Chapter 2

NOTES ON SELECTED ANTIBIOTICS

BETA-LACTAMS

This important group of cell wall-active antibiotics includes the penicillins, cephalosporins, carbapenems, monobactams, and some ß-lactamase inhibitors. They all contain an active ß-lactam ring in their chemical structure from which their collective name is derived.

The best predictor of bacterial killing by ß-lactam antibiotics is the time during the dosage interval when the free (non-protein bound) drug concentration exceeds the MIC of the target organism. Where parenteral ß-lactam therapy is indicted, either a prolonged infusion of each dose, or continuous infusion over 24 hours, has been shown to be efficacious and cost saving. Expense is reduced both by a reduction in the amount of drug needed per day and lower labour expenses with simplified regimens. A recent meta-analysis demonstrated that the administration of beta-lactam antibiotics by continuous infusion is also associated with decreased hospital mortality and a higher rate of clinical cure compared with intermittent dosing in critically ill patients.

PENICILLINS

Penicillin V and penicillin G have activity against susceptible aerobic Gram-positive organisms. Ampicillin and amoxycillin have activity against some Gram-negative rods, and the Gram-negative spectrum is increased with piperacillin. Some anaerobes are susceptible to penicillin, with the notable exception of *Bacteroides fragilis*.

- **Benzylpenicillin (penicillin G)** remains the antibiotic of choice for infections due to susceptible streptococci, staphylococci, meningococci, gonococci, *Treponema pallidum*, *Pasteurella*, *Actinomyces* and *Clostridium perfringens*. It is used in combination with aminoglycosides for serious enterococcal infections and endocarditis.
- **Procaine penicillin G** is a longer-acting, intramuscular alternative to benzylpenicillin, given 12 hourly. Levels achieved are lower than those for benzylpenicillin and it should therefore not be used to treat meningitis.
- **Benzathine penicillin G** is the longest acting form and provides very low levels for three weeks or more. It is used almost exclusively to prevent streptococcal pharyngitis (hence the prevention of rheumatic fever) and to treat syphilis, other than neurosyphilis.
- **Phenoxymethylpenicillin (penicillin V)** is administered orally and achieves much lower levels than parenteral benzylpenicillin. It is used primarily against *Streptococcus pyogenes* in the treatment of pharyngitis and the prevention of rheumatic fever. In other situations it has tended to be replaced by amoxycillin, whose oral absorption is more reliable and less dependent on an empty stomach.
- **Cloxacillin** is the agent of choice for methicillin-susceptible staphylococci. Flucloxacillin is equivalent, but is better absorbed after oral administration. Both cloxacillin and flucloxacillin are examples of penicillinase-resistant penicillins.

- **Amoxicillin and ampicillin** are equivalent, but amoxicillin is better absorbed after oral administration. These penicillins are effective against penicillin-susceptible organisms and more effective than penicillin against *Enterococcus* spp., *Listeria* spp., ß-lactamase negative *Haemophilus influenzae*, *Salmonella typhi*, *Proteus mirabilis* and some strains of *Escherichia coli*.
- **Amoxicillin plus clavulanate** (a ß-lactamase inhibitor) extends the spectrum of amoxycillin to include otherwise resistant strains of *Haemophilus influenzae, Moraxella catarrhalis*, some Enterobacteriaceae and most anaerobes including *Bacteroides fragilis*. However, uncertain CSF penetration by clavulanate precludes the use of this antibiotic in meningitis and brain abscesses.

  The following new formulations of amoxicillin/clavulanic acid have recently been registered:
  - For children: 90 mg/kg amoxicillin/6,4 mg/kg clavulanic acid divided into two doses per day.
  - For adults: sustained release tablets of 1 g amoxicillin/62,5 mg clavulanic acid, two tablets given twice daily.

  Both these formulations alleviate the need to use standard doses of amoxicillin/clavulanic acid plus additional amoxicillin as recommended in several previous South African guidelines.
- **Piperacillin** has the most extensive Gram-negative activity of the penicillins. Its activity spectrum is that of amoxicillin or ampicillin plus activity against some strains of *Pseudomonas aeruginosa*.
- **Piperacillin plus tazobactam** combination uses another ß-lactamase inhibitor (tazobactam) which enhances the activity of piperacillin against plasmid-mediated ß-lactamase-producing Gram-negative bacilli such as *Klebsiella* spp. and some *E. coli* strains. However, an increase in inhibitor-resistant extended spectrum ß-lactamase (ESBL) production amongst Gram-negative bacilli has impacted on the empiric use of this antibiotic. Furthermore, this combination is not able to fully overcome the enormous concentrations of chromosomally-mediated ß-lactamase produced by derepressed mutant strains of *Enterobacter* spp., *Citrobacter freundii*, *Morganella morganii, Serratia* spp., *Proteus* spp. and *Providencia* spp.

