Pneumonia in the developing world: Characteristic features and approach to management.

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Abstract

Community-acquired pneumonia (CAP) is a common cause of morbidity and mortality in adults worldwide, but its epidemiology varies markedly by region. Whilst in high-income countries, the predominant burden of CAP is in the elderly and those with chronic cardiovascular and pulmonary comorbidity, CAP patients in low-income settings are often working age and, in sub-Saharan Africa, frequently HIV-positive. Although region-specific aetiological data are limited, they are sufficient to highlight major trends: in high-burden settings, tuberculosis (TB) is common cause of acute CAP; Gram-negative pathogens such as *Klebsiella pneumoniae* are regionally important; HIV-associated opportunistic infections are common but difficult to diagnose. These differences in epidemiology and aetiological profile suggest modified approaches to diagnosis, severity assessment and empirical antimicrobial therapy of CAP are necessary, but tailored, individualised management approaches are constrained by limitations in the availability of radiological and laboratory diagnostic services, as well as medical expertise. The widespread introduction of the Xpert MTB/RIF platform represents a major advance for TB diagnosis, but innovations in rapid diagnostics for other opportunistic pathogens are urgently needed. Severity-assessment tools (e.g. CURB65) that are used to guide early management decisions in CAP have not been widely validated in low-income settings and locally adapted tools are required. The optimal approach to initial antimicrobial therapy choices such as the need to provide early empirical cover for atypical bacteria and TB remain poorly defined. Improvements in supportive care such as correcting hypoxaemia and intravenous fluid management represent opportunities for substantial reductions in mortality.

Keywords

Community-acquired pneumonia; developing countries; low-income countries; tuberculosis; HIV

1 Introduction

Pneumonia is a common cause of morbidity and mortality in adults worldwide. Our understanding of pneumonia is however largely based on research from high-income Western countries. In these settings, the epidemiology of disease, the spectrum of causal pathogens and key prognostic factors are well characterised and the approach to clinical management is standardised through national management guidelines. Clinicians in developing countries are left to decide whether the findings and recommendations are applicable in their local context. Is, for example, the spectrum pathogens identified in community-acquired pneumonia (CAP) patients in North America informative for selecting empirical antibacterial management in Niger? Does a CAP severity assessment tool developed in United Kingdom accurately predict outcome in Uganda? This narrative review summarises data on the epidemiology and aetiology of CAP in developing countries, where available giving priority to recent data, and considers how differences in disease within the broader healthcare context of resource limitations might impact upon the approach to diagnosis, assessment and management. The scope of the review is restricted to CAP in adults and it does not discuss the huge burden of childhood pneumonia that is present in many developing countries.

2 What is a developing country?

There is no universally accepted definition of what constitutes a developing country. The term has been used loosely and inconsistently to describe those countries with relatively poorer standards of living and economic prosperity. Until 2016, the World Bank classified all low- and middle-income countries (LMICs) as the Developing World.[1]

Whilst providing a convenient classification for analytical purposes, this 'developed' *vs.* 'developing' dichotomy is out-dated as economic growth in some developing countries accelerates rapidly and the Developing World becomes increasingly dissimilar. The World Bank now groups countries into four strata based solely on gross national income.[1] The United Nations classification incorporates measures of human capital (e.g. under-five mortality, adult literacy) as well as economic indices. It identifies 48 least developed countries (LDCs), defined as low-income countries with severe structural impediments to sustainable development.[2] The list includes all 31 low-income economies defined by the World Bank with the exception of Zimbabwe: 34 are in sub-Saharan Africa with most others in Southeast Asia (e.g. Cambodia, Bangladesh, Laos). Whilst still diverse, LDCs share many characteristics including high infant and under-five mortality, low adult life expectancy, food insecurity, incomplete access to electricity and limited health care expenditure.[2] Most LDCs lie within tropical or sub-tropical regions. The global burden of HIV both in terms of numbers of people living with HIV and new HIV infections, disproportionately affects sub-Saharan Africa.[3] Many LDCs also face a high burden of tuberculosis (TB).[4] Detailed understanding of disease epidemiology within LDCs is restricted by the paucity of available data. Therefore, whilst attempting to maximise use of data from LDCs, this review includes relevant data from lower-middle-income countries within sub-Saharan Africa and Southeast Asia. For convenience the term low-income country has been used throughout.

