Introduction

Although widely accepted as broad-spectrum antibiotics, cephalosporins are not active against all the bacteria commonly isolated in a hospital microbiology laboratory. Patients newly admitted to hospital tend to acquire hospital CNS within hours of their admission, especially if prescribed antibiotic therapy. Experimental models show that the selective pressure exerted by broad-spectrum cephalosporins brings about a rapid overgrowth of staphylococci that are resistant to the antibiotics used. This is also seen clinically, as most antibiotic-resistant hospital CNS are resistant to methicillin.

Inherently resistant microorganisms

Coagulase-negative staphylococci

CNS are the most prevalent skin commensals. Hospitals are a source of CNS, which includes carriage by patients and staff, and a reservoir in the hospital environment. There appears to be a relationship between antibiotic usage and antibiotic resistances of CNS in hospitals. Isolates from patients are generally multiply-resistant due to the continued heavy exposure of the hospital, staff and patients to antibiotics. Patients newly admitted to hospital tend to acquire hospital CNS within hours of their admission, especially if prescribed antibiotic therapy. Experimental models show that the selective pressure exerted by broad-spectrum cephalosporins brings about a rapid overgrowth of staphylococci that are resistant to the antibiotics used. This is also seen clinically, as most antibiotic-resistant hospital CNS are resistant to methicillin.
and are therefore relatively unaffected by cephalosporins. They consequently proliferate upon and within patients receiving these antibiotics. This property is not exclusive to the cephalosporins, as any antibiotic could theoretically have the same effect. It is very difficult to rank antibiotics, let alone individual β-lactam agents, according to their selective ability, but there have been studies showing that methicillin resistance in CNS is significantly associated with therapeutic and prophylactic use of cephalosporins.

Methicillin-resistant CNS encouraged by cephalosporin therapy may have clinical implications for some patients. CNS are commonly associated with infections of artificial prostheses, including plastic catheters, and will generate persistent low-grade infections unless the prosthesis is removed. Current management usually involves removal of such prostheses under glycopeptide cover, which increases the overall usage of these antibiotics.

Many hospitals in developed countries consume large amounts of cephalosporin antibiotics, particularly in surgical departments as the preferred choice for prophylaxis. This is being questioned at the present time for some specialities, because of concerns about the increasing prevalence of methicillin-resistant staphylococci. Some centres are already advocating a change from first- and second-generation cephalosporins to glycopeptides, but this move may be premature for others. These antibiotics are both expensive and toxic, and their use has been discouraged following the emergence of glycopeptide-resistant enterococci (GRE) and more recently, glycopeptide-intermediately resistant .

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### Oxidative non-fermentative Gram-negative bacilli

**P. aeruginosa** is another common isolate from patients. Ceftazidime and some newer cephalosporins aside, most cephalosporins encourage overgrowth of this organism because it is inherently resistant to these agents. Consumption of cephalosporin antibiotics in a hospital is associated with development or acquisition of resistance to these strains, and the only effective oral agents (quinolones) are losing ground because of increasing resistance.

**Enterococci**

Enterococci are also associated with cephalosporin therapy. These faecal-type streptococci first provoked interest as emerging pathogens in both hospital and community in the 1980s. Most infection occurs in the urinary tract, but patients who have received, or are receiving, parenteral cephalosporins appear to be at risk from enterococcal infections in a variety of sites, including blood. This is because enterococci are inherently resistant to cephalosporins and are able to colonize gastrointestinal sites previously populated by cephalosporin-susceptible organisms. This is particularly well illustrated by current theories regarding colonization resistance. Prescribing an antibiotic that decreases colonization resistance of the alimentary canal allows increased population densities (overgrowth) of potentially pathogenic bacteria. This correlates with mucosal invasion followed by translocation to lymph nodes. Overgrowth may also be associated with development or acquisition of resistance to the antibiotic prescribed.

The majority of healthy volunteers given cephalosporins acquire a substantially increased proportion of enterococci in the gastrointestinal tract. This is also seen in patients. Animal studies describe profound effects of cephalosporin agents on colonization resistance, although antibiotics other than cephalosporins are also implicated. It is difficult to apportion the effects of different antibiotics on colonization resistance because there are so few detailed studies specifically examining this. Some antibiotics, however, seem to be better able to maintain the status of the indigenous gastrointestinal flora than others.

Patients tend to be more vulnerable than volunteers to changes in colonization resistance and enterococcal overgrowth because the urinary tract, wounds, catheter sites and/or blood. With *Pseudomonas*, therapeutic options for clinically significant isolates are limited, and management has been further complicated by an increase in resistance to amoxicillin and gentamicin. GRE are virtually untreatable, and are discussed further below.

