COMMUNITY-AcQUIRED PNEUMONIA: EVIDENCE-BASED MANAGEMENT AND ANTIBIOTIC STEWARDSHIP

Introduction
Community-acquired pneumonia (CAP) is a common infectious disease with a high mortality rate. In South Africa, pneumonia, influenza and tuberculosis are the leading causes of natural death.1 Hospitalised patients with severe pneumonia are especially at risk of poor outcome. One-fifth of those admitted to the intensive care unit (ICU) and more than half of ventilated patients over the age of 65 with pneumonia will die.

Aetiology of CAP
In data collected from adults with CAP who required hospitalisation in the USA, a causative pathogen was identified in only 38%, which in the majority of cases (23%) was a virus. The most common viral pathogens were rhinovirus (9%) and influenza virus (6%). Bacterial causes were identified in 11% and mixed infection with a bacterial pathogen and virus in 3%. The most common bacterial cause was Streptococcus pneumoniae (5%), whereas less common bacterial pathogens included Mycoplasma pneumoniae, Staphylococcus aureus, Legionella pneumophila and Enterobacteriaceae.2 In the ICU setting, Haemophilus influenzae is extremely uncommon.

While the pneumococcal vaccine, which has in recent years been administered to both children and adults, may account for the decrease in incidence of infection with S pneumoniae, the continued predominance of infections caused by the influenza virus underscores the importance of annual vaccinations against this pathogen, especially among vulnerable individuals, e.g. elderly.

In HIV-positive patients, CAP becomes more common as the CD4 cell count falls. S pneumoniae and Mycobacterium tuberculosis are important pathogens. In general, the aetiology is similar to that in HIV-negative individuals, but H influenzae, S aureus, Gram-negative bacteria (GNB) and antibiotic-resistant bacteria are more common. Opportunistic pathogens may occur alone or in combination with conventional pathogens.3

Diagnosis
In patients where CAP is suspected, there are no individual clinical findings or combinations of findings that can confirm the diagnosis. However, the absence of abnormal vital signs or abnormalities on chest auscultation essentially rules out the diagnosis (Table 1).4 A chest X-ray is indicated in the presence of any of the signs listed in Table 1 or if a cough has been present for longer than three weeks. Comorbidities and age may complicate a

Table 1. Clinical features consistent with a diagnosis of CAP4

<table>
<thead>
<tr>
<th>Feature</th>
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<tbody>
<tr>
<td>Fever ≥38°C</td>
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<tr>
<td>Tachypnoea ≥24 breaths per minute</td>
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<tr>
<td>Tachycardia ≥100 beats per minute</td>
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<tr>
<td>Evidence of consolidation on examination: crackles, bronchial breathing, fremitus</td>
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clinical diagnosis. Confusion may be the only symptom in elderly patients with pneumonia.

Factors that increase the likelihood of infection with antibiotic-resistant organisms are listed in Table 2 and clinical features suggestive of infection with methicillin-resistant \textit{S aureus} (MRSA) are listed in Table 3.

Examination of expectorated sputum has a low yield and is generally not useful, so it is usually only recommended for a subset of hospitalised patients before initiation of antibiotic therapy (Table 4). Nevertheless, care must be taken when interpreting culture results, so as not to confuse colonising bacteria with causative pathogens.

### C-reactive protein

In conjunction with clinical examination, raised C-reactive protein (CRP) may be useful to support the diagnosis of CAP (cut-off value 33mg/l). Raised CRP values are especially high in patients with pneumonias caused by \textit{S pneumoniae} or \textit{L pneumophila} and CRP is higher in more severe disease. In patients with severe CAP, serial CRP measurement during the first week of treatment may be useful to monitor recovery. Decline in CRP <60\% in three days or <90\% in seven days indicates that empirical antibiotic treatment is inappropriate or that complications have developed.

### Point-of-care CRP testing in the community setting

The majority of antibiotic use occurs in the community (80\%), with prescribing for respiratory tract infections (RTIs) accounting for a considerable proportion of this. Most community RTIs are viral infections and self-limiting, so antibiotics are unnecessary. 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. However, it is estimated that 80\% of patients with acute RTIs receive an antibiotic, 60\% of which are unnecessary.

