How and when to manage respiratory infections out of hospital

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Shareable abstract (@ERSpublications)
Management principles for patients with lower respiratory infections include knowledge of local surveillance data, strategic use of diagnostic tests according to surveillance data, and judicious use of antimicrobials. https://bit.ly/3ziuPGS

Abstract

Lower respiratory infections include acute bronchitis, influenza, community-acquired pneumonia, acute exacerbation of COPD and acute exacerbation of bronchiectasis. They are a major cause of death worldwide and often affect the most vulnerable: children, elderly and the impoverished. In this paper, we review the clinical presentation, diagnosis, severity assessment and treatment of adult outpatients with lower respiratory infections. The paper is divided into sections on specific lower respiratory infections, but we also dedicate a section to COVID-19 given the importance of the ongoing pandemic. Lower respiratory infections are heterogeneous entities, carry different risks for adverse events, and require different management strategies. For instance, while patients with acute bronchitis are rarely admitted to hospital and generally do not require antimicrobials, approximately 40% of patients seen for community-acquired pneumonia require admission. Clinicians caring for patients with lower respiratory infections face several challenges, including an increasing population of patients with immunosuppression, potential need for diagnostic tests that may not be readily available, antibiotic resistance and social aspects that place these patients at higher risk. Management principles for patients with lower respiratory infections include knowledge of local surveillance data, strategic use of diagnostic tests according to surveillance data, and judicious use of antimicrobials.

Introduction

Acute respiratory infections can be divided into upper and lower respiratory infections. The focus of this review is lower respiratory infections in adults. Lower respiratory infections comprise acute bronchitis, influenza, community-acquired pneumonia, acute exacerbation of COPD and acute exacerbation of bronchiectasis [1]. They are responsible for 13% of all deaths in children aged <5 years and 4.4% of all deaths in the whole population. They are the leading cause of death in children aged <5 years old and the sixth cause of death overall. In the adult population, the absolute number of deaths from lower respiratory infections has been increasing in those aged ⩾70 years, mostly as a result of an ageing population. Lower respiratory infections markedly affect the vulnerable: children, elderly and the impoverished [2]. In a prospective cohort study that included 587 participants aged 85 years, independent risk factors for development of lower respiratory tract infections included smoking, systemic corticosteroid use, history of COPD, history of stroke, severe cognitive impairment and declined functional status [3]. In another prospective study that included 475 residents in nursing homes, independent risk factors for development of pneumonia included older age, male sex, swallowing difficulty and inability to take oral medications. Independent risk factors for lower respiratory tract infections other than pneumonia included older age and immobility. Vaccination against influenza was protective against pneumonia and other lower respiratory tract infections [4]. The majority of devastating pandemics and outbreaks are due to respiratory viruses and

manifest as lower respiratory tract infections [5]. Analysis from the pre-COVID-19 era identified *Streptococcus pneumoniae* as the leading pathogen responsible for lower respiratory tract infection mortality [2]. The main sections of this paper are divided into specific lower respiratory tract diseases rather than aetiologies, but we dedicate a section to COVID-19 given the importance of the ongoing pandemic.

Acute bronchitis

Definition

Acute bronchitis is defined as an acute illness causing cough and other symptoms and signs suggestive of lower respiratory tract infection. These include sputum production, wheezing, dyspnoea and chest discomfort or pain [1]. The absence of underlying lung disease distinguishes acute bronchitis from acute exacerbation of COPD or bronchiectasis, which will be covered in later sections.

Clinical examination and diagnostic work-up

When assessing a patient with suspected acute bronchitis, it is important to attempt to clinically exclude pneumonia. The latter should be suspected in the presence of tachycardia, tachypnoea, fever, low oxygen saturation or chest pain. Additionally, clues for the presence of undiagnosed underlying lung disease, particularly asthma, should be elicited in the clinical assessment. This is illustrated by a longitudinal cohort study that found that 19% of patients without known underlying lung disease who present with an isolated episode of acute bronchitis are subsequently diagnosed with asthma [6]. Complementary tests such as chest radiography, procalcitonin or sputum culture are not routinely obtained [7]. They can be obtained on a case by case basis if there is suspicion of pneumonia or another underlying lung disease. Testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently indicated for patients with acute respiratory illness, and this applies to all lower respiratory infections discussed. Testing for influenza is also indicated in patients with acute respiratory illness if the result will lead to a change in management or if there are epidemiological reasons for testing. For both SARS-CoV-2 and influenza, a nucleic acid detection test is preferred, but an antigen detection assay test can be used in the absence of a nucleic acid detection test [8].

Microbiology

In one representative study, an aetiologic diagnosis was established in 68% of the patients. The detection rate was 63% for viruses and 26% for bacteria. The most common virus was rhinovirus followed by influenza. The most common bacterium was *S. pneumoniae* [9].

Treatment

Antibiotics lead to shorter cough duration and reduction in days feeling ill and days with impaired activity. However, there is no difference in clinical improvement between patients who receive antibiotics and those who receive placebo [10]. The recognition that acute bronchitis is commonly self-limited, and that antimicrobial therapy is not indicated in immunocompetent patients, should prompt avoidance of antibiotic prescription in these patients. There is evidence that the majority of the antibiotic prescriptions for patients with acute respiratory tract infection are unnecessary [11]. Additionally, community antimicrobial intake represents 85–95% of the entire antimicrobial intake [12]. Currently, there are no data supporting the use of other therapies such as antitussives, inhaled bronchodilators, inhaled corticosteroids or systemic corticosteroids [7]. In adult outpatients diagnosed or suspected to have influenza, antiviral treatment is indicated for those with severe or progressive illness, high risk of complications (*e.g.* immunocompromised status or chronic medical conditions), pregnancy or post-partum status within 2 weeks. Treatment for influenza should also be considered for those with an early diagnosis (<2 days), household contacts of at-risk persons (*e.g.* immunocompromised) and healthcare providers [13]. Treatment for COVID-19 is discussed in a section below.

Community-acquired pneumonia

Epidemiology

The incidence of community-acquired pneumonia (CAP) is higher in men and rises considerably with age [14]. High-deprivation areas have higher incidence of CAP [15]. COPD and heart failure are the underlying diseases most commonly associated with CAP [16–18]. The mortality of outpatients with CAP is <1% [19]. However, for those requiring hospitalisation, the in-hospital and 1-year mortalities are 6.5% and 30.6%, respectively [17]. For those admitted to the intensive care unit (ICU), the in-hospital and 1-year mortalities are 17% and 47%, respectively [20]. Underlying diseases associated with increased mortality include diabetes mellitus, neoplastic disease, neurological disease [21] and congestive heart failure [22]. Increasing deprivation is also associated with increased mortality [15].