**Clostridium difficile**

*C. difficile* has long been associated with a range of clinical diseases, from antibiotic-associated diarrhoea to pseudomembranous colitis. Overgrowth of *C. difficile*, with or
without clinical symptoms, is not exclusively associated with cephalosporins and has been reported following administration of many other antibiotics. However, overgrowth occurs more commonly after cephalosporin therapy. Healthy volunteers given oral cephalosporins virtually all excrete C. difficile after 10 days of therapy. Treatment options for compromised patients usually include oral vancomycin or metronidazole, or both. Treatment failures occur frequently and precipitate the patient into and out of isolation, such is the propensity for spread of this spore-forming anaerobe. The organism may also be associated with outbreaks, which are debilitating to patients and costly for the hospital.

There has been a substantial increase of C. difficile in the UK over the last decade. It is possible that the British Thoracic Society endorsement of cephalosporins as first-line treatment for community-acquired pneumonia has played some part in the increase of this organism. A recent review states that the association between cephalosporins and C. difficile overgrowth is now so well established that cephalosporins should not be prescribed in care of the elderly units. This view has already been successfully transcribed into clinical practice, whereby restriction of cephalosporin use has resulted in a decrease in the numbers of patients with C. difficile.

**Candida albicans**

Overgrowth is not solely a bacterial domain. C. albicans awaits any opportunity afforded by antibacterial therapy, yeast infections often following a course of antibiotics. Antibacterial therapy has consistently been shown to be a major independent risk factor for the development of systemic candidosis. By no means exclusive to treatment with cephalosporins, Candida overgrows following exposure to most antibiotics. It is those with the broadest spectrum of cover, however, that are more likely to encourage overgrowth. Quinolones and aminoglycosides, for example, do not induce candidosis as rapidly or as often as cephalosporins. When volunteers are given oral cephalosporins, most become colonized by yeasts within 2 or 3 days of starting therapy; in another study, a group given amoxicillin did not show any increase in colonization with Candida. Patients treated with cefaclor, cefadroxil, cefuroxime, ceftriaxone, latamoxef or ceftazidime have an increased risk of developing Candida. Volunteers receiving parenteral ceftriaxone also show an overgrowth of yeasts in faecal flora. Surgical patients treated with cephalosporins demonstrate increased colonization with Candida. Patients are commonly found to have Candida from a throat swab soon after cefotaxime is initiated. Such patients are also at risk of candiduria, especially if the patient is catheterized. Candidaemia may follow if colonization of superficial sites and/or the urine is ignored. The more sites growing Candida, the higher the risk of invasive candidosis. Treatment clinically significant candidal overgrowth is difficult, especially when there are so few antifungal agents available.

There has been a huge increase in infections due to Candida over the past 20 years and there is no sign that numbers are abating. In hospital patients, the rate of blood-stream infection due to Candida spp. increased by almost 500% during the 1980s. Whilst there may be several different reasons for this, including greater awareness, more clinical interventions and better laboratory techniques, the increasing amount of Candida mirrors the increasing use of cephalosporins introduced over this period.

**Recent trends in the aetiology of hospital-acquired infections**

There has been a major shift in the aetiology of hospital-acquired infections during the 1980s in contrast to the 1970s, that is, an increase in the laboratory isolation of CNS, Candida, S. aureus, enterococci, P. aeruginosa and Enterobacter between 1980 and 1986–1989. Taken as a whole, the shifts are away from more easily treated pathogens towards more resistant pathogens with fewer options for therapy.

With the complexity and choice of antibiotic therapy nowadays, it is difficult to find specific evidence for the association of commensal overgrowth with the cephalosporin antibiotics alone. One study looked at hospital-acquired bacteraemia in an adult intensive care unit over 25 years (1971–1995). The use of amoxicillin plus gentamicin was gradually replaced by cephalosporins as first-line choice for the treatment of bacteraemic patients. During the last 5 years of the study, the number of bacteraemias increased two-fold, largely owing to increased isolation of enterococci, CNS, intrinsically antibiotic-resistant Gram-negative organisms (particularly P. aeruginosa) and Candida. Whilst the cephalosporins were introduced in the early 1980s, their prescribing frequency did not equal that of gentamicin until the 1990s. The organisms highlighted are the same as those already mentioned as being associated with cephalosporin therapy. The authors attributed the change in the spectrum of organisms to the changes in antibiotics used over the time period studied.

An additional study shows that if cephalosporin usage is reduced as part of an overall reduction in antimicrobial prescribing, there is a decrease in hospital-acquired infections, namely, enterococcal and selected Gram-negative bacteraemias, and MRSA and S. maltophilia colonization or infection. Others have documented the association of cephalosporins with staphylococci, enterococci, multiply-resistant Gram-negative bacilli, yeasts and C. difficile.

The next section describes a group of multiply-resistant bacteria rapidly increasing in hospitals throughout the world. It appears that cephalosporin usage selects for and encourages propagation of these organisms. It is even
possible that the cephalosporin antibiotics play a role in the molecular initiation of resistance for some.

