CLINICAL APPROACHES OF THE ANTIBIOTIC STEWARDSHIP PROGRAMME IN SOUTH AFRICA

Practical and responsible antibiotic use in hospital and in the community

KEY MESSAGES

- Early use of antibiotics in the first 6 months of life is associated with altered gut microbiota, impaired immunity and the emergence of atopic, immune-mediated and metabolic diseases and possibly also cancers and neuropsychiatric disorders in later life.

- Selection of an appropriate antibiotic for hospital patients with infection must be based on knowledge of likely pathogens and resistance patterns in the specific surgical/high care unit.

- 10 general principles for the selection of empiric therapy for postoperative peritonitis are insightful.

- In general practice, upper respiratory tract infections rarely require antibiotics. Antibiotics may be necessary in acute exacerbations of chronic bronchitis and are always indicated for the treatment of community-acquired pneumonia.

- Meticulous infection control and attention to general principles of patient care are essential for prevention of infections in ICU, which, when they do occur, are frequently highly antibiotic-resistant. Knowledge of local epidemiology and resistance patterns is essential when considering treatment options.

- In carefully selected patients with chronic obstructive pulmonary disease, long-term macrolide therapy may be helpful to reduce the occurrence of acute exacerbations and improve quality of life.

- For most surgical procedures that require antibiotic prophylaxis, a single dose of antibiotic is sufficient and a 1st generation cephalosporin is the preferred choice.

- Fluoroquinolones should not be used as first line antibiotics in general practice.

Abdominal sepsis

The gut microbiome: Its role in health and disease

Based on a presentation by Prof Marc Mendelson
Professor of Infectious Diseases, University of Cape Town, Co-Chairman of SAASP

The microbiota sharing the human body comprise a diverse ecological community of commensal, symbiotic and pathogenic micro-organisms, weighing around 2.2 kg. The microbial to human cell ratio is approximately 10:1 and gene ratio 100: 1.

In healthy people, the range of organisms is diverse, both between individuals and in the same individual, and variable depending on body location, such as vagina, gut and skin. The reason for such diversity is not fully understood, but diet, environment, host genetics and early microbial exposure play a role. In contrast, disease states are characterised by lack of microbial diversity.1-3

The human gastrointestinal tract is residence for a mixed population of
micro-organisms that play an essential role in the development of the immune system and maintenance of health.

The gut microbiome (collective genomes of micro-organisms) represents that of approximately 10^{14} organisms, of which about 95% are bacteria. It becomes established during the first 3 years of life (the foetal gut is sterile), deriving from maternal vaginal and faecal micro-organisms after vaginal delivery and evolving with breast feeding and transition to solid foods. Cesarean section (CS) is associated with reduced diversity and altered bacterial composition during infancy and childhood, which might help to account for the increased incidence of obesity and atopic disorders that is observed in children delivered in this way. Prolonged admission in neonatal care units and possible use of broad-spectrum antibiotics delays the establishment of beneficial microbiota and enables the growth of potentially pathogenic organisms.

The gut microbiota play essential roles in many aspects of health. These include colonic fermentation of dietary fiber; extraction of nutrients; vitamin synthesis; prevention of colonisation by pathogenic organisms; maturation of the intestinal epithelium; maturation and modulation of local and systemic immune responses; release of metabolites to the systemic circulation; and modulation of gastrointestinal hormone release and nerve function. The bacterial colonisation after birth is essential for normal development of a healthy immune system and different species of bacteria have different effects on immune maturation and function. Microorganisms regulate thickness and composition of the intestinal mucus layer; they induce development of lymphoid structures, including Peyer’s patches, mesenteric lymph nodes and splenic white pulp; they modulate immune cell differentiation and promote homeostasis by decreasing the number of pro-inflammatory cells (e.g., natural killer [NK] T cells) and modulating the balance between pro- and anti-inflammatory T cells and the expression of chemokines, cytokines and other soluble immune mediators. The gut microbiota regulates the production of antimicrobial peptides (AMPs) produced by intestinal epithelial cells. These include defensins, C-type lectins, ribonucleases, and S100 proteins, which regulate the composition of the microbiota and rapidly kill or inactivate micro-organisms that may breach the mucosal barrier and threaten the stem cell niche in the crypts of Lieberkühn.

Considering the importance of the gut microbiome in physiological development and homeostasis, it is not surprising that disruption of the microbiota by broad spectrum antibiotics may influence health outcomes. Depletion of gut microbiota in mice which were subsequently infected with *S. pneumoniae* was associated with increased bacterial dissemination, inflammation, organ damage and mortality compared with controls. Alveolar macrophage activity was disrupted with diminished capacity to phagocytose the bacteria. Faecal microbiota transplant (FMT) in gut microbiota-depleted mice was associated with normalisation of pulmonary bacterial counts and tumour necrosis factor (TNF)-α and interleukin (IL)-10 levels 6 hours after pneumococcal infection.

