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Pneumonia

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Introduction

Pneumonia remains a major contributor to mortality and morbidity worldwide in all age groups and is the leading cause of death in infants and children globally, exceeding the combined mortality of malaria, tuberculosis and HIV infection. The lung is constantly exposed to microorganisms and the combined effects of pathogen, host, and environmental factors determine whether or not the clinical condition known as pneumonia occurs. Pneumonia is generally more prevalent in low- and middle-income countries. Incidence is highest at the extremes of ages such as the elderly and infants. The overwhelming majority of pneumonia deaths in infants and young children occur in low-income settings.

There are a number of classifications of pneumonia in use that have implications for etiology, management, and prognosis, such as classification based on the origin of the infection or its severity. The term 'community-acquired pneumonia' (CAP) refers to the appearance of infection in a non-hospitalized population with no risk factors for multi-drug-resistant pathogens whereas the term 'hospital acquired pneumonia' or 'nosocomial pneumonia' is used when there is no evidence that the infection was present or incubating at the time of hospital admission. The latter type of pneumonia is most frequently found in patients receiving mechanical ventilation, hence the term 'ventilator-associated pneumonia.' Another classification in common use in children with community-acquired pneumonia in resource-limited settings is based on clinical severity, and is used to guide management decisions such as antibiotic treatment, hospitalization and oxygen therapy.

Pneumonia in Children

Pneumonia is the leading cause of death in infants and young children between 1 month and 5 years of age worldwide and a common cause of death in newborns (<1 month of age). Pneumonia accounted for around one-fifth of under-five mortality globally in 2011 (Walker et al., 2013), more than malaria, HIV and tuberculosis combined. In 2010, there were ≈120 million episodes of pneumonia, 14 million severe pneumonia episodes and 1·3 million deaths due to pneumonia in infants and children younger than 5 years, those under 2 years being most at risk. The overwhelming burden of pneumonia is in low-income countries and around half of deaths occur in sub-Saharan Africa. It is estimated that only half of children with pneumonia receive appropriate medical care.

Risk Factors

In addition to young age, there are a number of other established risk factors for incidence and mortality – **Table 1** (Rudan et al., 2008). There is a high prevalence of low birth weight (<2500 g) babies and of protein-energy malnutrition in early childhood in many resource-poor settings that greatly increases pneumonia risk. Not being breast-fed increases the risk of pneumonia as well as diarrhea and malnutrition. Vitamin A deficiency increases the risk of pneumonia-related mortality due to measles, and there is evidence to suggest that zinc deficiency is associated with more severe disease.

In low-income countries, community-based interventions such as the promotion of regular hand-washing in young children can reduce the spread of respiratory viruses and decrease the incidence of pneumonia as well as diarrhea (Luby et al., 2005; Jefferson et al., 2011). In these same settings, exposure to indoor air pollution due to the burning of unprocessed solid fuels for cooking and heating is common (Smith et al., 2000). Nearly half of the households worldwide are thought to cook daily with unprocessed solid fuels, such as biomass or coal that can release 50 times more pollution during cooking than gas stoves.

The HIV epidemic has had a major impact on child pneumonia, particularly in the high-burden settings in eastern, central and southern Africa. Prior to the routine use of cotrimoxazole preventive therapy and early antiretroviral therapy,

Table 1 Risk factors for child pneumonia incidence and mortality

Young age	Especially <2 years
Poor nutritional status	Low birth weight
	Malnutrition
	Not breast fed
	Micronutrient deficiency, e.g., vitamin A, zinc
Not immunized	Pneumococcal conjugate vaccine
	Measles
	Hib conjugate vaccines
	Pertussis
Presence of comorbidities	HIV infection
	Neurological conditions, e.g., severe cerebral palsy
	Cardiac disease
	Genetic conditions, e.g., down syndrome
Poor socioeconomic and environmental circumstances	Indoor air pollution
	Overcrowding
	Poor hygiene
	Poor access to health services

the incidence of severe pneumonia was at least 20-times higher in HIV-infected compared to HIV-uninfected infants and children (Madhi et al., 2000). Pneumonia-related mortality risk was also much higher, particularly in HIV-infected infants in whom *Pneumocystis jirovecii* pneumonia (PCP) was a leading cause of fatal pneumonia (Enarson et al., 2010).

Etiology

Childhood pneumonia can be caused by a wide range of pathogens, and knowledge of the common causative pathogens in high-burden settings is important to inform the choice of antibiotic therapy and potential preventive strategies, such as immunization. However, it is difficult to accurately determine etiology because of limitations concerning both clinical samples and laboratory analysis. It is difficult to obtain clinical samples for microbiological examination from the lower respiratory tract: percutaneous transthoracic fine needle lung aspiration is regarded as the gold standard sample and while relatively low-risk is little practiced (Scott and Hall, 1999); bronchoalveolar lavage is generally not done only in low-income country settings; and sputum samples obtained by nebulized saline induction can be contaminated during passage through the upper respiratory tract limiting their diagnostic value. Blood culture and chest radiograph are the traditional mainstays of diagnosis but blood culture is insensitive and chest radiography poorly specific. In addition, it is increasingly recognized that etiology can be complex and involve multiple pathogens.