In the case of lower RTIs, 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 CAP. An accurate diagnosis is therefore essential.

In the primary care setting, in the case of diagnostic uncertainty, point-of-care tests (POCTs) for CRP may be helpful in

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**Table 2. Factors associated with higher likelihood of infection with antibiotic-resistant bacteria\textsuperscript{a}\textsuperscript{5}**

- Age > 65 years
- Alcoholism
- Immune suppression (including corticosteroids and HIV infection)
- Bronchiectasis/severe COPD with previous administration of multiple antibiotics
- Exposure to children in day care
- Antibiotics in the last three months, especially fluoroquinolones and macrolides

**Table 3. Clinical features suggesting infection with MRSA\textsuperscript{6}\textsuperscript{7}**

- Cavitary infiltrate or necrosis
- Rapidly increasing pleural effusion
- Gross haemoptysis (not just blood streaked)
- Concurrent influenza
- Neutropenia
- Erythematous rash
- Skin pustules
- Young, previously healthy patient
- Severe pneumonia during summer months

**Table 4. Indications for culture of expectorated sputum in hospitalised patients\textsuperscript{5}\textsuperscript{6}\textsuperscript{7}\textsuperscript{8}\textsuperscript{9}**

- ICU admission
- Failure of antibiotic therapy
- Cavitary lesions (tuberculosis, anaerobes)
- Active alcohol abuse
- Severe obstructive or structural lung disease
- Immunocompromised individuals
- Pleural effusion
- Suspected \textit{Legionella}, MERS/SARS-CoV, H5N1, H7N9, GNB, MRSA

MERS/SARS-CoV: Middle East respiratory syndrome/severe acute respiratory syndrome coronavirus; GNB: Gram-negative bacteria; MRSA: Methicillin-resistant \textit{S aureus}
Community Acquired Pneumonia

making management decisions when used to support clinical examination. CRP >100mg/l is consistent with a diagnosis of CAP and antibiotics would be appropriate, whereas CAP is unlikely and antibiotics are generally unnecessary with CRP <20mg/l. It is, however, important to note that viral infections, including uncomplicated influenza may also present with CRP >100mg/l.

When CRP lies between 20 and 100mg/l, an antibiotic should be considered if the patient deteriorates clinically, has comorbidities, or if there are risk factors present for a complicated course (Table 5).²

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age &gt;75 years</td>
<td>• Age &lt;3 months</td>
</tr>
<tr>
<td>• Heart failure</td>
<td>• Cardiovascular conditions</td>
</tr>
<tr>
<td>• Severe COPD</td>
<td>• Pulmonary conditions (except asthma)</td>
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<tr>
<td>• Diabetes mellitus (especially with use of insulin)</td>
<td></td>
</tr>
<tr>
<td>• Neurological conditions</td>
<td></td>
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<tr>
<td>• Severe renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>• Compromised immunity</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Risk factors for a complicated course in patients with acute RTI and POCT CRP 20-100mg/l²

In patients with an acute exacerbation of chronic bronchitis (AECOPD), CRP may also be helpful to differentiate who might benefit from antibiotic therapy. AECOPD is defined as an acute event characterised by a worsening of the patient’s respiratory symptoms (sputum production, dyspnoea and reduced effort tolerance) that is beyond normal day-to-day variations and leads to a change in medication.¹⁰ In such a patient CRP >40mg/l suggests that antibiotics are likely to be beneficial.⁹

Principles of antibiotic therapy in CAP

The South African Antibiotic Stewardship Programme (SAASP) has published guidelines for antibiotic prescribing, which are available on the FIDSSA website (www.fidssa.co.za) and as an app for smart phone or tablet.¹¹

In patients with CAP, antibiotic therapy should be started as quickly as possible at the time of diagnosis, with an appropriate empirical antibiotic chosen according to the most likely pathogen and the likelihood of resistance. In this regard, it is essential to be aware of local resistance patterns as these can vary quite markedly from one region to another, and sometimes even between units in the same hospital. Where the diagnosis is made in a community setting and especially if the patient is in shock, antibiotics should be administered in the doctor’s rooms before transporting the patient to hospital.