Clinical manifestations

Patients with pneumonia often present acutely with a combination of the following: cough, sputum production, dyspnoea, pleuritic chest pain, fever and crackles on lung auscultation [23]. The most common respiratory symptom is cough (86%) followed by dyspnoea (72%), sputum production (64%) and pleuritic chest pain (46%). Most common nonrespiratory symptoms include fatigue (91%), fever (91%) and chills (73%). The most common signs include tachypnoea (49%), tachycardia (41%) and hyperthermia (34%) [24]. The value of specific symptoms and signs for the diagnosis of pneumonia has been evaluated. The following symptoms and signs are independently predictive of radiograph-confirmed pneumonia: temperature >37.8°C (RR 2.6, 95% CI 1.5–4.8), heart rate >100 per minute (RR 1.9. 95% CI 1.1–3.2), crackles on auscultation (RR 1.8, 95% CI 1.1–3.0), and oxygen saturation <95% (RR 1.7, 95% CI 1.0–3.1) [25]. Older patients can have a different presentation. They often do not report pleuritic chest pain or dyspnoea, but tachypnoea is a more commonly seen [24].

Diagnostic work-up

A routine chest radiograph in every patient presenting to a primary care clinic with lower respiratory infection is not warranted. Most of these patients do not have pneumonia. Chest radiography should be reserved for selected patients when the pre-test probability of pneumonia is moderate to high. In the primary care setting, a chest radiograph changed the probability of pneumonia in half of the patients. In most patients, the chest radiograph result decreased the probability of pneumonia, leading to less frequent use of antibiotics and more frequent reassurance of the patients [26]. Chest radiography can also at times provide valuable information about the severity of the pneumonia such as when there is pleural effusion or bilateral infiltrates [27]. It is, however, important to recognise the limitations of chest radiography in pneumonia. In most cases, the pattern seen on the chest radiograph cannot be used to predict the aetiology of pneumonia although at times it can be suggestive (*e.g.* multiple cavities in a patient with history of intravenous drug use is suggestive of *Staphylococcus aureus* infection) [28].

Lung ultrasound has emerged as an important imaging tool for the diagnosis of lung diseases, including pneumonia. It has high accuracy for the diagnosis of pneumonia, but most of these studies were performed in the ICU or emergency department [29]. As the technology becomes more omnipresent and clinicians more proficient, we anticipate increasing use of ultrasound in primary care.

Routine sputum culture in patients with CAP is unlikely to yield an aetiologic diagnosis in most cases [30]. In the outpatient setting, we reserve sputum culture for select cases depending on factors such as ease of obtainment, severity of the pneumonia, the pre-test probability of unusual pathogens, and the presence of structural lung disease.

Microbiology

Atypical bacteria, respiratory viruses and typical bacteria are the three major categories of pathogens causing CAP. Atypical pathogens have been identified in 22–31% of patients in cohorts of CAP treated in the outpatient setting. In aggregate, they have been the most common cause of CAP treated in the outpatient setting in some studies [31–33]. Of the atypical pathogens, *Mycoplasma pneumoniae* is the most commonly identified [31, 32, 34, 35], but in some series *Chlamydia pneumoniae* was also prevalent [33, 36]. There is a range of prevalences of the respiratory viruses in the different cohorts, which reflects the varying extent of testing for different viruses. In a study in an outpatient population with CAP, the prevalence of viral infection detected by PCR was 12.1% [37]. However, a meta-analysis of studies that included mixed inpatient and outpatient populations with CAP showed a prevalence of viral infection of 22.4% [38]. Typical pathogens have been detected in 9–56% of the cases in different studies [31–36]. *S. pneumoniae* remains the most common typical pathogen. Other common typical pathogens include *Haemophilus influenzae*, *Moraxella catarrhalis* and Enterobacteriaceae (*e.g. Klebsiella spp.*, *Escherichia coli*, *Enterobacter spp.*, *Serratia marcescens*, *Proteus mirabilis* and *Morganella morganii*) [39]. Anaerobic pathogens are not common causes of CAP even in the setting of aspiration. However, they should be considered in the setting of lung abscess or empyema [40].

Among the organisms usually causing CAP, resistance to antimicrobials has been a concern with *S. pneumoniae* and *H. influenzae*. *S. pneumoniae* resistance to macrolides, which has increased over time [41], is mostly secondary to target alteration promoted by ribosomal methylation and an efflux mechanism [42]. *H. influenzae* is classified into encapsulated (with six serotypes from a to f) and nonencapsulated or nontypeable. The use of *H. influenzae* type b conjugate vaccines has led to a marked decrease in invasive disease caused by *H. influenzae* type b [43], but infection by other serotypes and mainly by nontypeable *H. influenzae* remains common. Antibiotic exposure has led to an increase in *H. influenzae* resistance to β-lactam antibiotics, which occurs mainly *via* expression of β-lactamase enzyme or change in

penicillin-binding proteins. In a cohort of 92 patients who developed 95 episodes of CAP with isolates of nontypeable *H. influenzae*, COPD was the most common underlying disease, present in 28% of the patients. Resistance and intermediate resistance to ampicillin were present in 10.5% and 23.2% of the isolates, respectively [44].

Multidrug-resistant organisms, including *Pseudomonas aeruginosa*, extended-spectrum β-lactamase-producing Enterobacteriaceae and methicillin-resistant *S. aureus* (MRSA), have been identified in 3.3–6.0% of patients with CAP requiring hospitalisation [45, 46]. Previously, patients with a set of risk factors for multidrug-resistant organisms (*e.g.* hospitalisation for 2 or more days within 90 days, nursing home or long-term care facility residence, recent receipt of intravenous antibiotics or chemotherapy, wound care within the last 30 days, or dialysis treatment) were labelled as having health care-associated pneumonia [47]. The recognition that these risk factors are individually weak predictors of multidrug-resistant organisms has led to the abandonment of this categorisation [40]. It is, however, still important to recognise the subset of patients at higher risk of multidrug-resistant organism infection. To this end, a number of studies have developed scores for better prediction [45, 46, 48–50]. As pointed out by the 2019 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines, patients with CAP and risk factors for *P. aeruginosa* and MRSA are not commonly managed as outpatients [40].

Immunocompromised status has become increasingly common [51, 52]. At least one risk factor for immunocompromise was present in 18% of patients from the community with pneumonia requiring hospitalisation [53]. Immunocompromised patients develop infection not only from the same pathogens as nonimmunocompromised patients, but they are also susceptible to opportunistic pathogens such as fungi (*e.g. Aspergillus* species, *Pneumocystis jirovecii*), viruses from the Herpesviridae family, parasites (*e.g. Strongyloides stercoralis*), mycobacteria and other multidrug-resistant bacteria [54]. Patients with immunocompromised status are generally managed as inpatients.

Coccidioidomycosis, blastomycosis and histoplasmosis are endemic mycoses that often present as CAP. Unfortunately, diagnosis is often late and commonly suspected when there is no resolution of the pneumonia despite a course of antibiotics. Although immunocompromised patients are particularly susceptible, these endemic mycoses are also often present in nonimmunocompromised patients [55]. Knowledge of the geographical distribution of these endemic mycoses can be valuable for the clinician. Coccidioidomycosis is found mostly in the United States (Southern Arizona and the San Joaquin Valley region in California), Central America (Guatemala and Honduras) and South America (Argentina, Brazil, Colombia, Paraguay and Venezuela). Blastomycosis is found in the United States (mid-west, east, south east and south central), Canada, the African continent and, to a lesser extent, India. Histoplasmosis is endemic in areas of the United States (Ohio and Mississippi River Valleys), Canada (Quebec and Ontario), Central America and South America, but its geographical reach is global in part because of the HIV pandemic and immunosuppressive diseases and medications [56].