**Microorganisms with acquired resistance**

Extended-spectrum \(\beta\)-lactamase-producing coliforms

\(\beta\)-Lactamases are the major determinants of resistance to \(\beta\)-lactam antibiotics.84 All Gram-negative bacteria elaborate chromosomally mediated \(\beta\)-lactamase enzymes. These are typically low level in coliforms isolated from human-free environments but may be induced in a wide variety of species by exposure to \(\beta\)-lactam drugs.85,86

The prevalence of \(\beta\)-lactamases has forced pharmaceutical companies to seek alternative agents that are resistant to \(\beta\)-lactam attack.87 Cefotaxime and ceftazidime were initially regarded as indestructible from plasmid-mediated \(\beta\)-lactamases, but this belief has since been shattered following a cascade of reports describing plasmid-mediated resistance to both of these drugs.88,89 There are now increasing numbers of plasmid-mediated ESBLs described every year. Almost all of them are derivatives of the well-known TEM and SHV-1 \(\beta\)-lactamases.90 Variants of these inactivate third-generation cephalosporins and monobactams, having arisen by spontaneous mutation and being only marginally different in amino acid sequence from the parent enzymes.1 An additional mechanism of resistance is the capture on plasmids of normally chromosomal genes from *Enterobacter cloacae*, *Citrobacter freundii* or *P. aeruginosa*, which can provide *Klebsiella pneumoniae* or *Escherichia coli* with resistance to \(\alpha\)-methoxy-\(\beta\)-lactams (cefoxitin and cefotetan) as well as to oxyimino-\(\beta\)-lactams (cefotaxime, ceftriaxone and ceftazidime).91 A resistant organism isolated during therapy to one cephalosporin may thus demonstrate reduced susceptibility to other antibiotics, not necessarily within the same chemical class.92

Multiply-resistant coliforms are associated with high-level usage of cephalosporins, particularly cefotaxime, ceftriaxone and ceftazidime.5,9,44,87,93–97 These antibiotics induce and select for ESBL coliforms (ESBLC).87,95,98 If cephalosporins are avoided, there is less chance of selecting these highly resistant bacteria, and coliform susceptibility rates rise.5,98 At a hospital in New York, multiply-resistant *E. cloacae* isolates from the intensive care unit increased dramatically between 1988 and 1990.91 As a response, use of ceftazidime was severely restricted in favour of piperacillin in combination with an aminoglycoside. Following this change, susceptibility of *E. cloacae* isolates to ceftazidime increased from 54% to 75%, whilst the total number of multiply-resistant *E. cloacae* fell. No other major changes in susceptibility patterns were seen.97

Some resistant coliforms merely colonize patients; others invade to cause infection.8 Yet other epidemic strains spread to cause outbreaks of virtually untreatable disease.100,101 The location of antibiotic resistance mechanisms on plasmids facilitates easy spread between species and genera, and is most likely to occur in the gastrointestinal tract.46,102

Some physicians have already recognized the fact that cephalosporin usage may play a role in the selection of ESBL and therefore prescribe amoxicillin in conjunction with an antibiotic of another class for first-line treatment of community-acquired pneumonias.87 Similarly, some surgeons have reverted to the ‘old-fashioned’ combination of amoxicillin and gentamicin for surgical patients.87 The latter combination is less likely to encourage overgrowth of susceptible enterococci, yeasts and *C. difficile*, than would occur if a cephalosporin was the antibiotic of choice.3,19,57,72

Hospitals contain a concentrated reservoir of resistant coliforms, but a dilute version exists in the community. The path between the hospital and the community runs both ways.103 Even patients with no prior hospital contact can display clinically significant infection with multiply-resistant coliforms.104 Critically ill patients in intensive care units rapidly acquire such organisms, even if not previously colonized, and a battle often ensues between microbiologist and organism for time to allow the patient to recover from initial pathology before succumbing to hospital-acquired resistant microbes.

**Penicillin-resistant pneumococci**

Clinically significant infection with penicillin-resistant pneumococci (PRP) is prevalent worldwide.105 At present, the median MIC for strains in the USA lies between 0.05 and 0.1 mg/L and is continuing to rise. Most infections with intermediate-resistant pneumococci (MIC 0.1–1.0 mg/L penicillin) are treatable with increased doses of penicillin, but isolates are now showing high-level resistance (>2.0 mg/L).106 Some of these demonstrate resistance to third-generation cephalosporins, and this proportion is also increasing.106

PRP are associated with extensive prior antimicrobial therapy,107 particularly with \(\beta\)-lactam antibiotics.108–112 They may be selected at the infection site or in the nasopharynx.109 Resistant strains may even reside in the nasopharynx before treatment is initiated and are then encouraged by the antibiotic given. It is also possible that penicillin-susceptible strains are transformed *in vivo* to strains that have a lower susceptibility to penicillin.113 Any antibiotic in theory has the potential to select resistant strains provided that the local concentration of the drug is high enough to inhibit susceptible cells whilst encouraging a resistant subset.109 The risk of selection is increased if patients are under-dosed or given prolonged courses of antibiotics, or if drugs with inadequate activity against pneumococci are prescribed.114,115

