*Journal of Antimicrobial Chemotherapy* (2009) **64**, *Suppl. 1*, i29–i36
doi:10.1093/jac/dkp255

JAC

# Has the era of untreatable infections arrived?

**David M. Livermore***

*Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK*

**Antibiotic resistance is a major public health concern, with fears expressed that we shortly will run out of antibiotics. In reality, the picture is more mixed, improving against some pathogens but worsening against others. Against methicillin-resistant *Staphylococcus aureus* (MRSA)—the highest profile pathogen—the range of treatment options is expanding, with daptomycin, linezolid and tigecycline all launched, and telavancin, ceftobiprole, ceftaroline and dalbavancin anticipated. There is a greater problem with enterococci, especially if, as in endocarditis, bactericidal activity is needed and the isolate has high-level aminoglycoside resistance; nevertheless, daptomycin, telavancin and razupenem all offer cidal potential. Against Enterobacteriaceae, the rapid and disturbing spread of extended-spectrum β-lactamases, AmpC enzymes and quinolone resistance is forcing increased reliance on carbapenems, with resistance to these slowly accumulating via the spread of metallo-, KPC and OXA-48 β-lactamases. Future options overcoming some of these mechanisms include various novel β-lactamase-inhibitor combinations, but none of these overcomes all the carbapenemase types now circulating. Multiresistance that includes carbapenems is much commoner in non-fermenters than in the Enterobacteriaceae, depending mostly on OXA carbapenemases in *Acinetobacter baumannii* and on combinations of chromosomal mutation in *Pseudomonas aeruginosa*. No agent in advanced development has much to offer here, though there is interest in modified, less-toxic, polymyxin derivatives and in the siderophore monobactam BAL30072, which has impressive activity against *A. baumannii* and members of the *Burkholderia cepacia* complex. A final and surprising problem is *Neisseria gonorrhoeae*, where each good oral agent has been eroded in turn and where there is now little in reserve behind the oral oxyimino cephalosporins, to which low-level resistance is emerging.**

Keywords: β-lactamases, MRSA, *Escherichia coli*, *Acinetobacter baumannii*, *Neisseria gonorrhoeae*

## Introduction

Antibiotic resistance is subject to frequent press comment, with fears expressed that we shall soon 'run out' of antibiotics and that classical infections will regain their status as major sources of mortality.[1] It is suggested, too, that a swathe of modern medical procedures—from transplants to immunosuppressive cancer management—may collapse, as each depends crucially on our ability to treat infection. How justifiable are these fears?

This article reviews these concerns as they apply to the community and hospital bacteria prevalent in the developed world. Resistance presents different challenges in developing countries, for here the drift to untreatability often reflects issues of drug cost and supply as well as of resistance *per se*; moreover, the relative importance of classical pathogens is far greater.[2] Contrarily, developing countries sometimes have treatments not available in the West. These include various combinations of cephalosporins and β-lactamase inhibitors, with cefoperazone/sulbactam available across much of Asia, and with ceftriaxone/sulbactam and cefepime/tazobactam in India.[3] These may be useful in the battle against bacteria with extended-spectrum β-lactamases (ESBLs).

As will be seen, the resistance landscape is not as bleak as is sometimes painted, particularly against Gram-positive pathogens, but there must be concern about the situation with many Gram-negative opportunists. Although these mostly have low inherent pathogenicity, they are a major problem in intensive care. There is also (more surprisingly) scope for concern about gonococci, where we are running out of convenient oral treatment options.

