The growing burden of antimicrobial resistance

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Since the first usage of antimicrobials, the burden of resistance among bacteria has progressively increased and has accelerated within the last 10 years. Antibiotic resistance genes were present at very low levels prior to the introduction of antibiotics and it is largely the selective pressure of antibiotic use and the resulting exposure of bacteria, not only in humans but also in companion and food animals and the environment, which has caused the rise. The increasing mobility across the globe of people, food and animals is another factor. Examples of this are the international pandemic of different genotypes of CTX-M extended-spectrum β-lactamas (particularly CTX-M-14 and -15) and the emergence of the carbapenemase KPC-1 in both the USA and Israel. This review details examples of both the emergence and dissemination through different genetic routes, both direct and indirect selective pressure, of significance resistance in Staphylococcus aureus, Enterococcus species, Enterobacteriaceae and Pseudomonas/Acinetobacter. The response made by society to reduce resistance involves surveillance, reduced usage, improved infection control and the introduction of new antimicrobial agents. Although efforts are being made in all these areas, there is an urgent need to increase the effectiveness of these interventions or some bacterial infections will become difficult if not impossible to treat reliably.

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The emergence, spread and globalization of antimicrobial resistance

Antibacterial therapy has only emerged over the last 60 years as a practical proposition and has become one of the pillars of modern medicine. The removal of the scourge of premature death due to bacterial infection is now taken for granted in the developed world, but this is threatened by the development of resistance to antimicrobials. As bacteria are thought to have evolved 3500 million years ago,1 60 years is but ‘a second in a day’ in evolutionary time. Despite this, we have seen the development, even since their early use, of antibiotic resistance in many bacterial species. The first description of the clinical use of penicillin was contemporaneous with a report of an enzyme (named penicillinase by the authors)—a specific member of the family of β-lactamas—that destroyed benzylpenicillin and conferred resistance to penicillin.2

Surprisingly, penicillinase production in Staphylococcus aureus spread rapidly, and by the late 1940s, ~50% of the S. aureus in the UK were positive for this trait. This was closely followed by the accumulation of resistance to penicillin, tetracycline and macrolides in the 1950s, creating strains of S. aureus that caused considerable problems in the management of nosocomial infection. In contrast, vancomycin has been used for nearly 50 years and yet significant numbers of S. aureus isolates with high-level resistance are yet to emerge. Thus, the emergence of resistance to antibiotics is associated with their use, although the precise correlation can be highly variable.

The mechanisms by which antibiotic resistance can both appear de novo and spread among medically important bacteria are now better understood. It is clear that the horizontal gene pool, which consists of genes present on a plethora of diverse mobile genetic elements, results in the lateral transfer of genes both among strains of an individual species and among different species of both Gram-negative and Gram-positive bacteria and is the process whereby we arrive at multiresistant bacteria. The engine driving this process is the selective pressure of antimicrobial use; this is obvious in the hospital environment where clear relationships between antimicrobial use and the emergence of multiresistant strains can be seen.3–5 There is also increasing evidence being collected for the influence of community use of antimicrobials and in cases where reductions have been achieved in usage, reductions in resistance can be seen (e.g. reduction in penicillin resistance in pneumococci in the UK). However,
Emerging resistance—challenges from specific pathogens