Mycobacterium tuberculosis infection is suspected with a more protracted respiratory course, but it can present acutely. A large pneumonia cohort study showed it occurred in 0.9% of patients with CAP requiring hospital admission. The following factors were independently associated with CAP caused by *M. tuberculosis*: haemoptysis; upper lobe infiltrate localisation; weight loss, or 10% or less of ideal body weight; prior history of tuberculosis (TB) or recent exposure to TB or history of positive purified protein derivative (PPD) test; and night sweats [57].

Burkholderia pseudomallei is a Gram-negative bacterium and the cause of melioidosis, which presents as pneumonia in half of all cases. In 91% of melioidosis pneumonia cases, presentation is acute or subacute. Chronic pneumonia, which resembles TB, occurs in 9% of cases. Mode of acquisition is mainly *via* percutaneous inoculation or inhalation. Geographical distribution is mainly Southeast Asia and northern Australia [58].

Francisella tularensis is an intracellular Gram-negative coccobacillus and the cause of tularemia. Modes of acquisition include vector-borne transmission (ticks and mosquitoes), direct contact with animals (*e.g.* hare), ingestion of contaminated food or water, and inhalation of aerosols [59]. The presentation is largely dependent on the mode of transmission. For instance, while the ulcero-glandular form tends to occur after a bite from an infected tick, the pneumonic form often occurs after inhalation of contaminated aerosols [60]. The disease is found in the North American and Eurasian continents [59].

Acinetobacter baumannii is a Gram-negative aerobic bacillus that traditionally causes nosocomial infection. More recently, there have been reported cases of CAP caused by *A. baumannii* from the United States,

Australia, China and Taiwan [61–64]. Community-acquired *A. baumannii* causes severe disease [63], but community-acquired isolates are less likely to be multidrug-resistant than the nosocomial isolates [64]. Excessive alcohol consumption, smoking, COPD, renal disease and diabetes mellitus are commonly reported in patients with community-acquired *A. baumannii* [65].

Chlamydia psittaci is an obligate intracellular bacterium that causes the zoonotic disease psittacosis. The most common presentation of psittacosis is CAP. A pooled analysis showed that psittacosis is responsible for approximately 1% of the cases of CAP, but most patients in the analysis were hospitalised [66]. The most common modes of transmission have been exposure to infected birds and their droppings [67, 68] followed by contact with poultry [69].

Assessment of need for admission

Hospitalisation is required in 39–45% of patients with CAP [18, 70]. The decision to admit a patient with CAP can be helped by clinical prediction rules. The two most commonly used clinical prediction rules are CURB-65 and the pneumonia severity index. The CURB-65 was initially developed by the British Thoracic Society and subsequently validated in a modified form. It consists of five variables: confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant$30·min^{-1}, blood pressure (systolic blood pressure <90 mmHg or diastolic blood pressure $\leqslant$60 mmHg) and age $\geqslant$65 years. A more simplified version, CRB-65, omits urea. A score is computed by the sum of the variables, each of which is assigned a point of 0 or 1 (if abnormal). In an early cohort study, a CURB-65 score of 0 or 1 was associated with a mortality of 1.5% and these patients were deemed suitable for home treatment; a score of 2 was associated with a mortality of 9.2% and these patients were deemed to require hospital-supervised treatment (short inpatient admission or hospital-supervised outpatient treatment); and a score of 3 or more was associated with a mortality of 22% and these patients were deemed to require hospitalisation [71].

A version of CURB-65 using weighed and continuous variables available through the electronic medical record was tested against the traditional, dichotomous CURB-65 and showed a superior area under the curve to predict mortality [72]. The advantage of CURB-65 and its interactions is the simplicity, but that comes at a cost. For instance, criteria for admission other than the variables present in the CURB-65 were identified in a large retrospective cohort study of patients with CAP. In patients with CURB-65 score of 1, an oxygen tension <60 mmHg was identified in 28.7%, comorbidity in 22.8%, bilateral or multilobe radiographic involvement in 14.1% and pleural effusion in 8.2% [73]. This demonstrates that in patients with low CURB-65 score other physiological and clinical parameters need to be carefully assessed before a decision is made on whether patient can be treated as outpatient.

The pneumonia severity index (PSI) variables include age, comorbidities, physical examination findings and laboratory and radiographic parameters. A point score is computed by the sum of the score assigned to each variable. Patients are then categorised into one of five risk classes according to the total score [19]. PSI is computation intensive and may be more widely used if integrated into the electronic health record [74]. In prospective studies, the use of a critical pathway that included PSI led to a modest decrease in the rate of hospitalisations without affecting clinical outcomes [75, 76]. However, in one study, 5% of patients required late hospitalisations despite the use of PSI [76]. Social aspects such as homelessness, lack of health insurance and health illiteracy should be taken into account in the decision making. In summary, the use of prediction rules can serve as guidance, but they should not override clinical judgement in the decision to admit patients with CAP.

Treatment

The 2019 IDSA/ATS guidelines recommend amoxicillin or doxycycline as first choices for outpatient treatment of CAP in patients without comorbidities. Macrolide monotherapy is an option only when *S. pneumoniae* resistance to macrolide is less than 25%. In patients with comorbidities, the recommendation is combination therapy of amoxicillin/clavulanate and macrolide, or monotherapy with a respiratory fluoroquinolone [40].

The use of amoxicillin as one of the first-choice antibiotics in the most recent IDSA/ATS guideline is in line with the 2015 annotated version of the British Thoracic Society [77] and the 2011 European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases [1] guidelines and is a change from the 2007 IDSA/ATS guidelines in which macrolide was the first-choice antibiotic for previously healthy patients without risk factors for drug-resistant *S. pneumoniae* [78] (table 1).