MONOBACTAMS

Aztreonam is a monobactam antibiotic with a novel single nuclear ring structure which makes it highly resistant to hydrolysis by ß-lactamases and does not induce ß-lactamase activity. Aztreonam is only active against Gram-negative aerobic bacteria and displays synergy in combination with the newer fluoroquinolones, the other ß-lactams and aminoglycosides for many strains of Enterobacteriaceae and most strains of *P. aeruginosa*. Aztreonam lacks significant nephrotoxicity, with no significant effect on normal intestinal flora.

As aztreonam is not currently registered for routine use in South Africa, requests have to be made to the Medicines Control Council (MCC) on compassionate grounds. Its current role in South Africa appears to be that of salvage therapy in patients with multidrug-resistant *Pseudomonas aeruginosa* infections.

CEPHALOSPORINS

The cephalosporins are a group of broad-spectrum antibiotics which are conveniently grouped into four generations, with increasing activity against Gram-negative aerobes, and somewhat decreasing Gram-positive activity. The table below shows a simplified grouping based on their spectra of activity.

GENERATION	SPECTRUM	PARENTERAL	ORAL
1st	Staphylococci (except MRSA) Streptococci (not Enterococci) *E. coli, Proteus mirabilis, Klebsiella pneumoniae*	Cefazolin	Cephalexin Cefadroxil
*2nd	As for 1st generation AND *Haemophilus* (including ß-lactamase producers)	Cefuroxime	Cefaclor Cefprozil Cefuroxime Loracarbef
2nd	As for *2nd generation AND *Bacteroides*	Cefoxitin	
*3rd	As for *2nd generation AND other Gram-negative bacilli except *Pseudomonas* and *Acinetobacter* spp.	Cefotaxime Ceftriaxone	Cefpodoxime Cefixime
3rd	As for the *3rd generation AND methicillin-resistant *Staphylococcus aureus*	Ceftaroline	
3rd	As for the *3rd generation AND *Pseudomonas*	Ceftazidime	
4th	As for the *3rd generation including *Enterobacter* spp. and *Pseudomonas*	Cefepime	

All cephalosporins are active against most streptococci, except *Enterococcus* spp. (which are all intrinsically resistant). Importantly, they also have no activity against *Listeria* or methicillin-resistant staphylococci (except ceftaroline). Most penicillin-allergic patients will tolerate cephalosporins, but this group of antibiotics should be avoided if there is a definite history of anaphylaxis after penicillin administration. In general, the third-generation cephalosporins are significantly less active against staphylococci than the first-, second- and fourth-generation cephalosporins. All cephalosporins are hydrolysed by extended-spectrum ß-lactamases produced by Gram-negative pathogens.

- **First-generation cephalosporins** are effective alternatives for treating staphylococcal and streptococcal infections. They are therefore alternatives for skin and soft-tissue infections, as well as for streptococcal pharyngitis. It is important to stress that the members of this generation are not indicated for empiric treatment of otitis media or sinusitis. Although these agents have some activity against *E. coli*, *Klebsiella* and *Proteus*, their use is limited to urinary tract infections caused by susceptible strains of these organisms.
- **Second-generation cephalosporins** have increased activity against Gram-negative bacteria, including *H. influenzae, N. meningitidis* and *M. catarrhalis*. They are therefore useful agents for treating upper and lower respiratory tract infections, sinusitis and otitis media. These agents are also active against *E. coli*, *Klebsiella* and *Proteus*, which makes them potential alternatives for treating urinary tract infections caused by these organisms. Cefoxitin is a second-generation cephalosporin with anaerobic activity, and although seldom used as a therapeutic agent, it may have a role for prophylaxis in abdominal and pelvic surgery.

