

Current resistance issues in anti-microbial therapy

The consequences of increasing bacterial antimicrobial resistance during the last few decades cannot be overestimated.

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The human gut contains 10^{13} - 10^{14} bacteria that are exposed to selection pressure whenever antibiotics are administered.¹ The same selection pressure applies to respiratory flora, which is one of the reasons why antimicrobial therapy prescribed for the treatment of respiratory tract infection should aim to eradicate pathogenic bacteria from the site of infection and from the nasopharynx.

How resistance occurs

Antimicrobial-resistant bacteria have been selected as the subject of this article, as they are either inherently resistant to a drug, or they have acquired resistance via DNA transfer or mutation. Resistance may not be confined to a single antibiotic, but may affect multiple antimicrobial classes. Bacterial adaptation to antimicrobial therapy has now reached a point where it poses serious clinical therapeutic challenges.

One of the consequences of bacterial resistance is that primary empiric therapy may fail to be active against potential pathogens. In severe infection, inadequate therapy is associated with delayed resolution and significantly increased mortality.²

Clinically significant resistance among Gram-positive and Gram-negative pathogens that cause infection in the community and hospital is increasing. Rice³ recently described these pathogens by using the acronym ESKAPE, as they can effectively escape the effects of most antimicrobial drugs. ESKAPE comprises *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.

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Gram-positive resistance

Streptococcus pneumoniae is a common cause of otitis media, sinusitis, community-acquired pneumonia, meningitis and bacteraemia. Penicillin-resistant *S. pneumoniae* (PRSP) has emerged during the last few decades, complicating therapy for

such infections. However, because of a recent change in penicillin breakpoints and the way in which these susceptibilities are subsequently reported, PRSP is currently a lesser problem than before.

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S. aureus has evolved from a susceptible organism to penicillin resistant, methicillin resistant (MRSA), and low-level vancomycin resistant (VISA), followed by high-level vancomycin resistant (VRSA) (currently confined to a few cases). VRSA, like MRSA, is often resistant to multiple antimicrobials. The mechanism of resistance for VISA and VRSA is thickening of the cell wall with substitution of the last amino acid of peptidoglycan precursors. There are several alternative therapies for the treatment of VISA or VRSA, of which linezolid therapy is one, but mutations in the 23S ribosomal RNA genes may also lead to linezolid resistance. Quinupristin-dalfopristin, tigecycline, ceftobiprole, daptomycin and the new lipoglycopeptides, e.g. oritavancin, are seen as agents with potential clinical use in this setting.

MRSA has recently emerged as a community-acquired (CA-MRSA) cause of skin and soft-tissue infection. These infections may resemble spider bites, or present as necrotising fasciitis or pneumonia. CA-MRSA strains are particularly virulent as they often produce a cytotoxic toxin, the Panton-Valentine leucocidin toxin. CA-MRSA is generally susceptible to clindamycin, co-trimoxazole, tetracycline, rifampicin and the quinolones.⁴

Enterococcus is the third most common cause of both nosocomial bloodstream infection and bacterial endocarditis. With the emergence of vancomycin-resistant enterococci (VRE), especially *E. faecium*, no appropriate therapy for VRE endocarditis has been defined.

The mechanism of vancomycin resistance in these organisms is mediated by different genes known as vanA, vanB, vanC, vanD and

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vanE. The vanC gene is found intrinsically in some non-pathogenic enterococci, but more pathogenic species may also acquire genetic material conferring resistance to the glycopeptides. These genes alter the binding site for vancomycin and the drug can therefore not inhibit synthesis of the cell wall. The administration of vancomycin and the cephalosporins has been shown to select for VRE.

Gram-negative resistance

Gram-negative resistance currently poses an even greater therapeutic challenge.

Gram negatives have now evolved from multidrug resistance (resistance to 3 or more classes of antimicrobials) to extreme drug resistance (susceptibility to 2 or fewer classes) to pan drug resistance (diminished susceptibility to all classes), the last seen especially in *Pseudomonas* spp. and *Acinetobacter* spp.

MRSA has recently emerged as a community-acquired (CA-MRSA) cause of skin and soft-tissue infection.

Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae is of specific concern in South Africa, with certain regions currently reporting an incidence of 55% in all *Klebsiella* tested in the laboratory. ESBLs are commonly seen in *Klebsiella* and *Escherichia coli*, but are also prevalent in most Enterobacteriaceae, e.g. *Enterobacter*, *Salmonella*, *Serratia*, *Proteus*, etc. This mechanism of resistance inactivates all beta-lactam antimicrobials, with the exception of the carbapenems (ertapenem, imipenem, meropenem and doripenem). Quinolone resistance is also common in these organisms.

The selection of this mechanism of resistance is a reflection of antimicrobial utilisation, especially with regard to the cephalosporins (particularly parenteral third-generation drugs, e.g. ceftriaxone) and the quinolones (e.g. ciprofloxacin, levofloxacin), although the carbapenems have also been implicated.

ESBL-producing Gram negatives are no longer confined to nosocomial infections and have emerged as a source of community-acquired infection, particularly *E. coli* producing the CTX-M enzyme. Risk factors associated with colonisation and infection

with ESBL organisms are the following: age >60 years, co-morbidity, catheterisation, diabetes, antimicrobial exposure during the last 3 months, hospitalisation during the last 3 months, and patients admitted from a frail care centre or a health care-associated environment.^{5,6}

Outcomes in bacteraemic infection caused by ESBL-producing organisms are worse than those in patients with non-ESBL-producing Enterobacteriaceae, with an increase in mortality and length of stay in hospital seen in the ESBL-producing group.⁷

The carbapenems are recommended as first-line therapy for severe infections caused by ESBL-producing organisms. The emergence of carbapenem-resistant Enterobacteriaceae is therefore of great concern, as therapeutic options for this group are very limited.