## Staphylococci and streptococci

The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemias is now falling in England (Figure 1),[4,5] with a reduction in MRSA infection also achieved in some US hospitals.[6] Factors contributing to these improvements include

*Tel: +44-20-8327-7223; Fax: +44-20-8327-6264; E-mail: david.livermore@hpa.org.uk

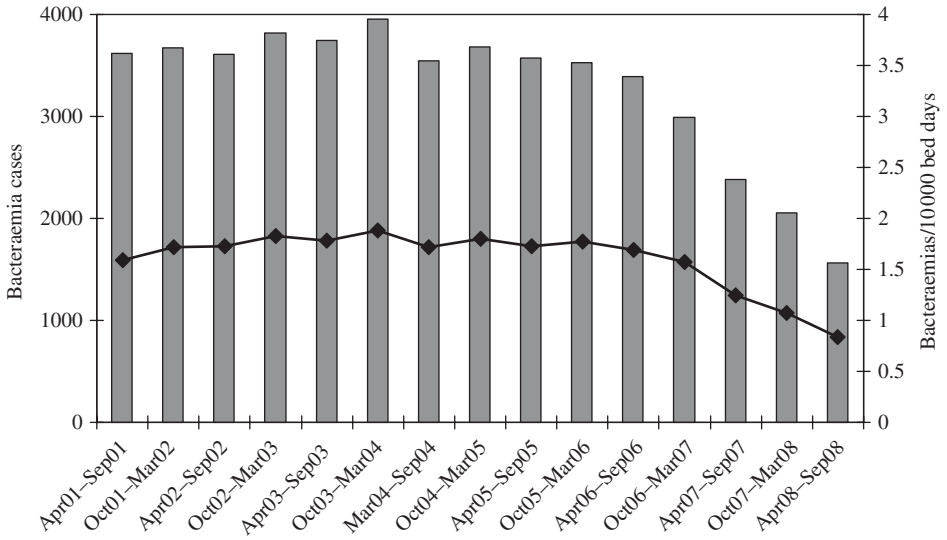


**Figure 1.** Numbers of MRSA bacteraemias in England by 6 month periods from 2001 to 2008 (bars, left axis) and rates of bacteraemia per 10000 bed days (line, right axis). Based on mandatory reporting to the HPA.

greater emphasis on infection control, mupirocin-based decolonization of patients and better management of intravenous lines, which often provide the entry portal. There is some evidence that EMRSA-16, which is one of the two most prevalent MRSA clones in the UK, is in particular decline (HPA, data on file). What is more, there is a growing range of new anti-MRSA drugs, with linezolid, quinupristin/dalfopristin, daptomycin and tigecycline marketed, with ceftobiprole, ceftaroline, telavancin, dalbavancin and oritavancin in advanced development,[7] and with razupenem (PZ-601) in Phase II trials.[8] The problem with MRSA is no longer a shortage of therapies, but whether new—and more costly—therapies offer significant advantages over established glycopeptides. Here the data are ambiguous, with most trials powered to show equivalence not superiority, but with hints that linezolid may be superior to vancomycin in MRSA pneumonia[9] and that daptomycin may approach superiority in bacteraemia.[10]

In the case of pneumococci, the introduction of a heptavalent conjugate vaccine (Prevnar; Wyeth) is reducing the incidence of severe disease among vaccinated children and their elderly contacts.[11] Moreover, since this vaccine targets those serotypes in which resistance is most prevalent, it is also reducing the proportion of resistant isolates,[12] though it also seems gradually to be selecting for penicillin-resistant strains belonging to non-vaccine serotypes, notably 19A.[13] This limitation is being addressed by the development of new 11- and 13-valent vaccines, with the latter protecting against serotype 19A.[14] In addition, and as with MRSA, new treatment options are emerging, including quinolones, ketolides, linezolid, tigecycline and, potentially, ceftobiprole and ceftaroline.

## Enterococci

Although enterococci account for 10-fold fewer infections than *S. aureus*, and have much less pathogenic potential, they are problematic in immunosuppressed patients and are frequent agents of endocarditis. *Enterococcus faecalis*—the commoner species—is almost always susceptible to ampicillin,[15] whereas *Enterococcus faecium* generally is resistant. Vancomycin resistance, too, is mostly seen in *E. faecium* and is largely confined to a few specialist centres in the UK (Table 1), though it is more widespread in the USA. A greater practical problem is that ~30%–50% of both *E. faecalis* and *E. faecium* have high-level gentamicin and/or streptomycin resistance, precluding the synergy upon which standard endocarditis therapy depends. Several new agents, including linezolid and tigecycline, have good *in vitro* activity against enterococci (including vancomycin-resistant strains) but are bacteriostatic, making them of limited value in endocarditis or neutropenic patients. Daptomycin is bactericidal, but, at presently licensed dosages, is marginal against *E. faecium*.[16] This might be overcome with higher dosages, presently under evaluation. Telavancin may provide a further cidal option, though not against those isolates with VanA.[17] Further back in the development cycle, razupenem (PZ-601) is unique among β-lactams in retaining activity against many ampicillin-resistant *E. faecium*.[18]