- **Third-generation cephalosporins** are active against most enteric Gram-negative organisms, including ß-lactamase producers, salmonellae and shigellae. They have less activity against staphylococci and therefore are not recommended for treating staphylococcal infections nor for prophylaxis in surgery. The parenteral third-generation cephalosporins (ceftriaxone and cefotaxime) have excellent activity against most strains of *Streptococcus pneumoniae*, including the vast majority of those with intermediate resistance and high level resistance to penicillin. These agents also have activity against *N. meningitidis* and *N. gonorrhoeae*. Their use should be limited to infections resistant to first choice agents, empiric treatment of meningitis, gonococcal infections and infections caused by penicillin-resistant pneumococci. Ceftazidime has useful antipseudomonal activity.
  - **Oral third-generation cephalosporins** cefixime and cefpodoxime are available in South Africa. These agents have greater efficacy against Gram-negative organisms than the first- and second-generation cephalosporins, but are less effective against *Staphylococcus aureus*. They are also active against penicillinase-producing strains of *Neisseria gonorrhoeae*. They have no activity against *Pseudomonas aeruginosa*, enterococci or *Campylobacter jejuni/coli*. They offer no significant advantage over amoxycillin for otitis media and sinusitis, or over penicillin for pharyngotonsillitis.
  - **Novel third-generation cephalosporin** Ceftaroline is a parenteral third-generation cephalosporin with a Gram-negative spectrum similar to that of ceftriaxone. In addition, ceftaroline is active against methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSP) due to its affinity for the altered PBPs (penicillin-binding proteins) found in these organisms. It is indicated for complicated skin and skin structure infections, including those caused by MRSA, as well as community acquired pneumonia.
- **Fourth-generation cephalosporins:** These drugs have a spectrum of activity, which includes the antipseudomonal activity of ceftazidime and the Gram-positive activity of cefotaxime and ceftriaxone including excellent cover against methicillin sensitive *S. aureus*. They have enhanced activity against *Enterobacter spp, Citrobacter* spp.*, Serratia* spp.*, Morganella* spp.*, Providencia* spp. and *Proteus* spp. because they are less susceptible to inactivation by AmpC beta-lactamases. Cefepime is currently the only drug in this class available in South Africa.

CARBAPENEMS

- **Imipenem/cilastatin** is one of the broadest spectrum antibiotics available. It is combined with cilastatin to prevent its degradation by renal tubular dehydropeptidase. Its spectrum covers the Enterobacteriaceae, *Pseudomonas*, *Bacteroides fragilis* and most Gram-positive cocci. However, it lacks activity against methicillin-resistant staphylococci, *Enterococcus faecium, Corynebacterium jeikeium*, *Listeria*, *Clostridium difficile and Stenotrophomonas maltophilia.* Seizures have been reported, especially with higher doses and in patients with impaired renal function. The use of this agent should be restricted to the treatment of life-threatening infections caused by highly resistant bacteria.
- **Meropenem** is a similar drug to imipenem but does not require combination with a dehydropeptidase inhibitor. It has slightly less activity against Gram-positive pathogens compared to imipenem. This drug has been suggested as an alternative to ceftriaxone for the management of meningitis caused by penicillin-resistant *Streptococcus pneumoniae*.
- **Ertapenem** is a broad-spectrum carbapenem, active against most common pathogens including anaerobes except enterococci, non-fermenters (e.g. *P. aeruginosa*) and methicillin-resistant staphylococci. It remains active against most Enterobacteriaceae with extended-spectrum ß-lactamases (ESBLs). In contrast to the other carbapenems it is administered once a day, either intravenously or intramuscularly.

- **Doripenem** has a spectrum of activity similar to meropenem, although it appears to have more potent in-vitro activity against *Pseudomonas aeruginosa*. Doripenem is stable in normal saline at room temperature for eight hours, allowing for prolonged infusion times.

AMINOGLYCOSIDES

This group includes:

- Amikacin
- Kanamycin
- Tobramycin
- Streptomycin
- Gentamicin

The aminoglycosides are active against aerobic Gram-negative bacilli, including *Pseudomonas* spp. These antibiotics have no activity against anaerobes, and alone they are inactive against streptococci. When the aminoglycosides are used in combination with penicillin or ampicillin, a synergistic effect is obtained against most streptococci, including enterococci. Although the aminoglycosides are active against most staphylococci, they should not be considered first choice agents and should not be used alone to treat staphylococcal infections.

Aminoglycosides are accordingly used in combination therapy for the treatment of serious infections with aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa*, complicated urinary tract infections, nosocomial respiratory tract infections, complicated intra-abdominal infections, enterococcal endocarditis and tuberculosis.

The principal side effects of the aminoglycosides are otovestibular toxicity and nephrotoxicity. They should be avoided when possible in the elderly and those with impaired renal function. Serum levels should be monitored in all patients receiving treatment for longer than two days. Administration once daily is as effective as divided doses and is the regimen of choice in most situations as the aminoglycosides ability to kill microorganisms is 'concentration dependent'.

See Annexure A regarding monitoring of serum aminoglycoside levels.