*S. aureus*

Penicillinase-producing hospital strains of *S. aureus* that were also resistant to the commonly available antimicrobials, as exemplified by the phage type 80/81 strain, caused considerable clinical problems in the 1950s. These problems were solved initially by the introduction of methicillin and then by the introduction of the related semi-synthetic penicillins, cloxacillin and flucloxacillin, which resulted in a marked decline in these strains. Very shortly after the introduction of methicillin in 1960, three resistant isolates were noted from the same hospital in southern England. This marked the start of our battle with methicillin-resistant *S. aureus* (MRSA). Interestingly, despite an early surge in cases in the 1960s, MRSA rates generally fell in Europe through to the early 1980s. The cause of this decline is not clear, but may relate to reductions in the prescribing of tetracyclines (which it had been argued were a co-selecting agent) and vigorous infection control. However, the hull was not to last for long. In the 1980s, a rise in the frequency of gentamicin-resistant MRSA was reported from the USA, Ireland and the UK. Subsequently, a series of well-characterized hospital-associated clones of MRSA have arisen. In the UK, EMRSA-15 and -16 have proved to be the dominant strains in healthcare-associated infections caused by MRSA. In other parts of the world, other dominant strains have emerged, and in some countries, the frequency of occurrence of MRSA among *S. aureus* exceeds 50%. Few routine surveillance data exist internationally for MRSA, but prevalence data do exist for many countries and reveal a wide variation in the prevalence of MRSA as a proportion of significant *S. aureus* isolates, ranging from <1% in countries such as the Netherlands to rates of 25% to 50% in much of the Americas, Australia and some countries in southern Europe. MRSA was initially thought to have arisen by a single genetic event in which a large piece of mobile DNA (the staphylococcal cassette chromosome, SCCmec) was transferred from a coagulase-negative staphylococcus into the *S. aureus* genome and inserted close to the origin of replication (oriT). It is now clear that this event has occurred on a number of occasions as there are multiple types of SCCmec cassette arrangements, which represent separate horizontal gene transfers. The SCCmec element has a unique mechanism of mobilization by which it excises and integrates into the new host chromosome, the element itself carrying recombinases for the cassette (ccrAB and ccrC).

The dramatic increase in the occurrence of infections caused by MRSA led to substantial increases in use of vancomycin, but surprisingly, no resistance was seen prior to 1997. The first resistant strains identified were designated vancomycin-intermediate *S. aureus*, and these have now been reported worldwide. There is evidence that these strains have a thickened cell wall, which results in the elevation of MICs of vancomycin to 8–16 mg/L. The biggest fear with regard to resistance in MRSA has been the possibility of transfer of the vanA gene complex from glycopeptide-resistant enterococci into *S. aureus* to produce vancomycin-resistant strains (VRSA) and the rapid dissemination of the clone or clones that have acquired these genes. An early in vitro experiment showed that it was possible to transfer and express vanA in *S. aureus*, and between 2002 and 2007, six clinical isolates of VRSA—all carrying the vanA gene complex—have been reported in the USA. Worryingly, VRSA has also been reported from India where two strains were found in a recent survey. It is interesting that this event did not occur earlier or more frequently; the explanation may be the recent description of a specialized lineage-specific restriction system (*Sau*I type 1 restriction modification system hsdR), which destroys incoming DNA into particular *S. aureus* lineages. Strains that have this system are unlikely to receive foreign DNA from bacteria such as enterococci, and *S. aureus* lab-strain RN4220 has a missense mutation in the hsdR gene that could allow gene transfer.

MRSA is usually thought of as being associated with hospitals or those who have had prolonged periods in hospital, although transmission of hospital strains among family members is well recognized. The emergence, therefore, of true community-associated strains (CA-MRSA) since the late 1990s is a further
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challenge to the effective treatment of *S. aureus* infections. Early strains of CA-MRSA were initially noticed in North America where rates have now risen to as high as 70% of community-acquired *S. aureus* infections, as reported in a survey undertaken at Houston Children’s Hospital. Outbreaks have been seen particularly among inpatients in jails, but the occurrence of sometimes rapidly fatal necrotizing pneumonia, particularly among children, is of particular concern. CA-MRSA strains typically belong to different multilocus sequence typing lineages compared with the common nosocomial strains and often produce Panton–Valentine leukocidin (PVL) toxin. The role of PVL toxin in producing the severe clinical manifestations that are seen is controversial; a recent report suggested that it may be only one of several important toxins. However, more recent experiments with isogenic strains in a mouse infection model suggest that PVL is a significant virulence factor. In contrast to the nosocomial strains, CA-MRSA strains are frequently susceptible to antimicrobials such as clindamycin, trimethoprim/sulfamethoxazole, tetracyclines, gentamicin, fluoroquinolones and chloramphenicol. However, resistance to the macrolides is common (which may also undermine the clinical efficacy of clindamycin), and there are increasing reports of resistance to older oral agents which will pose substantial problems in the future for the empirical treatment of moderate or serious *S. aureus* infections in the community.