**Table 1.** Distribution of bacteraemias due to glycopeptide-resistant enterococci (GRE) among English hospital trusts, October 2005–September 2006

| Total no. GRE bacteraemias | No. trusts falling in stated range |
|---|---|
| 0 | 41 |
| 1–10 | 111 |
| 11–20 | 12 |
| 21–30 | 0 |
| 31–40 | 4[a] |
| >40 | 4[a] |

[a]These eight trusts account for 39% of all GRE bacteraemias; all were specialist centres, four were in London.

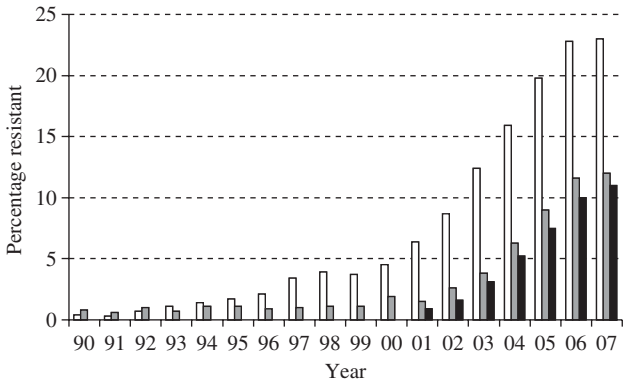


**Figure 2.** Rise in the proportions of *E. coli* from bacteraemias in England, Wales and Northern Ireland resistant to fluoroquinolones (white), oxyimino-cephalosporins (grey) and both (black). Based on laboratories' reports to the HPA.

## Enterobacteriaceae

It is much harder to be positive about the situation with Enterobacteriaceae, where major recent shifts have occurred, with the accumulation of ESBLs in *Escherichia coli* and *Klebsiella* spp., and a generalized rise in fluoroquinolone-resistant organisms (Figure 2).[19,20]

Until 2000, most ESBL producers were hospital *Klebsiella* spp. with TEM and SHV mutant β-lactamases. Now, in contrast, the dominant ESBLs across most of Europe and Asia are CTX-M enzymes, which originated as genetic escapes from *Kluyvera* spp. These have proliferated not only in hospital *Klebsiella pneumoniae* but also in *E. coli*, including those from 'complicated' community patients, generally with a history of recent hospitalization and antibiotic therapy. The urinary tract is the commonest site infected.

Different CTX-M ESBL variants have become prevalent in different countries; also, the degree of clonality among producer *E. coli* varies with locale, though a sequence type (ST)131, serotype O25:H4 lineage with CTX-M-15 enzyme has disseminated globally (Figure 3).[21] Irrespective of enzyme type and strain, most producer Enterobacteriaceae are multiresistant: >80% of ESBL-positive *E. coli* from bacteraemias in the UK and Ireland are resistant to fluoroquinolones and >40% are resistant to gentamicin.[22] Consequently, the likelihood of a urosepsis case, (say), being empirically treated with a compound to which the isolate proves resistant is increased. This is important and, in a meta-analysis, Schwaber and Carmeli[23] found that the death rate among patients with bacteraemias caused by ESBL producers was 1.85-fold higher than among those with bacteraemias due to non-producers, principally owing to longer delays in the initiation of effective therapy. A similar conclusion was reached by Rodriguez-Baño *et al.*,[24] who found 9% mortality among patients receiving appropriate empirical therapy for bacteraemias due to *E. coli* with ESBLs versus 35% among those receiving drugs to which the isolates were subsequently found to be resistant.