The etiologic spectrum for childhood pneumonia varies between settings and changes over time. Respiratory viruses are more prominent than bacterial pathogens in populations with better socioeconomic conditions and widespread use of bacterial conjugate vaccines, and pneumonia-related mortality is low in such settings. Etiology studies undertaken in the 1980s in low-income settings identified *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) as the common bacterial pathogens causing pneumonia in children (Shann, 1995). These studies also identified a range of viral pathogens such as respiratory syncytial (RSV) and influenza viruses, but showed that the majority of pneumonia-related deaths were due to bacterial rather than viral pneumonia, with the exception of measles. In the past, pneumonia was a common cause of death in children with measles, either directly due to measles virus (giant cell pneumonia) or more commonly due to secondary bacterial pneumonia such as due to *S. pneumoniae* or *Staphylococcus aureus*.

Children that are immunosuppressed such as those that are severely malnourished or HIV-infected are susceptible not only to a higher incidence and mortality from pneumonia, but also to a wider spectrum of pathogens. In addition to a very high risk of pneumonia due to common bacterial pathogens, they also develop pneumonia due to uncommon Gram negative bacteria such as *Klebsiella pneumoniae* or *Acinetobacter*, to opportunistic pathogens such as *Pneumocystis jirovecii*, and to *Mycobacterium tuberculosis*. It is also likely that these children are more susceptible to pneumonia from nosocomial infection in settings such as overcrowded nutritional rehabilitation units, but this has not been well quantified or described. HIV-infected infants with pneumonia often have more than one potential pathogen identified such as bacteria with viruses or *M. tuberculosis*, or PCP with CMV infection. While tuberculosis is generally thought to be associated with chronic respiratory symptoms, in infants it can present as an acute severe pneumonia with bacterial co-infection. This is likely to be common and responsible for the initial improvement frequently observed with standard antimicrobial therapy in childhood tuberculosis.

Viruses are common causes of child pneumonia, and in high and middle income settings, are the predominant cause. In addition to viruses such as RSV, influenza, parainfluenza, adenoviruses, and rhinoviruses, human metapneumovirus and bocavirus have been more recently identified. While viral pneumonia is a major cause of morbidity causing a huge burden to health services, mortality is generally low unless that are underlying comorbidities and co-infection with other pathogens. Other causes of pneumonia in children that are usually self-limiting are atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydophila* species.

Current efforts to provide an update on the etiologic spectrum of pneumonia in the era of widespread use of conjugate Hib and pneumococcal vaccines include the multi-country Pneumonia Etiology Research in Child Health (PERCH) study which has been conducted in a range of settings in Africa and Asia (Levine et al., 2012). Recent studies are employing a wider range of more sensitive diagnostics than earlier studies (Howie et al., 2014).

Clinical Manifestations

Fever and cough are common in children with respiratory tract infections, such as pneumonia. Clinical findings that indicate lower respiratory tract infection or pneumonia on inspection include increased respiratory rate and chest indrawing or recession, with lower costal indrawing being the focus of WHO clinical definitions. On auscultation focal abnormalities such as crackles or reduced air entry may be present, but are commonly not found. Infants with viral pneumonia, for instance due to RSV, will commonly have generalized wheeze. The definition of tachypnea or fast breathing is age-dependent: 0–1 month, $\geq$60 breaths per minute; 2–11 months, $\geq$50 breaths per minute; and 12–59 months, $\geq$40 breaths per minute. Chest indrawing is generally lower costal, although retractions may be noted sternally, suprasternally, or intercostally. Children with severe pneumonia may have additional features such as poor feeding, head nodding, grunting, altered mental state and direct evidence of hypoxemia by way of pulse oximetry or the presence of cyanosis.

The WHO has established a simple case-management approach that classifies severity of pneumonia to guide appropriate management, and that relies on a few features readily identifiable by trained health workers such as fast breathing and lower chest indrawing (**Table 2**). The overall aims of the WHO case-management strategy are twofold. The first is to improve outcomes for child pneumonia by providing prompt and appropriate care with antibiotics and oxygen therapy when needed. The second is to avoid unnecessary use of antibiotics for those children with respiratory symptoms that do not have pneumonia, and to avoid unnecessary hospitalizations for children that can receive antibiotics at home.

Table 2 Case-management approach for diagnosis and management of pneumonia according to the World Health Organization (WHO, 2013)

Sign or symptom	*Classification*	*Treatment*
Cough or difficulty in breathing with: ● Oxygen saturation <90% or central cyanosis ● Severe respiratory distress (e.g., grunting, very severe chest indrawing) ● Signs of pneumonia with a general danger sign (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions)	Severe pneumonia	Admit to hospital Give oxygen if saturation <90% Manage airway as appropriate Give recommended antibiotic Treat high fever if present
● Fast breathing: ≥50 breaths/min in a child aged 2–11 months ≥40 breaths/min in a child aged 1–5 years ● Chest indrawing	Pneumonia	Home care Give appropriate antibiotic Advise the mother when to return immediately if symptoms of severe pneumonia Follow up after 3 days
● No signs of pneumonia or severe pneumonia	No pneumonia: cough or cold	Home care Soothe the throat and relieve cough with safe remedy Advise the mother when to return Follow up after 5 days if not improving If coughing for more than 14 days, refer to chronic cough

Chest radiography is not required routinely in the clinical assessment of children with pneumonia, and is not a diagnostic tool that can distinguish bacterial from viral pneumonia. Chest radiography is indicated if there is uncertainty about diagnosis (e.g., suspected pneumothorax, empyema or cardiac failure) or if there is an unsatisfactory response to first-line antibiotics.

