Emerging antibiotic resistance in gram positive bacteria: return to the pre-antibiotic era?

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This is a brief summary of four problems of antibiotic resistance in gram positive bacteria. Methicillin-resistant *Staphylococcus* spp. remain a major nosocomial threat and have become even more important with the increased use of foreign material (e.g. vascular catheters). There has been a rapid increase in penicillin-resistant *Streptococcus pneumoniae* isolates. This will lead to a reevaluation of the therapy of common respiratory tract infections such as otitis, sinusitis, and pneumonia, and will create major problems for the empirical treatment of bacterial meningitis. In Group A ß-haemolytic *Streptococcus* spp., resistance to penicillin is unlikely to emerge, but increasing use of erythromycin and other macrolides has resulted in widespread macrolide resistance. Finally, the appearance of multi-resistant *Enterococcus* spp. shows that we have returned to the pre-antibiotic era. These strains are resistant to all available antibiotics and have caused hospital outbreaks of untreatable and fatal infections.

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Introduction

Antibiotic resistance has been a problem since the introduction of penicillin G and the sulphonamides in the 1940s. During the 1970s and 1980s, emergence of antibiotic resistance was a clinical problem mainly with gram negative bacteria, such as *Pseudomonas aeruginosa*, *Enterobacter* spp. and *Klebsiella* spp. At that time, these species were also the most common aetiologies of hospital-acquired infections.

Until recently, resistance in gram positive bacteria was mainly a problem involving *Staphylococcus* spp. Shortly after penicillin G became available, penicillin-resistant strains of *Staphylococcus aureus* and coagulase-negative *Staphylococcus* spp., such as *Staphylococcus epidermidis*, appeared in hospitals and have subsequently spread into the community. The problem with this type of resistance—caused by the bacterial production of penicillinase (an enzyme hydrolysing many penicillins)—was solved with the development of penicillinase-resistant penicillins, the cephalosporins, and several other groups of antibiotics active against *Staphylococcus* spp. However, soon methicillin-resistant *Staphylococcus* spp. (MRS) appeared, and again the source was the hospital environment. This time, resistance was mediated by modification of the penicillin binding proteins (PBPs) of the bacteria, and conferred resistance to all available ß-lactam antibiotics, including carbapenems such as imipenem. In addition, methicillin-resistance was often combined with resistance to other types of antibiotics, e.g. the aminoglycosides. The only antibiotic uniformly active against MRS is vancomycin. This group remains a major clinical problem and is likely to do so for many years to come.

There has been a rapid increase in resistance problems in gram positive bacteria other than *Staphylococcus* spp. Simultaneously, there has been a switch from a dominance of gram negative to gram positive aetiology of hospital-acquired infections. Four major clinical concerns include MRS, particularly the strains which are also resistant to glycopeptide antibiotics such as teicoplanin; penicillin-resistance in *Streptococcus pneumoniae*; the emergence of resistance in Group A ß-haemolytic *Streptococcus* (GAS)

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spp. and multi-resistant *Enterococcus* spp. This seminar article discusses these problems and possible ways to reduce them.

Methicillin-resistant *Staphylococcus* spp.

Methicillin-resistant *S aureus* (MRSA) strains vary in prevalence from less than 1% to 80% of clinical isolates of *Staphylococcus* spp. from hospitalised patients.[1-4] Examples of countries with very low prevalence are Denmark, Finland, Norway, Sweden, and the United Kingdom. High or very high MRSA frequencies are seen in Spain, Italy, and other Mediterranean countries and also in Southeast Asia (including Hong Kong, where MRSA seems to be endemic in most hospitals).[5,6] In countries with high prevalence, there are now indications that MRSA has spread outside the hospital environment and that community-acquired *S aureus* infections may be caused by MRSA.[7] However, in most countries, MRSA is still a problem confined to the hospital environment and nursing homes.[8,9]