In humans, early use of antibiotics in the first 6 months of life has been associated with transient or persistent alterations in immunity, altered microbial control, impaired colonisation resistance and emergence of pathobionts and pathogenic microorganisms. Persistent loss of dominant microbial regulators of host immunity, aberrant immunological responses to altered commensal microorganisms, and alterations in host and microbial metabolism after exposure to antibiotics may provide an explanation for the emergence of atopic, immune-mediated and metabolic diseases and possibly also cancers and neuropsychiatric disorders in later life (Table 1).

| Table 1. Possible clinical consequences in later life of antibiotic use in early infancy  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Inflammatory bowel syndrome</strong></td>
<td><strong>Atopic dermatitis</strong></td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td><strong>Multiple sclerosis</strong></td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td><strong>Cancer?</strong></td>
</tr>
<tr>
<td><strong>Type 1 diabetes</strong></td>
<td><strong>Autism?</strong></td>
</tr>
</tbody>
</table>
Antibiotic prescribing in colorectal sepsis

Dr Adrian Brink
Clinical Microbiologist, Ampath NLS, Milpark Hospital, Johannesburg, Ex Officio President of Federation of Infectious Diseases Societies of Southern Africa (FIDSSSA); Co-Chairman SAASP.

Depending on the experience of the surgeon and surgical site, the incidence of postoperative peritonitis (POP) after colorectal surgery varies between 1% and 10%, and associated mortality may be as high as 10%.

The key to management of POP is effective surgical source control in combination with appropriate empiric antibiotic treatment. Because patients undergoing colorectal surgery are high risk at the outset, many of them are at risk of failing surgical control per se (Table 2) and choice of antibiotic is critical.

Because pathogens and antibiotic susceptibility vary not only between hospitals, but also between units within the same hospital, selecting an appropriate antibiotic requires knowledge of which pathogens are likely in the specific unit. Broad spectrum antibiotics should be avoided and treating colonisation is inappropriate (Table 3). The most frequent reason for using inappropriate empirical therapy is bacterial resistance to the selected antibiotic.

Data collected in South Africa during 2004-2009 for the Study for Monitoring Antimicrobial Resistance Trends (SMART), which follows trends in resistance among aerobic and facultative anaerobic gram-negative bacilli (GNB) isolated from complicated intra-abdominal infections (cIAIs) in patients around the world, showed that antibiotic-resistant bacteria were common. Enterobacteriaceae comprised 83.7% of the isolates, with *Escherichia coli* being the most common isolate (46.4%), and 7.6% of these were extended-spectrum beta-lactamase (ESBL)-positive. The highest ESBL rate was documented for *Klebsiella pneumoniae* (41.2%). Approximately 90% of the isolates were susceptible to ertapenem, amikacin, piperacillin-tazobactam and imipenem-cilastatin, whereas rates of resistance to ceftriaxone and cefotaxime were approximately 30% and to ciprofloxacin and levofloxacin approximately 20%. Approximately one quarter of *K. pneumoniae* and 5% of *E. coli* and *Proteus mirabilis* isolates were multi-drug resistant (MDR; defined as resistance to three or more antibiotic classes). Susceptibility to ertapenem, but not imipenem-cilastatin was reduced significantly in ESBL-positive vs. ESBL-negative isolates (91% vs. 98% and 95% vs. 99%, respectively).

Patients with postsurgical intra-abdominal infections who have had a close association with an acute care hospital or who reside in a chronic care setting (healthcare-associated infections) are at increased risk of infection due to *Pseudomonas aeruginosa, Acinetobacter, ESBL-producing bacteria, methicillin-resistant Staphylococcus aureus* (MRSA), Enterococci and *Candida* species and infections also due to multi-drug resistant organisms (Table 4). Consequently, because adequate empiric therapy is an

### Table 2. Clinical factors predicting failure of source control

1. Delay in initial intervention beyond 24 hours
2. High severity of illness (APACHE II score ≥15)
3. Advanced age
4. Comorbidity and degree of organ dysfunction
5. Low albumin
6. Poor nutritional status
7. Degree of peritoneal involvement or diffuse peritonitis
8. Inability to achieve adequate debridement or control of drainage
9. Malignancy

### Table 3. Risk factors for inappropriate antibiotic therapy

1. Not using local data (i.e., antibiotic resistance)
2. Use of broad spectrum antibiotics (e.g., vancomycin) when not absolutely necessary
3. Broad treatment of contamination, including surgical prophylaxis
4. Aggressive treatment of bacterial colonisation
5. Excessive antimicrobial treatment (i.e., continuation of antibiotics when infection is cured)
General principles when selecting empiric therapy for postoperative peritonitis are as follows:

1. Knowledge of local epidemiology & syndromic antibiograms are key to choosing empiric cover for colorectal sepsis.
2. Considerations in determining appropriate therapy should take account of
   - Site of perforation
   - Dose and dosing frequency
   - Severity of illness
   - Potential for antibiotic resistance, considering prior antibiotic treatment and nosocomial vs. health-care associated vs. community onset, and subsequently prevalent pathogens (e.g. ESBL-producing Enterobacteriaceae vs. P. aeruginosa).
3. Monotherapy is preferred.
4. If risk factors for MDR organisms are not present, narrow spectrum empiric cover such as amoxicillin-clavulanate would suffice.
5. Recommended options for patients at risk of ESBL-positive organisms (Table 5) include ertapenem and tigecycline, which also have a spectrum of activity appropriate for anaerobes.
6. Hospital-acquired (HA) peritonitis (e.g., due to anastomotic failure) may be associated with worse prognosis and, whilst enterococci are more frequently cultured, P. aeruginosa has to be considered and requires therapy such as piperacillin-tazobactam, meropenem, imipenem or doripenem.
7. Routine empiric coverage for enterococci is not necessary for community-acquired intra-abdominal infections. Recommended options for those at high risk for poor outcome due to enterococcal infections (Table 6) are piperacillin-tazobactam, tigecycline or the addition of ampicillin or vancomycin to regimens lacking sufficient enterococcal activity (e.g., carbapenems).
8. Duration of empiric therapy should be guided by clinical findings. For most patients 2 to 7 days appears to be an adequate. Longer therapy is not associated with improved outcomes and it is reasonable to discontinue therapy if the patient is afebrile with a normal white cell count.
9. Although C. albicans or other fungi are cultured from approximately 20% of patients with acute perforations of the gastrointestinal tract, antifungal treatment is usually unnecessary. However, patients in whom Candida is associated with increased mortality include those who have recently received immunosuppressive therapy for a neoplasm, have had perforation of a gastric ulcer on acid suppression, those with malignancy, transplantation or inflammatory disease, and those who have postoperative or recurrent intra-abdominal infection. Empiric antifungal therapy is highly dependent on the local susceptibility patterns and the local laboratory should be contacted for advice before starting treatment.
10. Patients should be reassessed regularly. A guide to clinical decision making at 72 hours is illustrated in Table 7.

### Table 4. Healthcare-associated infections

<table>
<thead>
<tr>
<th>Community-onset healthcare-associated infection</th>
<th>Patients have at least one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Presence of invasive device at time of admission</td>
</tr>
<tr>
<td></td>
<td>• History of MRSA infection or colonisation</td>
</tr>
<tr>
<td></td>
<td>• History of surgery, hospitalisation, dialysis or residence in a long-term care facility in the 12 months preceding the culture date</td>
</tr>
</tbody>
</table>

| Hospital-onset infection | Patients with positive culture results obtained >48 hours after admission ± risk factors for community-onset infection |

### Table 5. Risk factors for ESBL-producing bacterial infection

- Treatment with 2nd or 3rd generation cephalosporin
- Hospitalisation in the past 3 months
- Treatment with fluoroquinolones
- Treatment with penicillin
- Antibiotic treatment in the previous 3 months
- Age ≥60 years
- Diabetes
- Male gender
- Infection with Klebsiella species

### Table 6. Risk factors for enterococcal infections

- Immunocompromised patients
- Patients with health care-associated post-operative peritonitis
- Patients with severe sepsis of abdominal origin who have previously received cephalosporins and other broad-spectrum antibiotics selecting for Enterococcus species
- Patients with peritonitis and valvular heart disease or prosthetic intravascular material, which place them at high risk of endocarditis
New modalities in the prevention and management of *Clostridium difficile* infection

**Professor Debra A Goff**

*Clinical Associate Professor, Infectious Diseases Specialist, Ohio State University Medical Center, Columbus, Ohio, USA*

Effective antibiotic stewardship requires identification of high risk patients, confirmation of an accurate diagnosis, use of effective antibiotics and coordination of care.

In this context, general principles for the diagnosis and management of *C. difficile* infection (CDI) are as follows:

1. **Careful patient selection.** Risk factors include antibiotic use, hospital patient or nursing home resident, age >65 years, serum albumin <2.5g/dl, increasing serum creatinine, ICU admission.

2. **Only liquid stools** (in patients not receiving laxatives) should be considered for testing (≥3 unformed watery stools in a 24 hour period). It should be noted that tube feeding causes liquid stools.

3. **There is no consensus** as to which diagnostic laboratory test is best. PCR is quick, with high specificity and sensitivity, but is expensive.

4. **The necessity of all treatments** (e.g., antibiotics, proton pump inhibitors, H₂-receptor antagonists) should be re-evaluated.

5. **Gloves and gowns** should be worn when treating patients with CDI. Hand sanitizer does not kill *C. difficile*.

6. **C. difficile** severity scores may be useful to guide treatment. Severe disease is associated with increased white cell count (>15-20 cells/mm³), age >65 years, rising serum creatinine, fever ≥38.5°C and clinical or radiological evidence of severe colitis.12,13

   • Mild or moderate: start with metronidazole;
   • Severe: start with vancomycin;*
   • Combinations may considered for very high risk patients with comorbidities.

7. **Antibiotics should be discontinued** if possible. If this is not possible, an alternative antibiotic with low risk of antibiotic-associated CDI should be considered (e.g., aminoglycoside, sulphonamide, macrolide, vancomycin, and tetracycline).

8. **Assess need for surgical intervention.**

*Professor Richards added that combination IV and oral metronidazole may be used for severe CDI, with de-escalation as necessary to oral metronidazole monotherapy.