The role of companion or agricultural animals as reservoirs for both hospital-acquired strains and CA-MRSA is increasingly recognized. A study of food animals in Korea demonstrated that a number of animal isolates of MRSA, particularly from cattle and chickens, had substantial similarities and were identical by random amplified polymorphic DNA (RAPD) typing to human isolates of nosocomial MRSA. More recently, a particular lineage of MRSA, sequence type ST398, has been found in both companion animals and humans in Germany and Austria. MRSA ST398 has recently been recognized, particularly in the Netherlands, as causing colonization and disease in pigs with subsequent spread to humans, emphasizing the growing importance of animals and the environment in the epidemiology of MRSA. EMRSA-15, the dominant UK strain in nosocomial infections, has also been found as a common colonizer of both veterinary staff and companion animals.

*Enterococci*

Although enterococci are part of the normal gut flora and have a low virulence, colonization followed by infection can readily occur in compromised patients and those with serious injuries, particularly if they have been given selecting antibiotics. The appearance of vancomycin-resistant *Enterococcus faecium* in 1986 in the UK presaged an expansion, particularly in the USA, of a highly resistant and potentially difficult-to-treat pathogen. Resistance to vancomycin is mediated by two major classes of gene clusters, *vanA* and *vanB*. Although problems with *vanB*-carrying vancomycin-resistant enterococci (VRE) have been reported and may be locally dominant, it is the *vanA* gene that has caused the greatest problems globally. It has been recently suggested that enterococci may have acquired the *vanA* gene by horizontal transfer from the chromosomes of glycopeptide-producing *Actinomyces/Streptomyces* such as *Streptomyces tovocaensis* and *Actinoplanes teichomyceticus*. Intriguingly, *Streptomyces coelicolor*, although not a glycopeptide producer, has been found to carry *van*-like genes encoding vancomycin resistance. It is likely that soil-inhabiting antibiotic-producing bacteria are the reservoir of *vanA*, although other investigators have suggested that *Pseudomonas* spp. may be the source.

Data from The Surveillance Network database indicate that during the 1990s, species-specific vancomycin resistance among isolates of *E. faecium* from blood increased rapidly in the USA from 26.2% in 1995 to 48.8% in 1996. In the early days of VRE infection in hospitals, when single clonal outbreaks occurred, it was often possible to control an outbreak by prompt application of contact precautions with infected patients and screening for asymptomatic carriers of VRE. This situation still pertains in the UK. However, in the USA, it has now been found that multiclonal outbreaks, with high levels of carriage among asymptomatic patients and admissions from the community, have meant that effective control is extremely difficult; this is typified by an outbreak described at the University of Maryland Medical Centre. The reason for the rapid and progressive spread of *E. faecium* has been hypothesized to be the agricultural use of glycopeptides such as avoparcin, the use of which was banned in the EU. Following the EU ban, there has been a significant decrease in the faecal carriage of vancomycin-resistant *E. faecium* in chickens, for example, in Denmark. However, a delay was noted in pigs due to the continued use of tylosin, which, although not a glycopeptide, nonetheless co-selects for glycopeptide resistance due to linked macrolide resistance genes. Within the hospital environment, the use of certain antibiotics has been demonstrated to cause selection by association in case–control studies, particularly tetracycline/trimethoprim and third-generation cephalosporins. Interestingly, the same study showed the potentially protective effect of piperacillin/tazobactam, and this effect has been confirmed in a mouse model. Mice were challenged with VRE orally, and ceftriaxone or ticarcillin/clavulanate-pre-treated animals had high levels of colonization, whereas those treated with piperacillin/tazobactam or saline were not heavily colonized. The intensive use of oral vancomycin in hospitals for the treatment of *Clostridium difficile* infection is also likely to select for increased faecal carriage of VRE. It seems likely that a combination of good antibiotic stewardship and infection control may be the best way of controlling VRE in the hospital setting, although the influence of the veterinary use of antibiotics may continue to be felt in the European environment where there has been an increase in the VRE rates in humans. The recent report of a substantial clonal outbreak of VRE resistant to linezolid (a critical antibiotic for the treatment of VRE) in Birmingham, AL, USA, is a cause for concern. In the Netherlands, it has been suggested that the emergence of multidrug-resistant, hospital-adapted *E. faecium* clonal complex CC17 without a community reservoir can be explained by cross-transmission and selective antibiotic pressure and may precede the emergence of VRE.