QUINOLONES

The classification of the quinolones into 'generations', on the basis of microbiological activity is controversial, but is useful for clinicians.

According to this classification, nalidixic acid is a **first-generation quinolone**. Because of its reliable activity against most Enterobactericeae, it became a popular choice for the treatment of uncomplicated urinary tract infections. Nalidixic acid is also used to treat shigellosis in children. It requires dosing four times a day and is available only as an oral agent and does not achieve significant tissue levels. It has no activity against *Pseudomonas aeruginosa*, anaerobes, chlamydiae, mycoplasmas or Gram-positive bacteria.

The **second-generation quinolones** expanded the bacterial coverage to include *Pseudomonas aeruginosa* and staphylococci. These quinolones have modest-to-poor activity against streptococci (notably *Streptococcus pneumoniae* and enterococci) and anaerobes. They exhibit high intracellular penetration, allowing for therapy against intracellular organisms such as chlamydiae, mycoplasmas and legionellae.

A significant problem has been the emergence of resistance during therapy for infections caused by *Staphylococcus aureus* and *Streptococcus viridans*. The second-generation quinolones can be divided into two subgroups. One group contains ciprofloxacin and ofloxacin, which are available in both oral and parenteral formulation, and can be used to treat minor and severe infections such as urinary tract infections, severe enteric infections caused by salmonellae, shigellae and

typhoid fever. The other group contains agents available only as oral formulations (e.g. enoxacin, lomefloxacin, norfloxacin), which are used primarily for urinary tract infections. In general, these agents should be reserved for the treatment of significant infections caused by *Pseudomonas aeruginosa* or other Gram-negative bacteria which are resistant to conventional antibiotics.

The **third-generation quinolones** have similar activity to the second-generation quinolones, plus increased activity against *Streptococcus pneumoniae*. However, they are less active than the second-generation quinolones against Gram-negative bacteria. Activity against anaerobes is modest-to-poor. Levofloxacin belongs to this group of quinolones. This quinolone should ideally be reserved for use as an alternative to other agents for acute exacerbations of chronic bronchitis and bacterial pneumonia in elderly patients. To achieve the recommended 24 hour AUC/MIC targets for pneumococci, levofloxacin doses of 500 mg twice daily are required.

Gemifloxacin and moxifloxacin can be considered **fourth-generation quinolones** owing to their increased activity against *Streptococcus pneumoniae*. In addition, moxifloxacin has excellent activity against anaerobes, and hence might be considered for the treatment of intra-abdominal infections (of intestinal or pelvic origin) in addition to respiratory tract infections (as for the third-generation quinolones).

GENERATION	GENERIC NAME	MICROBIOLOGICAL ACTIVITY
1st	Nalidixic acid	Enterobacteriaceae, including *Shigella*
2nd	Ciprofloxacin Ofloxacin Enoxacin Lomefloxacin Norfloxacin	As above AND *Pseudomonas* *Neisseria* spp. *Haemophilus* spp. *Moraxella catarrhalis* *Chlamydia* and *Chlamydophila* *Mycoplasma* *Legionella*
3rd	Levofloxacin	As above AND *Streptococcus pneumoniae*
4th	Moxifloxacin Gemifloxacin	As above AND *Streptococcus pneumoniae* Anaerobes (moxifloxacin) *Mycobacterium tuberculosis* (moxifloxacin)

TETRACYCLINES

- Tetracycline
- Doxycycline
- Minocycline

The antimicrobial spectra of all tetracyclines are nearly identical. They have activity against Gram-positive cocci, *Escherichia coli, Neisseria gonorrhoeae*, *Brucella* spp., vibrios, rickettsiae, coxiellae, mycoplasmas, chlamydiae and chlamydophilae, and spirochaetes including *Treponema pallidum* and *Borrelia burgdorferi*.

Tetracyclines are the treatment of choice for chlamydial, rickettsial, *Brucella* and *Ureaplasma* infections and are an alternative to erythromycin for *Mycoplasma pneumoniae* infections. Tetracyclines are also used for the treatment of inflammatory acne. Both doxycycline and minocycline have long half-lives and are therefore given once daily or twice daily. Unlike most other tetracyclines, they are reliably absorbed in the presence of food. Tetracyclines are contraindicated in children younger than eight years and in pregnancy (except for serious *Rickettsia* and *Brucella* infections) as they discolour developing teeth and may depress skeletal growth in premature infants. Only doxycycline can be used safely in renal insufficiency, and this agent is also less likely to stain the teeth. Gastrointestinal side effects and photosensitivity are relatively common with all tetracyclines; vertigo is common with minocycline.