The current preference for β-lactam monotherapy, which comes at the expense of not covering atypical bacteria, is based on two premises. On the one hand, there is the concern for high rates of *S. pneumoniae*

TABLE 1	Treatment recommendations for outpatient management of community-acquired pneumonia according to different guidelines	
ATS and IDSA guidelines, 2019 [40]	Recommendation	Amoxicillin 1 g three times a day or doxycycline 100 mg twice a day
	Alternative choices for areas with pneumococcal resistance to macrolide <25%	Azithromycin 500 mg first day followed by 250 mg daily or clarithromycin 500 mg twice a day
	Recommendations in patients with comorbidities (chronic heart, lung, liver or renal disease; diabetes mellitus; alcohol use disorder; cancer; and asplenia)	Amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/ clavulanate 875 mg/125 mg twice daily, or 2000 mg/125 mg twice daily, or a cephalosporin (cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily) AND macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin (500 mg twice daily or extended release 1000 mg once daily))
		Respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily)
BTS guidelines, 2015 [77]	Preferred agent	Amoxicillin 500 mg three times a day
	Alternative choices	Doxycycline or clarithromycin
ERS/ESCMI guidelines, 2011 [1]	First choice	Amoxicillin or tetracycline
	Hypersensitivity to penicillin	Tetracycline or macrolide

ATS: American Thoracic Society; IDSA: Infectious Diseases Society of America; BTS: British Thoracic Society; ERS: European Respiratory Society; ESCMI: European Society for Clinical Microbiology and Infectious Diseases.

resistance to macrolide. Indeed, 54.9% of the *S. pneumoniae* isolates in the United States were resistant to macrolides in 2018 and 2019 [41]. On the other hand, resistance and intermediate susceptibility to penicillin were 2% and 1.6% [79]. It is important to recognise there is marked geographical variation in the susceptibility profile to both macrolide and penicillin [42]. In Europe, invasive isolates of *S. pneumoniae*, for which benzylpenicillin has a minimal inhibitory concentration >0.06 mg·L^{-1} ranged from below 5% in three countries to equal or above 25% in nine countries in 2020. Resistance to macrolides occurred in 16.9% in aggregate, but there was also large variation among countries [80].

In addition, the clinical relevance of atypical bacteria in outcomes of outpatients has been questioned [81]. However, it is well established that *Legionella pneumophila* causes severe pneumonia [82]. Other atypical pathogens can also cause severe pneumonia [83, 84]. One review estimated that 0.5–2.0% of patients with *M. pneumoniae* pneumonia present in a fulminant form, and these severe cases occur more often in young patients [85]. In one study, patients with severe *M. pneumoniae* pneumonia had significantly longer times to initiation of adequate antibiotic therapy [83]. In one cohort of 276 hospitalised patients with CAP, *Chlamydia pneumoniae* was identified in 24 patients (8.7%). Of these, four had severe pneumonia upon presentation [86].
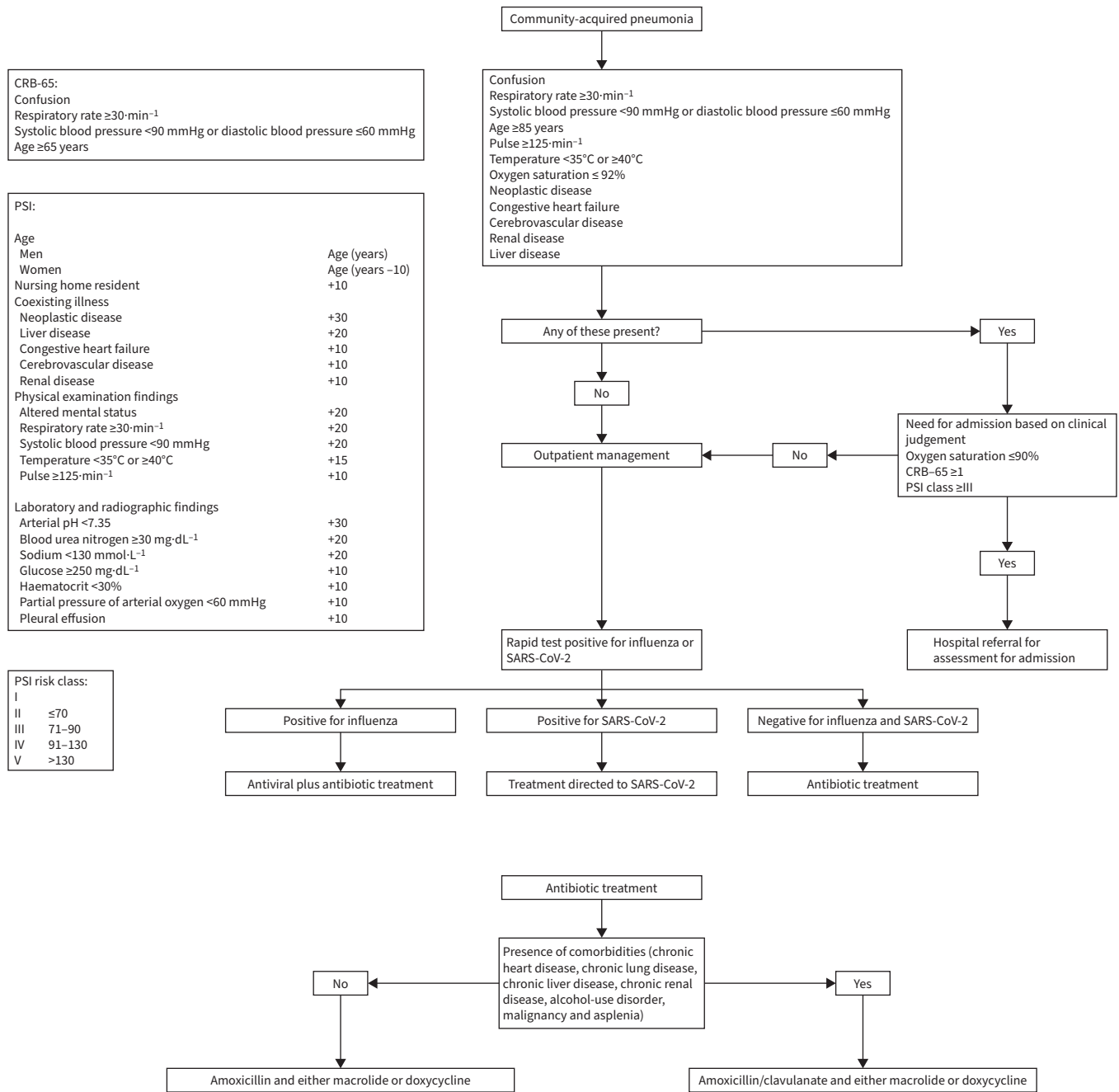
Our approach has been to treat patients without comorbidities with amoxicillin for appropriate coverage of *S. pneumoniae* with the addition of a second agent (*e.g.* macrolide or doxycycline) to cover atypical pathogens. The combination therapy approach is not supported by randomised clinical trials, but is based on epidemiological and clinical data demonstrating the relevance of atypical pathogens in the aetiology of CAP.

We treat patients with comorbidities with amoxicillin/clavulanate to cover both *S. pneumoniae* and other bacterial pathogens with the addition of either a macrolide or doxycycline to cover atypical pathogens. If a microbiological work-up is obtained and a pathogen is identified, we generally provide pathogen-directed therapy. Bacterial co-infection has been found in a third of patients diagnosed with influenza pneumonia [87]. Thus, we treat patients diagnosed with influenza pneumonia with both antiviral and antibiotic therapies. We treat patients with pneumonia diagnosed with other respiratory community-acquired viruses with antibiotic therapy because bacterial co-infection is common in this setting as well. In patients diagnosed with SARS-CoV-2 infection, we generally provide targeted therapy only (see section below) since bacterial co-infection is uncommon [88] (figure 1).

