Multiresistant organisms at the front line

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Summary

Multiresistant bacterial pathogens such as methicillin-resistant *Staphylococcus aureus*, multiresistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci and multiresistant *Pseudomonas aeruginosa* are being seen with increasing frequency in the community and not just in hospital practice. Treatment options for infections caused by these pathogens are limited, but in most cases a suitable drug can be found. In particular, there are options for the treatment of the community-associated strains of MRSA, such as trimethoprim-sulfamethoxazole, and often macrolides or lincosamides.

Key words: antibiotic resistance, MRSA.

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Introduction

General practitioners are often faced with patients suffering from infections caused by bacteria harbouring some kind of antibiotic resistance. Many of these resistances are so common that we take them for granted – for example, penicillin resistance in *Staphylococcus aureus* occurs in about 90% of community strains, and amoxycillin resistance in about 50% of *Escherichia coli*. Usually there are options for antibiotic treatment (see Table 1), and laboratories attempt to provide susceptibility data. However, for some resistant organisms the options are limited, problematic or both. The generic term for these strains is multiresistant organisms.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Even though methicillin itself is no longer used, the term methicillin-resistant is still used to identify these very important multiresistant organisms. The general practitioner is likely to encounter two types of MRSA. These are the multiresistant MRSA strains that are hospital-associated which are found colonising or occasionally infecting patients who have previously been hospitalised, and the non-multiresistant community-associated MRSA strains which are found in all those common circumstances where one would expect to see susceptible *S. aureus*, namely boils, furuncles, cellulitis and wound infections. Purulent forms of staphylococcal skin infection respond best to drainage, and for small lesions drainage without antibacterial treatment will be usually adequate.[1]

When antibacterial treatment is required for MRSA infection, the choice is driven by whether the infecting strain is hospital- or community-associated. Choices for hospital-associated MRSA are quite limited. Serious infection requires hospitalisation and intravenous vancomycin, while less serious infections require an oral combination of rifampicin and fusidic acid. This oral combination is essential to avoid the selection of further resistance during treatment. Unfortunately, the Pharmaceutical Benefits Scheme (PBS) only subsidises rifampicin for indications other than staphylococcal infection, while fusidic acid – which the PBS states must be used in combination – is available for just such an indication. Hence, adequate treatment for hospital-associated MRSA often requires a return visit to hospital to ensure timely access to appropriate drugs.

There are usually more treatment options for community-associated MRSA than for hospital-associated infections. Most strains are susceptible to macrolides (erythromycin, roxithromycin, clarithromycin and azithromycin) and lincosamides (clindamycin and lincomycin), as well as trimethoprim/sulfamethoxazole and tetracyclines. Susceptibility to erythromycin predicts susceptibility to clindamycin, which is considered the drug of choice (when one is required) for mild to moderate community-associated MRSA. The other drug for which there is most experience in less severe infection is trimethoprim/sulfamethoxazole. This is recommended for young children as clindamycin suspension is not available, or when resistance to erythromycin (which more often than not predicts resistance to clindamycin) is suspected or proven. Tetracyclines such as doxycycline can be used for minor community-associated MRSA, although their use should probably be reserved for patients allergic to a trimethoprim/sulfamethoxazole component, and only in those more than eight years of age. Patients with serious infections caused by community-associated MRSA should be hospitalised and treated with vancomycin initially.