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**Table 7. Guide to management at 72 hours after commencing empiric antibiotics for colorectal sepsis**

<table>
<thead>
<tr>
<th>Culture result</th>
<th>Clinical assessment</th>
<th>Recommended course of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Better</td>
<td>• De-escalate</td>
</tr>
<tr>
<td>Positive</td>
<td>Worse</td>
<td>• Consider fungal infection, enterococci or MRSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Adjust therapy according to microscopy, culture and sensitivity result</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If appropriate: source control</td>
</tr>
<tr>
<td>Negative</td>
<td>Better</td>
<td>• Stop therapy</td>
</tr>
<tr>
<td>Negative</td>
<td>Worse</td>
<td>• Consider fungal infection, enterococci or MRSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If appropriate: source control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Extra-abdominal source</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Genetic polymorphisms/systemic inflammatory response syndrome (SIRS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reconsider diagnosis. If clinical condition is unlikely to be due to sepsis, discontinue antimicrobials</td>
</tr>
</tbody>
</table>

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  Click on ‘Accredited CPD modules’.
Respiratory tract infections
The rationale for diagnostic tests to prevent inappropriate prescribing in respiratory tract infections

Dr Tom Boyles
Senior Specialist in Infectious Diseases & HIV Medicine, Groote Schuur Hospital, Cape Town

Prescribing for respiratory tract infections (RTI) accounts for a considerable portion of antibiotic use, especially in the community setting. Furthermore, in most RTIs, both antibiotics and diagnostic tests are unnecessary and inappropriate, where history and clinical examination are sufficient for diagnosis and management decisions.

This is especially true of upper RTIs, including sore throat, otitis media and sinusitis, which are relatively simple to diagnose clinically and are usually self-limiting.

Antibiotics may be considered in the case of streptococcal pharyngitis to limit the development of complications, including rheumatic fever and acute post-streptococcal glomerulonephritis. Where available, culture from a throat swab specimen is helpful to confirm the diagnosis (Figure 1). Rapid antigen tests are not helpful in South Africa.

In the case of lower RTI, acute bronchitis is invariably viral and antibiotics are of no value. In contrast, an antibiotic may be necessary in acute bacterial exacerbations of chronic bronchitis (AECB) and is always indicated for community-acquired pneumonia (CAP). Clinical findings that favour a diagnosis of CAP include fever, tachypnea, tachycardia and evidence of consolidation. Where there is doubt about the diagnosis, a chest X-ray should be done.

In the primary care setting, where there is diagnostic uncertainty, point-of-care C-reactive protein (CRP) may also be helpful in making management decisions. CRP >100mg/l is consistent with diagnosis of CAP, whereas antibiotics are generally unnecessary when CRP <20mg/l. When CRP is between these values, an antibiotic

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**Figure 1. Diagnostic and treatment criteria for acute pharyngotonsillitis.**


**Diagnose all-cause pharyngotonsillitis when the following are present:**
- Sore Throat
- Fever

**Viral features**
- Coryza
- Cough
- Conjunctivitis
- Hoarseness

**Bacterial features**
- Anterior stomatitis
- Discrete ulcerative lesions
- Diarrhoea

- Tender anterior cervical lymphadenopathy
- Pharyngeal erythema
- Pharyngeal oedema or exudate

**GABHS unlikely**
- Symptomatic treatment only
- No antibiotic prescribed

**GABHS more likely**
- Perform throat swab
- No antibiotic prescribed

- Symptomatic treatment
- Provide delayed antibiotic script

- If GABHS grown, contact patient to have antibiotic dispensed

- Symptomatic treatment
- Provide antibiotic script, only if 3–21 years old

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should be considered if there are risk factors present for a complicated course or if the patient deteriorates clinically.

Procalcitonin levels, which are upregulated in bacterial and downregulated in viral infections may be helpful under certain circumstances to differentiate aetiology of AECB. However, this test is expensive and is not available as point-of-care.

**Strategies for prevention and management of ventilator-associated pneumonia**

**Professor Guy Richards**  
*Academic Head and Professor of the Division of Critical Care at the University of the Witwatersrand, Director of the Department of Critical Care at the Charlotte Maxeke Johannesburg Academic Hospital and Chief Physician in the Department of Medicine and Pulmonology*

Hospital and ventilator-associated pneumonias are those arising more than 48 hours after admission or intubation for mechanical ventilation, respectively. Although there is no gold standard for diagnosis of ventilator associated pneumonia (VAP) and clinical features are subjective and nonspecific, the CDC has proposed defining symptoms and signs for VAP (Table 8). However, the sensitivity and specificity of these criteria are questionable and there is poor correspondence between clinical signs and histological pneumonia. Consequently, there is a high rate of misdiagnosis and the actual incidence and prevalence of VAP remain difficult to quantify. Nevertheless, it is estimated that the incidence approximates 15-20% and peaks at around day 5. Similarly, although reported mortality rates among these patients may be as high as 70%, because of the critical nature of their illness and high rate of comorbidities, it is difficult to determine what proportion of deaths are attributable directly to VAP.