COVID-19 infection
Epidemiology
SARS-CoV-2, the aetiology of COVID-19 pandemic, has emerged as a major cause of death. In the United States, it was the third leading cause of death in 2021, behind only heart disease and cancer [89]. The total

CRB-65:
Confusion
Respiratory rate ≥30·min^{-1}
Systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg
Age ≥65 years

PSI:

Age	
Men	Age (years)
Women	Age (years −10)
Nursing home resident	+10
Coexisting illness	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical examination findings	
Altered mental status	+20
Respiratory rate ≥30·min^{-1}	+20
Systolic blood pressure <90 mmHg	+20
Temperature <35°C or ≥40°C	+15
Pulse ≥125·min^{-1}	+10
Laboratory and radiographic findings	
Arterial pH <7.35	+30
Blood urea nitrogen ≥30 mg·dL^{-1}	+20
Sodium <130 mmol·L^{-1}	+20
Glucose ≥250 mg·dL^{-1}	+10
Haematocrit <30%	+10
Partial pressure of arterial oxygen <60 mmHg	+10
Pleural effusion	+10

PSI risk class:

I	
II	≤70
III	71–90
IV	91–130
V	>130

FIGURE 1 Triage and treatment of patients with community-acquired pneumonia. PSI: pneumonia severity index; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

number of COVID-19 deaths since the beginning of the pandemic is nearing 1 million in the United States [90]. There have been five waves of the COVID-19 pandemic in the United States. Early in the pandemic, the more densely populated urban areas were predominantly affected. The less densely populated areas were more affected later in the pandemic [91]. While most infected patients have either asymptomatic or mild disease, a subset of patients develop severe disease. Increasing age and comorbidities are risk factors for more severe disease [92].

More than 2 years after the pandemic onset, SARS-CoV-2 infection persists. Because immunity to coronaviruses decreases over time, re-infection occurs. It is thus likely that SARS-CoV-2 will become one of the endemic community-acquired pathogens causing respiratory infections. The endemic phase does not necessarily mean a decreased burden from SARS-CoV-2. Rather, it represents a stable level of infection.

The extent of severity of infection in individual patients will depend on the protection generated by immunity, either *via* prior natural infection or vaccination [93].

Clinical manifestations

In the outpatient setting, the most common symptoms include fatigue (65.7%), cough (58.8%), headache (45.6%), chills (38.2%) and anosmia (27.9%). Symptoms peak at day 10 and recede at day 20 from the onset of clinical manifestations. One characteristic feature that distinguishes COVID-19 from most other viral respiratory infections is that symptoms associated with COVID-19 are often protracted. Some patients have symptoms that last weeks. Those are more often fatigue, cough, dyspnoea and anosmia [94]. In a comprehensive review of the diagnostic accuracy of signs and symptoms, the following were found to be more predictive of COVID-19 infection: headache, myalgia, fever, arthralgia and fatigue [95]. Less severe disease and thus changing clinical presentations are expected with the increasing number of individuals who acquire immunity to SARS-CoV-2 *via* vaccination or natural infection [96].

Assessment of need for admission

If initial triage of patients with confirmed or suspected COVID-19 is *via* telehealth, the following should prompt a referral to in-person visit either in the emergency department or in a dedicated COVID-19 clinic: dyspnoea, oxygen saturation ⩽94% or mental status change [97]. The use of outpatient oxygen saturation monitoring has received special consideration as a triage tool during the pandemic because of the recognition that some patients with COVID-19 do not experience worsening respiratory symptoms upon development of hypoxia. Patients with hypoxia have higher odds of requiring hospitalisation, and those with hypoxia have worse outcomes [94, 98]. However, the use of a home pulse oximeter requires attention to technical aspects. The device should be a finger oximeter approved by the United States Food and Drug Administration. Smart phone applications are not sufficiently accurate for safe use. Patients should be reminded that the measurement is to be performed at rest, using the index or middle finger and waiting at least 30 s before recording the results. Nail polish and cold extremities can lead to misleading results [99]. Lower thresholds for in-person evaluation should also be used in older people or those with high-risk medical conditions [97]. A clinical trial did not show an improvement in the number of days alive and out of the hospital at 30 days for patients who received monitoring of oxygen saturation *via* a home pulse oximeter [100]. In this study, however, both the intervention and control groups were being closely monitored by automated text messages and, if needed, callbacks from nurses. It is unclear whether the findings of the trial can be generalised to other practices.

The decision to admit a patient with COVID-19 relies on clinical judgement and is influenced by several factors, including vital signs, oxygen saturation, imaging findings, comorbidities, age, frailty and social aspects. In that decision, one should bear in mind that, for the same degree of illness severity as assessed by PSI or CURB-65, hospitalised patients with COVID-19 pneumonia have a much higher mortality as compared with hospitalised patients with CAP due to other aetiologies [101]. A clinical prediction rule for adverse events in outpatients has been developed and may have a role in the future if integrated with the electronic medical record [102].

Treatment

There are now two oral antiviral agents for which the Federal Drug Administration issued Emergency Use Authorizations: ritonavir-boosted nirmatrelvir and molnupiravir. Nirmatrelvir is an antiviral agent with inhibitory activity against SARS-CoV-2-3CL protease. The latter is an enzyme used by SARS-CoV-2 for replication. A slower metabolism and longer metabolic activity of nirmatrelvir is achieved by adding ritonavir [103]. Molnupiravir is a ribonucleoside that is converted into N-hydroxycytidine, which in turn binds to the viral genome. As a result, deleterious errors occur and SARS-CoV-2 replication is inhibited [104].

Remdesivir is an intravenous antiviral agent that directly inhibits the SARS-CoV-2 RNA-dependent RNA polymerase [105]. Bebtelovimab is an intravenous recombinant neutralising human monoclonal antibody that binds to spike protein of SARS-CoV-2. The Federal Drug Administration issued an Emergency Use Authorization of bebtelovimab for the treatment of mild to moderate COVID-19 based on the results of a phase 2 trial (BLAZE-4) showing safety [106].

Outpatient treatment is more likely to benefit three major categories of patients: immunocompromised, unvaccinated or partially vaccinated (including those who have not received a booster), and vaccinated with risk factors for severe disease (*e.g.* age ⩾65 years or age <65 years with comorbidities or risk factors for severe disease) [107]. The clinical trials testing the above outpatient treatments were conducted predominantly in unvaccinated patients [103–106]. The efficacy of these treatments is thus unclear in

vaccinated patients, but we agree that vaccinated patients with risk factors for severe disease should be offered treatment if available.