In children with severe pneumonia, it is important to assess whether they are hypoxemic. Hypoxemia (SaO2<90%) is common in children with severe pneumonia and is associated with mortality (Subhi et al., 2009). The most accurate diagnostic tool is pulse oximetry but this is not always available. Clinical features indicating hypoxemia such as cyanosis or altered mental state have poor sensitivity.

Management

The treatment of CAP in children is empirical with the selection of antimicrobials determined by evidence-based knowledge of the common bacterial causes, severity of pneumonia, and the presence of underlying risk factors such as severe malnutrition. Most children with CAP can be treated with oral therapy (Addo-Yobo et al., 2004). WHO recommends home care for cases that are not 'severe' including those with chest indrawing, though randomized trial evidence for the safe home treatment of pneumonia with chest indrawing is largely from South Asia (Ashraf et al., 2010; Hazir et al., 2008) and further evidence from elsewhere, notably Africa, would be beneficial.

The WHO recommends the following antibiotic therapy for pneumonia in children (WHO, 2013).

For pneumonia that is not 'severe': oral amoxicillin

- In settings with high HIV infection rate, give oral amoxicillin at least 40 mg kg^{-1} per dose twice a day for 5 days.
- In areas with low HIV prevalence, give amoxicillin at least 40 mg kg^{-1} per dose twice a day for 3 days.

Give the first dose at the clinic and teach the mother how to give the other doses at home.

For 'severe' pneumonia: intravenous ampicillin (or benzylpenicillin) and gentamicin.

- Ampicillin 50 mg kg^{-1} or benzylpenicillin 50 000 U kg^{-1} IM or IV every 6 h for at least 5 days
- Gentamicin 7.5 mg kg^{-1} IM or IV once a day for at least 5 days.

If the child does not show signs of improvement within 48 h and staphylococcal pneumonia is suspected, switch to gentamicin 7.5 mg kg^{-1} IM or IV once a day and cloxacillin 50 mg kg^{-1} IM or IV every 6 h (p. 83). Use ceftriaxone (80 mg kg^{-1} IM or IV once daily) in cases of failure of first-line treatment.

In high and middle income country settings empiric antibiotic regimens tend to differ from the WHO guidelines. Macrolides such as roxithromycin and azithromycin are often used for the outpatient management of pneumonia, particularly in school-aged children due to the prevalence of pathogens such as *Mycoplasma pneumoniae* in this group. For the inpatient treatment of complicated pneumonias, broad-spectrum coverage is commonly achieved with cephalosporins or beta-lactamase inhibiting antimicrobials such as a combination of amoxicillin and clavulanic acid, while for suspected staphylococcal pneumonias agents such as clindamycin or vancomycin may be added to conventional first line anti-staphylococcal agents such as cloxacillin or flucloxacillin where the prevalence of methicillin-resistant *S. aureus* (MRSA) is appreciable or its presence confirmed.

A meta-analysis of nine studies that investigated the impact of introducing community-based case management of pneumonia showed a reduction in pneumonia-related mortality of 42%, 36%, and 36% among neonates, infants, and children of 0–4 years, respectively (Sazawal et al., 2003). A community-based pneumonia case-management strategy should be part of an integrated approach to the care of sick children at community and primary health care levels in resource-limited settings. Improvements can also be made at the secondary care facility (district hospital) with the introduction of a structured approach to pneumonia

case-management and hypoxaemia, ensuring availability of antibiotics and oxygen (Enarson et al., 2014; Duke et al., 2008).

Integrated community case management (iCCM) of pneumonia, malaria, and diarrhea has been increasingly adopted as a strategy to improve access of the poorest, most underserved children to treatment for these diseases. The WHO and UNICEF released a joint statement justifying the need for iCCM and making recommendations on its implementation in 2012 (WHO, 2012). The integration of pneumonia with malaria management in rural Zambia resulted in 68% of children with pneumonia receiving treatment within 24–48 h of symptom onset, as opposed to only 13% of children referred to health centers for evaluation (Yeboah-Antwi et al., 2010). In rural Uganda, a cluster-randomized trial that compared malaria management only versus malaria and pneumonia iCCM demonstrated that children in integrated case management areas were more likely to receive prompt and appropriate antibiotics for pneumonia compared to children in areas where only malaria management was offered (Kalyango et al., 2013). While these and other studies have demonstrated an impact on early treatment and have demonstrated that iCCM is safe, there are limited high quality data on the impact of this strategy on all-cause child mortality.