Carbapenems are accepted as the drugs of choice for serious infections caused by ESBL producers and are often the only widely used antibiotics to remain active.[22,25] This must drive their use and, also, the selection pressure for carbapenem resistance. Although carbapenem resistance currently is seen in <2% of UK Enterobacteriaceae, there are growing problems overseas. In particular, there has been substantial spread of *K. pneumoniae* with KPC carbapenemases in the USA, Israel and Greece,[26–28] with those from the first two countries often belonging to a single highly successful ST258 clone.[29] Metallo-β-lactamases (MBLs), too, are becoming scattered among Enterobacteriaceae, though they remain less of a problem than in *Pseudomonas aeruginosa* (see below).[30] In Greece, plasmids and integrons encoding VIM-1 MBL have spread widely among *K. pneumoniae*, with 42% of bloodstream isolates now carrying these enzymes or KPC types.[31] Elsewhere, the prevalence seems much lower, but assessment is complicated by the fact that MICs for some producers are below current European Committee on Antimicrobial Susceptibility Testing (EUCAST) or CLSI breakpoints. A study of 209 cephalosporin-resistant Enterobacteriaceae from Bolzano (Northern Italy) revealed 24 with VIM MBLs, including 10 clonal *K. pneumoniae*. MICs of imipenem and meropenem ranged from 2 to >32 and from 0.25 to >32 mg/L, respectively.[32] If such organisms are present in Bolzano (with a population of 120000), it is likely that they are widespread in larger Italian centres. In Turkey there are multiple reports of OXA-48, a plasmid-mediated carbapenemase, in *K. pneumoniae* and, less often, *E. coli*. *K. pneumoniae* strains with this enzyme have caused sizeable hospital outbreaks.[33]

Up to December 2007, the UK Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) had received just eight carbapenemase-producing Enterobacteriaceae: five with MBLs, two with KPC carbapenemases and one *K. pneumoniae* with OXA-48 enzyme. MICs for six of these are shown in Table 2, underscoring their multiresistance. During 2008 we received 21 further producers from UK patients, doubling the total for all previous years combined. These comprised: (i) five *K. pneumoniae* with KPC carbapenemases, two epidemiologically linked to Greece and one to Israel; (ii) nine *K. pneumoniae* with OXA-48 enzyme, none with defined overseas links but including two identical isolates from different residents at the same nursing home; (iii) two *K. pneumoniae* with a VIM-type MBL, both linked to Greece; (iv) a *Pantoea* sp. with an IMP-type enzyme and no overseas link; and (v) four with NDM-1, a novel metallo-enzyme strongly linked to India and Pakistan. All of the six KPC-positive *K. pneumoniae* to date belong to the international ST258 clone (ARMRL, data on file).

Whilst these numbers were far fewer than the ~150 Enterobacteriaceae referred in the same period with ertapenem resistance contingent on combinations of ESBL or AmpC and impermeability,[34] the potential risk is greater since: (i) carbapenemases are a more efficient resistance mechanism; (ii) their genes may achieve horizontal spread; and (iii) strain ST258 is a fit lineage demonstrably able to disseminate widely. In contrast, strains with carbapenem resistance via combinations of β-lactamase plus impermeability have not been associated with cross infection or outbreaks.

Treatment of severe infections due to carbapenemase-producing Enterobacteriaceae presents major challenges. Members of the ST258 KPC-positive *K. pneumoniae* clone usually are susceptible to gentamicin, polymyxin and tigecycline, but other lineages with KPC carbapenemases may carry gentamicin-modifying enzymes. Enterobacteriaceae with MBLs are similarly multiresistant and, although aztreonam is stable to hydrolysis, many producers are resistant owing to co-production of ESBLs or AmpC enzymes.[32] Isolates with OXA-48 enzyme

**Figure 3.** International distribution of *E. coli* O25:H4 ST131 with CTX-M-15 ESBL and multiresistance to other antibiotics. In many cases the only drugs to remain active are polymyxins and tigecycline.