Dissemination of MRSA in the hospital environment is a major nosocomial infection problem. Factors increasing the risk of MRSA outbreaks include high patient density (both in the hospital as a whole and the individual ward), low numbers of hospital staff per patient, poor hospital hygiene (especially with regard to hand-washing routines), and frequent referrals of patients from other hospitals.[3,4,8,10,11] The use of intravascular catheters has been identified as an independent risk factor for bacteraemic infections caused by MRSA.[12] Epidemiological surveys using modern molecular techniques have demonstrated that MRSA outbreaks are often caused by single clones of *S aureus* spreading rapidly in the hospital environment, particularly in intensive care units.[13-15] As with other infections caused by *S aureus*, the manifestations of MRSA infections may be serious, but the virulence of MRSA does not seem to differ from that of methicillin-sensitive strains.[16,17] Treatment of MRSA is with antibiotics active against the strain causing the infection. At present, only vancomycin is active against all MRSA strains. Most strains are also susceptible to other antibiotics (Table 1). A promising development is the new class of carbapenem antibiotics—the acyl-carbapenems—which are active against all MRS strains so far tested.[18]

For prevention and containment of MRSA, high level hospital hygiene is of paramount importance.[10,19] Strict isolation of patients who are carriers of, or infected with MRSA, is possible only in hospitals with low frequencies of the organisms, but is an effective measure. In an outbreak situation, topical use of mupirocin, an antibiotic with high activity against MRS, should be considered. However, since mupirocin resistance is becoming increasingly common, routine prophylactic use of this antibiotic should be avoided.[20-22]

With coagulase-negative *Staphylococcus* spp., the antibiotic resistance problems are similar to those of *S aureus*. Methicillin-resistant strains are common in all countries and are still mainly a hospital problem. A major difference is that while all strains still seem to be vancomycin-susceptible, teicoplanin resistance has been reported especially among coagulase-negative *Staphylococcus* spp. other than *Staphylococcus epidermidis*, e.g. *Staphylococcus haemolyticus*.[18,23,24] Coagulase-negative *Staphylococcus* spp. are generally less virulent than *S aureus*. If resistant strains are not covered by the initial antibiotic treatment given, patients are not at major risk of dying from their infections if active treatment is commenced when the antibiotic sensitivity pattern becomes known.

A major threat in this area is emergence of general glycopeptide resistance in MRS, i.e., resistance to both vancomycin and teicoplanin, in addition to the resistance against ß-lactam antibiotics. Theoretically, such resistance is possible since resistance to glycopeptide antibiotics in *Enterococcus* spp. is transferable and these organisms and *Staphylococcus* spp. often coexist in the same body sites.[25]

Penicillin-resistant *Streptococcus pneumoniae*

Streptococcus pneumoniae remains the most important and common bacterial aetiology of community-acquired pneumonia, otitis media, and sinusitis. For decades, the standard treatment for pneumococcal infections has been penicillin. This is no longer the case in those countries where penicillin-resistant *S pneumoniae* have increased rapidly in frequency.[26-30] Such resistance is chromosomally coded and results in altered PBPs which have markedly reduced capacity to bind all commercially available ß-lactam antibiotics.[31] However, they are highly susceptible to the new acyl-carbapenems under development.[18] There are degrees of penicillin-resistance and one should carefully separate strains which are highly resistant to penicillin from those which have intermediate sensitivity (Table 2). The latter are often treatable with parenteral benzylpenicillin or oral phenoxymethylpenicillin if high doses are used and if the infection is not located in the central nervous system. Of other ß-lactam antibiotics, cephalosporins have varying

Table 1. Antibiotics active against methicillin-resistant strains of *Staphylococcus* spp.

Antibiotic	Comments
Vancomycin	Resistance not seen
Teicoplanin	Resistance rare but may occur
Clindamycin	Resistance occurs
Fusidic acid	Resistance occurs
Rifampicin	Resistance occurs
Aminoglycosides	Resistance common
Fluoroquinolones	Resistance common

activity against intermediately sensitive *S pneumoniae*, with cefotaxime and ceftriaxone being the most active, and ceftazidime one of the less active of the third generation cephalosporins.[32,33] Cefotaxime may be somewhat more active than benzylpenicillin against strains which are intermediately susceptible to penicillin. However, treatment failures have been reported when cefotaxime was used as empiric treatment of meningitis caused by pneumococcal strains not fully susceptible to penicillin.[34,35]

The problem with decreased susceptibility of *S pneumoniae* isolates to ß-lactam antibiotics has been further emphasised by a parallel development towards more frequent resistance to other antibiotics. Thus, resistance to macrolides (erythromycin, dirithromycin, roxithromycin, clarithromycin, and azithromycin) has increased dramatically in some countries—especially France and Spain.[36,37] It is not uncommon to find macrolide resistance coupled to penicillin resistance. Such coupling is very common in *S pneumoniae* isolates resistant to co-trimoxazole.[38,39] So far, the only antibiotics to which resistance in this species has not been described, are the glycopeptides; vancomycin and teicoplanin.