Potential toxicity and contraindications to specific antibiotics must be considered. History of maculopapular rash after a previous exposure to amoxicillin means that all penicillins should be avoided, but risk of cross-allergy to second- or third-generation cephalosporins is only approximately 0.1%. However, a type I sensitivity reaction (urticaria) after previous exposure indicates that all beta-lactam antibiotics should be avoided in future. Wherever possible, a single antibiotic should be used, ensuring the correct dose and route of administration. For time-dependent antibiotics, such as beta-lactams, blood concentrations must remain above the bacterial minimal inhibitory concentration (MIC) for at least 50-60%, and ideally 100%, of the dosing interval. To achieve this, high doses may be necessary. Similarly, with concentration-dependent antibiotics (e.g. fluoroquinolones, aminoglycosides), sufficient doses should be considered to achieve an appropriate area under the concentration-time curve (AUC) to inhibit bacterial growth (AUC/MIC ratio [AUIC]). Some examples of appropriate doses for oral antibiotics are listed in Table 6.
Table 6. Oral therapy: optimal drug doses for CAP\textsuperscript{11,12}

<table>
<thead>
<tr>
<th>Oral antibiotic</th>
<th>Recommended dose for CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>2g 12-hourly or 1g 8-hourly</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>2g 12-hourly</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1g 12-hourly</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>200mg 8-hourly</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>800mg daily</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500mg 12-hourly or 750mg daily</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400mg daily</td>
</tr>
</tbody>
</table>

Appropriate choices for outpatient therapy of CAP include oral amoxicillin (agent of choice) or amoxicillin-clavulanate ± macrolide/azalide/telithromycin; or moxifloxacin or levofloxacin.\textsuperscript{11-13}

**Severe CAP requiring hospitalisation**

Patients older than 65 years and those with comorbidities or severe pneumonia require hospitalisation and should be treated with parenteral antibiotics. Early admission to hospital and, where necessary, to ICU, adherence to treatment guidelines and early administration of antibiotics improve survival and reduce length of hospital stay.

Various severity-of-illness and prognostic scores are used to determine which patients may be candidates for outpatient therapy, or alternatively when hospitalisation is required. The CRB-65 is a simple set of criteria that helps to identify patients with high mortality risk and who would benefit from admission to hospital. It assigns a score of 1 point to each of the following positive criteria: age ≥65 years; confusion (based on a specific mental test or disorientation to person, place or time); respiratory rate ≥30 breath/minute; and low blood pressure (systolic <90mmHg or diastolic ≤60mmHg). A score of 2 or more indicates that admission to hospital is necessary.

Recommended inpatient antibiotic therapy includes amoxicillin-clavulanate or a second- or third-generation cephalosporin ± macrolide as first line; or a fluoroquinolone (moxifloxacin or levofloxacin).\textsuperscript{12,13} In addition to their antibiotic effect, macrolides have immunomodulating properties and macrolide-based regimens have been shown to reduce mortality in hospitalised patients with CAP.\textsuperscript{14}

Early switch from IV to oral therapy reduces hospital length of stay and the potential for catheter site complications. Consequently, IV therapy should be discontinued as soon as possible and all patients who are stable and can take oral medication should receive oral treatment. Guidelines recommend that an appropriate duration of antibiotic therapy is 7-10 days, depending on the severity of disease.