TIGECYCLINE

Tigecycline, the first of a new class of broad-spectrum antibiotics, the glycylcyclines, is licensed in South Africa for the parenteral treatment of adult patients with complicated intra-abdominal and skin and soft tissue infections. Tigecycline is highly active against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *S. epidermidis* (MRSE) and enterococci, including vancomycin-resistant enterococci. It is also highly active against Enterobacteriaceae including multidrug-resistant strains such as extended-spectrum ß-lactamase (ESBL) producing *Klebsiella pneumoniae*. The spectrum of activity also includes anaerobes and atypical pathogens. It is not reliably active against *Pseudomonas aeruginosa.*

MACROLIDES

- **Erythromycin** is used for *Legionella*, *Campylobacter*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* infections, and for the treatment and prevention of whooping cough. It is used to treat chlamydial and *Ureaplasma* infections in pregnancy or childhood, when a tetracycline is contraindicated. Erythromycin has only marginal activity against *Haemophilus influenzae*. It is a useful drug for treating infections caused by *Streptococcus pyogenes* and pneumococci in patients allergic to penicillin.
- **Roxithromycin** has similar antibacterial activity to erythromycin but has a longer half-life and has improved activity against *Haemophilus influenzae*. It is given twice a day.
- **Clarithromycin** has significantly increased activity against organisms traditionally considered susceptible to erythromycin, plus good activity against *Mycobacterium avium* complex, *Vibrio cholerae*, *Neisseria gonorrhoeae*, *Campylobacter jejuni* and *Helicobacter pylori*. The major advantage over erythromycin includes better gastrointestinal absorption and tolerance and activity against *Haemophilus influenzae*. It is given once or twice a day and is available in an extended-release formulation.
- **Azithromycin** is less active than erythromycin against staphylococci and streptococci but more active against *Haemophilus influenzae*. It has a long half-life, allowing once-daily dosing. It is also available in an injectable form.

NOTE

There is complete cross-resistance between erythromycin, roxithromycin, clarithromycin and azithromycin.

KETOLIDES

Telithromycin is a novel antibacterial that belongs to a new chemical family; the ketolides. Telithromycin has a broad spectrum of antibacterial activity, which encompasses penicillin-resistant and erythromycin-resistant *Streptococcus pneumoniae*, as well as atypical or intracellular microorganisms. Telithromycin's low propensity for resistance may be attributable to its high degree of binding to two sites on the bacterial ribosome. Consequently, modification at a single site may not be sufficient to block telithromycin binding and therefore induce resistance to telithromycin. Telithromycin was specifically developed to provide optimal therapy for patients with antibiotic-resistant community-acquired respiratory tract infections.

CLINDAMYCIN

Clindamycin is active against Gram-positive bacteria such as staphylococci, pneumococci, *Streptococcus pyogenes*, and against most anaerobes including *Bacteroides fragilis*. Clindamycin is able to reduce toxin production in toxin-elaborating strains of streptococci and staphylococci and is used in patients with toxic shock syndrome. It is considered by some to be superior to penicillin in anaerobic pulmonary infections. It is an alternative to metronidazole for anaerobic infections (except those in the CNS), and bacterial vaginosis (topical) in pregnant women. Principal adverse effects are allergy (rash), antibiotic-associated diarrhoea including pseudomembranous colitis and, rarely, hepatotoxicity.

CHLORAMPHENICOL

This agent is active against salmonellae, *Haemophilus influenzae*, *Streptococcus pneumoniae, Neisseria meningitidis*, rickettsiae, and anaerobic bacteria (including *Bacteroides fragilis*). It is now seldom used because of rare irreversible marrow aplasia (approximately one per 20 000) and dose-related reversible circulatory collapse in infants ('grey baby syndrome'). Chloramphenicol is well absorbed, has broad spectrum activity and excellent CSF penetration. Chloramphenicol has a place in the treatment of brain abscess, meningitis in those allergic to ß-lactams, and is also effective in typhoid fever. It is a reasonable alternative to a tetracycline for rickettsiae infections in children younger than eight years.

GLYCOPEPTIDES

- **Vancomycin** is active against *Staphylococcus aureus*, *Staphylococcus epidermidis*, including strains resistant to methicillin (therefore also oxacillin and cloxacillin). Other Gram-positive bacteria such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, enterococci, *Corynebacterium jeikeium*, and *Clostridium difficile* are all sensitive to vancomycin. Ototoxicity, nephrotoxicity, allergy and, when infused rapidly, 'red-man syndrome' (erythroderma and hypotension), are principal adverse effects. Vancomycin is not absorbed from the gastro-intestinal tract. As an IV infusion it is used for the treatment of serious methicillin/oxacillin-resistant staphylococcal infections. In the penicillin-allergic patient it is used in combination with an aminoglycoside for the treatment of enterococcal endocarditis. Given orally, vancomycin is an alternative to metronidazole for the treatment of *Clostridium difficile* infections.