The aminopenicillins have been widely regarded as being disproportionately responsible for selecting PRP, but this may be only because the emergence of this pathogen
coincident with increased consumption of these antibiotics.\textsuperscript{116} It is entirely possible that increased prescribing of other antibiotics, e.g. cephalosporins, macrolides and co-trimoxazole, is equally or more important than amoxicillin in the promotion of PRP.\textsuperscript{116–119} Studies examining the effect of antibiotics on the carriage of PRP are often flawed in their design and conclusions.\textsuperscript{109} Authors do not often calculate the relative selective pressures of different classes of antibiotics;\textsuperscript{117–119} in many studies, investigators fail even to identify the specific antibiotics given, referring only to the generic term “antibiotics.”\textsuperscript{109} Even more unusually, some authors identify the classes of antibiotics that select resistant strains, but fail to complete the analysis. In one of these studies, co-amoxiclav was shown to be associated with a minimal increase in the incidence of PRP carriage (from 14\% to 16\%) whilst the use of other unidentified antibiotics was associated with a much greater increase in PRP incidence (from 39\% to 70\%).\textsuperscript{120}

It is indisputable that aminopenicillins promote the carriage of PRP, because in common with other \beta-lactams, they select PRP strains already present in the oropharynx. It is also the case that there are other penicillin-resistant streptococci present in the oral cavity, which could serve as reservoirs for resistance genes that lead to alterations in pneumococcal penicillin-binding proteins (PBPs).\textsuperscript{121}

There are some studies that detail a connection between cephalosporins and PRP.\textsuperscript{2,105,109,122–124} One compares the efficacy of cefixime versus co-amoxiclav in children with acute otitis media.\textsuperscript{134} Cefixime was associated with a rate of selection of PRP of 41.9\%, compared with 15.9\% for co-amoxiclav.\textsuperscript{124} The selection of PRP by oral cephalosporins, both in vitro and in vivo, can be explained by their reduced activities against PRP, as well as by the fact that the modification of a single penicillin-binding protein, PBP 2x, may result in a marked increase in MICs.\textsuperscript{124,126} Selection by cephalosporins occurs at higher frequencies than that by amoxicillin.\textsuperscript{125} Even very potent broad-spectrum cephalosporins are capable of selecting PRP.\textsuperscript{117} In a study whereby a single dose of ceftriaxone was compared with a 10 day course of co-amoxiclav for children with acute otitis media in an area of high PRP prevalence, nearly twice as many PRP were selected by the cephalosporin as by co-amoxiclav (27.4\% and 14.5\%, respectively).\textsuperscript{117}

Other work indicates that oral cephalosporins promote mutants with higher MICs of parenteral third-generation cephalosporins than of penicillin.\textsuperscript{115} Oral cephalosporins are often prescribed for streptococcal pharyngitis, where colonizing pneumococci normally reside. Use of these agents may be responsible for the sudden increase in PRP recorded by a community survey in Northern Ireland.\textsuperscript{127} Consumption has certainly been correlated with the prevalence of high-level penicillin resistance in Spain.\textsuperscript{128} The inference is, therefore, that cephalosporins select for and encourage resistance to \beta-lactam antibiotics in pneumococci colonizing the oropharynx.\textsuperscript{109} Furthermore, PRP have greater potential to spread than susceptible strains.\textsuperscript{129} Concurrent resistance to other antibiotics, including macrolides and co-trimoxazole in multiply-resistant strains, will not only select still greater numbers of resistant populations in the nasopharynx, but may also lead to clinical failures, thereby increasing the risk of dissemination of PRP.\textsuperscript{130} The pathogenicity of this organism is such that the increasing incidence worldwide is of major concern to clinicians.

**MRSA**

The prevalence of MRSA is also giving cause for concern.\textsuperscript{131} \textit{S. aureus} itself has always been regarded as a pathogen and now there are only a few remaining antibiotics effective against resistant strains. Potential usage of any member of the \beta-lactam group is excluded once \textit{S. aureus} becomes resistant to methicillin.\textsuperscript{1} There is a steady increase of new cases nationally and an increasing proportion of MRSA from total numbers of staphylococcal bacteraemias.\textsuperscript{132}

MRSA was first described in 1961 in Britain, but despite fear of spread, there were only sporadic outbreaks in the 1960s and 1970s.\textsuperscript{133–135} Cephalosporins were widely introduced in 1980 and the first epidemics of MRSA were reported in London during the middle 1980s.\textsuperscript{136} By 1990, most parts of the UK were affected.

