Chapter 10

LOWER RESPIRATORY TRACT INFECTIONS

ACUTE BRONCHITIS

Acute bronchitis in otherwise healthy individuals is extremely common.

Viral causes (most common)	Influenza A and B, parainfluenzavirus, coronavirus, rhinovirus, respiratory syncytial virus, adenoviruses and human metapneumovirus
Bacterial causes (less common)	*Bordetella pertussis/Bordetella parapertussis* *Mycoplasma pneumoniae* *Chlamydophila pneumoniae*

TREATMENT

- Acute viral bronchitis requires symptomatic treatment only, there are no reports in the literature to suggest that such patients benefit from antibiotics, with the exception of those with acute exacerbations of chronic bronchitis.
- *Bordetella pertussis* typically presents as a persistent cough (> 14 days) and antibiotics provide clinical benefit only if started early (in the first week of onset). However, antibiotic treatment should be instituted, even if later in the course of the illness to limit the spread of infection, despite minimal effect on the clinical course.
- Confirmed *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* should be treated with either azithromycin or doxycycline.

℞ TREATMENT: BORDETELLA PERTUSSIS

Clarithromycin 500 mg PO 12 hourly or 1g XL PO daily for 7 days

OR

Azithromycin 500 mg PO on day 1, then 250 mg PO daily for 4 days

ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Acute exacerbation of chronic obstructive pulmonary disease or COPD (i.e. underlying airflow obstruction) is defined as an acute increase in symptoms beyond normal day-to-day variation, and includes one or more of the following cardinal symptoms, whilst the CXR is usually unchanged:

- Cough increases in frequency and severity
- Sputum production increases in volume and/or changes character
- Dyspnoea increases

Viruses are often implicated, at least initially. Secondary infections may occur and are caused by bacteria such as *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*, with *Pseudomonas aeruginosa* and Enterobacteriaceae in severe cases.

TREATMENT

Although most clinicians treat patients in this setting with antibiotics, studies comparing antibiotics with placebo have shown little difference in the rate of resolution of symptoms. If antibiotics are prescribed (usually to those with an exacerbation with increased sputum purulence and either increased dyspnoea or increased sputum volume or requiring mechanical ventilation), these should ideally be based on culture and sensitivity results.

EMPIRIC TREATMENT: ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Amoxicillin-clavulanate 1 g PO 12 hourly or 1.2 g IV 8 hourly

OR

Ceftriaxone 2 g IV once daily

OR

Moxifloxacin 400 mg PO once daily

Treat for 7–10 days

NOTE

COPD patients require annual influenza vaccination as well as pneumococcal polysaccharide vaccination.

BRONCHIOLITIS

Bronchiolitis occurs in children younger than two years old and is typically caused by a virus. Respiratory syncytial virus (RSV) is the most common cause followed by parainfluenza viruses and human metapneumovirus. The inflammation partially or completely blocks the bronchioles causing wheezing. Bronchiolitis is the leading cause of hospitalisation in infants and young children. Management is supportive and oxygen should be given when needed. Antibiotics are not necessary. Nebulised ribavirin may be considered in immunosuppressed children with severe RSV infection and may be beneficial in adult hematopoietic stem-cell transplant recipients. Refer to the chapter ‘Pre-exposure and post-exposure prophylaxis’ for details on RSV pre-exposure prophylaxis.

PNEUMONIA

The current South African guideline on the management of community-acquired pneumonia (CAP) was published in 2007 and is due for review shortly.

TYPE OF PATIENT	LABORATORY INVESTIGATIONS	TREATMENT
Outpatient	Not necessary	Empiric treatment
Hospitalised (high risk) • Admitted to ICU • Sepsis or septic shock • Immunosuppressed patients (HIV, asplenia, alcoholism) • At risk of resistant pathogens • Failed initial therapy	• Sputum MC&S • Blood cultures • Influenza virus PCR during influenza season • Respiratory virus multiplex PCR-consider • Atypical bacteria multiplex PCR-consider	Empiric and guided treatment

The choice of empirical antibiotic therapy depends on the age of the patient, the severity of the illness (i.e. requiring hospitalisation or ICU care) and presence of any underlying or comorbid disease.

COMMUNITY-ACQUIRED PNEUMONIA (CAP)

It is important to note that in > 50% of CAP cases no causative organism is found.