<table>
<thead>
<tr>
<th>Two or more serial radiographs with at least one of the following</th>
<th>One of the following</th>
<th>Two of the following</th>
</tr>
</thead>
</table>
| • New or progressive and persistent infiltrate  
• Consolidation  
• Cavitation | • Fever (>38°C)  
• Leukopenia (<4000 WBC/μl) or leukocytosis (>12 000 WBC/μl)  
• For adults ≥70 years old, altered mental status with no other recognized cause | • New onset of purulent sputum or change in character of sputum or increased respiratory secretions or increased suctioning requirements  
• New onset or worsening cough, or dyspnea, or tachypnea  
• Rales or bronchial breath sounds  
• Worsening gas exchange (e.g. oxygen desaturations, increased oxygen requirements, or increased ventilator demand) |

The pathogens associated with VAP derive from both endogenous and exogenous sources, including aspiration of gastric contents, inhalation of airborne pathogens, extension from a contiguous site and translocation via the circulation. Enteric gram-negative bacilli are common, whereas, at least in Johannesburg, *Staphylococcus aureus* is rarely isolated. Because they emanate from the ICU environment, organisms are frequently highly antibiotic-resistant. Biofilm production is essential for colonisation and adherence to the endotracheal tube and airways, and presents a challenge to treatment, because biofilm structures are resistant to both antimicrobials and host defences. Quorum sensing, in which organisms release molecules that enable intra- and interspecies communication, causes upregulation of genes that stimulate biofilm production and antimicrobial resistance, resulting in complex biofilms of mixed and antibiotic-resistant pathogens.
Prevention of VAP

Meticulous infection control (e.g., hand washing) and attention to general principles of patient care are essential for prevention of infections in ICU. General principles, characterised by the acronym FAST HUGS BID, are listed in Table 9.

Table 9. General principles for prevention of infection in ICU

<table>
<thead>
<tr>
<th>Comments</th>
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<tbody>
<tr>
<td>Feeding and fluids</td>
</tr>
<tr>
<td>Analgesia</td>
</tr>
<tr>
<td>Sedation</td>
</tr>
<tr>
<td>Ulcer prophylaxis</td>
</tr>
<tr>
<td>Thromboprophylaxis</td>
</tr>
<tr>
<td>Head up position</td>
</tr>
<tr>
<td>Indwelling catheter removal</td>
</tr>
<tr>
<td>De-escalation of antibiotics</td>
</tr>
</tbody>
</table>

In carefully selected patients, early tracheostomy improves outcomes when the duration of MV is expected to exceed a week. Careful attention should be paid to tube cuff pressure, where <20cm H₂O favours aspiration and >30cm H₂O causes mucosal injury. Using an ultrathin polyurethane cuff (7 mm) reduces aspiration and significantly decreases early and late VAP.

Careful attention should be paid to oral hygiene and care of the endotracheal tube (ETT). Oral chlorhexidine wash, especially in higher concentrations (2%) can help reduce the incidence of VAP.

Management of VAP

As in other hospital-acquired infections, pathogens are unit specific and knowledge of local epidemiology and resistance patterns is essential. The type of pathogen is usually consistent regardless of time from ICU admission to onset of VAP.
Long-term macrolides in COPD: Risk/benefit analysis

*Professor Charles Feldman*

*Professor of Pulmonology, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand*

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with worsening of symptoms, admission to hospital and impaired quality of life. Associated mortality is very high - approximately 10% die in hospital and up to 43% die within 1 year of the event.

COPD comprises a cycle of impaired mucociliary clearance, acute and chronic respiratory infection and persistent inflammation that, in turn, increases susceptibility to infection, both acute and chronic. Although their full mechanisms of action are not completely understood, there are multiple mechanisms that might account for the potential of chronic macrolide therapy to break the chronic cycle of inflammation-infection in COPD and to strengthen the airways defence mechanisms to prevent infective exacerbations. Macrolides reduce bacterial load and virulence, reduce airway secretions, improve mucociliary clearance, and exert various anti-inflammatory and immunomodulatory effects (Table 10).17,18

**Table 10. Potential beneficial effects of macrolides in chronic respiratory diseases**18

<table>
<thead>
<tr>
<th>Reduced airway secretion</th>
<th>Reduced chronic inflammation</th>
<th>Antibacterial effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduced water secretion</td>
<td>• Increased phagocytosis of apoptotic neutrophils</td>
<td>• Inhibition of bacterial protein synthesis</td>
</tr>
<tr>
<td>• Modulation of mucin gene expression</td>
<td>• Increased β-defensin levels</td>
<td>• Suppression of quorum sensing proteins</td>
</tr>
<tr>
<td></td>
<td>• Reduced production of pro-inflammatory cytokines</td>
<td>• Reduced bacterial adherence</td>
</tr>
<tr>
<td></td>
<td>• Reduced neutrophil chemotaxis</td>
<td>• Reduced bacterial toxin production</td>
</tr>
<tr>
<td></td>
<td>• Downregulation of adhesion molecule expression</td>
<td>• Inhibition of bacterial biofilm function</td>
</tr>
<tr>
<td></td>
<td>• Reduced production of oxygen species</td>
<td>• Reduced generation of oxygen free radicals</td>
</tr>
</tbody>
</table>

In carefully selected patients with COPD, chronic use of macrolide antibiotics reduces the duration of individual exacerbations, extends periods between exacerbations, reduces the number of hospitalisations and improves quality of life.17

There are, however, potential risks associated with long-term macrolide therapy.18,19

• Chronic use increases the emergence of bacterial antibiotic resistance, including resistance in nontuberculous mycobacterial diseases for which macrolides, and in particular clarithromycin, are commonly used.