According to the National Institutes of Health guidelines, the preferred therapy should be ritonavir-boosted nirmatrelvir. Remdesivir is considered second choice. Alternative therapies in the absence of ritonavir-boosted nirmatrelvir or remdesivir include bebtelovimab or molnupiravir [107]. Globally, we believe feasibility favours oral medications. Based on efficacy and ease of administration, ritonavir-boosted nirmatrelvir is our first choice. However, the ritonavir component inhibits the cytochrome P450 (CYP) 3A4, leading to several drug interactions and limiting its use in some occasions. If the interaction is not expected to be clinically relevant, ritonavir-boosted nirmatrelvir can still be administered. If the interaction is expected to be clinically significant, strategies can be used to minimise it. Those include temporarily withholding the concomitant medication or the prescription of an alternative therapy for COVID-19. More information on medications that interact with ritonavir-boosted nirmatrelvir and strategies to minimise drug–drug interactions can be found in the drug–drug interactions information given on the National Institutes of Health's COVID-19 Treatment Guidelines webpage [108]. Ritonavir-boosted nirmatrelvir is currently not recommended in patients with estimated glomerular filtration rates <30 mL·min^{-1} or with severe hepatic impairment [109]. Molnupiravir is a reasonable alternative despite an efficacy that is not as high by indirect comparison. Molnupiravir should not be administered during pregnancy as data from animal studies indicate it may cause fetal harm. Females of childbearing potential should be assessed for pregnancy and should use an effective method of contraception during treatment and for 4 days after treatment completion. Sexually active males with partners of childbearing potential should use an effective method of contraception during treatment and for at least 3 months after treatment completion [110] (figure 2).
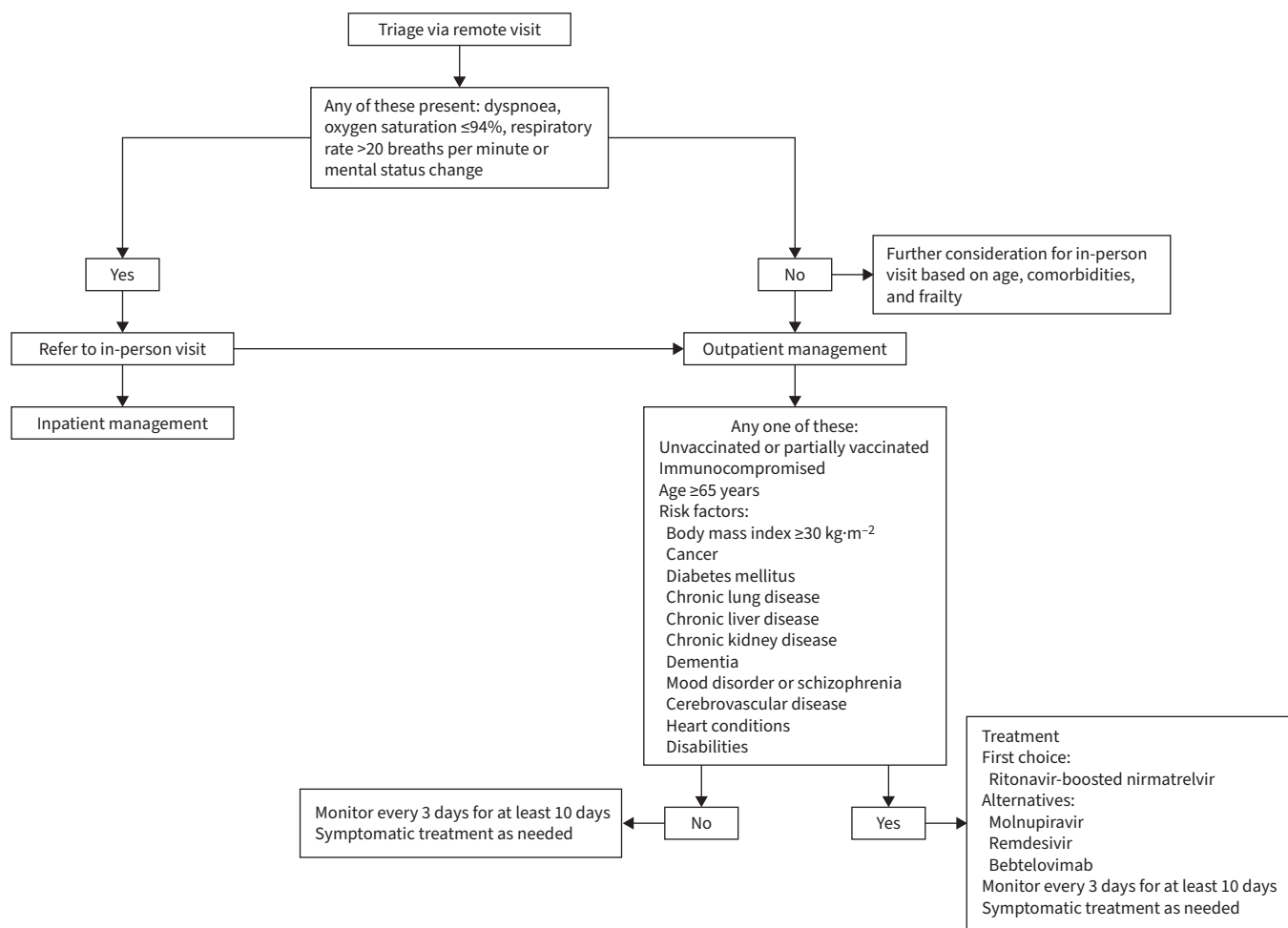

FIGURE 2 Triage and treatment of patients with COVID-19.

Acute exacerbation of COPD

Definition

Exacerbation of COPD has been defined as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD" [111]. Thus, the distinctive feature of acute exacerbation is the need for additional therapy [112]. Commonly, patients present with one or a combination of the following: purulent sputum or increase sputum amount, increased dyspnoea, wheezing and chest tightness. In mild exacerbations, patients do not need typically require further medical care. In a moderate exacerbation, patients need further medical assistance (*e.g.* a clinic visit). In a severe exacerbation, patients require hospitalisation [111].

Conditions that commonly mimic COPD exacerbation include heart failure [113, 114] and pulmonary embolism [115]. A potential pitfall is the nonrecognition of asthma features (*e.g.* asthma-COPD overlap syndrome) in some patients with COPD [116, 117] (table 2).

Epidemiology

The annual frequency of exacerbation increases with the severity of COPD: 0.85 per person for patients with moderate disease, 1.34 for those with severe disease, and 2.00 for those with very severe disease. The prevalence of hospitalisation in a year also increases with severity of disease: 7% for moderate disease, 18% for severe disease and 33% for very severe disease. A prior exacerbation is the most predictive variable for a future exacerbation. Other factors predictive of an exacerbation include worsening lung function, history of reflux or heartburn, increasing white cell count, and increasing health impairment [118].