Prevention

Vaccines increasingly have a role to play in the prevention of pneumonia. Hib is an important cause of pneumonia and meningitis in high-burden, low-income countries. In The Gambia, the Hib conjugate vaccine demonstrated an efficacy of 100% for Hib pneumonia, 95% for prevention of invasive Hib disease, and 21% reduction in radiologically confirmed pneumonia (Mulholland et al., 1997). The Hib conjugate vaccine has become part of the routine immunization program for infants of many countries since 2000, with marked reductions in invasive Hib disease noted.

The pneumococcal conjugate vaccine has even greater potential to reduce the burden of bacterial pneumonia and meningitis in children. Vaccine trials in South Africa and The Gambia demonstrated efficacy of the 9-valent vaccine to reduce pneumonia hospitalizations, radiological confirmed pneumonia, and in the case of The Gambia, a 16% reduction in all-cause mortality (Cutts et al., 2005). There is increasing evidence that vaccination of young children with the pneumococcal conjugate vaccine also provides protection to the adult population by reducing transmission.

Pneumonia is a serious complication of measles, and until recently was a common cause of death associated with this disease. A safe and effective measles vaccine has been available for decades. While measles-related pneumonia is not the scourge it once was as a result of immunization, the optimal timing and vaccine strategy will vary between populations. In addition, infants in low-income settings routinely receive vitamin A at 6 months of age which protects against measles-related mortality. If a child does develop measles, then they should receive additional doses of vitamin A to reduce the risk of complications including pneumonia.

In addition to vaccines, efforts to improve early childhood nutrition, notably through exclusive breast-feeding in the first 6 months, can help protect against pneumonia and pneumonia-related mortality (Victora et al., 1999). Reduction in exposure to indoor air pollution, primarily from cooking smoke in low-resource settings (Smith et al., 2000), and to household overcrowding may also reduce the risk of pneumonia, while improvements in access to healthcare services reduce morbidity and mortality.

There is great potential to reduce the impact of HIV on child pneumonia. The numbers of new HIV infections in babies globally is falling each year due to antenatal HIV screening and prevention of mother-to-child transmission. Cotrimoxazole preventive therapy for all HIV-exposed or infected infants protects against PCP which was a common cause of severe pneumonia and deaths in HIV-infected infants from 2 to 6 months of life. Early antiretroviral therapy for HIV-infected infants will reduce pneumonia risk even further. While bacterial conjugate vaccines are not as protective in HIV-infected infants as HIV-uninfected infants, they still do provide some protective efficacy, and this is important given the high burden of bacterial pneumonia in HIV-infected infants. Furthermore, it may be that vaccine efficacy may be improved further if the infant is receiving antiretroviral therapy at the time of immunization, but there are no data to confirm this. Finally, infants that are exposed to tuberculosis in the household setting should be screened for tuberculosis, and if well should receive preventive therapy to reduce the risk of developing tuberculosis.

Overall, it is projected that known interventions can have an increasingly substantial impact on pneumonia mortality if scaled up successfully, with increased investment leading to more lives saved more rapidly (Bhutta et al., 2013).

Pneumonia in Adults

Community-Acquired Pneumonia (CAP)

In adults, the incidence of pneumonia differs among countries ranging from 1.6 to 11 per 1000 adults per year. In the United States, CAP affects more than 4 million adults and accounts for more than 1 million hospital admissions each year, pneumonia and influenza are the sixth leading cause of death, and the age-adjusted mortality attributed to this disease is on the rise. Several populations are at risk of CAP, especially due to *Streptococcus pneumoniae*: people 65 years and older, and those with immunocompromising conditions, such as anatomic or functional asplenia, congestive heart failure, COPD, diabetes mellitus, liver disease, and alcoholism. Smoking is the strongest risk factor for invasive pneumococcal disease in immunocompetent non-elderly adults. HIV infection is a major risk factor for CAP in adults due to a wide range of pathogens including pneumococcus, and in tuberculosis endemic settings, *M. tuberculosis* is important, either as a direct cause or because adults with pulmonary tuberculosis are at greater risk of secondary bacterial pneumonia. Long-term care facility residents represent a unique high-risk group as they often have infections that mirror hospital-acquired pneumonia but may also suffer from community-acquired pathogens such as *S. pneumoniae*.

Clinical Features

Adults and adolescents with CAP usually present a constellation of symptoms and signs that include cough, dyspnea, sputum production, and pleuritic chest pain, although non-respiratory symptoms (mainly in elderly patients who may report fewer symptoms) such as changes to mental state may also predominate. Diagnosis relies on clinical findings from patient history and physical examination and radiological abnormalities (Metlay et al., 1997; Wunderlink and Waterer, 2014). While the presence of an infiltrate on chest X-ray supports the diagnosis, there are no clinical or radiological features that can accurately predict a specific etiologic agent.