  See Annexure A regarding dosing and monitoring of serum vancomycin levels.
- **Teicoplanin** is a glycopeptide antibiotic with a molecular structure related to that of vancomycin. Gram-positive bacteria such as staphylococci (including methicillin-resistant strains), streptococci, enterococci and many anaerobic Gram-positive bacteria are susceptible to teicoplanin in-vitro. Rare species of coagulase-negative staphylococci may be resistant to teicoplanin yet sensitive to vancomycin. Teicoplanin has an exceptionally long half-life, allowing once daily intramuscular or intravenous administration. Recent studies suggest twice daily loading doses for 48 hours are required to rapidly achieve steady state concentrations in patients with serious infections.

OXAZOLIDINONES

Linezolid (IV, tablets and oral suspension) is the first member of the novel oxazolidinone class of antibiotics. Linezolid is a broad-spectrum antibiotic for the treatment of resistant Gram-positive infections such as community-acquired and nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*. Linezolid is also indicated in complicated skin and soft tissue infections caused by MRSA and vancomycin-resistant enterococcal infections. Oral linezolid demonstrates 100% bioavailability. Linezolid dosage is 600 mg twice daily and does not require a loading dose.

FOSFOMYCIN

This is a bactericidal antibiotic that inhibits the early stage of peptidoglycan synthesis in the cell wall and shows broad-spectrum activity against both Gram-positive and Gram-negative bacteria. In-vitro activity has also been documented for carbapenem-resistant Gram-negative bacteria including *Klebsiella pneumoniae* and multidrug-resistant *Pseudomonas aeruginosa*. Low levels of toxicity have been reported.

- Fosmomycin is only available as an oral preparation in South Africa for the treatment of urinary tract infections.
- The recommended dose for a urinary tract infection is 3 g as a single dose.
- As is the case with colistin, fosfomycin is increasingly being used abroad as salvage therapy for multidrug-resistant Gram-negative infections.

COTRIMOXAZOLE (TRIMETHOPRIM PLUS SULPHAMETHOXAZOLE)

Cotrimoxazole is active against a broad spectrum of Gram-negative and Gram-positive bacteria, as well as *Nocardia*, *Toxoplasma*, *Burkholderia cepacia, Stenotrophomonas maltophila* and *Pneumocystis*. This combination is used to treat Gram-negative urinary tract infections, and is the agent of choice for *Nocardia* infections. Cotrimoxazole is also used to treat and prevent *Pneumocystis jirovecii (carinii)* and *Toxoplasma* infections. Both the sulphonamide and trimethoprim may cause skin rashes, including Stevens-Johnson syndrome.

POLYMIXINS

Colistin is available in South Africa as Colymycine® which contains colistimethate sodium (CMS). It is available in vials that are measured in international units and one vial contains one million international units (1 MU). Colistin is increasingly being used as salvage therapy to treat multidrug-resistant nosocomial infections, particularly those caused by carbapenemase-producing Enterobacteriaceae, *P. aeruginosa* and *A. baumannii*.

Colistin should always be used as part of combination antibiotic therapy and never as monotherapy when used to treat multidrug-resistant organisms.

ADULT DOSING

Colistin should be administered as soon as possible after reconstitution as it is unstable in aqueous solutions

LOADING DOSE FOR ALL CRITICALLY ILL PATIENTS OR PATIENTS WITH SEVERE SEPSIS (REGARDLESS OF RENAL FUNCTION)

Loading dose is calculated as:

Dose of colistin base activity (mg) = target plasma concentration (mg/L) x 2.0 x ideal body weight

- Desirable target steady state plasma concentration of colistin is 2 mg/L
- 33 mg colistin base activity = ~ 1 million IU

Recommended maximum loading dose is 9 MU IV infused over 60 minutes, followed by the first maintenance dose 12 hours later

MAINTENANCE DOSING

Normal renal function (eGFR > 60): 4.5 MU 12 hourly infused over 15–30 minutes

DOSE ADJUSTMENT IN RENAL IMPAIRMENT

Refer to the 'look-up' table below for the daily dose required to achieve a steady state average target concentration of 2 mg/L based on the patient's creatinine clearance as determined by the Cockcroft and Gault equation:

Creatinine clearance (CrCl)* = (140 - age × ideal weight) ÷ serum creatinine

*For women, multiply the total by 0.85

DOSE OF CMS FOR PLASMA COLISTIN CSS, AVG OF 2 MG/DL

CREATININE CLEARANCE ML/MIN	COLISTIN BASE ACTIVITY MG/DAY	COLISTIN BASE ACTIVITY MILLION IU/DAY
0	130	3.95
15 to < 10	145	4.40
10 to < 20	160	4.85
20 to < 30	175	5.30
30 to < 40	195	5.90
40 to < 50	220	6.65
50 to < 60	245	7.40
60 to < 70	275	8.35
70 to < 80	300	9.00
80 to < 90	340	10.3
≥ 90	360	10.9

PATIENTS RECEIVING RENAL REPLACEMENT THERAPY

- The standard loading dose should be given
- The baseline daily dose to acheive an average steady state concentration of 2 mg/L in a patient with a CrCl of 0 mL/min is 130 mg/day (3.95 million IU/day) colistin base activity.
- Supplement the daily baseline dose by 10% for every one hour of dialysis

INTERMITTENT HAEMODIALYSIS

- Non-dialysis days give the baseline daily dose of 130 mg/day (3.95 million IU/day)
- On dialysis days supplement the baseline dose by 10% for every one hour of dialysis. Dialysis should occur towards the end of the colistin dosing interval. The supplement to the baseline daily dose should be given with the next regular dose once dialysis has ended.

CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

- Add 10% for one hour of CRRT to the baseline dose
- The suggested colistin base activity dose is 440 mg/day (~13 million IU/day)

NEBULISED COLISTIN

Nebulised colistin can also be in used in conjunction with intravenous colistin in cases of nosocomial pneumonia or ventilator-associated pneumonia. Standard adult dose is 2 MU 8 hourly (dissolved in 4 mL 0.9% sodium chloride solution or sterile water). The solution should be nebulised at an oxygen flow rate of 8 L/min via a face mask.

Nation RL, Garonzik SM, et al. 2017. Dosing Guidance for intravenous Colistin in critically ill Patients. *Clin Infect Dis* 64:565-571.

The most important adverse effect of colistin is nephrotoxicity due to acute tubular necrosis. Other side effects include dizziness, paresthesia, muscle weakness, ataxia, peripheral neuropathy and respiratory paralysis.

Colistin is not registered in South Africa but is obtainable via the Medicines and Related Substances Act through a Section 21 application process to the Medicines Control Council (MCC).

(www.mccza.com, tel. 012 312-0000)

The following is needed to apply:

- Application form filled in by the attending doctor
- A consent form (patient or family, if not possible by the attending doctor)
- A script
- A deposit into the MCC bank account

Please contact your local hospital pharmacist to assist with the application.

FUSIDIC ACID

This is essentially an antistaphylococcal agent. It should always be used in combination with another antibiotic to prevent the emergence of resistance e.g. cloxacillin, or in the case of MRSA, rifampicin, cotrimoxazole or even a quinolone should be considered. The only common side effects are gastric irritation when taken orally and skin rashes.

METRONIDAZOLE

Metronidazole has excellent activity against anaerobic bacteria, including *Bacteroides fragilis* and against several intestinal protozoa. It has no activity against aerobic bacteria. It is the agent of choice for bacterial vaginosis, trichomoniasis, giardiasis, amoebiasis, *Clostridium difficile* and balantidiasis.

Although it does have activity against *Helicobacter pylori*, a significant percentage of strains are resistant to metronidazole with reduced eradication rates in those treated. Unlike clindamycin, metronidazole effectively penetrates the blood-brain barrier. Nausea, metallic taste, and disulfiram-like effect with alcohol are side effects, which may be less common with the related agent tinidazole.

NITROFURANTOIN

This orally administered agent does not achieve significant blood and tissue levels but is excreted in the active form in urine. It is therefore only used for the treatment or prophylaxis of uncomplicated lower urinary tract infections, due to most Gram-positive or Gram-negative bacteria. *Pseudomonas aeruginosa* and *Proteus* species are intrinsically resistant. Pulmonary reactions may be problematic.