Airway inflammation

The airways of patients with stable COPD are characterised by an increased number of T-lymphocytes and macrophages in the bronchial mucosa [119]. Patients with an exacerbation phenotype have further airway inflammation at baseline [120]. Colonisation of the airways by bacterial pathogens has been associated with higher levels of interleukin-8 and worse respiratory symptoms [121]. During an exacerbation, the number of inflammatory cells (lymphocytes, neutrophils and eosinophils) and levels of cytokines, eosinophil cationic protein and neutrophil elastase in the sputum increase [122]. Sputum levels of leukotriene B4 [123], tumour necrosis factor-α and interleukin-8 [124], and gene expression epithelial-derived neutrophil attractant-78 [125] increase and appear to play a role in neutrophil recruitment during an exacerbation. The antioxidant capacity is decreased whereas oxidant products are increased in patients with COPD exacerbation [126]. Recently, basic research has shown that altered microbiota induces lung inflammation [127]. Additionally, bacterial load has been shown to correlate with airway inflammation and symptoms in stable state [128].

Diagnostic work-up

Similar to the work-up for patients with CAP, we reserve sputum culture for select cases such as patients with recurrent exacerbation or recent hospitalisation.

TABLE 2 Conditions that are commonly associated with COPD exacerbation	
Heart failure	Heart failure is a common trigger of COPD exacerbation. Additionally, heart failure exacerbation may be misdiagnosed in up to 13% patients with asthma or COPD and acute dyspnoea [113]. Proper heart failure management may reduce the risk of COPD exacerbation [114]. Past medical history of heart failure, paroxysmal nocturnal dyspnoea, third heart sound, jugular venous distension, crackles, pulmonary venous congestion on chest radiography, presence of atrial fibrillation on electrocardiogram, and elevated brain natriuretic peptide are findings more strongly associated with heart failure in patients with dyspnoea [160].
Pulmonary embolism	In patients admitted for acute exacerbation of COPD, the prevalence of pulmonary embolism is 12.9%. Risk factors for pulmonary embolism include recent immobilisation, lower extremity oedema, concomitant deep venous thrombosis and elevated d-dimer [115].
Asthma-COPD overlap syndrome and COPD with peripheral eosinophilia	Features of asthma-COPD overlap syndrome include persistent airflow obstruction, history of at least 10 pack-years of tobacco smoking, bronchodilator response of at least 400 mL in forced expiratory volume in 1 s, and peripheral blood eosinophil count >300 cells·μL^{-1} [116]. In patients with COPD, higher blood eosinophil counts predict better response to inhaled corticosteroids [117].

Aetiology

Infection is the major trigger of COPD exacerbations, although exposure to pollutants is also an important contributor [129]. Respiratory viruses are responsible for approximately 50% of the infections [130]. Commonly identified viruses include rhinovirus and influenza. Other less common viruses include parainfluenza, adenovirus, coronavirus and human metapneumovirus [131]. Typical bacteria, identified in 24–42% of the infections [130, 132], commonly include *M. catarrhalis*, *H. influenzae* and *S. pneumoniae*. As the severity of COPD increases, patients are at higher risk of infection by *P. aeruginosa* [16]. Atypical bacteria are variably identified.

Bacterial pathogens can often be identified in the airway of patients with COPD when they are in stable conditions [133]. This finding casts doubt on the pathogenic role of bacteria in exacerbation of COPD. However, molecular analysis shows that exacerbations are often associated with a new strain of a bacterial pathogen, endorsing the pathogenic role of bacteria [134].

Assessment of need for admission

Criteria for hospital admission include a change in mental status, marked increase in dyspnoea, tachypnoea, worsening hypoxia or hypercapnia, inadequate response to outpatient treatment, and lack of social support for safe outpatient treatment [112, 135]. Factors to be considered in the decision to admit a patient include presence of comorbidities, the underlying severity of the COPD, history of prior admissions for exacerbation, need for home oxygen therapy, and adherence to treatment [136].

Treatment

The pharmacological treatment of COPD exacerbation centers on the use of short-acting bronchodilators, systemic glucocorticoids and antibiotics. Antibiotics are more likely to be beneficial in patients with severe exacerbations requiring hospitalisation [137]. In outpatients with exacerbation of mild to moderate severity, antibiotics have a modest effect on the reduction of treatment failure [138]. The core symptoms indicating the need for antibiotics in COPD exacerbation include increase in dyspnoea, sputum volume, and sputum purulence [139]. Accordingly, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of antibiotics in patients with increases in dyspnoea, sputum volume and sputum purulence, or in the presence of increased sputum purulence plus an additional criterion (increase in dyspnoea or sputum volume) [112]. We favour a 5-day course of amoxicillin-clavulanic acid, which led to a higher rate of symptom improvement as compared with placebo in a clinical trial [140].

Treatment with systemic glucocorticoid leads to fewer treatment failures [141] and lower relapse rates [142]. A clinical trial demonstrated noninferiority of a 5-day course compared with a 14-day course of prednisone [143]. Our approach has been to treat with a 5-day course of 40 mg of prednisone daily. Nebulised budesonide has been evaluated as an alternative to systemic glucocorticoids with promising results in hospitalised patients [144, 145], but more studies are needed before routine use.

Acute exacerbation of noncystic fibrosis bronchiectasis

Definition

A consensus statement defined an acute exacerbation of bronchiectasis as a worsening of three of the following symptoms for at least 2 days: cough, sputum volume, sputum purulence, dyspnoea, fatigue and haemoptysis. Additionally, a clinician must establish that a change of treatment is needed [146]. The British Thoracic Society guidelines have highlighted that is in not uncommon for adults with bronchiectasis to have variations in daily symptoms of cough and sputum production. Neither the usual variation in daily symptoms nor the isolated finding of mucopurulent (pale yellow) or purulent (yellow to green) sputum establish an exacerbation. Rather, it is the combination of an increase in respiratory or systemic symptoms (*e.g.* cough, wheezing, dyspnoea or fatigue), increased volume or change in viscosity of sputum, and increased sputum purulence that indicate an exacerbation [147].

Epidemiology

In a cohort of 1826 patients with bronchiectasis included in a US registry, the mean age was 64 years, 79% were women and 60% were never-smokers. The most common comorbidities were history of pneumonia (68%), gastroesophageal reflux disease (47%), asthma (29%), COPD (20%), rheumatologic disease (8%), primary immunodeficiency (5%), prior TB (4%), primary ciliary dyskinesia (3%) and inflammatory bowel disease (3%). In 63% of the patients, nontuberculous mycobacteria (NTM) was identified or previously reported. Patients with NTM more often had tree-in-bud and mucoid impaction on CT. An exacerbation in the prior 2 years was present in 64% of the patients, and the average number of exacerbations in the prior 2 years was three [148]. Table 3 shows the aetiologies or diagnoses associated with bronchiectasis based on a mutinational study [161].