*Enterobacteriaceae*

Following the introduction of ampicillin in the 1960s, plasmid-mediated resistance caused by the production of the TEM and SHV serine β-lactamases became a major clinical problem. A survey of *E. coli* in the faeces of patients presenting for elective surgery in West London in 1968 showed a 17% resistance rate to ampicillin, the majority of which was plasmid-mediated as demonstrated by conjugation to *E. coli* K12. The
When third-generation cephalosporins are used to treat infections with bacteria such as Citrobacter spp. and Enterobacter spp., high-level resistance develops in ~20% of the cases due to the over-production of the chromosomal AmpC-type β-lactamase. Subsequently, it has been found that ampC β-lactamase genes from a variety of Gram-negative bacteria have been mobilized onto plasmids and have spread worldwide. Although not as substantial a problem as the CTX-M-type ESBLs, these plasmid-encoded AmpC enzymes are continuing to increase in number and diversity.54,55 (regularly updated tables can be accessed at the Lahey web site: http://www.lahey.org/Studies/). When ampC-bearing plasmids are present in the same isolate of Enterobacteriaceae as an ESBL gene, the detection of the ESBL gene can be difficult; this requires the use of AmpC-stable cephalosporins, such as cefepime or ceftepirome combined with clavulane or boronic acid as an inhibitor, although detection is not 100% reliable even using these combinations.56 Multiresistant Enterobacteriaceae, which are resistant to most currently available antimicrobials, are heavily treated with carbapenems, and the increased use of these carbapenems does raise fears for the development and spread of resistance. Plasmid-mediated transferable carbapenemases, mainly of the IMP and VIM families, have been described from a wide range of locations and in many different bacterial hosts, particularly in Pseudomonas, but they have also been described in Enterobacteriaceae.57 The spread of KPC-2 carbapenemases among Klebsiella pneumoniae, E. coli, Salmonella spp. and Enterobacter spp. in the USA and recent reports of KPC-2- and KPC-3-producing K. pneumoniae from Israel suggest that we will see widespread dissemination of this gene.58,59

Pseudomonas and Acinetobacter

Pseudomonas aeruginosa is a widespread environmental organism that can cause considerable problems in both immunocompromised patients and intensive care unit patients in hospitals where there are environmental sources. Patients who are admitted and given broad-spectrum antibiotics develop gut colonization either with their own community-acquired or nosocomially transmitted strain leading to infection in some cases. β-Lactam antibiotics such as ceftazidime and piperacillin/tazobactam have been traditionally used to treat infections, but resistance to these agents is now common in many parts of the world. The rise in quinolone resistance, not only in Enterobacteriaceae but also in P. aeruginosa, has further undermined the number of available agents to treat such infections, and carbapenems are used increasingly to treat Pseudomonas infections. Worryingly, the VIM-2 metallo-carbapenemase, which was originally described in Italy, is now widely spread across the world and has been found in substantial numbers in Pseudomonas spp. isolates in a number of surveys.60 In one survey from China, the blaVIM-2 integron-associated gene was found in 14 of 140 imipenem-resistant isolates.61 Resistance to carbapenems can occur through a range of mechanisms, which include the loss of specific porins and the expression of efflux pumps, for which the mex A/B and X/Y systems are very important.62 A worrying survey from Canada—a country generally considered to have low levels of antibiotic resistance—of all P. aeruginosa isolates from the Calgary area between 2002 and 2006 revealed 14% of the strains to be resistant to imipenem. A metallo-β-lactamase phenotype was found in 35%
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of those, with 96% (i.e. 178/185) positive for blaVIM genes and the remaining 4% positive for blaIMP genes.63 Such a high incidence in a country with comparatively few problems of antibiotic resistance must indicate the possibility of the rapid spread and dissemination of these integron-associated metallo-
carbapenemases elsewhere in the future.

Acinetobacter spp., particularly Acinetobacter baumannii, are well recognized as a cause of infection, particularly in intensive care units where their resistance to drying can pose substantial problems in their eradication from the environment. Acinetobacter produce a wide range of β-lactamases and have a formidable spectrum of intrinsic resistance mechanisms, which can mean that some strains are resistant to all known antibiotics with the exception of colistin.64 The rapid spread of the OXA carbapenemases in the UK and elsewhere has eroded the activity of the carbapenems,65 while recent reports of the development of heteroresistance to colistin in an in vitro pharmacokinetic/pharm-
macodynamic model may compromise the use of colistin as a therapeutic option.66 Although the number of patients infected by Acinetobacter is small, there is a great need for novel agents that are active against these multiply resistant strains. Tigecycline has shown particular promise in this area,67 although recently decreased susceptibility has been reported in the literature.68,69