• Drug-drug interactions are important. Macrolides inhibit the cytochrome P450 3A4 isoenzyme, and may increase the serum concentrations of other drugs metabolised by this enzyme, including statins, amiodarone and warfarin.

• Ototoxicity that is reversible on discontinuation may occur with chronic administration of macrolides. It is usually described as sensorineural, bilateral hearing loss involving the lower or speech frequencies.

• Macrolides increase the QTc interval, which increases the risk of *torsades de pointes*, ventricular fibrillation and sudden death. Older patients (especially those >80 years of age) with cardiac disease and those taking other medications that also prolong the QTc interval are especially at risk. Other risk factors include conditions associated with reduced drug elimination, hypokalaemia and hypomagnesaemia, prolonged QTc interval before starting therapy, bradycardia and genetic predisposition.

• Gastrointestinal side effects, although typically mild in severity, are the most common adverse effect reported by patients receiving macrolides.

**Which patients should be considered for chronic macrolide therapy?**

Guidelines for COPD management recommend smoking cessation, enrolment in a rehabilitation program, and optimal use of medications including long-acting inhaled beta-agonists, long-acting inhaled...
Anticholinergic agents and inhaled glucocorticosteroids. Education and regular assessment is also required to ensure correct use of inhalers and compliance with therapy.²⁰,²¹

Patients who continue to experience exacerbations despite optimal COPD management are potential candidates for chronic macrolide therapy, taking care to ensure that there are no contraindications.²⁰,²²

The exact patient population that will benefit and the optimal dose and duration of therapy is at present uncertain, but proposed criteria for selecting patients with COPD for long-term macrolide therapy are summarised in Table 11.

### Table 11. Proposed criteria for selecting patients for long-term macrolide therapy and contraindications²⁰,²²

<table>
<thead>
<tr>
<th>Proposed selection criteria</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Moderate to severe COPD (GOLD stage 2, 3 or 4)</td>
<td>• Prolonged QTc interval on electrocardiography (&gt;450ms), or receiving drug therapy that prolongs QTc interval</td>
</tr>
<tr>
<td>• At least 2 exacerbations treated with antibiotics or systemic steroids in the past year, or at least one exacerbation that resulted in admission to hospital</td>
<td>• Unstable or uncontrolled cardiovascular disease (congestive heart failure, angina pectoris)</td>
</tr>
<tr>
<td>• Management of COPD already optimal</td>
<td>• Hearing impairment documented previously or apparent on audiometry</td>
</tr>
<tr>
<td>• Compliant with current therapy and using proper inhaler technique</td>
<td>• Allergy to macrolides</td>
</tr>
</tbody>
</table>

GOLD: Global Initiative for Chronic Lung Diseases

Any acute exacerbations should be treated with comprehensive standard antibiotic therapy before initiating chronic therapy. Patients should be reassessed at 12 months.


### Controversies in antibiotic stewardship

**What is the evidence for anything other than single dose antibiotic prophylaxis for surgical site prophylaxis?**

**Professor Natie Botha**

*General Surgeon, Laparoscopic, Open Surgery and Surgical Oncology, Cape Town*

**Timing and duration of surgical prophylaxis**

Timing of antimicrobial administration in surgical prophylaxis is critical to ensure that good tissue levels of drug are present for the duration of the procedure and for the first 3 to 4 hours after the surgical incision. Most parenteral antibiotics should therefore be administered within 30 to 60 minutes of incision. Although they are rarely used for prophylaxis, vancomycin and fluoroquinolones require longer infusion times and administration should begin 2 hours before surgical incision.

For most surgical procedures a single dose of an antimicrobial agent will provide adequate tissue levels. However, where it is necessary to continue for longer, most experts agree that prophylaxis should be discontinued within 24 hours postoperatively.

**Organisms involved in surgical site infections**

Most surgical infections are acquired from the patient’s own microbial flora, but exogenous infection may also occur by contamination during surgery from medical staff, the environment and instruments.

*S. aureus* is the major pathogen associated with wound infections following...
clean surgery. Gram negative bacteria are important causes of wound infection following surgery involving the colon or genitourinary tract and gynaecological procedures.

**Choosing the appropriate antimicrobial agent**

Due to their appropriate spectrum of activity (including *S. aureus* and streptococci), low potential for side effects and allergic reactions, and low cost, first generation cephalosporins are preferred for surgical prophylaxis. The half-life of cefazolin is 1.8 hours, which is ideal for prophylaxis. It should be used at a dosage of 2g for a 70kg adult, or 3 g for adults weighing more than 120kg.

Because colorectal surgery requires gram negative and anaerobic cover (including *Bacteroides fragilis*), cefoxitin or cefuroxime plus metronidazole is the preferred choice for this type of surgery.

Third generation cephalosporins have limited anti-staphylococcal activity and may select for extended spectrum gram negative resistance and should not be used for surgical prophylaxis.