Although they may be associated with reduced incidence of adult respiratory distress syndrome (ARDS), corticosteroids are of doubtful benefit in most patients with CAP. However, low-dose corticosteroid use may reduce short-term mortality in patients with CAP complicated by septic shock and it is recommended that they be reserved for this subgroup of patients.\textsuperscript{15-17}

**Resistance to antibiotics and antibiotic stewardship**

Bacterial resistance to antibiotics is one of the biggest global threats facing the world today.\textsuperscript{18} Infections that in the past were treatable are becoming difficult to cure, resulting in in an increase in both healthcare costs and patient mortality. Antibiotic-resistant bacteria, including MRSA, extended-spectrum beta-lactamase (ESBL) producers, and carbapenem-resistant Enterobacteriaceae, are increasing in prevalence worldwide. Many pathogens are now resistant to more than
one antibiotic and bacterial strains are emerging that are susceptible to none of the currently available first-line or last-resort antibiotic agents. Patterns of resistance vary by geographic region and country.

Antibiotic resistance is a direct result of antibiotic use. All over the world, antibiotics are used liberally in both human medicine and agriculture. The problem is compounded by a limited research pipeline with few new antibiotic molecules expected in the immediate future. Furthermore, when they do become available, new drugs are frequently expensive and unavailable to poorer communities and low- and middle-income countries. \(^1^9\)

Antibiotic stewardship programmes, which focus on ensuring proper use of antimicrobials to optimise patient outcomes while minimising the emergence of resistant organisms, have been effective in some high-income countries, leading to stabilisation of or a reduction in antibiotic resistance levels. Key to these efforts is reduced utilisation of antibiotics – where antibiotic use declines, the levels of resistance decline. However, although antibiotic usage in some high-income countries has declined, global consumption of antibiotics in human medicine increased by 36% between 2000 and 2010. South Africa and the BRIC countries accounted for 76% of this growth. Of particular concern was the increased consumption of last-resort antibiotics, including carbapenems (45%) and polymixins (13%).\(^2^0\)

The World Health Organization (WHO) and Global Antibiotic Resistance Partnership (GARP) recommend six strategies to help slow resistance and maintain the effectiveness of current antibiotic agents:\(^1^8\),\(^1^9\)

1. Vaccines and improved water and sanitation. These have reduced demand for antibiotics in higher-income countries.
2. Improved hospital infection control (including hand washing) and antibiotic stewardship.
3. Change from incentives (in medicine and agriculture) that encourage antibiotic overuse and misuse to incentives that encourage antibiotic stewardship.
4. Reduce and eventually phase out antibiotic use in agriculture.
5. Educate and inform health professionals, policymakers and the public on sustainable antibiotic use.
6. Ensure political commitment to meet the threat of antibiotic resistance.

Stewardship principles of particular concern to prescribing doctors and other healthcare workers are listed in Table 7.

### Table 7. Antimicrobial stewardship principles for healthcare workers\(^2^1^–^2^3\)

- Prescribe antibiotics, antifungal medications and antiviral medications appropriately:
  - Discourage self-prescription;
  - Use antimicrobial medications only when indicated;
  - Right drug, right dose, right duration of therapy appropriate to the individual patient;
  - Rely on the clinical microbiology laboratory;
  - Consider local susceptibility trends and previous recent exposure to antibiotic/antimicrobial therapy;
  - Adhere to treatment guidelines;
  - Precise targeting is preferable to ‘shotgun’ therapy;
  - Consider the pharmacokinetic and pharmacodynamic characteristics of antimicrobial therapy to ensure that the agents used are appropriate to the individual patient and the site of infection;
  - Use the shortest antimicrobial course with proven efficacy;
  - Use combination therapy only when indicated;
  - Understand definitions and indications of empirical/directed therapy vs prophylaxis;
  - Use step-down therapy where indicated;
  - Use clinical experience guided by evidence-based guidelines;
  - Encourage patient compliance;
- Document the dose, duration and indication for every prescription;
- Stay aware of local resistance patterns and current treatment recommendations;
- Participate and lead efforts within the hospital/prescribing community to improve prescribing practices;
- Follow hand hygiene and other infection control measures with every patient;
- Restriction and well-defined indications for prophylaxis (e.g. with azoles, antibiotics).
Under the auspices of SAASP, an online training course in rational prescribing and antibiotic stewardship for South African doctors and pharmacists is available free of charge at https://www.openlearning.com/courses/

References