TABLE 3 Aetiologies or diagnoses commonly associated with bronchiectasis

Aetiologies or associated diagnoses [161]	Remarks
Post-infectious (20%)	Other aetiologies of bronchiectasis should be excluded. Tuberculosis is the most common cause and is more prevalent in developing countries [162].
COPD (15%)	Prevalence of bronchiectasis of 29% in a cohort of patients with COPD; the most common pattern is tubular [163]. May represent primary bronchiectasis in the setting of COPD or bronchiectasis secondary to COPD. Investigation for aetiology of bronchiectasis may be warranted on a case by case basis [164].
Connective tissue disease (10%)	Bronchiectasis has been present in up 35% of patients with rheumatoid arthritis [165]. Patients with connective tissue disease may also have traction bronchiectasis as a result of fibrotic lung disease [166].
Immunodeficiency (5.8%)	Most frequent immunodeficiency is common variable immune deficiency [167]. As such, different guidelines suggest obtaining serum immunoglobulins as part of the work-up of the aetiology of bronchiectasis [154, 168].
Allergic bronchopulmonary aspergillosis (4.5%)	Suspect in patients with difficult to control asthma or cystic fibrosis, eosinophilia (often >500 cells·mm^{-3}) and elevated total serum IgE levels (often >417 IU·mL^{-1}). On chest CT, bronchiectasis tends to be central and there may be mucus plugs in central bronchi and high attenuation mucus in the bronchi. Other corroborating tests include cutaneous reactivity or specific IgE antibody to filamentous fungal antigen, precipitating antibodies or IgG antibodies against filamentous fungal antigen, and filamentous fungal growth in respiratory cultures [169].
Asthma (3.3%)	In one cohort, bronchiectasis was present in 67.5% of patients with severe asthma. Those with bronchiectasis are more likely to have growth of pathogens in sputum culture and consume more antibiotics. The most common type of bronchiectasis is cylindrical [170].
Inflammatory bowel disease (1.9%)	Most common thoracic manifestation of inflammatory bowel disease. Bronchiectasis is seen more often with ulcerative colitis [171].
Ciliary dysfunction (1.7%)	Primary ciliary dyskinesia is an autosomal recessive disorder that manifests as chronic rhinosinusitis, recurrent respiratory infections, male infertility and bronchiectasis. Half of all patients have defects in organ laterality [172].
Aspiration/oesophageal reflux (0.6%)	Gastrointestinal symptoms are common in patients with bronchiectasis [173]. There is also high prevalence of IgG against *Helicobacter pylori* in serum of patients with bronchiectasis [174]. Bronchiolitis may also be present with chronic aspiration [175].
α_1-antitrypsin deficiency (0.6%)	Clinically significant bronchiectasis has been identified in 27% of patients with α_1-antitrypsin deficiency. Bronchiectasis is more often tubular and in the lower lobes. Panlobular emphysema is common [176].
Yellow nail syndrome (0.1%)	Yellow nail syndrome is characterised by lower extremities lymphoedema, bronchiectasis, pleural effusion, and yellow nail discolouration [177].

CT: computed tomography.

Airway inflammation

The pathogenesis of bronchiectasis is characterised by a vicious cycle that includes impaired mucus clearance, recurrent infection, dysregulated inflammatory response, and airway dilatation and damage [149]. Patients with bronchiectasis have a predominantly neutrophilic airway inflammation profile. However, it is now established that 20% of patients with bronchiectasis have blood eosinophil count >300 cells·µL^{-1}. Such a peripheral eosinophilic profile may be a risk factor for exacerbation in patients who previously received antibiotics for infection. However, the presence of low blood eosinophil count (<100 cells·µL^{-1}) may indicate higher neutrophilic inflammation and portends a higher mortality in patients with bronchiectasis [150].

The concept that a single pathogen overgrowth causes infection may not fully explain why some patients are more predisposed to recurrent bronchiectasis exacerbation. The interaction between microbes (interactome), rather than the microbe itself, may better predict risk of exacerbations. Interactomes may also explain why antimicrobials that are not effective against the prevailing pathogen may still lead to clinical improvement in some patients [151].

Aetiology

In a cohort study of 186 patients with bronchiectasis exacerbation, a microbiological aetiology was obtained in 98 (68.5%) patients. *P. aeruginosa* was the most common pathogen (39%) followed by respiratory viruses (26%), *S. pneumoniae* (16%), *H. influenzae* (15%), *S. aureus* (12%) and *Enterobacteriaceae* (7%), *Aspergillus* sp. (7%) and NTM (3%) [152].

Diagnostic work-up

Whenever feasible, a sputum culture for routine pathogens, mycobacterium and fungus is obtained. Prior culture results should be reviewed if available.

Assessment of need for admission

Hospitalisation is indicated in the presence of worsening respiratory failure (respiratory rate >25·min^{-1}), substantial decrease in oxygen saturation, temperature >38°C or other signs of sepsis, haemodynamic instability, development of cyanosis, inability to take oral antibiotic, need for intravenous antibiotics in the absence of a home intravenous antibiotics programme and lack of social support [153, 154].

Treatment

Empiric antimicrobials are initiated while waiting for the culture results [154]. A previously isolated pathogen should be covered [155]. When *P. aeruginosa* has been previously isolated, we suggest oral levofloxacin. Oral ciprofloxacin is an alternative to oral levofloxacin against *P. aeruginosa*, but we reserve it for pathogen-directed therapy because of its lower antimicrobial activity against *S. pneumoniae* [156]. In nonsevere exacerbations, and when there is no evidence of prior *P. aeruginosa* isolation, we suggest oral amoxicillin-clavulanic acid. If the culture reveals a pathogen, empiric antibiotic therapy can be switched to pathogen-directed therapy [154]. In a recent trial of hospitalised patients, antibiotic course based on bacterial load count led to a shorter antibiotic course length (8 days) and, in those colonised with nonpseudomonas organisms, a longer time to another exacerbation as compared with a fixed 14-day antibiotic course [157]. While the trial indicates that an antibiotic course shorter than the traditionally recommended 14-day course is feasible in these patients, the proof-of-concept design and small sample size make the findings preliminary. The length of treatment, thus, remains a contentious topic. A 14-day course of antibiotics is still recommended when treating patients for *P. aeruginosa* while a shorter course may be applied in patients without *P. aeruginosa* [158].

Conclusion

Lower respiratory infections encompass a range of diseases that are heterogenous and require different management strategies. Much progress has been made in the field of respiratory infections, including better surveillance systems, development of clinical prediction rules, new molecular diagnostic tests and novel treatment options. Perhaps the greatest scientific breakthrough we have recently witnessed was the development of effective vaccines against COVID-19. Those achievements are to be celebrated, but they should not distract us from the ongoing challenges, including medical misinformation [159], antibiotic resistance [41] and more importantly health disparities and lack of access to healthcare [2].

The outpatient management of patients with respiratory infections is better achieved with comprehensive clinical assessment for precise clinical diagnosis, knowledge of local surveillance data (*e.g.* the circulating pathogens), strategic use of diagnostic tests according to surveillance data, assessment of illness severity and need for admission using clinical data integration and prediction rules when available, judicious use of antimicrobials, recognition of those at higher risk due to disability, poverty or health illiteracy and patient follow-up.

Questions for future research in respiratory infections

- Development and application of clinical pathways for site triage and treatment.
- Development and testing of new molecular diagnostic tests for both viral and bacterial pathogens.
- Development of new antimicrobial agents, including antiviral agents.
- Development and testing of vaccines against respiratory pathogens.

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