The Japanese experience cites the introduction of second- and third-generation cephalosporins in the early 1980s as playing a significant part in the emergence and spread of MRSA in Tokyo hospitals.\textsuperscript{137–139} The steady increase of MRSA in Europe, including Britain and Italy, has also been attributed to the use of cephalosporins.\textsuperscript{140–142} A report from America describes a community outbreak of MRSA among iv drug abusers who self-administered cephalosporins for prophylactic purposes.\textsuperscript{143}

At least three mechanisms account for methicillin resistance in \textit{S. aureus}: production of PBP 2a or 2’ encoded by the chromosomal mec(A) gene, production of modified PBPs and inactivation of methicillin by \beta-lactamase.\textsuperscript{144} There is insufficient evidence to prove the molecular role played by antibiotics in the acquisition of these mechanisms but it is widely believed that antibiotics are associated with the induction, selection and propagation of MRSA.\textsuperscript{137,138,140,145–151} The induction hypothesis originates firstly from training procedures, whereby methicillin-susceptible \textit{S. aureus} (MSSA) is cultured in broth containing sub-MIC levels of \beta-lactam antibiotics, in particular, cefazolin and cefotaxime.\textsuperscript{138} It is possible to create MRSA (MIC > 1000 mg/L) from such experiments, although rather more difficult to transpose them into a clinical context. Methicillin-resistant clones can also be identified from \textit{S. aureus} specifically resistant to cephamycin antibiotics,\textsuperscript{146} and serial exposure of \textit{S. aureus} to cefalexin disc induces the development of staphylococci cross-resistant to cefalexin and methicillin.\textsuperscript{152} The latter work also showed that once induced, the capacity for methicillin resistance was not easily lost.\textsuperscript{152} Considering selection, some authors

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specifically cite cephalosporin therapy as a major factor in the appearance of MRSA.149–151 Once established, continued use of cephalosporins encourages the spread of the organism.137,151

It is reasonable to assume that all members of the \( \beta \)-lactam class of antibiotics have some ability to induce methicillin resistance in staphylococci, albeit difficult to prove.152 It is even more difficult to ascribe the ability for the selection process between individual \( \beta \)-lactam agents.15,153 If the capacity for generating MRSA is regarded as similar between \( \beta \)-lactam agents, however, then cephalosporins shoulder much of the responsibility owing to the frequency of their use.

There are further issues that may be important in the evolution of MRSA. We may accept that the most plausible hypothesis is repeated exposure of \( S. aureus \) to \( \beta \)-lactam antibiotics,152,154 but it is also possible that inadequate doses, or too short a course, of the same agents may fail to eradicate infection with MSSA whilst presenting the \( \beta \)-lactam ring to the organism as a template or trigger. Poor prescribing, or non-compliance on the part of the patient, would encourage bacterial mutation to produce effective resistance mechanisms or, more likely, facilitate the clonal expansion of a member of the population already with the genetic capabilities for methicillin resistance.154 But these are probably not the only factors by which MSSA becomes MRSA. It is also possible that the methicillin resistance genes are transferred to \( S. aureus \) from \( Staphylococcus epidermidis \).138,155,156

Antibiotic resistance characteristics can be transferred between coagulase-negative and coagulase-positive staphylococci and this includes methicillin resistance.156 Most hospitals have endemic methicillin-resistant \( S. epidermidis \) (MRSE) in the environment as well as colonizing staff and patients,10,12,13,157 and newly admitted patients soon become colonized with multiply-resistant CNS.3,11,12,16,17 Patients may even be admitted with MRSE on the skin at the proposed operation site, which, the authors suggested, should question the use of prophylactic cephalosporins.22 This particular study concerned patients admitted for prosthetic hip implants, in whom it was shown that the most common post-operative infections were caused by methicillin-resistant coagulase-negative staphylococci.22

The consequence of cephalosporin prophylaxis is illustrated by two clinical studies of surgical patients, the first of which showed that MRSE was detected in high numbers on the skin of surgical patients within 5 days of exposure to per-operatively administered cephalosporins.18 The second showed that just three doses of cefuroxime encouraged the appearance of MRSE from aortic graft recipients within 1 week.156 Once colonized, further usage of \( \beta \)-lactam antibiotics exerts the selection pressure required for continued increase in methicillin-resistant staphylococci.14,15,137,147,151 As it is the case that all persons are colonized with \( S. epidermidis \) and one in three persons are colonized with \( S. aureus \), the propensity for selection and spread of methicillin-resistant staphylococci and the potential for genetic exchange between staphylococcal species becomes immediately apparent.137,155,156

There is a direct association between MRSA and cephalosporins. Asensio et al.159 showed that patients who had received treatment for >5 days with cephalosporins were three times more likely to acquire MRSA than those who had not received these agents. This agrees with other studies, which detail a significant association of cephalosporins with the acquisition of MRSA.149–151,160 Conversely, a study demonstrating the effects of reducing cephalosporin usage in three acute medical wards for the elderly showed that the number of MRSA infections was reduced by half; there was also a 42% drop in the number of \( C. difficile \) infections.90 Another reported a decline in the number of MRSA isolates from 35% to 23%, following the introduction of control strategies including a decision to decrease the use of cephalosporins in favour of piperacillin–tazobactam.161 MRSA appears to be a sensitive indicator of the quality of hospital hygiene overall,162 as it is associated with other hospital organisms of concern.66,81,161 If a hospital manages to control MRSA, it controls other hospital organisms as well.162