Etiology

Most cases of CAP in adults are due to a few key pathogens out of a plethora of causative agents. The most predominant pathogen observed is *S. pneumoniae* (pneumococcus), which historically accounts for about two thirds of all cases of bacteremic pneumonia. The widening use of conjugate pneumococcal vaccines in adults, together with indirect benefits from their use in children (reducing adult exposure), is changing the epidemiology of adult pneumococcal pneumonia. Other agents vary according to the severity of the disease (**Table 3**) and the epidemiological condition or risk factors (**Table 4**; Mandel et al., 2007). Concurrent infection by multiple microorganisms may lead to CAP; for example, influenza A may be followed by a secondary infection with *S. pneumoniae* or *S. aureus*. *Chlamydophila pneumoniae* may also be followed by *S. pneumoniae* (File, 2003).

Pneumonia is a common complication and cause of mortality in adolescents and young adults during epidemics of some new influenza strains such as the recent avian influenza (H5N1) or swine flu (H1N1) epidemics.

Risk Stratification

The most important issue in the management of a patient with CAP concerns the most appropriate care setting: outpatient, hospitalization on a medical ward, or admission to a high-dependency unit (HDU) or intensive care unit (ICU). Between 30% and 50% of adults with CAP are at low risk of death and may potentially be managed at home. The decision regarding hospitalization is usually based on the stability of the clinical condition, the risk of death and complications, and the presence or absence of other medical problems and social characteristics. Severity or prognostic scores have been developed and evaluated that are used to identify patients who may be candidates for outpatient treatment.

The most widely used prediction score is the 'pneumonia severity index' (PSI), which stratifies the patients to five risk categories; the higher the score, the higher the risk of death (Fine et al., 1997). The PSI categorizes those that can be safely managed as outpatients, those that require a short period of observation in the emergency department, and those that should be hospitalized, considering the presence of severe CAP markers. An easy-to-use version of the PSI is available on the internet (see Relevant Websites). An alternative score used at the bedside is the CURB 65 (Lim et al., 2003).

Other considerations such as the presence of hypotension (systolic blood pressure lower than 90), hypoxemia, exacerbation or active comorbidities, inability to reliably take oral

Table 3 Most common causative factor in community-acquired pneumonia by patient care setting (Mandel et al., 2007)

	Non-ICU patients	*ICU patients*
Streptococcus pneumoniae	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*
Mycoplasma pneumoniae	*Mycoplasma pneumoniae*	*Legionella* species
Haemophilus influenzae	*Chlamydophila pneumoniae*	*Haemophilus influenzae*
Chlamydophila pneumoniae	*Haemophilus influenzae*	Gram-negative bacilli
Respiratory viruses[a]	*Legionella* species	*Staphylococcus aureus*
	Respiratory viruses[a]	

[a]Influenza A and B, adenovirus, respiratory syncytial virus (RSV), parainfluenza.

Table 4 Risk factors related to specific pathogens in community-acquired pneumonia (Mandel et al., 2007)

Alcoholism	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* species, *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* species, *S. pneumoniae, Moraxella cararrhalis, Chlamydophila pneumoniae*
Aspiration	Enteric gram-negative, anaerobes
Lung abscess	Community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), oral anaerobes, *M. tuberculosis*, atypical mycobacteria
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Hotel or cruise ship stay in previous 2 weeks	*Legionella* species
Travel to or residence in South-East and Eastern Asia	*Burkholderia pseudomallei*, avian influenza, severe acute respiratory syndrome (SARS) caused by coronavirus infection)
Active influenza in the community	Influenza, *S. pneumoniae, Staphylococcus aureus, H. Influenzae*
Structural lung disease (bronchiectasis)	*P. aeuruginosa, S. aureus*
Injection drug use	*S. aureus*, anaerobes, *S. pneumoniae*, *M. tuberculosis*
Endobronchial obstruction	Anaerobes, *S. pneumoniae, H. influenzae, S. aureus*
HIV infection (early)	*S. pneumoniae, H. influenzae, M. tuberculosis*
HIV infection (late)	All of the above, plus *Pneumocystis jirovecii, Cryptococcus, Histoplasma, Aspergillus,* atypical mycobacteria (especially *Mycobacterium kansasii*)

medications, or social characteristics that compromise treatment compliance, should all be taken into account when evaluating the need for hospital admission (Metlay and Fine, 2003).

Diagnostic Testing

The choice of diagnostic tests appropriate to use in pneumonia cases are based on the probability that findings would significantly alter standard (empirical) management decisions, the severity and care setting of patients, and suspicion of a specific pathogen on an epidemiological basis.

Extensive tests for outpatients with suspected bacterial CAP are optional because of the low probability of treatment failure and good prognosis with recommended empirical antibiotic treatment. The presence of epidemiological variables that point to a specific pathogen requiring different treatment clearly justifies extensive testing.

Blood cultures have low sensitivity (5–14%) but should be done in hospitalized patients, especially in cases of severe CAP, ICU patients, asplenia, liver disease, or alcohol abuse or other forms of immunusuppression, and in the presence of cavitary infiltrates with the suspicion of MRSA (**Figure 1**).

A valid expectorated sputum sample for microbiologic processing requires more than 25 polymorphonuclear cells and less than 10 epithelial squamous cells per high-power (×1000) microscopic field and should be obtained whenever possible, especially in the group of patients mentioned earlier. However, the collection of pretreatment expectorated sputum should not delay the initiation of antibiotic administration. A respiratory sample (endotracheal aspiration or bronchoscopically obtained) is recommended for patients intubated for severe CAP in settings where obtaining a lower respiratory sample is feasible.