Carbapenem resistance generally involves several mechanisms of resistance, including the production of carbapenem-hydrolysing enzymes (carbapenemases), up-regulation of efflux systems, and mutations to outer-membrane proteins affecting permeability. There is a variety of different carbapenemases that can be chromosomally or plasmid encoded. The most frequent class A carbapenemase is the *Klebsiella pneumoniae* carbapenemase (KPC). These enzymes are mostly plasmid encoded and confer decreased susceptibility to all beta-lactam antimicrobials. KPC isolates are also usually resistant to other classes of antimicrobials, but most isolates are still susceptible to colistin and tigecycline.

Several risk factors are associated with acquiring KPC, including exposure to quinolones, carbapenems, anti-pseudomonal penicillins and glycopeptides, admission to an ICU, mechanical ventilation, tracheostomy and surgery with the use of prosthetic material.⁸

Pseudomonas is an important cause of nosocomial infection, including pneumonia, urinary tract infection, wound, burn and intra-abdominal infection, and bacteraemia. It is frequently isolated from patients with co-morbid disease. Because of its virulence and ability to form biofilms, *Pseudomonas* is a remarkably pathogenic organism. Besides its intrinsic resistance to a number of antimicrobial agents, *Pseudomonas* has acquired resistance via inactivating enzymes, antimicrobial binding-site mutations and increased expression of efflux pumps. Of concern are recent reports documenting reduced susceptibility and resistance to polymyxins, regarded as reserve therapy for multidrug-resistant *Pseudomonas*.^{9,10}

Enterobacter is another important health care-associated pathogen with increasing

resistance to antimicrobial agents. A variety of mechanisms may be involved in conferring resistance in these organisms, including inducible chromosomal cephalosporinases, ESBLs and carbapenemases.

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Azole resistance seen in *Candida* spp.

Fungal infection has increased during the last few years owing to an increase in immunocompromised hosts because of HIV infection, oncotherapy, transplant surgery and auto-immune disease.

Although *Candida albicans* resistance to fluconazole is uncommon, some *Candida* spp. are less susceptible.

Both *Candida krusei* and *Candida glabrata* are of clinical importance. They are associated with haematological malignancies and azole prophylaxis. *C. krusei* is particularly resistant to fluconazole.

New antimicrobials coming to the market in South Africa

Antimicrobial resistance is developing at a rate far exceeding the development of new antimicrobial drugs. Although several alternative therapies for the treatment of Gram-positive infections will become available in the future, the same cannot be said for the treatment of Gram-negative infections.

Tigecycline

Tigecycline, the first of a novel class of broad-spectrum antibiotics, the glycylcyclines, was recently licensed in South Africa for the parenteral treatment of adult patients with complicated skin

and soft-tissue infections (cSSTIs) and complicated intra-abdominal infections (cIAIs).

Of importance is the drug's activity against ESBL-producing Enterobacteriaceae, *Acinetobacter*, MRSA, and enterococci. It does however not have activity against *Pseudomonas* spp., *Proteus* spp., *Providencia* spp. or *Morganella* spp.

Because of high tissue levels but low serum levels caution is advised if the drug is utilised in bacteraemic patients.

Doripenem

Doripenem is a class 2 carbapenem with Gram-negative activity similar to that of meropenem, and Gram-positive activity similar to that of imipenem.

Doripenem exhibits rapid bactericidal activity against *Pseudomonas*, with 2 - 4-fold lower MIC values compared with meropenem.

Although registered for the treatment of complicated intra-abdominal infection and complicated urinary tract infection, this drug will increase the options for treating hospital-acquired pneumonia and ventilator-associated pneumonia.

Mutational loss of outer membrane protein OprD is often described during imipenem treatment of *Pseudomonas* infection, but doripenem retains activity against these strains.

Of interest is that doripenem will be the first beta-lactam antimicrobial to be registered as an extended infusion, each dose given over 4 hours.

Ceftobiprole

Ceftobiprole is a novel 5th-generation cephalosporin with enhanced Gram-positive cover, including anti-MRSA cover.

It has *in vitro* activity against Gram-negative organisms, including *Pseudomonas*, compared with cefepime. It is currently licensed in some countries as a parenteral drug for the treatment of complicated skin and skin-structure infections.

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In a nutshell

- The use of antimicrobial agents has been shown to be one of the major determinants in the shift towards resistant strains.¹¹
- Gram-negative resistance, particularly ESBL- and carbapenem-resistant Enterobacteriaceae, MDR *Pseudomonas* and *Acinetobacter*, and the recently described polymyxin-resistant *Pseudomonas*, poses significant therapeutic challenges.
- Unless current antimicrobial resources are managed more responsibly we will shortly face a spectre of untreatable Gram-negative infection.
- All antimicrobials are not equal.
- There are significant differences between drugs, even between those in the same class.
- Choice of antimicrobial agent and dosage should be optimised to ensure clinical resolution of infection and eradication of carrier status.
- However, extended duration of therapy for most community-acquired infections is undesirable owing to selection of resistance and should be avoided.