Epidemiologically, it seems clear that pneumococcal strains which are intermediately sensitive or resistant to penicillin are spread clonally.[40,41] Unpublished Icelandic studies (Kristinsson KG, personal communication) have demonstrated a reservoir of penicillin-resistant pneumococci in children aged between six months to five years, who carried the organisms in the oropharynx. A striking finding was that all of the carriers had received antibiotic treatment during the preceding six months, and that co-trimoxazole treatment and possibly also macrolide treatment (but not treatment with ß-lactam antibiotics—penicillin or cephalosporins) predisposed for carriership with resistant *S pneumoniae* organisms. The paradoxical conclusion of this observation is that penicillin is less likely to select for penicillin-resistance than are macrolides and co-trimoxazole.

Little published information is yet available on the frequency of penicillin-resistant *S pneumoniae* in Hong Kong. However, recent unpublished studies at the Prince of Wales Hospital indicate that the problem is increasing rapidly and that up to 45% of these strains may not be fully penicillin-susceptible.

The consequences of penicillin resistance in *S pneumoniae* are serious. Two of the cheapest and less toxic groups of antibiotics, the ß-lactams and erythromycin, lose their general usefulness. There might even be cases of otitis media which have to be admitted to hospital solely for the purpose of administering intravenous vancomycin or teicoplanin treatment. In patients with bacterial meningitis, monotherapy with a third generation cephalosporin (e.g. cefotaxime or ceftriaxone), is no longer guaranteed to cover all pathogens. It is recommended to add rifampicin in the empiric treatment of purulent meningitis with a third generation cephalosporin, if penicillin-resistant pneumococcal strains are common in the general population.

Table 2. Penicillin susceptibility of *Streptococcus pneumoniae*

Sensitivity	Definition*	Consequences
Sensitive	MIC <0.1 mg/L	All infections treatable with normal doses of penicillin
Intermediately sensitive	MIC 0.1-1 mg/L	Most infections (not meningitis) treatable with high penicillin doses
Resistant	MIC >1 mg/L	Most infections not treatable with penicillins

* Definitions are given in terms of minimal inhibitory concentrations (MICs) of benzylpenicillin

Presently, the most promising approach to this problem seems to be the development of effective vaccines against pneumococcal infections. The currently available 23-valent polysaccharide pneumococcal vaccines have several deficiencies; they are poorly immunogenic in immunodeficient subjects and they are not immunogenic in children aged below 18 to 24 months, i.e. the age when recurrent otitis media is most common.[42-44] However, as with *Haemophilus influenzae* type b, for which protein conjugation of its capsular polysaccharide resulted in a highly immunogenic and effective vaccine, a protein-conjugated pneumococcal polysaccharide vaccine has been developed which is immunogenic in newborns.[44-46] Large-scale field trials are ongoing with several such vaccines and within five years, it is likely that we will have access to vaccines which can drastically reduce the incidence of both invasive pneumococcal infections, and less serious respiratory tract infections caused by these organisms.

Resistance in Group A ß-Haemolytic *Streptococcus* spp.

Group A ß-haemolytic *Streptococcus* spp. (*Streptococcus pyogenes*) have received increased attention in recent years. Reasons for this include a marked increase in life-threatening GAS infections (septicaemia and necrotising fasciitis) and increased frequencies of antibiotic resistance, mostly against erythromycin and other macrolides.[47-50] It is now clear that in patients without immunity to the erythrogenic toxins of GAS, a so-called superantigen reaction, i.e., a severe syndrome similar to the septic shock syndrome described for *Staphylococcus* spp. and with a high mortality rate, may develop.[51]

Therapeutic recommendations for GAS infections have been to use benzylpenicillin or phenoxymethylpenicillin as first-line drugs and to give patients with a history of penicillin allergy, erythromycin or another macrolide. Penicillins can and should still be used as first-line treatment. Resistance to penicillin in GAS by alterations of PBPs seems not to be possible; transfer of the gene rendering *S pneumoniae* isolates resistant to GAS cells resulted in a marked reduction of their reproductive capacity (Tomasz A, personal communication).