RIFAMPICIN

Rifampicin is active against a wide range of microorganisms. Apart from its important role as an antituberculous and antilepromatous agent, rifampicin is used to eradicate nasopharyngeal carriage of *Neisseria meningitidis* and *Haemophilus influenzae* following meningitis, and as an adjunct to doxycycline (in brucellosis), and fusidic acid (in serious staphylococcal infection). The agent causes red/orange discoloration of body fluids and occasional influenza-like symptoms and hepatotoxicity. Rifampicin is a potent inducer of specific metabolic enzymes in the liver and intestine. The levels of several drugs are markedly reduced such as phenytoin, warfarin, HIV protease inhibitors and oral contraceptives. Due to its primary value as an antimycobacterial agent, its use for other purposes should be restricted.

ANNEXURE A: RECOMMENDATIONS REGARDING DOSING AND 'DESIRABLE' SERUM LEVELS OF THE AMINOGLYCOSIDE ANTIBIOTICS AND VANCOMYCIN

Both the aminoglycoside group of antibiotics and vancomycin have narrow therapeutic indices and monitoring of serum levels is required to (i) assess adequacy of therapy and (ii) detect/avoid potential dose-related toxicity.

AMINOGLYCOSIDES

These may be administered by the intravenous (IV) or intramuscular (IM) route. It should be noted that comparative studies have confirmed the efficacy of single daily dosing (extended-interval administration) compared to intermittent dosing. In general, extended-interval dosing is preferred and takes advantage of the pharmacodynamic properties of the aminoglycosides, and offers greater ease of preparation, administration and monitoring. Certain patient groups exhibit altered pharmacokinetics and traditional intermittent dosing may be preferable in burn patients, patients with ascites, pregnant women and those with a creatinine clearance < 40 mL/min (including patients requiring dialysis) OR > 120 mL/min.

INTRAMUSCULAR (IM) ADMINISTRATION

- Predose (trough) level: Take serum (clotted blood) specimen within 15–30 minutes before the next dose
- Postdose (peak) level: Take serum (clotted blood) specimen one hour (60 minutes) after IM administration

INTRAVENOUS (IV) ADMINISTRATION

- Bolus (IV 'push') is not recommended – the preferred practice is to infuse the aminoglycoside in 5% dextrose or 0.9% NaCl over 15–30 minutes
- Predose (trough) level: Take serum (clotted blood) specimen within 15 minutes before the next dose
- Postdose (peak) level: Take serum (clotted blood) specimen 30 minutes after completion of the IV infusion

'DESIRABLE' SERUM ANTIBIOTIC LEVELS (MG/L): AMINOGLYCOSIDES

	PEAK (MULTIPLE DAILY DOSES)	TROUGH (MULTIPLE DAILY DOSES)	TROUGH (ONCE DAILY DOSING)
Gentamicin	4–10	1–2	< 1
Tobramicin	4–10	1–2	< 1
Netilmicin	4–10	1–2	< 1
Amikacin	15–30	5–10	< 1
Kanamycin	15–30	5–10	< 1

NOTE

- Once-daily dosing of aminoglycosides makes monitoring of peak levels unnecessary
- It is important that the specimens are clearly identified and labeled as 'peak' or 'trough' as appropriate

VANCOMYCIN

The only parenteral route is intravenous administration. Bolus (IV 'push') administration is contraindicated. The recommended practice is to infuse vancomycin in doses of 15–20 mg/kg every twelve hours in a patient with normal renal function. In a setting where rapid clearance is anticipated (e.g. burn patients), the dose may be administered every eight hours. In general, the drug should be infused over 30 minutes for each 500 mg increment (e.g. 500 mg over 30 minutes, 1 000 mg over one hour, etc.). A loading dose of 25–30 mg/kg must be given in patients with serious infections such as sepsis, endocarditis, pneumonia and meningitis.

Nephrotoxicity and ototoxicity associated with vancomycin monotherapy is uncommon; toxicity appears to increase in patients with underlying renal dysfunction, concomitant nephrotoxic therapies (e.g. aminoglycosides), and co-morbidities. Hence the clinical utility of monitoring vancomycin serum concentration continues to be the subject of ongoing debate. However, most would agree that trough concentrations are considered the most accurate and practical method to monitor vancomycin levels regarding toxicities, and should always be performed in patients receiving vancomycin therapy for longer than three days.

There is little role for the routine monitoring of peak vancomycin concentrations, given the lack of data correlating peak concentrations with efficacy or toxicity.

- Predose (trough) level: Take serum (clotted blood) specimen within 15–30 minutes before the next dose.
- Postdose (peak) level: Take serum (clotted blood) specimen 30 minutes after completion of the IV infusion.

'DESIRABLE' SERUM ANTIBIOTIC LEVELS (MG/L): VANCOMYCIN

	PEAK	TROUGH
Vancomycin	20–40	< 15–20