ORGANISMS COMMONLY ASSOCIATED WITH CAP

ORGANISM	DESCRIPTION
Streptococcus pneumoniae	The leading cause of CAP worldwide across all settings (outpatient, inpatients and ICU patients), although a decline has been noted as a result of the introduction of pneumococcal conjugate vaccines
Haemophilus influenzae	More common in outpatients and in patients with COPD.
'Atypical pathogens': *Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *Legionella* species	True incidence in South Africa is unknown. A few studies suggest that they may represent up to 30% of cases where an aetiologic agent cannot be found
Aerobic Gram-negative bacilli e.g. *Klebsiella*	Usually elderly patients and those who are severely ill
Staphylococcus aureus	May cause severe disease
Respiratory viruses e.g. influenza and RSV	Usually seasonal
Mycobacterium tuberculosis	Should always be considered in the South African setting
Pneumocystis jirovecii (PJP)	Typically in HIV-infected patients

Others e.g. *Bordetella pertussis*, *Coxiella burnetti* (Q fever), and *C. psittaci*	

TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Over the last 15 to 20 years, there has been a dramatic increase in the prevalence of *Streptococcus pneumoniae* with resistance to penicillin, however most are of intermediate resistance. Because the mechanism of resistance to penicillin and other β-lactams is a result of alterations of penicillin-binding proteins, it is common to encounter 'cross-resistance' among the ß-lactams, including amoxicillin and cephalosporins.

Suboptimal dosing of oral β-lactam antibiotic therapy, e.g. amoxicillin and second-generation cephalosporins have been implicated as the cause of treatment failures, and hence we recommend higher doses of amoxicillin (or amoxicillin-clavulanate), second-generation cepalosporins and parenteral penicillin, which will provide more than adequate cover for these resistant isolates, if present.

Amoxicillin-clavulanate may be preferred for empirical treatment of *H. influenzae*, due to the increase in β-lactamase production (rates above 10-15%), that have been seen in certain South African provinces.

The prevalence of macrolide/azalide resistance in *Streptococcus pneumoniae*, especially high-level resistance, is very common in the private sector, and hence we do not recommend these agents as monotherapy for CAP. The macrolides/azalides and tetracyclines, however still remain the antibiotics of choice for the 'atypical' organisms.

Ciprofloxacin has poor cover against *Streptococcus pneumoniae,* whilst the newer 'respiratory' quinolones (moxifloxacin, gemifloxacin and levofloxacin) provide good cover against *Streptococcus pneumoniae, Haemophilus influenzae* and the atypical organisms.

TREATMENT: COMMUNITY-ACQUIRED PNEUMONIA – OUTPATIENTS

PATIENTS YOUNGER THAN 65 YEARS WITHOUT UNDERLYING DISEASE (COMORBIDITIES)

High dose amoxicillin 1 g PO 8 hourly (children: 80–100 mg/kg/day in two doses)

Addition of atypical cover (clarithromycin 500 mg PO 12 hourly OR azithromycin 500 mg PO daily) is considered optional.

Treat for at least five days or 36–48 hours after the temperature has normalised.

Alternative, but more expensive agents include new fluoroquinolones, cefuroxime axetil and amoxicillin-clavulanate. There is little or no place for routine use of oral or parenteral third-generation cephalosporins such as cefpodoxime, ceftibutin or cefixime for CAP in this age group.

PATIENTS OLDER THAN 65 YEARS WITH OR WITHOUT UNDERLYING DISEASE (COMORBIDITIES)

High dose amoxicillin-clavulanate 1 g PO 12 hourly or 2 g sustained release PO 12 hourly

Addition of atypical cover (clarithromycin 500 mg PO 12 hourly OR azithromycin 500 mg PO daily) is considered optional.

Alternatively, use a respiratory fluoroquinolone (levofloxacin 750 mg PO once daily OR moxifloxacin 400 mg PO once daily).

Treat for at least five days or 36–48 hours after the temperature has normalised.

In patients with a penicillin allergy, use a respiratory quinolone.