**When is more than a single dose appropriate for surgical prophylaxis?**

Although it is generally unnecessary to administer prophylactic antibiotics postoperatively, there are certain circumstances in which multiple doses of antibiotic may be appropriate.

1. Procedures exceeding 2-3 hours. A second dose equal to the first may be administered.
2. Massive blood loss (more than 1500 ml).
3. Cardiac surgery. In addition to pre-operative antibiotics, intra-operative re-dosing during procedures lasting more than 400 minutes has been associated with decreased risk of postoperative infections. Doses should be administered every 2 hours until closure. It may be appropriate to administer prophylactic antibiotics for 24 hours following cardiac or valve surgery.
4. Insertion of a prosthetic device. Antibiotics may be administered for at least 24 hours.
5. Orthopaedic surgery. Postoperative antibiotics can reduce the incidence of both early and delayed infection following joint replacement, repair of closed fractures and insertion of plates and screws. Most guidelines suggest 24 hours prophylaxis for prosthetic devices.
6. Noncardiac thoracic surgery. Multiple doses of a cephalosporin can prevent infection after closed-tube thoracostomy for chest trauma with haemo- or pneumothorax.
7. Vascular surgery. Prophylaxis should be administered 6-8 hourly for 24 hours after surgery.
8. Colon and colorectal surgery. Intraoperative repeat dosing is recommended to prevent surgical wound infection.

Alternative prophylactic agents for patients with allergy to beta-lactam antibiotics

**Fluoroquinolones should be the antibiotics of last resort for community and hospital prescribing**

**Prof Marc Mendelson & Prof Charles Feldman**

The effectiveness of the fluoroquinolones has made them one of the most commonly prescribed antibiotics in general practice. In comparison to public sector use, in the private sector the number of prescriptions for quinoline antibiotics has been disproportionately increasing year on year. Although they are widely used for respiratory and urinary tract infections, for the most part, their use is inappropriate and unnecessary. The collateral damage associated with inappropriate fluoroquinolone use includes the following:
1. Emergence of resistant bacteria. Fluoroquinolone resistance rates have increased in almost all bacterial species, including pneumococcus (especially in South Africa where fluoroquinolones are used to treat multidrug resistant tuberculosis), gram-negative pathogens (including Enterobacteriaceae, Pseudomonas, Klebsiella and Neisseria sp.), and Mycobacterium tuberculosis. Furthermore, because of the association of genes encoding fluoroquinolone resistance and resistance to other drug classes, fluoroquinolone resistance is strongly associated with resistance to other antibiotics, including ESBL production and resistance to aminoglycosides. Fluoroquinolones, such as levofloxacin and ciprofloxacin, select for methicillin resistance among staphylococci (MRSA).

2. High degree of disruption of the gut microbiota

3. Clostridium difficile-associated diarrhoea

4. Fluoroquinolone-associated tendonitis

Although they are therefore generally not to be used as a first-line antibiotic choice, there are specific clinical conditions in which fluoroquinolones might be considered. These include:

1. Community-acquired pneumonia, in the case of severe allergy to beta-lactam antibiotics, failed response to initial therapy, suspected or known resistance to alternative antibiotics and atypical pneumonias.

2. Acute exacerbation of chronic bronchitis where the patient has received non-fluoroquinolone antibiotics in the previous 90 days, or complicated chronic bronchitis with or without chronic bronchial sepsis.

3. Community-acquired intra-abdominal infections, as part of combination antibiotic therapy in stable, non-critical patients with no ESBL-associated risk factors.

Stopping antibiotics: Should patients in the community setting be told to stop taking their antibiotics when they feel better?

Longer exposure to antibiotics is a risk factor for the development of antibiotic resistance in the community. It has therefore been suggested that patients should be advised to stop taking prescribed antibiotics when they feel better.

However, ‘feeling better’ is subjective, and this advice may leave the patient in an uncertain situation where, from a clinical standpoint, it may be appropriate or inappropriate to discontinue therapy. For example, some conditions such as HIV, TB, osteomyelitis, pyelonephritis, endocarditis or switching from IV to oral antibiotics require longer-term therapy, despite the subjective impression of wellness. Therefore it is inappropriate to leave the patient without guidance.

The key to appropriate antibiotic use is rational, carefully considered prescribing, taking stewardship principles into consideration:

1. Only prescribe antibiotics when they are absolutely necessary

2. Prescribe for shortest possible duration of therapy appropriate to the indication. In community infections especially, it is unnecessary to prescribe antibiotics for 5, 7 or 10 days when a shorter course will be sufficient (e.g. 2-3 days)

3. Patients should be given clear instructions on how, and for how long, to take prescribed medication.
IN PHARMACY

Special Report: South African Antibiotic Stewardship Programme Annual Meeting

The annual meeting of the South African Antibiotic Stewardship Programme (SAASP) on 5 February 2016 was highlighted by the launch of the 2016 SAASP pharmacist-initiated collaborative study on adherence to the South African community-acquired pneumonia (CAP) guidelines. The purpose of the study is to foster ongoing antibiotic/antimicrobial stewardship (AMS) in South Africa in an era of escalating antibiotic resistance worldwide, with a view to preserving the utility of these life-saving medications for future generations.