With the high frequencies of erythromycin resistance seen in some countries, the recommendation to use a macrolide as the first alternative to penicillin becomes doubtful. A study from Finland[50] indicated a strong correlation between the total macrolide consumption and the frequency of resistant GAS strains. In agreement with this is the observation that in Japan (where the first wave of macrolide-resistant GAS was reported) resistance frequencies are now among the lowest in the world.[52] Most probably this is the result of a marked reduction in the use of macrolides in Japan.

What to use in penicillin-allergic patients with GAS infections? Probably the best alternative is to use an oral cephalosporin. The risk of cross-hypersensitivity is most likely minimal and the frequencies of serious allergic reactions to oral cephalosporins are very low.[53] Moreover, in patients with recurrent streptococcal pharyngitis, oral cephalosporins give considerably higher cure rates than does penicillin.[54,55] It should be noted that lincosamides (lincomycin and clindamycin) are not alternatives when macrolide resistance is common, since cross-resistance is prevalent.

Multi-resistant *Enterococcus* spp.

This is at present the most serious antibiotic resistance problem and can truly be described as a return to the pre-antibiotic era. In the United States and elsewhere, nosocomial outbreaks of infections caused mainly by *Enterococcus faecium*, but also by other enterococcal species (athough not yet the most prevalent enterococcal species, *Enterococcus faecalis*) resistant to all commercially available antibiotics, have been reported and have resulted in several deaths which could have been avoided had effective treatment been available.[55-60] These organisms have caused endocarditis, urinary tract infections, and most frequently, septicaemia in compromised patients. Previously, multi-resistant strains of these species were not uncommon in the hospital environment but such strains were uniformly susceptible to glycopeptide antibiotics such as vancomycin. The problem now is that they are capable of acquiring resistance to glycopeptide antibiotics.

The reasons for the emergence of multidrug-resistance in *Enterococcus* spp. is not entirely known. One possibility is that resistance to glycopeptide antibiotics may be related to the use of oral vancomycin for treatment of *Clostridium difficile*-associated diarrhoea. When given orally, vancomycin is not absorbed, nor destroyed in the intestines. Hence, very high concentrations reach the colon i.e. the main reservoir for enterococci. This might lead to selection of resistant subpopulations of enterococcal strains. Indirect evidence for this hypothesis is that glycopeptide resistance has so far been seen mainly in the United States, where oral use of vancomycin has been more common than in Europe.

Before the development of new antibiotics active against multi-resistant enterococci, one therapeutic possibility might be to try combinations of three or more antibiotics. In vitro studies have indicated that such treatment may be effective.[61,62] However, the selection of which antibiotics should be used will require very extensive microbiological investigation, which is not normally done in routine laboratories. Other measures which may slow down or even stop the dissemination of resistant enterococci include improved hospital hygienic routines (for detection and containment of the problem) and the reassessment of antibiotic use, especially with regard to glycopeptides.

Comments

These four examples of current problems with antibiotic resistance illustrate a new situation in the treatment of bacterial infections. For as long as we have had access to antibiotics, there has been a race between the bacteria developing mechanisms for resistance and the scientists developing new antibiotics active against resistant organisms. Until now, that race has invariably been won by science. That is no longer the case. We have been outsmarted by the microbes and are in the position where we may lack effective antibiotics, while there are still several years before new drugs will be available for clinical use.

One important lesson is that antibiotic resistance problems tend to diminish or even disappear as soon as use of an antibiotic decreases. Hence, a general reduction of antibiotic usage both in outpatients and in the hospitals would be likely to lessen the problems with antibiotic resistance. This requires a change in attitudes. The physicians and surgeons must learn to markedly limit their use of antibiotics. It is also important to avoid use of one antibiotic for all types of infections; rotation between antibiotics of various types is likely to reduce the risks of resistance development. Patients must be taught that antibiotics are not the solution to all infections. Most infections heal by themselves and most respiratory tract infections are caused by viruses, against which we lack effective drugs. In addition, the pharmaceutical industry must refrain from marketing activities which may encourage the overuse of antibiotics.

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