TREATMENT: COMMUNITY-ACQUIRED PNEUMONIA – HOSPITALISED PATIENTS (NON-ICU)

Amoxicillin-clavulanate 1.2 g IV 8 hourly

AND

Atypical cover (clarithromycin 500 mg IV 12 hourly OR azithromycin 500 mg IV daily)

OR

Ceftriaxone 2 g IV once daily

AND

Atypical cover (clarithromycin 500 mg IV 12 hourly OR azithromycin 500 mg IV daily)

OR

Ceftaroline 600 mg IV 12 hourly

AND

Atypical cover (clarithromycin 500 mg IV 12 hourly OR azithromycin 500 mg IV daily)

OR

Ertapenem 1 g IV once daily

AND

Atypical cover (clarithromycin 500 mg IV 12 hourly OR azithromycin 500 mg IV daily)

In patients with a penicillin/cephalosporin allergy, use moxifloxacin 400 mg IV OR levofloxacin 750 mg IV once daily **AND** atypical cover.

NOTE: COMMUNITY-ACQUIRED PNEUMONIA IN HOSPITALISED PATIENTS (NON-ICU)

An alternative choice is a fluoroquinolone with enhanced cover against *Streptococcus pneumoniae* or telithromycin. Antibiotics should be given parenterally initially and replaced with oral agents once the temperature has settled. The recently launched 5th generation cephalosporin, ceftaroline (Zinforo®) is highly bactericidal against *S. pneumoniae* (and other Gram-positive bacteria, including MRSA). In addition, its Gram-negative cover is similar to that of ceftriaxone. Treat for a total duration of 5–7 days.

Although some authorities recommend the addition of an aminoglycoside in suspected *Pseudomonas aeruginosa* infections, studies in South Africa have shown that *Pseudomonas aeruginosa* is rarely encountered in this group of patients, while *Klebsiella pneumoniae* is seen more often.

COMMUNITY-ACQUIRED PNEUMONIA IN ICU PATIENTS (SEVERELY ILL PATIENTS)

As a generalisation, the presence of two or more of the parameters listed below indicates severe illness:

CLINICAL FEATURES	LABORATORY PARAMETERS:	OTHER
• Confusion/decreased consciousness • Low blood pressure (systolic < 90 mm Hg, diastolic < 60 mm Hg) • Respiratory rate > 30 breaths/minute • Multilobular consolidation • Extra-thoracic systemic complications • Comorbid disease	• Hypoxaemia (pO2 < 8 kPa) • White cell count < 4 or > 30 x 10^9/L • Abnormal renal function (e.g. urea > 7 mmol/L) • Abnormal liver function (e.g. albumin < 30 g/L)	• Rapidly expanding infiltrates • Multilobar consolidation • Cavitation

TREATMENT: COMMUNITY-ACQUIRED PNEUMONIA IN ICU PATIENTS

Amoxicillin-clavulanate 1.2 g IV 8 hourly OR ceftriaxone 2 g IV once daily OR ceftaroline 600 mg IV 12 hourly OR ertapenem 1 g IV once daily

AND

Atypical cover (clarithromycin 500 mg IV 12 hourly OR azithromycin 500 mg IV daily)

AND

An aminoglycoside, i.e. amikacin 15 mg/kg IV OR gentamicin 7 mg/kg IV OR tobramycin 7 mg/kg IV once daily

Treat for 5–7 days. Exceptions include *S. aureus* pneumonia and *Legionella* pneumonia (14 days treatment recommended).

In patients with a penicillin/cephalosporin allergy, use moxifloxacin 400 mg IV OR levofloxacin 750 mg IV once daily together with atypical cover.

NOTE: COMMUNITY-ACQUIRED PNEUMONIA – HOSPITALISED PATIENTS

Recent evidence suggests that combination therapy with a macrolide and β-lactam compared to β-lactam monotherapy decreases mortality and/or length of hospital stay for patients with CAP requiring hospitalisation. Similar findings were shown in *S. pneumoniae* bacteraemia and severe CAP. This is most likely due to the immunomodulatory effects that are seen with macrolides.

Recent evidence also supports the use of adjunctive steroids in patients with severe CAP. An exception is influenza CAP, where it has been associated with increased mortality.

ATYPICAL PNEUMONIA

Atypical pneumonia refers to a pneumonia caused by *Mycoplasma pneumoniae, Chlamydophila pneumoniae* or rarely *Legionella* spp. These bacteria are referred to as 'atypical' because the pneumonia caused by these organisms may have different symptoms, appear different on a chest X-ray, or respond to different antibiotics than the typical bacteria that cause pneumonia. Even though these infections are called 'atypical', they are not uncommon.