**Table 2.** MICs for carbapenemase-producing Enterobacteriaceae referred to ARMRL between 2003 and 2007

| | | MIC (mg/L)[a] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Species | Enzyme | AMP | ETP | IPM | IPM–EDTA | MEM | CAZ | TZP | ATM | CIP | GEN | TOB | AMK | CST |
| *Klebsiella* spp. | IMP | >64 | >16 | >32 | 0.5 | >32 | >256 | **(16)** | **1** | **≤0.125** | >32 | >32 | 32 | **≤0.5** |
| *Klebsiella* spp. | IMP | >64 | 8 | **(2)** | 0.125 | 4 | >256 | **(16)** | **≤0.125** | 4 | 16 | >32 | 16 | **≤0.5** |
| *E. coli* | IMP | >64 | 8 | **(2)** | 0.125 | **(2)** | 256 | **(8)** | **0.25** | >8 | >32 | >32 | **2** | **≤0.5** |
| *Enterobacter* spp. | KPC-4 | >64 | >16 | >32 | >16 | >32 | >64 | >64 | >64 | >8 | **1** | **1** | **2** | **1** |
| *Klebsiella* spp. | KPC-3 | >64 | >16 | 32 | >16 | >32 | 256 | >64 | >64 | >8 | **1** | 32 | 32 | **≤0.5** |
| *K. pneumoniae* | OXA-48 | >64 | >16 | 16 | 8 | 8 | 256 | >64 | >64 | >8 | **1** | 32 | **8** | **1** |

AMK, amikacin; AMP, ampicillin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CST, colistin; ETP, ertapenem; GEN, gentamicin; IPM, imipenem; MEM, meropenem; TOB, tobramycin; TZP, piperacillin/tazobactam.

[a]Values indicating susceptibility are shown in bold font, but are shown in parentheses for β-lactams where, allowing the hydrolytic activity, we would be sceptical about using the agent therapeutically.

have very variable resistance profiles, contingent on the other mechanisms frequently being present (ARMRL, data on file).

Although tigecycline and polymyxins are active *in vitro* against most carbapenemase-producing Enterobacteriaceae, neither seems a panacea. Tigecycline has low blood levels and its efficacy in severely-ill patients remains to be established unequivocally.[35] It proved inferior to imipenem/cilastatin in nosocomial pneumonia, largely owing to poorer outcomes in patients with ventilator-associated infection.[36] Polymyxins, too, have questionable performance in pneumonia, owing to poor pulmonary penetration; they also have a reputation for nephrotoxicity, though recent experience suggests this is exaggerated. Moreover, pulmonary levels can be increased by co-administration of the nebulized formulation.[37,38] Among antibiotics in clinical development, one showing promise against carbapenem-resistant Enterobacteriaceae is ceftazidime with NXL104, a novel 'suicide' β-lactamase inhibitor. This combination was active at ≤4 mg/L, against most strains with KPC and OXA-48 enzymes,[39] but lacked activity against strains with MBLs. Similar performance would be expected for ceftaroline/NXL104, which is earlier in the development pathway. Otherwise, the novel aminomethyl tetracycline PTK-0796 (Paratek) evades efflux-mediated tetracycline resistance and has now completed Phase II clinical trials, although it is not clear whether its serum levels are superior to those of tigecycline.

Other possibilities, still in pre-clinical development, include Basilea's BAL30376, which combines a dihydroxypyridone monobactam (BAL19764), inherently stable to MBLs, with a bridged monobactam (BAL29880) and clavulanate, to protect against AmpC β-lactamases and ESBLs, respectively.[40,41] The combination's main gap is a lack of cover against strains with KPC enzymes, but minorities of β-lactamase-negative,

AmpC-producing and ESBL-producing Enterobacteriaceae have reduced susceptibility.[42] The reasons for this variability are unclear, but may relate to strain-variable expression of iron uptake pathways, which are accessible to dihydroxypyridone and catechol-linked β-lactams.[43] The possibility of modifying polymyxins to detoxify them, whilst retaining antimicrobial activity, is also under investigation and may prove effective.[44]