Recently, there has been a report published detailing the deaths of four children from MRSA infections, three of whom had originally received a cephalosporin.163 Cephalosporins are only poorly active against MRSA,154–166 it is possible that usage of these antibiotics not only selects for cephalosporin usage in three acute medical wards for the elderly.161 If a hospital manages to control MRSA, it controls other hospital organisms as well.162

-one hospital-acquired infection over the past 20 years.4 Natural resistance to penicillin and cephalosporins has been further complicated by additional resistance to amoxicillin, co-amoxiclav, gentamicin and now glycopeptides.53,168 There are virtually no antibiotics available for the treatment of clinically significant resistant enterococci and no means whereby asymptomatic carriers can be cleared.28,169

The association between cephalosporin therapy and enterococcal overgrowth has already been discussed. It follows, therefore, that vancomycin-resistant enterococci (VRE) are also associated with cephalosporin usage.170,171 A recent report describes how hyperendemic VRE in a haematology unit was effectively eradicated by changing from ceftazidine to piperacillin–tazobactam as first-line treatment for febrile neutropenics. The reintroduction of ceftazidine was accompanied by a return of VRE, despite continued attention to hygiene and surveillance.170 A study previously mentioned witnessed a drop in the number of VRE isolates from 16% to 5% after restricting cephalosporins in favour of piperacillin–tazobactam.161 Outbreaks of vancomycin-resistant enterococci have increased exponentially in recent years.172–175

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Enterococci have also become a significant cause of hospital-acquired infection over the past 20 years.4 Natural resistance to penicillin and cephalosporins has been further complicated by additional resistance to amoxicillin, co-amoxiclav, gentamicin and now glycopeptides.53,168 There are virtually no antibiotics available for the treatment of clinically significant resistant enterococci and no means whereby asymptomatic carriers can be cleared.28,169

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of VRE may be controlled by switching from cephalosporins to aztreonam,\textsuperscript{172} or from cephalosporins to aminoglycosides.\textsuperscript{173}

VRE are also linked with the use of glycopeptides in hospitals\textsuperscript{151,168,174} and in animals,\textsuperscript{174,175} and this has been assumed to be the most important factor in the selection of these organisms.\textsuperscript{71} However, if the indications for vancomycin therapy are examined, it is apparent that some of these indications are actually generated by the use of cephalosporins,\textsuperscript{3,6,151,176} i.e. there is not only a direct association of cephalosporins with VRE, but an indirect one, whereby cephalosporins select other organisms that require treatment with vancomycin, which then leads to the selection of VRE.\textsuperscript{151} Methicillin-resistant staphylococci, for example, already linked to the widespread use of \(\beta\)-lactam antibiotics, including cephalosporins, warrant treatment with iv vancomycin for seriously infected patients.\textsuperscript{23,168,177} Even more vancomycin is used, for prophylactic purposes, if patients at risk are admitted to a hospital with endemic methicillin-resistant staphylococci.\textsuperscript{22,26} Glycopeptide-susceptible enterococci, selected by cephalosporin use, occasionally require treatment with vancomycin, especially if resistant to aminoglycosides.\textsuperscript{3,52} Patients with \textit{C. difficile} colitis, another sequela of cephalosporin therapy, also require treatment with vancomycin.\textsuperscript{171,178}

Thus, cephalosporin use is associated with several different organisms, the management of which may include vancomycin. Increased vancomycin usage could then select for vancomycin-resistant organisms including VRE. The \textit{C. difficile} scenario can be considered further regarding the evolution of VRE, because a patient treated with cephalosporin antibiotics suffers concurrent overgrowth of both \textit{C. difficile} and enterococci.\textsuperscript{176,179} If severe diarrhoea ensues, therapy is usually with oral vancomycin. Thereby an abundance of naturally resistant enterococci are exposed to non-absorbable vancomycin and the gut provides an excellent site for selection.\textsuperscript{46} (Vancomycin-resistant pediococci, leuconostoc and lactobacilli inhabit the mouth, gut and genital tract, but these do not appear to be the source of the genes encoding acquired resistance in enterococci.\textsuperscript{180}) When faeces are screened for VRE, those patients found to be positive are often colonized with \textit{C. difficile} as well; some even have MRSA to complete the package.\textsuperscript{179} In summary, therefore, it may be that heavy usage of cephalosporins is the main driving force behind the increasing prevalence of VRE, rather than glycopeptides.

This hypothesis is also supported by studies that report that parenteral vancomycin does not appear to be an important risk factor for acquisition of VRE,\textsuperscript{181,182} nor did the administration of copious amounts of oral vancomycin for an outbreak of \textit{C. difficile} appear to generate a problem with VRE.\textsuperscript{173} Furthermore, successful restriction of vancomycin prescribing has had no effect upon the occurrence of VRE in some centres.\textsuperscript{183,184}