TREATMENT: ATYPICAL PNEUMONIA

Clarithromycin 1 g PO XL daily or 500 mg PO/IV 12 hourly

OR

Azithromycin 500 mg PO/IV daily

OR

Doxycycline 100 mg PO 12 hourly

OR

Moxifloxacin 400 mg PO/IV daily

OR

Levofloxacin 750 mg PO/IV daily

Treat for 14 days (especially in the case of *Legionella* pneumonia)

PNEUMONIA DURING INFLUENZA EPIDEMICS

The clinical findings of influenza overlap those of community-acquired bacterial pneumonia, and influenza infection can be complicated by secondary bacterial infections, typically *Staphylococcus aureus, Streptococcus pneumoniae*, *Streptococcus pyogenes* or *Haemophilus influenzae*. Antiviral treatment, typically with oral oseltamivir (Tamiflu®) should be started in all patients with

suspected or laboratory-confirmed influenza who have a lower respiratory tract infection or those at risk of developing a severe or complicated infection. The selection of antimicrobial agent depends upon the patient's severity of illness and comorbid conditions and typically includes a β-lactam and a macrolide.

ASPIRATION PNEUMONIA

Aspiration pneumonia is a particular problem in the elderly and in the presence of conditions such as alcoholism, epilepsy, and cerebrovascular accidents. It is usually due to anaerobes alone or with facultative or aerobic bacteria. The most common aerobes in community-acquired cases are *Streptococcus* spp., whilst Gram-negative bacilli and *Staphylococcus aureus* are prominent in hospital-acquired aspiration pneumonia.

TREATMENT: ASPIRATION PNEUMONIA

Amoxicillin-clavulanate 1.2 g IV 8 hourly

OR

Metronidazole 500 mg IV 8 hourly **AND** ceftriaxone 2 g IV once daily

OR

Ertapenem 1 g IV daily

OR

Piperacillin-tazobactam 4.5 g IV 6 hourly (or as a continuous infusion of 18 g over 24 hours)

Clindamycin 600 mg IV 8 hourly can be used as an alternative to metronidazole

Duration of therapy is based on clinical grounds and is typically 7–10 days

PNEUMONIA IN THE IMMUNOCOMPROMISED PATIENT (E.G. HIV-INFECTED PATIENTS)

In addition to organisms typically responsible for CAP, also consider *Pneumocystis jirovecii*, fungi and cytomegalovirus, especially in those with CD4 counts less than 100 cells/μL.

TREATMENT: PNEUMOCYSTIS JIROVECII PNEUMONIA

Treat with high dose cotrimoxazole to cover PJP in addition to empiric antibiotics

Orally: TMP 320 mg/SMX 1600 mg = 2 double strength tablets PO 8 hourly for 21 days

Intravenously: 15–30 mg TMP and 75–100 mg SMZ per kg per day in 4 divided doses = 4 ampoules (trimethoprim 320 mg and sulfamethoxazole 1600 mg) 6 hourly for 21 days

Hypoxic patients with PJP should also be given adjunctive corticosteroid therapy

HEALTHCARE-ASSOCIATED PNEUMONIA (HCAP), HOSPITAL-ACQUIRED PNEUMONIA (HAP) AND VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

	DEFINITION	PATHOGENS
HCAP	Pneumonia in a patient: • Who has been hospitalised in an acute care hospital for 2 or more days within 90 days of the current infection • Who has been residing in a nursing home or long-term care facility • Who has been receiving IV antibiotics, chemotherapy or wound care within the past 30 days of the current infection	• Typical respiratory pathogens • Gram-negative bacilli e.g. *Klebsiella* spp., *Serratia* spp. (including ESBL producers) • Anaerobes • Staphylococci (methicillin-sensitive and resistant)
HAP	Pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission	• Typical respiratory pathogens • Gram-negative bacilli e.g. *Pseudomonas aeruginosa*, *Acinetobacter* spp., multidrug-resistant *Klebsiella* spp., *Serratia* spp • Staphylococci, including MRSA
VAP	Pneumonia that develops more than 48 hours after endotracheal intubation	

GUIDELINES FOR THE MANAGEMENT OF HCAP, HAP AND VAP

It is important to know the usual expected pathogens in your unit/hospital as well as their typical susceptibility patterns to guide empirical antibiotic treatment. These organism profiles and susceptibility patterns may differ significantly between wards/units and hospitals. Before an empiric regimen is chosen, determine whether the patient is at risk for infection due to a multidrug-resistant (MDR) pathogen.