Response to the increasing burden of antimicrobial resistance

The first response to high levels of antimicrobial resistance must be to reduce the selective pressure generated by antibiotic usage. As patients require treatment, it is not always possible to modify substantially or reduce antimicrobial use. However, there have been some clear examples of good antibiotic stewardship leading to reductions in antimicrobial resistance, notably the reduction in penicillin resistance among pneumococci in the UK following a 30% reduction in pharmacy sales of oral β-lactams.6 However, the correlation between reduced prescribing and resistance is not clear cut. The same study reported that a fall in macrolide usage was not associated with a fall in macrolide resistance. There are large numbers of studies that show a correlation between increasing usage over time of particular antimicrobial classes either with resistance to that agent or to co-selective resistance to other agents. A recent well-constructed study followed trends in antimicrobial resistance in a hospital in Taiwan over a 12 year period and concurrently collected data on usage. A rise in cefotaxime-resistant/ciperoxacin-resistant E. coli and meropenem-resistant P. aeruginosa was significantly associated with increasing consumption of extended-spectrum cephalosporins, carbapenems, fluoroquinolones and aminoglycosides. Interestingly, increases in ceftripoxicin-resistant K. pneumoniae and meropenem-resistant Acinetobacter were significantly associated with increased use of extended-spectrum cephalosporins, but not with other antimicrobials.71 In contrast, some other studies have failed to show a correlation with formulary control. One such study reports the spread of ESBLs within a hospital despite antibiotic restriction, suggesting that infection control may be a better control method for antibiotic-resistant bacteria.72 A confounding variable in this study may have been the fact that many ESBL-producing strains were introduced from the community following admission of patients colonized with such strains in their bowel. These strains may then have been selected following administration of a range of antimicrobials and caused endogenous infections.

In understanding the control of antibiotic-resistant bacteria, it is important to have surveillance mechanisms in place that are both accurate and comprehensive. Programmes such as EARSS (European Antimicrobial Resistance Surveillance System) and ESAC (European Surveillance of Antimicrobial Consumption) have generated data to reveal broad correlations between usage and national resistance rates and also rapid changes in patterns of resistance. Surveillance systems in the future will have to use standardized methodology, particularly in relation to suscepti-
bility testing; the currently used range of commercial, automated and non-automated systems can generate apparently discrepant data. There are also large parts of the world where little, if any, surveillance is undertaken, and surveys supported by the pharmaceutical industry, such as SENTRY73 and SMART,74 have revealed very useful data in those parts of the world. These data suggest that antimicrobial resistance in areas where control of antimicrobial prescribing (particularly in the community) is poor is much higher. These data are confirmed by studies specifically of community isolates, for example, the occurrence of high levels of fluoroquinolone and third-generation cephalosporin resistance in community isolates of Enterobacteriaceae in China.75

Infection control is possibly the single most important control measure that can be applied to the containment of antibiotic-resistant bacteria in a hospital setting, and there are a number of reports of successful control in the literature. One of the problems can be of making a clear case to hospital management for the deployment of scarce resources in infection control. Money spent in this area almost invariably results not just in the control of antibiotic-resistant bacteria but also in reductions in death rates.

Finally, the development and introduction of new agents have often in the past resulted in substantial reductions in the occurrence of resistance to antibiotics already in use due to the elimination of those strains that carry the resistance genes. Following the introduction of penicillin, there was a rapid rise in resistance to penicillin in S. aureus and other drugs such as chloramphenicol, tetracycline and erythromycin through the 1950s.11 The development and widespread use of penicillinase-
stable isoxazolyl penicillins such as methicillin, cloxacillin and flucloxacillin reduced the spread and occurrence of resistant strains of S. aureus in the 1960s. This effect was documented in a 6 year longitudinal study of the ecology of S. aureus in a Cincinnati hospital between 1964 and 1970.76 The subsequent rise of MRSA presumably indirectly selected by isoxazolyl penicillins and more recently by cephalosporins and fluoroquinolones has obliterated original reductions in MRSA infections. Recently, carriage of a strain of MRSA (TW) strongly associated with intravascular device-related bacteraemia has been eradicated in ICU patients by treatment with linezolid. The authors concluded that pre-emptive treatment of carriers led to the ter-
mination of the outbreak.77