Table 1

Treating multi-drug resistant infections in the community

Multiresistant organism	Resistance pattern	Infection	Drug of choice for mild to moderate infection
Hospital-associated MRSA	Pattern 1 Penicillin **R** Methicillin **R** Erythromycin **R** Tetracycline **R** Trimethoprim/sulfamethoxazole **R** Ciprofloxacin **R** or **S** Pattern 2 Penicillin **R** Methicillin **R** Erythromycin **R** mostly Tetracycline **S** Trimethoprim/sulfamethoxazole **S** Ciprofloxacin **R**	Any	Rifampicin plus fusidic acid
Community-associated MRSA	Penicillin **R** Methicillin **R** Erythromycin **S** mostly Tetracycline **S** Trimethoprim/sulfamethoxazole **S** Ciprofloxacin **S**	Any	Clindamycin
Multiresistant *Streptococcus pneumoniae*	Penicillin **R** Amoxycillin **S** or **R** Erythromycin **R** Tetracycline **R** Trimethoprim/sulfamethoxazole **R**	Otitis media, sinusitis, acute exacerbations of chronic bronchitis, pneumonia	Amoxycillin Moxifloxacin for adult patients (≥18 years) with penicillin allergy
Vancomycin-resistant enterococci	Penicillin and/or amoxycillin **S** or **R** Vancomycin **R**	Urinary tract	Nitrofurantoin or norfloxacin
Multiresistant *Escherichia coli*	Amoxycillin **R** Amoxycillin/clavulanate **S** / **I** / **R** Cefazolin/cephalexin **R** Trimethoprim/sulfamethoxazole **R** Cefotaxime or ceftriaxone **S** or **R**	Urinary tract	Amoxycillin-clavulanate if susceptible. Otherwise norfloxacin if susceptible.
		Other sites	Amoxycillin-clavulanate if susceptible. Otherwise ciprofloxacin if susceptible.
Other multiresistant enteric bacteria	*Klebsiella* species Amoxycillin **R** Amoxycillin/clavulanate **S** or **R** Cefazolin/cephalexin **R** Trimethoprim/sulfamethoxazole **S** or **R** Cefotaxime or ceftriaxone **S** or **R** *Enterobacter* species Amoxycillin **R** Amoxycillin/clavulanate **R** Cefazolin/cephalexin **R** Trimethoprim/sulfamethoxazole **S** or **R** Cefotaxime or ceftriaxone **S** or **R**	Urinary tract	Amoxycillin-clavulanate if susceptible. Otherwise norfloxacin if susceptible.
		Other sites	Amoxycillin-clavulanate if susceptible. Otherwise ciprofloxacin if susceptible.
Multiresistant *Pseudomonas aeruginosa*	Ticarcillin **S** or **R** Ceftazidime **S** or **R** Meropenem **S** or **R** Gentamicin **S** or **R** Tobramycin **S** or **R** Norfloxacin **S** or **R** Ciprofloxacin **S** or **R**	Urinary tract	Norfloxacin or ciprofloxacin if susceptible

MRSA methicillin-resistant *Staphylococcus aureus*
R resistant
S susceptible
I intermediate

Colonisation

In general, treatment should not be administered to patients who are merely colonised with MRSA, even in long-term care facilities, where the risk of transmission is higher. Topical (nasal) mupirocin in particular has a very limited role because its effect is short-lived and confined to the nostrils. Eradication of the colonised state is difficult and treatment should only be considered if the patient has proven recurrent furunculosis due to nasal carriage of MRSA. Topical treatment should only be used as part of a more intensive regimen involving systemic antimicrobials not readily available in community practice.

Multiresistant *Streptococcus pneumoniae*

Before the introduction of a conjugate pneumococcal vaccine into the childhood immunisation schedule, the proportion of multiresistant *S. pneumoniae* strains in the community was increasing. They are less prevalent now, in part due to the overall decrease in pneumococcal infections as a result of the conjugate vaccine, but they will still be encountered.[2]

As many multiresistant *S. pneumoniae* strains are isolated from young children, the combination of multiresistance and a more restricted range of oral suspensions makes optimising treatment difficult. Resistance to macrolides, lincosamides, tetracyclines and trimethoprim/sulfamethoxazole is common in *S. pneumoniae*, especially in strains with reduced susceptibility to penicillins. Over 10% of Australian isolates have this resistance pattern. Paradoxically, strains with reduced susceptibility to penicillins generally remain susceptible to oral amoxycillin in higher doses (up to 1 g every eight hours). This makes amoxycillin the drug of choice for mild to moderate infections, even for the great majority of multiresistant strains, and it is currently recommended in Australian guidelines.[3]

Penicillin-allergic patients

Problems arise in the penicillin-allergic patient. Oral cephalosporins are ineffective against strains of *S. pneumoniae* with even slightly reduced susceptibility to penicillin. In adults, moxifloxacin is the most suitable choice, although this is not readily available on the PBS. For children with an allergy to beta-lactam antibiotics (12 years or younger) there is currently no entirely satisfactory oral treatment. Fortunately, penicillin allergy in young children is uncommon. Options range from trying a macrolide or trimethoprim/sulfamethoxazole if they are only mildly unwell, to hospitalisation for parenteral therapy in a sicker child.

Vancomycin-resistant enterococci

Vancomycin-resistant enterococci are usually hospital-associated multiresistant organisms. While they are unlikely to spread widely in the community, an increasing number of patients are becoming colonised in hospital and a small percentage will subsequently develop an infection with the colonising strain after being discharged. Most of these infections will be in the urinary tract.

Vancomycin-resistant enterococci strains are difficult to manage for a number of reasons, including their high transmissibility in the hospital setting, and more importantly because of the very limited range of antimicrobials available to treat them. Enterococci are naturally resistant to many antibacterial drugs including macrolides, lincosamides, cephalosporins and trimethoprim/sulfamethoxazole. There are two prominent vancomycin-resistant enterococci phenotypes: resistant to vancomycin and teicoplanin (so-called VanA), and resistant to vancomycin but susceptible *in vitro* to teicoplanin (so-called VanB). Unlike in other countries, the predominant phenotype in Australia is VanB.

