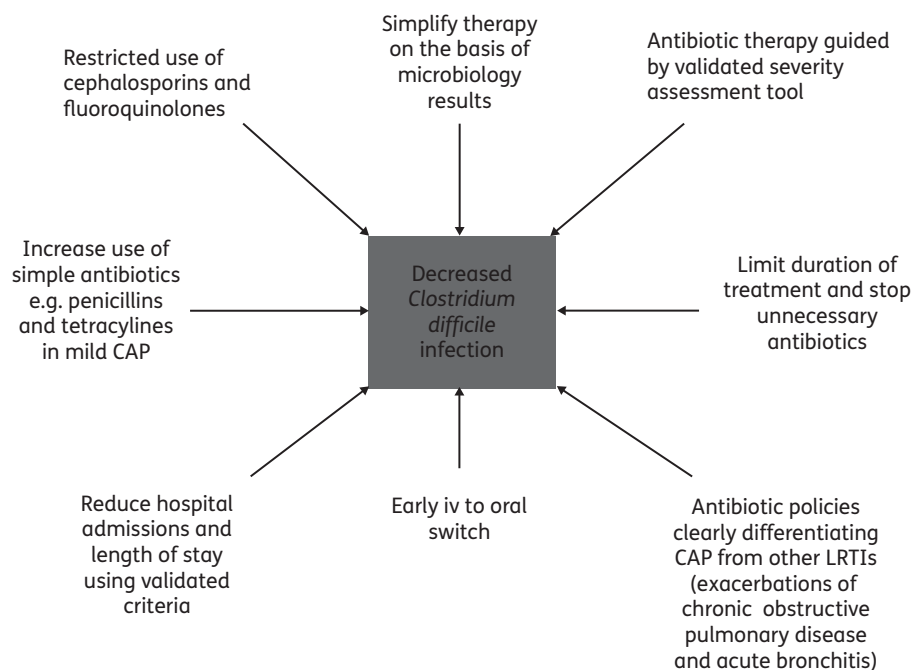
Figure 4. Management practices in CAP that may contribute to reducing CDI.

The BTS guidelines emphasize the importance of clinical judgement in making the decision to switch to oral antibiotics and note that there is a limited amount of evidence to guide when to make the iv to oral switch. In general, they recommend that in a patient who is clinically improving and is afebrile for 24 h, switching to oral therapy should be considered.

Studies have described clinical stability criteria that provide an objective means of classifying whether a patient has responded appropriately to therapy, and therefore an objective means of identifying patients who may be switched from iv to oral medication, or discharged from hospital (Table 2).[1,94] Evidence suggests that once patients reach clinical stability, switching to oral therapy and hospital discharge are safe and associated with a very low rate of relapse.[94,95] Audits suggest that up to 20% of patients are kept on iv therapy inappropriately in hospitals.[21] Patients may also be kept in hospital for longer than is necessary, with resultant increased exposure to hospital-acquired infections. Data from the UK are lacking, but data from the USA, in the landmark PORT study, found that 22% of patients were kept in hospital after they were clinically stable. Reasons included unavoidable delays (treatment of co-morbidities, delays in organizing long-term care), but also areas where discharge could be expedited (such as the belief that patients should remain in hospital to complete antibiotic courses).[96]