An added complication regarding VRE in a hospital concerns its ability to survive long-term in the environment.\textsuperscript{185} It is worth promoting environmental hygiene in a hospital, especially since there are no effective protocols for clearing VRE from the human gastrointestinal tract.\textsuperscript{26,186} The hospital environment may not be so temperate as the human gut, but may still provide an appropriate medium whereby organisms are able to transfer resistance genes.\textsuperscript{187,188} Exchange of genes between Gram-positive organisms is well documented\textsuperscript{189,190} MRSA is another organism noted for its ability to survive in the hospital environment, but there is no evidence that resistant enterococci have contributed towards the appearance of glycopeptide-tolerant strains of MRSA.\textsuperscript{191}

\textbf{In vitro studies on the pharmacodynamic effects of cephalosporins}

So far, this review has focused upon the problem of selection and overgrowth of organisms associated with cephalosporin therapy. A common theme underlying this problem is the inability of these antibiotics to eradicate effectively key organisms, thus encouraging survival either with or without enhanced resistance to antibiotics. In this context, recent work on the mechanism of action of cephalosporin antibiotics offers some \textit{in vitro} explanations for these clinical observations.\textsuperscript{192}

Microscopic studies on the effect of \(\beta\)-lactam antibiotics on the bacterial cell at concentrations in excess of the MIC are able to distinguish between amoxicillin and cefalexin.\textsuperscript{193} The sequence of events is inhibition of cell division followed by lysis; this occurs very quickly with amoxicillin, as cell growth barely reaches two cell units in length before the onset of lysis. With cefalexin, however, there is a significant period of filamentous growth before the cell lyses, usually as a result of a sudden rupture of the cell wall. Filaments can be observed in clinical specimens from patients with Gram-negative infections treated with a variety of \(\beta\)-lactams, and, in particular, the aminothiazolyl cephalosporins, e.g. cefuroxime, cefotaxime, ceftazidime and ceftriaxone. This property has prompted one author to state that bacterial growth is not actually inhibited by the filament-forming antibiotics and it follows that overall cell wall synthesis is not inhibited to any significant extent either.\textsuperscript{194} It could also be said that the time utilized for filament formation by the cephalosporins is time available for antimicrobial resistance induction, whereas the use of other agents, which induce early cell death, would reduce the risk of such an event.

Filamentous cells that develop in the presence of cephalosporins do eventually lyse as a result of a sudden rupture of the cell wall, usually at a point where cell division would normally have taken place.\textsuperscript{195} Round cell formation and rapid lysis can be achieved by using higher concentrations of predominantly filament-forming anti-
bactericidal effects more usually associated with $\beta$-lactam agents, but promote the generation of aberrant forms that are able to survive in vivo. This may have clinical implications; first, as some bacteria may persist in patients following a course of one of these antibiotics; secondly, as survival may include the generation of tolerant or even resistant progeny, and thirdly, when assessing endotoxin release following exposure to antibiotics. If there is difficulty in convincing colleagues of the clinical and long-term benefits of decreasing cephaplosporin use, then the funders of healthcare may offer a view. Aside from the cost benefits of reducing the amount of these drugs purchased, there are substantial savings to be made from lower numbers of patients who require treatment for the consequences of overgrowth resulting from cephaplosporin therapy.

It has been suggested that the clinical freedom enjoyed by the medical profession to prescribe what they like, when they like, should be reviewed for the prescription of antimicrobials. Even experienced practitioners may not realize that giving a patient antibiotics affects not just that patient, but also their environment, and all the other people who come into contact with that environment. Removing the right to prescribe antimicrobials freely would divide the medical profession and place a monumental burden upon microbiology and infectious disease specialists. There may also be repercussions for dentists and nurse prescribers. Even if this policy was implemented, inadequate infection control and antibiotic practices elsewhere in the world would erode any progress made in halting the increase of multiply-resistant organisms. The World Health Organization (WHO) must take some responsibility in promoting international discussion on antimicrobial use throughout the world.

A multifaceted approach to the control of multiply-resistant organisms is required. There are a variety of strategies, some of which have already been mentioned, i.e. antibiotic policies, judicious use of antimicrobials by clinicians, laboratory support, WHO involvement and a strengthening of the role of microbiologists and infectious diseases physicians. Education for everyone is vitally important and in particular, perhaps, for medical students, for whom microbiology teaching should be re-prioritized within the undergraduate curriculum.

Pharmacists play an important role in restricting over-the-counter sales and in the advice they offer. In the hospitals, they audit prescribing, evaluate adherence to policies and formulary and issue advice on iv-to-oral and antibiotic stop mechanisms. The microbiology laboratory cannot provide instant identification of all microorganisms, but there are an increasing number of rapid diagnostic techniques available and 24 h processing of non-urgent specimens from high-risk patients can be introduced in order to avoid a sample languishing until the next working day. Laboratory computers should provide the data required for multiple audit and surveillance strategies for infection control. Pharmaceutical research, better definitions of infection and the dangers of prolonged prescribing are other potential control issues.