The choice of treatment for vancomycin-resistant enterococci infection depends on the severity of the infection and which species is causing it. *Enterococcus faecalis* strains are mostly susceptible to penicillin and amoxycillin, and these drugs can be used (in higher dosages) provided the patient is not allergic to penicillin. On the other hand, most *Enterococcus faecium* strains are resistant to penicillin and amoxycillin, and drugs that are only available in hospital may be the only option. These important reserve drugs, such as linezolid and daptomycin, are effective parenteral drugs. Fortunately, nitrofurantoin and norfloxacin remain options for urinary tract infections caused by either VanA or VanB.

Colonisation

There are no effective treatments for the colonised state. Furthermore, if the isolate is from the urine of a patient with an indwelling catheter without any systemic symptoms, this represents colonisation rather than true infection and treatment is not warranted.

Multiresistant *Escherichia coli*

Over 5% of clinical *E. coli* isolates in Australia are resistant to more than three antibacterial drugs recommended for use – resistance to amoxycillin, cefazolin/cephalexin and trimethoprim/sulfamethoxazole is the commonest profile.[4] Reduced susceptibility or resistance to amoxycillin-clavulanate is also found in more than 8% of all *E. coli* and in up to 13% of amoxycillin-resistant strains, so strains with multiresistance are encountered in general practice. Fortunately, most strains at present still remain susceptible to the fluoroquinolones (norfloxacin and ciprofloxacin) and to nitrofurantoin. The recent increase in community strains harbouring extended-spectrum beta-lactamases is concerning – these enzymes make *E. coli* resistant to third-generation cephalosporins

(cefotaxime and ceftriaxone). These strains are often resistant to gentamicin and/or fluoroquinolones so when treating multiresistant *E. coli* infection, the susceptibility test results are required to ensure that an appropriate effective drug is chosen.

Other multiresistant enteric bacteria

Klebsiella species are found in similar clinical settings to *E. coli* in community practice. They are naturally resistant to amoxycillin, and have a higher propensity to acquire resistances than *E. coli*. Almost 10% of strains are multiresistant (more than three acquired resistances).[4] Treatment options are similar to *E. coli*, again taking careful heed of the susceptibility test results.

Less commonly encountered multiresistant enteric bacteria are *Enterobacter* species, which are naturally resistant to amoxycillin, amoxycillin-clavulanate and cefazolin/cephalexin. Furthermore, these species can become resistant to third-generation cephalosporins during treatment. Treatment choices are restricted to trimethoprim/sulfamethoxazole or fluoroquinolones if susceptible on testing, or carbapenems for serious infection.

Multiresistant *Pseudomonas aeruginosa*

P. aeruginosa is naturally resistant to many antibacterial drugs. Without acquired resistance, this species is only susceptible to a limited range of beta-lactams (ticarcillin, piperacillin, ceftazidime, cefepime and meropenem), aminoglycosides (gentamicin, tobramycin and amikacin) and fluoroquinolones (norfloxacin and ciprofloxacin). Furthermore, *P. aeruginosa* has a high propensity to mutate to or acquire resistance to any of these drugs. Hence, in certain clinical settings such as intensive care and in patients with cystic fibrosis, multiresistant strains of *P. aeruginosa* are common.

Multiresistant strains may be encountered in the community, most commonly in complicated urinary tract infection. Treatment of mild to moderate urinary infection caused by these strains will be defined by the results of susceptibility tests. If the isolate is susceptible to ciprofloxacin, this drug can be given orally to outpatients. Otherwise, all other drugs must be administered parenterally, and hospital management is usually required. Strains isolated from otitis externa will usually respond adequately to topical treatment.

Conclusion

Although there are limited treatment options for infections caused by multiresistant organisms, there are still drugs available in the community in many cases and hospitalisation for more complex parenteral therapy can be avoided. In general, treatment of colonisation with multiresistant organisms is not required.

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In the last two years, Professor Turnidge has sat on anti-infective advisory boards for Janssen-Cilag and Pfizer.

Dental notes

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The increasing prevalence of multiresistant bacteria in community-associated infections is most likely caused by over-prescription of antibiotics. The majority of dental infections can be successfully treated with an accurate diagnosis and timely dental treatment without antibacterial medication. When antibacterial drugs are needed, the principle of using a drug with the narrowest spectrum has long been held and is clearly outlined in recent guidelines.[1] Studies have shown that 85% of oral bacteria are susceptible to penicillin V. This is only marginally higher – 91% – with amoxycillin.[2] Over 10% of Australian *Streptococcus pneumoniae* isolates have reduced susceptibility to penicillins, yet these isolates paradoxically remain susceptible to higher doses of oral amoxycillin. Potentially life-threatening *S. pneumoniae* infections in children can be effectively treated with high-dose amoxycillin and this is one of the clinical reasons why amoxycillin is not recommended as the first drug of choice for oral infections.[1] Dentists should be aware of changing drug-resistance patterns and use antibiotics judiciously.

References

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