Table 3. Summary of evidence supporting changes to management of LRTIs

Recommendation	Evidence for reduction of *C. difficile*/hospital-acquired infection	Evidence of benefit/safety in CAP
Restricted use of:		
cephalosporins	meta-analysis suggests sustained reduction in CDI following restriction of cephalosporins[36]	there is no evidence that cephalosporins are superior to the alternative agents in the treatment of CAP
fluoroquinolones	strong association with epidemic 027 ribotype;[35] limited evidence on the effect of fluoroquinolone restriction	meta-analysis suggests no benefit of using fluoroquinolones compared with alternative agents[48]
co-amoxiclav	one study suggests reduced risk of CDI following co-amoxiclav restriction alongside cephalosporin restriction[65]	there is no evidence to suggest that co-amoxiclav is superior to other agents in the treatment of CAP
Treatment of mild LRTIs with:		
tetracyclines	identified as agents least likely to cause CDI in one meta-analysis[9]	limited evidence, but used successfully for many years in Scandinavian countries;[66] low rates of *S. pneumoniae* resistance in the UK[68]
oral penicillin	limited evidence; widely used in Scandinavian countries where rates of CDI and antibiotic resistance are low[67]	limited evidence, but used successfully for many years in Scandinavian countries;[67] low rates of *S. pneumoniae* resistance in the UK[68]
Severity-guided antibiotic therapy using validated severity tools	no evidence specifically related to CDI or antibiotic-resistant organisms	severity tools have been widely validated[72–79] and are recommended by national and international guidelines[1]
Increased outpatient management of mild LRTIs	*C. difficile* is predominantly hospital acquired;[2] although no trials exist, outpatient management is likely to be associated with reduced risk of acquiring CDI	outpatient management for mild CAP is equivalent to inpatient management in terms of mortality, complications and patient satisfaction with care[80]
Early discharge in clinically stable patients	*C. difficile* is predominantly hospital acquired;[2] although no trials exist, outpatient management is likely to be associated with reduced risk of acquiring CDI	length of hospital stay has been reduced in a number of clinical studies without compromising patient safety[83,93,95,101]
Early iv to oral switch therapy	no specific studies in reducing *C. difficile*, but will contribute to reducing broad-spectrum antibiotic use and length of hospital stay	a randomized controlled trial found early iv to oral switch in patients with severe pneumonia equivalent to 7 days iv therapy in terms of mortality and treatment success[93]
Shorter antibiotic courses	duration of antibiotic therapy is linked to CDI[2,89]	a meta-analysis of randomized controlled trials suggest that short versus longer course antibiotic regimes in mild–moderate CAP are at least as effective in terms of mortality and overall clinical efficacy[91]
Reduced inappropriate prescribing	measures to reduce inappropriate prescribing and reduce antibiotic use (particularly cephalosporins and clindamycin) are associated with reduced CDI[36]	none of the studies on restrictive antibiotic policies has reported increased mortality from infectious disease as a consequence

Early iv to oral switch and early hospital discharge are likely to reduce CDI rates, in addition to improving cost-effectiveness of care.

Reducing inappropriate antibiotic use in RTIs

It has been suggested that up to 50% of antibiotic use in hospitals is inappropriate.[36] Inappropriate antibiotic therapy is a broad term, but in the context of RTIs refers to the use of regimens that are unnecessary (e.g. antibiotic treatment in viral infections or upper RTI), excessive (such as cephalosporin use in mild CAP), inadequate for the likely organisms (e.g. ciprofloxacin, which has poor activity against *S. pneumoniae*) or insufficient (such as failure to cover atypical organisms or *S. aureus* in patients admitted to the ICU).

Changes in junior doctor practices and the expansion of the new speciality of acute medicine in the UK mean that a large proportion of CAP patients are now not managed initially by respiratory physicians.[1] Most studies suggest that concordance with national guidelines is low.[69,70]

Diagnosis of CAP is also suboptimal. One study found 29% of patients diagnosed with CAP in hospital had a normal chest X-ray.[97] In another UK study, 50% of patients enrolled in the 'CAP' cohort had a normal chest X-ray.[98] Although some of these patients with LRTI may require antibiotic therapy [e.g. infective exacerbations of chronic obstructive pulmonary disease (COPD)] there is evidence that patients without pneumonia are treated with cephalosporins and combination therapy. This is particularly the case for COPD where overtreatment with antibiotics is common.[99]

Despite clear guidelines from the BTS, inappropriate antibiotic therapy still appears widespread. The BTS recently re-audited local practices for the management of CAP as part of the preparations for the 2009 guidelines. Disappointingly, practices had not improved in the 7 years since the previous survey. Against the guidance of the BTS, 61% of respondent hospitals recommended β-lactam/macrolide combination therapy for mild hospitalized pneumonia. Forty-nine percent reported cephalosporins as first-line antibiotic therapy for severe CAP, with only 34% recommending the BTS first-line therapy of co-amoxiclav and macrolide. Only 38% of hospitals reported that local guidance was influenced by concerns over *C. difficile*.[100] A further concerted effort is required to reduce inappropriate prescribing and improve adherence to the guidelines. Figure 4 summarizes management practices in RTIs that may have a role in reducing CDI. There is little published evidence to suggest that manipulating CAP management can reduce CDI; however, in large part the recommendations in Figure 4 represent best practice for CAP patients, irrespective of the risk of CDI.

A summary of the evidence supporting the measures discussed in this review is shown in Table 3.

Conclusions

The CDI epidemic has forced us to re-evaluate how we use antimicrobials in hospitals and to examine management practices for RTIs. There are clear areas for improvement in the management of RTIs in the UK and elsewhere, improvements that may lead to a reduction in CDI.

Transparency declarations

None to declare.

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