RISK FACTORS FOR MDR PATHOGENS

IN PATIENTS WITH HCAP	IN PATIENTS WITH HAP AND VAP
• Hospitalisation for two days or more in the preceding three months • Residence in a nursing home or extended care facility • Home infusion therapy • Chronic dialysis • Home wound care • Family member with a MDR pathogen	• Antibiotic therapy in the preceding 3 months • Current hospitalisation of five days or more • High frequency of antibiotic resistance in the community or specific unit • Structural lung disease • Immunosuppressive disease and/or therapy (e.g. steroids)

TREATMENT: HCAP, HAP AND VAP

IF NO KNOWN RISK FACTORS FOR MDR PATHOGENS ARE PRESENT

Fluoroquinolones (moxifloxacin 400 mg IV daily or levofloxacin 750 mg IV daily)

OR

Ceftriaxone 2 g IV daily

OR

Cefepime 2 g IV 8 hourly (or 6 g over 24 hours as a continuous infusion)

OR

Piperacillin-tazobactam 4.5 g IV 6 hourly (or 18 g over 24 hours as a continuous infusion)

OR

Ertapenem 1 g IV daily

IF KNOWN RISK FACTORS FOR MDR PATHOGENS ARE PRESENT

Cefepime 2 g IV 8 hourly (or 6 g over 24 hours as a continuous infusion)

OR

Imipenem 1 g IV 8 hourly OR meropenem 1–2 g IV 8 hourly IV OR doripenem 1 g IV 8 hourly

OR

Piperacillin-tazobactam 4.5 g IV 6 hourly (or 18 g over 24 hours as a continuous infusion)

OR

Levofloxacin 750 mg IV daily

OR

Ertapenem 1 g IV daily

Addition of an aminoglycoside (amikacin 15 mg/kg IV OR gentamicin 7 mg/kg IV OR tobramycin 7 mg/kg IV once daily) is considered optional.

Note: Loading doses should be considered for some of the above antibiotics, especially when used as extended/continuous infusion, to facilitate rapid attainment of the target levels (e.g. cefepime, piperacillin-tazobactam).

IF MRSA IS SUSPECTED OR ISOLATED, ADD TO ABOVE REGIMEN

Vancomycin 15–20 mg/kg 8–12 hourly in patients with normal renal function (target serum trough concentration 15–20 mg/L)

Give a loading dose in seriously ill patients of 25–30 mg/kg to facilitate rapid attainment of the target trough concentration.

OR

Linezolid 600 mg 12 hourly IV or orally

Duration of therapy: De-escalation of therapy should be considered 48–72 hours after initiation of therapy, and should be based on results of initial cultures and the clinical response of the patient.

NOTE: EXTENDED INFUSIONS IN PATIENTS WITH HCAP, HAP AND VAP

Because of increasing resistance of pathogens associated with HCAP, HAP, and VAP, one potential strategy to enhance the antimicrobial action of a given agent is to optimise the pharmacodynamic effect. Such regimens can potentially provide effective therapy for pathogens with higher minimum inhibitory concentration (MICs), and may impede the emergence of resistance, and potentially provide a pharmacoeconomic benefit.

OPTIMISATION OF ANTIMICROBIAL EFFECT CAN BE ACHIEVED BY

MECHANISM OF ACTION	EXAMPLES	OPTIMISATION
Concentration-dependent	Aminoglycosides Fluoroquinolones	Increase doses
Time-dependent	β-lactams	Extended or continuous infusions

Extended infusions are generally more practical than continuous infusions, since dedicated intravenous catheters are required for continuous infusions.

TREATMENT: HCAP, HAP AND VAP EXTENDED INFUSIONS

Piperacillin-tazobactam: 4.5 g infused IV over 3 hours, administered 6 hourly

An alternative to the extended infusion is to administer piperacillin-tazobactam as a continuous infusion of 18 g IV over 24 hours

Meropenem: 1–2 g infused IV over 3 hours, administered 8 hourly

Doripenem: 1 g infused IV over 4 hours, administered 8 hourly

Cefepime: 2 g infused IV over 3 hours, administered 8 hourly