Aside from the challenges of carbapenem-resistant Enterobacteriaceae, there is a major issue about the treatment of community infections due to ESBL-producing Enterobacteriaceae. Nitrofurantoin and fosfomycin usually remain active in lower urinary infections but are not suitable in ascending infections;[45] mecillinam, too, may appear active but its activity is impaired if the inoculum is raised and there are few data on its clinical efficacy against ESBL producers.[46] Possible answers might include combination of an oral cephalosporin with a β-lactamase inhibitor.[3] Such combinations are marketed in India, but little has been published on their efficacy against ESBL producers. Other options include oral penems and carbapenems, with faropenem and tebipenem available in Japan, but not elsewhere. Tebipenem has MICs as low as those of meropenem for most Enterobacteriaceae,[47] whereas faropenem is less active[48] and had poor results given at 300 mg twice daily in a cystitis trial,[49] a deficiency that might be overcome by a higher dosage. The aminomethyl tetracycline PTK-0796 may be a further oral option, but only if (unlike tigecycline) it gives adequate urinary levels.

## Non-fermenters

*P. aeruginosa* is considerably the most important non-fermenter both as a nosocomial opportunist and as a colonist of the cystic fibrosis (CF) lung. Many CF isolates are multiresistant, reflecting the fact that the infection is essentially ineradicable and is exposed to repeated rounds of antibiotic selection pressure, co-selecting resistance and hypermutability, which facilitates development of further resistance.[50,51] It is common to see CF isolates of *P. aeruginosa* with multiple mutational mechanisms compromising all antibiotics except (usually) the polymyxins. The only mitigating factor is that the *in vitro*/*in vivo* resistance correlation is poor in CF and patients often respond even when the pulmonary flora contains a high proportion of resistant bacteria.

Multiresistance among *P. aeruginosa* isolates is less prevalent outside CF, but varies hugely with locale.[52] As in CF, it mostly reflects the accumulation of mutations variously affecting efflux, permeability and chromosomal β-lactamase expression.[53] Less often, this multiresistance reflects the presence of acquired genes and plasmids. TEM, SHV and CTX-M ESBLs all have been reported in *P. aeruginosa*, but are uncommon; VEB ESBLs are prevalent in the species in East Asia and are now scattered elsewhere,[54] and PER types are widespread in Turkey.[55]

Resistance to carbapenems, particularly imipenem, can arise by simple mutation in *P. aeruginosa*, mediated by loss of a carbapenem-specific porin, OprD. Less often, MBLs are responsible: VIM and IMP MBLs have been reported internationally,[30] whereas clones with SPM-1 enzymes have disseminated in Brazil.[56] Some producers have caused major outbreaks, with dozens to hundreds of patients affected over prolonged periods.[57,58] ARMRL has received >100 producer isolates, mostly with VIM MBLs, from UK clinical laboratories. These included representatives of several small outbreaks involving ≤16 patients.

**Table 3.** Susceptibilities (%) among 100 consecutive MBL-producing *P. aeruginosa* isolates referred to the ARMRL, 2001–7

| Antibiotic | Susceptible | Intermediate | Resistant | Not tested |
|---|---|---|---|---|
| IPM | 2 | 4 | 94 | |
| MEM | 2 | 1 | 97 | |
| CAZ | 6 | | 91 | 3 |
| PIP | 2 | | 95 | 3 |
| TZP | 6 | | 90 | 4 |
| ATM | 31 | | 62 | 7 |
| GEN | 3 | | 94 | 3 |
| TOB | 5 | | 79 | 16 |
| AMK | 14 | 5 | 78 | 3 |
| CIP | 12 | | 85 | 3 |
| CST | 95 | | 2 | 3 |

AMK, amikacin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CST, colistin; GEN, gentamicin; IPM, imipenem; MEM, meropenem; PIP, piperacillin; TOB, tobramycin; TZP, piperacillin/tazobactam.