One of the best documented examples of the phenomenon was the use of amikacin in hospitals with a high incidence of gentamicin resistance. One 3 year study demonstrated a statistically significant reduction in gentamicin resistance from 17.4% to 7.4%, with no rise in amikacin resistance.78 In another study in which gentamicin and tobramycin were restricted and
replaced with amikacin, similar reductions were seen, which were reversed when gentamicin was re-introduced. The introduction of second- and third-generation cephalosporins, which were highly active against the aminoglycoside-resistant Enterobacteriaceae, resulted in a massive reduction in hospital infections caused by them. *Serratia marcescens* frequently develops resistance to amikacin as all isolates carry a copy of the AAC(6’)-Ic aminoglycoside-inactivating enzyme resistance gene, which can become derepressed. In an outbreak of *S. marcescens* cross-infection on a urology unit, heightened control of infection resources failed, but treatment of patients with second/third-generation cephalosporins was successful. However, this has not always been the case as sometimes a newly introduced agent will be affected by existing resistance mechanisms (e.g. resistance to cefepime in ESBL-producing *E. coli*). There are a number of novel agents either introduced or on the point of introduction that are active against Gram-positive pathogens (e.g. tigecycline, ceftobiprole, oritavancin and dalbavancin), but in the case of Gram-negative infections, the choice is much smaller with the re-introduction of some older agents, such as temocillin, which has stability to both AmpC and ESBL β-lactams, but little activity against other pathogens such as *Pseudomonas* or stability to some other mechanisms of resistance, e.g. carbapenemases such as VIM-2.

Tigecycline was developed specifically to be unaffected by the common efflux-based mechanisms of resistance to tetracyclines, such as Tet(A/B) in Gram-negative bacteria, and those conferring ribosomal protection. In consequence, its activity is good against multiresistant *E. coli*, offering a potential new agent for ESBL/AmpC-producing multiresistant strains. The occurrence and mechanisms of resistance to tigecycline that have been reported have recently been reviewed. In a large survey of multidrug-resistant organisms in the USA, significant resistance was only seen in some isolates of *Klebsiella* (9% of *K. pneumoniae* isolates), and activity against multidrug-resistant strains was good, with no resistant *E. coli* strains reported (MIC₅₀ 0.5 mg/L and 0% resistant). Resistance has usually been attributed to the upregulation of efflux pumps, particularly the AcrAB system. Upr egulation of the AcrAB system has recently been identified in resistant isolates of *K. pneumoniae* and *Enterobacter cloacae*, with increased expression of the transcriptional regulator RamA. Carbenemase-producing Enterobacteriaceae are a major emerging therapeutic problem, and in a recent survey of 104 isolates from across the globe, no resistance to tigecycline was seen.

Performance of tigecycline against *A. baumannii* has been generally good, and it has shown promise when used clinically. Resistance has been noted on a number of occasions, and recent work suggests that this is due to upregulation of the AdeABC multidrug efflux pump. AdeABE efflux pumps belong to the resistance-nodulation-cell division family, which are capable of effluxing tigecycline, which is not a substrate for other efflux systems because of the glycylic substitution. A second efflux system AdeIJK has recently been identified in *A. baumannii*. The authors concluded on the basis of data from insertional mutants in the adeABC and adeIJK genes that both pumps contribute, in a more than additive fashion, to tetracycline and tigecycline resistance. The overexpression of AdeIJK was lethal so its precise contribution to high-level tigecycline resistance in clinical isolates is not entirely clear. The activity of tigecycline against Gram-positive bacteria is exceptionally good. Earlier reviews of resistance in *S. aureus* (including MRSA) failed to identify any resistant strains. This finding has been confirmed by two recent surveys from the USA and Europe, Asia/Pacific, Latin and North America. In both of the recent studies, no resistance among penicillin-non-susceptible *S. pneumoniae* and VRE was found (as judged by low MIC₉₀ as FDA/CLSI breakpoints for these organisms were not available). The useful activity against some multiresistant Gram-negative pathogens combined with very good activity against MRSA/VRE (for which no resistance has been yet reported) makes tigecycline a potentially useful agent for use in treating some nosocomial infections.

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