In defence of the cephaplosporin antibiotics, they provide useful activity against a number of common pathogens, and their low toxicity reassures clinicians and obviates the need for serum levels. Patients allergic to penicillin sometimes rely upon a cephaplosporin as the only agent available to

Filament formation leads to a rapid increase in endotoxin production and, ultimately, endotoxin release when these cells lyse. There are several studies to support this. Higher doses of filament-forming antibiotics may alternatively produce the more fragile spheroplasts, which would tend to lyse and thus reduce the propensity for endotoxic shock. It is possible, therefore, that the choice and dose of an antimicrobial agent for a patient with septic shock could be clinically crucial.

Conclusion

This review has attempted to piece together some of the suspicions surrounding a very widely used class of antibiotics. There is strong suggestive evidence that cephaplosporins have played a major role in encouraging the organisms discussed. Countries, and even individual hospitals, that have enforced low usage of cephaplosporins through education, strict antibiotic policies and prescribing penalties, are currently experiencing relatively low rates of multiply-resistant organisms. Countries where cephaplosporins are used more often have much higher rates of resistance. It is, however, difficult to determine whether it is specific restriction of cephaplosporin antibiotics in isolation that is responsible for the lower rates of resistance, or, indeed, an overall effect from controlling all antibiotic classes. In defence of the former view, most of the references cited specifically target cephaplosporins as key players in the link between antibiotic usage and prevalence of multiply-resistant organisms.

Compounding the problem is the fact that microbiologists have yet to define fully the mechanisms linking antibiotic usage and antibiotic resistance. Prescribing colleagues will almost certainly question how just one group of antibiotics alone, within the extensive $\beta$-lactam class, could be the most important driving force behind the continuing increase in resistant organisms, even allowing for broad-spectrum activity and popularity. Convincing clinicians that antibiotic therapy should be more closely tailored to the patient requires scientific proof and this is not yet evident. Changing current antibiotic prescribing practices demands a strong microbiology presence, robust antibiotic policies, education and laboratory support, as well as a more careful evaluation of the infected patient and potential pathogen, confirmed or otherwise.

If there are any doubts about the clinical freedom enjoyed by the medical profession to prescribe what they like, when they like, the peer, should be reviewed for the prescription of antimicrobials. Even experienced practitioners may not realize that giving a patient antibiotics affects not just that patient, but also their environment, and all the other people who come into contact with that environment. Removing the right to prescribe antimicrobials freely would divide the medical profession and place a monumental burden upon microbiology and infectious disease specialists. There may also be repercussions for dentists and nurse prescribers. Even if this policy was implemented, inadequate infection control and antibiotic practices elsewhere in the world would erode any progress made in halting the increase of multiply-resistant organisms. The World Health Organization (WHO) must take some responsibility in promoting international discussion on antimicrobial use throughout the world.

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Acknowledgements

Thanks are due to Mrs Su Byrne for secretarial services and Dr Shelley Heard for original teaching on antibiotics.

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them. They should not be used for routine prophylaxis, however, but have their efficacy preserved with more rational prescribing.22,213,214 There may well be an argument for revising the recommended adult doses of, in particular, the aminothiazolyl cephalosporins. Reduced bactericidal activity leading to the selection phenomena described may relate to inadequate dosing rather than an inherent therapeutic deficit. Tissue penetration and concentration at the site of infection are other factors to consider.

It is also pertinent to say that in the absence of cephalosporins, greater use of other antibiotics would have been required. Not only would these have very likely generated their own particular selection strategies, but also some agents would have almost certainly produced considerable toxic effects, far more so than the cephalosporins. It is unlikely, however, that we would have seen the prolific rise of multiply-resistant organisms if the cephalosporins had never been introduced. This is because few of the existing agents offered such broad-spectrum activity, with such low toxicity, and consequently would not have been universally prescribed. A greater range of antibiotics would have been utilized, diffusing the selection potential. It is the popularity of the cephalosporins, perhaps, that has become their downfall.

Resistance inevitably follows the introduction of a new antimicrobial. In intensive care units, the original promise offered by cephalosporins as broad-spectrum therapy was almost immediately eroded by the appearance of resistant organisms, and their use was supplanted by the use of quinolones. The legacy of heavy usage of these drugs, however, resulted in the appearance of multiply-resistant Acinetobacter. Now S. maltophilia flourishes, following the introduction of the carbapenems.215 This ominous progression, played out over the past 20 years, can be likened to a worldwide chess game; as one piece is captured, another moves to threaten.216 If we therefore shift prescribing choice away from the cephalosporins to another antibiotic group chosen.46 Resistance is the price one pays for having an antibiotic and using it, because nature abhors a vacuum and will fill it up if it can.134 Ultimately, the future therapy of infection may almost certainly depend upon the immune response, with continued work on the development of cytokine inhibitors.210 The latter are already showing positive benefits for patients in ITU.217,218

In conclusion, the selection pressure created by heavy usage of cephalosporin antibiotics over the last 20 years has generated a plethora of multiply-resistant organisms. The possible links between C. difficile, VRE and MRSA serve as a warning for potentially untreatable infection—with ESBL-C providing the Gram-negative equivalent. The risks posed by overuse of cephalosporins remain only speculative, unless specific proof is forthcoming. By then, though, we may be contemplating the post-antibiotic era.
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