The only agents still widely active were the polymyxins, exemplified by colistin in Table 3.

*Acinetobacter baumannii*, the next-most-important non-fermenter after *P. aeruginosa*, is more often resistant.[59] This resistance mostly reflects gene acquisition, though up-regulation of chromosomal AmpC and OXA-51-like β-lactamases arises via upstream migration of insertion sequences, notably IS*Aba-1*.[60]

Until 2000, carbapenem resistance remained rare in *A. baumannii*, though resistance to other antibiotics was widespread. Subsequently, carbapenem resistance has increased sharply, owing to the clonal spread of strains with IS*Aba-1*-mediated up-regulation of chromosomal OXA-51-like enzymes, or with acquired OXA-23, OXA-40 (OXA-24) or OXA-58-like carbapenemases. OXA-23, probably the commonest of these, originated in *Acinetobacter radioresistens* but has transferred to *A. baumannii*.[61] A few *Acinetobacter* strains have acquired MBLs.

Clones with OXA carbapenemases have spread between hospitals. Thus, different lineages with OXA-40 enzyme have disseminated in Northern Spain[62] and around Chicago,[63] whilst lineages with up-regulated OXA-51 enzyme have been transported to the UK and USA with military casualties repatriated from the Middle East.[64] In the UK, the Southeast (SE) clone, with an up-regulated OXA-51-like enzyme, and the 'OXA-23 clone 1',[65,66] with OXA-23 enzyme, have each reached >50 hospitals, mostly in the South East. The SE clone has variable resistance to imipenem, borderline susceptibility to tigecycline and full susceptibility to polymyxins, whereas the OXA-23 clone 1 is usually susceptible only to tigecycline and polymyxin. The OXA-40-producing ACB20 strain circulating around Chicago is consistently susceptible only to polymyxins.[63]

The attributable mortality risk of *A. baumannii* infections remains controversial, since many affected patients have complicated underlying disease;[59] nevertheless, some infections are life-threatening and, here, treatment increasingly depends on polymyxins. Positive outcomes are reported in approximately 60% of cases treated with these drugs, though rates are lower in pneumonia, a problem that may be addressed by co-administration of the nebulized formulation.[59,67]

Very few new antibiotics offer potential against *P. aeruginosa* and *A. baumannii*. Doripenem has ~2-fold lower MICs than meropenem for *P. aeruginosa*, but this advantage is offset by lower breakpoints (EUCAST S ≤ 1, R > 4 mg/L) than for meropenem (S ≤ 2, R > 8 mg/L) and imipenem (S ≤ 4, R > 8 mg/L), based on the lower dosages validated in clinical trials (500 mg three times daily for doripenem compared with up to 2 g three times daily for meropenem). The novel oxyimino-cephalosporin CXA-101 (FR264205)[68] is 4- to 8-fold more active than ceftazidime against *P. aeruginosa*, potentially overcoming most resistance caused by efflux or derepression of AmpC though not that due to ESBLs and MBLs. Resistance also remains in some CF strains with complex combinations of mechanisms.

A further interesting compound is the dihydroxypyridone monobactam BAL30072 (Basilea), which was found to have MICs of ≤8 mg/L for ~90% of isolates belonging to the *A. baumannii* OXA-23 clone 1 and the SE clone.[69] Values up to and above 128 mg/L, nevertheless, were seen for small minorities of these lineages and for greater proportions of carbapenemase producers belonging to other clones. BAL30072 was also active at 8 mg/L against 78% of multiresistant *Burkholderia cepacia* complex isolates from CF and deserves testing against *Burkholderia pseudomallei*. Against multiresistant *P. aeruginosa* from CF it was ~2-fold more active than aztreonam, thus offering a less dramatic gain.