Pharmacist-driven antibiotic stewardship

Infectious disease specialist Dr Debbie Goff, a founding member of the Antimicrobial Stewardship Program at Ohio State University (OSU), underscored that it’s up to pharmacists to make AMS happen. “We’re living in a world where many antibiotics no longer work. Consumers do not understand this and pharmacists need to take the lead in education. As far back as 1946, Alexander Fleming warned that the advent of penicillin would usher in an era of antibiotic abuse. ‘The thoughtless person playing with penicillin is morally responsible for the death of a man who finally succumbs to a penicillin-resistant organism’.

Dr Goff played a key role in the development of a collaboration between OSU and South Africa. Its purpose was to develop an antibiotic stewardship outreach program and facilitate an OSU-South Africa pharmacists’ network to lead antibiotic stewardship programmes, given South Africa’s lack of infectious-disease trained pharmacists. This ‘train the trainer’ mentoring programme, which started in 2013, provides local pharmacists with the skills necessary to implement antibiotic stewardship. Dr Goff expressed her pride at what South Africa has already accomplished on the global map of stewardship.

Several graduates of the programme gave feedback on their extremely positive experiences. Sonya Kolman, a clinical pharmacologist at Netcare Linksfield, said that it gave her the confidence to take on a leadership role in introducing AMS at her institution. “Our biggest achievement has been a decrease in antibiotic consumption and defined daily dosages through doctor consultation.”

Angeliki Messina, quality leadership manager: antibiotic stewardship, Netcare Hospitals, returned from the mentorship at OSU with the goal of training future generations of pharmacists in AMS. “My key learnings included never taking no for an answer, being aware that I work as part of a team, holding my peers accountable for achieving the next level of excellence and, most of all, that a candle loses nothing by lighting another. So let’s work together.”
Antibiotics

Introducing the 2016 SAASP pharmacist-initiated collaborative study on adherence to the South African CAP guidelines

Introducing the study, Dr Dena Van den Bergh, director: quality leadership at Netcare, invited all delegates to get involved as she outlined the quality improvement (QI) methodology. “Quality-driven methodology is the science of improvement,” she said. “Our goal is to evaluate current practice and identify the changes necessary for best practice. Working together, we can make an impact, so pharmacists need to take the lead to persuade their colleagues in hospitals. Do this respectfully in a way that inspires, rather than implies criticism, and frame it as an opportunity.”

The study aims to close ‘know-do’ gap in the management of CAP to achieve best practice and ensure that the right patients get the right treatment. “We’re building the collaborative as we speak and hope in time to publish the findings. Those who participate will be the first pharmacists in South Africa – or maybe the world – to look at this issue.”

Professor Guy Richards of the University of the Witwatersrand expressed his view that many doctors have no idea how to prescribe antibiotics and that pharmacists need to assume the role in the interests of maintaining the usefulness of these agents. CAP is a particularly appropriate subject of the study in that it is still the most widespread and fatal of human diseases. “It is the commonest cause of infectious death in the USA and the sixth commonest cause of death overall.”

Inappropriate therapy plays a key role in antibiotic resistance, with antibiotics frequently prescribed for viral infections. The minimum inhibitory concentrations (MICs) – the lowest amount of the drug required to kill the organisms – are increasing, meaning higher doses are required. If this trend is not addressed, many drugs could ultimately become unusable because of toxicity issues associated with high doses. It is therefore critical to prescribe appropriately.

Where an antibiotic is appropriate, it should be prescribed according to SAASP principles. “Choose an appropriate empirical antibiotic, targeting the most likely pathogen and assessing the likelihood of resistance. Review potential contraindications and consider hypersensitivity, potential toxicity, aim for a single drug at the correct dose/route of administration and start appropriate treatment rapidly, as each hour of delay is associated with a 7.6% decrease in survival. South African guidelines recommend oral amoxicillin as the agent of first choice.

“It’s also important to know the guidelines as therapy consistent with guidelines is associated with decreased time to stability, a shorter length of hospital stay and lower mortality,” he said.

Dr Pieter Ekermans, a clinical microbiologist at Ampath, Centurion, reviewed the importance of laboratory testing to determine antibiotic selection and thus promote antibiotic stewardship when treating CAP. “Although pathogen-directed therapy fosters antibiotic stewardship, and reduces costs and complications, a pathogen is only detected in about half of all CAP episodes,” he said.

There is a wide variety of tests available, but not all are appropriate for diagnosing pneumonia. He underscored that molecular test platforms have changed the way pneumonia is diagnosed, allowing for the assessment of multiple potential pathogens. He cautioned, however, that these tests don’t always provide data on antibiotic resistance or distinguish between colonisation and infection. Sampling is also a key concern – and when undertaking any laboratory test (especially for microbiological work-up), one requires samples that are appropriate, representative, of good quality and of adequate volume.

“Correlate laboratory findings with the clinical picture. Treat the patient, not the results. Microbiological work-up is required for severe CAP cases (notably patients who are hospitalised, and especially those in the ICU). Specimen quality determines the quality of your results and don’t interpret each of the haematological and chemical parameters in isolation,” he concluded.

“One person can make a difference – and that person can be you”
Dr Debbie Goff

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