The urinary antigen test for *S. pneumoniae* and *Legionella pneumophila* is a rapid tool that is able to detect a pathogen in adults with reasonable accuracy even after antibiotic therapy has been started (File, 2003). For *S. pneumoniae*, studies in adults have shown a sensitivity of 50–80% and a specificity of over 90%. For *Legionella*, all the assays available detect only *L. pneumophila* serogroup 1, which accounts for 80–95% of community-acquired cases of Legionnaire's disease and has a sensitivity ranging from 70% to 90% and a specificity of nearly 99%.

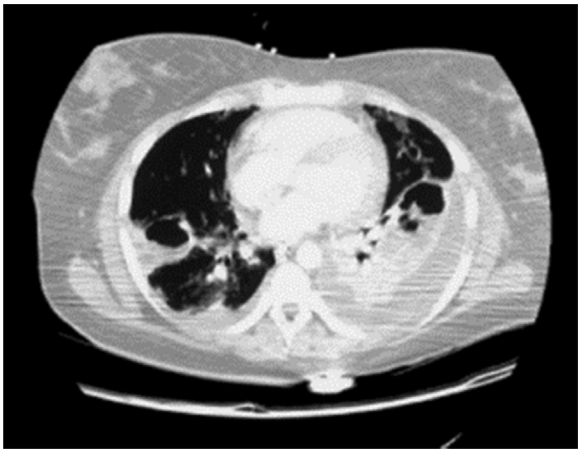

Figure 1 Necrotizing pneumonia on chest CT showing multiple bilateral nodules and cavitation, lower left lobe consolidation, and pleural effusion in a patient with methicillin-resistant *Staphylococcus aureus*.

Treatment

WHO recommendations for antimicrobial therapy for adults are based on the Integrated Management of Adolescent and Adult Illness (IMAI) (WHO, 2009). At lower levels of the health system, adolescents and adults with severe pneumonia (defined as very fast breathing, temperature ≥39 °C, pulse ≥120, lethargy, unable to walk unassisted, uncomfortable lying down, or severe chest pain), an initial dose of intramuscular ceftriaxone or ampicillin plus gentamicin should be administered; if both options are not available, chloramphenicol is the recommended second line agent. HIV-positive patients with 'adult danger signs' (e.g., very fast breathing or inability to walk unassisted) should be treated empirically for PCP with cotrimoxazole and supplemental oxygen as appropriate.

For patients with uncomplicated pneumonia (defined as two of the following: fast breathing, night sweats, or chest pain), an oral antibiotic should be administered (with the exception of pregnant women in their 2nd or 3rd trimester and HIV-positive individuals with stage IV disease or low CD4 counts who should be admitted). Recommended options include amoxicillin or cotrimoxazole or second line agents including erythromycin, azithromycin, or doxycycline.

Treatment recommendations for adults in developed country settings also depend on the level of severity of CAP. In previously healthy outpatients a macrolide (azithromycin, clarithromycin, or erythromycin) is recommended. However, the prevalence of drug-resistant *S. pneumoniae* worldwide has increased and the risk factors for β-lactam resistance have been defined: age over 65 or under 5, β-lactam treatment within the previous 3 months, alcoholism, medical comorbidities, and immunosuppressive disease or treatment; despite such findings its clinical relevance remains controversial because the outcomes of patients with 'beta-lactam resistance' (*S. pneumoniae*) usually do not result in treatment failures. Additionally, the rates of *S. pneumoniae* macrolide resistance have risen substantially in several parts of the world, contributing to an increased risk of macrolide treatment failure (Daneman et al., 2006). It is therefore prudent to treat these patients with a respiratory fluoroquinolone (levofloxacin, gatifloxacin) or β-lactam (amoxicillin 1 g tid or amoxicillin/clavulanate 2g bid or ceftriaxone) plus a macrolide in regions with recognized high-resistance rates. In non-ICU inpatients the following treatment options are recommended: a respiratory fluoroquinolone or β-lactam plus macrolide. In ICU inpatients the following regimen is the minimal treatment recommended: β-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) plus fluoroquinolone (Mandel et al., 2007).

Prevention

Vaccines against pneumococci and influenza remain the mainstay for preventing CAP. All persons 50 years and older, contact with high-risk persons and health-care workers should receive the influenza vaccine. The pneumococcal polysaccharide vaccine is recommended for people 65 years and older, the

immunocompromised, and patients with anatomic or functional asplenia and chronic disease with high-risk of pneumococcal disease (congestive heart failure, COPD, diabetes mellitus, liver disease, alcoholism). Smoking cessation should be a goal for all persons, particularly those with pneumonia because of the increased risk of invasive pneumococcal disease in immunocompetent non-elderly adults who smoke. The risk of pneumococcal disease in adults has fallen in countries that have introduced pneumococcal conjugate vaccine for infants, presumably by reducing transmission of pneumococcus from young children to adults. Antiretroviral therapy and cotrimoxazole preventive therapy reduce the risk of CAP in people living with HIV. Due to the increased recognition of atypical pertussis and the risk of adults transmitting pertussis, several countries are now advocating for the use of the acellular pertussis vaccine in adults.3.