Other potential future options against non-fermenters include peptides. Potential ways to detoxify polymyxins were mentioned earlier.[44] Many larger peptides with anti-*Pseudomonas* or anti-*Acinetobacter* activity have also been described; most cause membrane disruption and have been isolated from natural sources, ranging from phagocytes to amphibian skin, where they doubtless fulfil a protective role. The problems for pharmaceutical development are that they are difficult to manufacture in commercial quantities, are prone to rapid metabolism and may be immunogenic.

### *Neisseria gonorrhoeae*

*N. gonorrhoeae* may seem a strange candidate for inclusion on a list of pathogens where we are running out of treatments, for gonorrhoea has been an easy target throughout the antibiotic era. Nevertheless, *N. gonorrhoeae* has progressively accumulated resistance, and the spread of resistant strains among sexual networks led to abandonment of penicillin and, latterly, ciprofloxacin as standard therapies. There is now a slow accumulation of strains with resistance to azithromycin and of those with incremental reductions in susceptibility to cefixime.[70] Disturbingly, there is little in reserve behind these agents: spectinomycin can be used too, but is no longer readily available in the UK, its marketing authorization having lapsed. Pristinamycin can be used too, but is not readily available outside France and has not been tested against recently described strains with high-level azithromycin resistance.[71]

Few new drugs have been tested extensively against *N. gonorrhoeae*. Ertapenem was highly active *in vitro*, with MICs of mostly 0.004–0.06 mg/L and has a long half-life.[72] However, it is unclear whether its activity is impaired against strains with the penicillin-binding protein (PBP) mutations that compromise cefixime and this needs to be investigated, as does the anti-gonococcal activity of new oral penems and carbapenems, notably tebipenem. PTK-0796 should overcome Tet(M), which is the main source of high-level tetracycline resistance in *N. gonorrhoeae* and might be an oral treatment, although multiple doses would be needed.

## Conclusion

At present we can still treat most infections. Against staphylococci and streptococci our options are increasing; moreover, improved infection control is reducing the incidence of MRSA bacteraemias in the UK and new vaccines are reducing the incidence of severe pneumococcal disease. In these cases there is little likelihood of untreatable infection in the foreseeable future. There is more of a risk with enterococci, especially in settings (e.g. endocarditis) where bactericidal activity is mandatory; nevertheless, the absolute number of such infections is small and the risk to public health must be kept in proportion.

There should be far more concern about Gram-negative pathogens. It is now common to see Enterobacteriaceae susceptible only to carbapenems, tigecycline and polymyxin, and there is concern about the rise of carbapenem resistance caused by KPC and MBLs. Simultaneously, ESBL-producing, quinolone-resistant *E. coli* are seeping into the community, often causing urinary infections that are no longer easy to treat with oral agents. In the case of non-fermenters, strains resistant to carbapenems are already common, leaving polymyxins and tigecycline as the last agents active, neither of them ideal. Last, the gonococcus is making a remarkable and worrisome attempt to develop resistance to all the antibiotics that allow convenient oral therapy.

Some of these issues might be addressed by better infection control or by novel vaccines. Nevertheless, the inescapable reality is that there is a pressing need for new antimicrobials against Gram-negative bacteria. This is more challenging than the development of new agents active against Gram-positive bacteria, since an anti-Gram-negative drug must cross the outer membrane and evade efflux. It is likely that some of the new β-lactamase inhibitor combinations described here will prove useful, but none will address all of the resistance mechanisms now proliferating. The result will be a slowly growing minority of infections that become technically untreatable. Far more numerous, though, will be the seriously-ill patients who, because their pathogen is multiresistant, receive an ineffective antibiotic as primary empirical therapy. And this, as numerous studies have shown, *is* associated with increased mortality.[73]

## Transparency declaration

The author has shareholdings, or acts as enduring attorney for a shareholder, in AstraZeneca, Dechra, EcoAnimal Health, GlaxoSmithKline, Pfizer and Schering-Plough; he has had research contracts or conference finance in the past 3 years from AstraZeneca, Calixa, Cerexa, Johnson & Johnson, Merck, Novartis, Novexel, Pfizer, Phico, Theravance and Wyeth. He is employed by the HPA and is influenced also by their views on antibiotic usage.

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