Hospital-Acquired Pneumonia

Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 h or more after admission, which was not incubating at the time of admission. Pneumonia is a common nosocomial infection and remains the in-hospital acquired infection with the highest associated mortality. The overall incidence of HAP varies from 6 to 8.6 per 1000 admissions in high-income settings, and is substantially higher in resource-limited settings. The highest incidence is reported in the ICU, occurring in 12–29% of patients, of which 90% is ventilator-associated pneumonia (VAP). VAP-related mortality is high, between 33% and 50%. Host characteristics (advanced age and female gender), underlying diseases (higher-severity disease scores), and etiology (non-fermenting Gram-negative bacilli) are associated with a poor prognosis. Inappropriate or delayed antibiotic treatment is associated with higher mortality. The presence of HAP increases hospital stay by an average of 7–9 days per patient and accounts for a large proportion of antibiotics prescribed.

In addition to the definitions established earlier, a diverse population of patients have been found to have a spectrum of pathogens causing pneumonia that more closely resembles HAP, that is, multi-drug-resistant pathogens (Table 5). Pneumonia in this group of patients is known as 'health-care-associated pneumonia' and the diagnostic and therapeutic considerations are similar to the previously mentioned groups (HAP and VAP) (Bonten et al., 2005).

Table 5 Risk factors for multi-drug-resistant pneumonia

Antimicrobial therapy in the previous 90 days
Current hospitalization for 5 days or more
High frequency of antibiotic resistance in the community or hospital unit
Hospitalization ≥2 days in the preceding 90 days
Residence in a nursing home or extended care facility
Home infusion therapy
Chronic dialysis
Family member with multi-drug-resistant pathogen
Immunosuppressive disease and/or therapy

Adapted from Mandel, L.A., Wundernik, R.G., Anzueto, A., et al., 2007. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin. Infect. Dis. 44 (Suppl.), S27–S72.

Etiology

The time of onset of pneumonia is an important epidemiologic variable and risk factor for specific pathogens and outcomes in patients with HAP and VAP. Early-onset pneumonia is defined as occurring within the first 4 days of hospitalization. It usually has the best prognosis and is more likely to be caused by microorganisms that are already carried by the host ('community flora'): *S. pneumoniae*, *H. influenzae*, *S. aureus*, and anaerobes. 'Late-onset' pneumonia (5 days or more) is more likely to be caused by multi-drug-resistant pathogens and is associated with a poor prognosis: *Pseudomonas aeruginosa* (30%), *S. aureus* including methicillin-resistant (25%), Gram negative enteric bacilli (25%), *L. pneumophila* (5%), *S. pneumoniae* (5%), *H. influenzae* (5%), *Aspergillus* and *Candida* species (5%), and polymicrobial (30%).

Diagnosis

Clinical features that suggest nosocomial pneumonia include the presence of new and persistent pulmonary infiltrates, temperature greater than 38.3 °C or less than 36 °C, white blood cell count greater than 12 000 mm^{-3} or less than 4000 mm^{-3}, and purulent secretions. Unfortunately, many hospitalized patients present such findings for other reasons, especially intubated patients, thus making diagnosis difficult. Given the poor accuracy of an isolated clinical finding, a score of clinical findings (a 'modified clinical pulmonary infection score' – CPIS) can be used for initial decision-making. This score is based on previously mentioned findings and an oxygenation index (Table 6). If the sum is 6 or greater, a respiratory sample is justified and empirical antibiotic treatment is begun (Torres et al., 2006).

Blood cultures are recommended, as circumstances permit, when considering a diagnosis of nosocomial pneumonia. Unfortunately, similar to the situation with CAP, the sensitivity is low (10–20%) and specificity is reduced in critically ill patients who are at risk from multiple infectious foci.

The most important challenges in the management of suspected HAP are to avoid inappropriate or delayed antibiotic treatment with the higher mortality that this entails, and, on the other hand, to prevent the emergence of multi-drug-resistant microorganisms by avoiding indiscriminate antibiotic prescription. To achieve this dual purpose, when feasible, a lower respiratory tract sample should be obtained for Gram stain and culture along with *in vitro* antibiotic susceptibility testing to guide management (Bonten et al., 2005).

Table 6 Modified clinical pulmonary infection score (CPIS)

CPIS points	*0*	*1*	*2*
Tracheal secretions	Rare	Abundant	Abundant + purulent
Infiltrate on chest X-ray	None	Diffuse	Localized
Temperature (C°)	36.5–38.4	38.5–38.9	<36 to >39
WBC counts ($1000\ ml^{-1}$)	4–11	<4 to >11	<4 to >11 + >500 bands
PaO_2/FiO_2[a]	>240 or ARDS		<240 without ARDS

Abbreviations: ARDS, acute respiratory distress syndrome; WBC, white blood cell.
[a]Ratio between arterial pO_2 (mmHg) and inspired oxygen fraction.

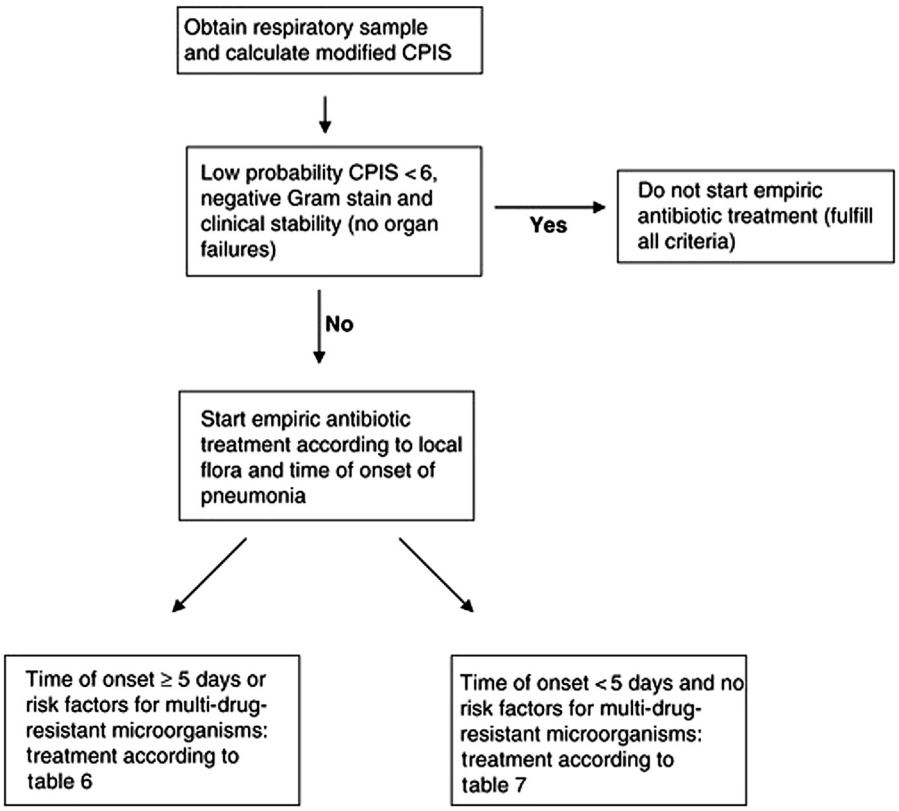

Figure 2 Summary of the management strategies for a patient with suspected hospital-acquired pneumonia.

In patients breathing spontaneously, respiratory secretions can be obtained by expectoration (with the same considerations as CAP for 'valid' sputum). The diagnostic accuracy of sputum in HAP has yet to be established. In intubated patients, lower respiratory tract cultures can be obtained via a bronchoscope or via suction, and can be cultured semiquantitatively or quantitatively with different cut-off points for discriminating 'colonization' from 'infection' according to the method. Quantitative cultures and more invasive methods increase the specificity of the diagnosis without deleterious consequences. In order to facilitate the diagnostic approach, a tracheobronchial aspirate with Gram stain and semiquantitative or quantitative culture (cut-off point to differentiate colonization from infection: $\geq 10^5$ colony forming units/mL for the quantitative method) (Canadian Critical Care Trials Group, 2006) should be obtained. **Figure 2** presents a summary of the management of these patients.

Therapy

Inappropriate therapy (where the microorganism is not sensitive to the antibiotic) is a risk factor for excess mortality, and multi-drug-resistant microorganisms are frequent pathogens commonly associated with inappropriate therapy. On the other hand, delay in starting antibiotic therapy may increase mortality, so it is important to treat the most probable etiologic pathogens promptly. Empiric therapy is more likely to be appropriate if the antibiotic selection is based on protocols designed based on local evidence. There are therapeutic guidelines available (Bonten et al., 2005) that may be adapted according to the local patterns of antibiotic resistance.

Conclusion

Pneumonia is an important cause of morbidity and mortality in both children and adults globally. Risk factors affecting incidence and outcome include extremes of age, poor nutrition, immunosuppression, environmental exposures and socioeconomic determinants. *S. pneumoniae* is the major cause of community-acquired bacterial pneumonia while Gram negative bacteria, often resistant to multiple antibiotics, are common causes of hospital-acquired pneumonia and pneumonia in immunosuppressed individuals. Diagnosis is generally clinical and management is based mainly on knowledge of likely causative pathogens as well as clinical severity and presence of known risk factors. Timely and effective antibiotic treatment and oxygen therapy if hypoxemic are critical to patient outcomes. Preventive measures range from improved nutrition and hygiene to specific vaccines that target common causes in children and adults such as the pneumococcal or influenza vaccines. Together, preventive and curative measures can have an increasingly substantial impact on mortality and morbidity as they are successfully scaled up globally.

See also: Bacterial Infections: Overview; Influenza; Influenza, Historical; Measles; Respiratory Diseases: Overview; Respiratory Infections, Acute; Respiratory Syncytial Virus; Rhinoviruses; Streptococcal Diseases.

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