3 Pneumonia epidemiology: A global perspective

3.1 Incidence and risk factors

In high-income countries, increasing age is clearly the dominant risk factor for CAP. In the United States, overall incidence in adults is around 2.5 per 1000 person years, rising to 6.3 and 16.4 per 1000 person years in adults aged 65 to 79 and 80 years or older, respectively.[5] In low-income settings, population-level pneumonia incidence data are sparse, but the major burden of disease is highlighted by hospital registry data in which pneumonia is amongst the commonest reasons for adult hospitalisation.[6, 7] Interpretation of incidence data is often complicated by variations in the source (e.g. hospital registry, community surveillance), the case definition used and, if cause-specific, the extent of the microbiological evaluation. In a prospective surveillance study of adults in Central Vietnam the incidence of all-cause CAP was estimated at 0.81 per 1000 person years, rising to 6.95 per 1000 person years in those aged 75 or older.[8] By comparison, the incidence of hospitalised pneumococcal pneumonia in a study from rural Thailand was relatively low: estimated at 0.31 and 1.5 per 1000 person years in all adults and those aged 70 or over, respectively.[9] In sub-Saharan Africa, the incidence of CAP is dominated by the effect of HIV which, if untreated, is associated with a 17- to 35-fold increase in pneumococcal pneumonia.[10, 11] In a community surveillance study in rural Kenya the incidence of pneumococcal acute respiratory infection (defined as a respiratory symptom with fever, hypoxia or hospitalisation) was estimated at 5 and 67 cases per 1000 person years in HIV negative and positive individuals, respectively.[12] In CAP cohorts from the region, HIV prevalence of 50 to 75% is typical.[13-16]

Malnutrition, household crowding and exposure to indoor air-pollution from domestic combustion of biomass fuels may also contribute to the burden of pneumonia in low-

income countries.[17, 18] Risk factors for CAP that are common in many high-income countries such as smoking, COPD, congestive heart failure and cerebrovascular disease[19] presumably pertain in low-income settings and may become more prominent as average life expectancies increase.

The overall effect of alternative dominant drivers of CAP incidence acting upon markedly younger populations means that *typical* CAP patient encountered by clinicians differs markedly between high- and low-income settings. Whilst in the former, the predominant and increasing burden of hospitalised CAP is in the elderly and individuals with chronic cardiovascular or pulmonary comorbidity [20], a major burden of hospitalised CAP in many low-income countries is in working-age adults.[10]

3.2 Outcome

Globally, pneumonia is the commonest infectious cause of death, the fourth commonest cause of death overall and the second leading cause of life years lost. In 2015, the Global Burden of Disease Study estimated that lower respiratory tract infection (LRTI) caused 2 million adult deaths and an estimated 37 million years of loss life.[21] In high-income countries, nearly 90% of all LRTI deaths occur in adults over 70. By contrast, in sub-Saharan Africa, 46% of all LRTI deaths occur in children under 5 and amongst adults, 55% of deaths occur in those under 70, including 22% in adults aged 15 to 49 years. These marked differences in mortality burden may, in large part, reflect differences in population age distributions, but cause-specific, age-standardised mortality data is lacking. Amongst CAP cohorts from Africa, however, the typical trend of increasing mortality rates with advancing age seen in high-income settings is not consistently found.[14-16, 22]

Within individual CAP cohorts, the observed mortality rate varies markedly with disease severity and treatment setting, ranging from <1% to nearly 50%.[23] Mortality in recently published cohorts from LDCs were: Cambodia, 23%;[24] Central African Republic, 16%;[24] Senegal, 19%;[24] Uganda, 18% [25]. Reported mortality rates from contemporaneous cohorts in high-income countries were: Australia, 6%,[26] Germany, 14%,[20] United States, 2%.[5] Differences in patient demographics, comorbidity profile and clinical practice, particularly in terms of hospitalisation rates, make meaningful comparisons of outcome between CAP cohorts difficult. For example, in a recent US study of hospitalised CAP, inpatient mortality was 2% but 65% of patients were assessed to have low severity disease.[5] By comparison, in a national audit of 154 UK hospitals, average inpatient mortality was 17%, but the proportion with low severity disease was considerably lower at 40%.[27] Sow *et al* recruited contemporary CAP cohorts in France and Guinea using an identical case definition that excluded patients with HIV and TB: despite being considerably older (mean age 62 *vs.* 38 years) and having a higher burden of comorbid disease, mortality was not significantly higher in the French cohort (8% *vs.* 6%).[28]

In high-income countries only around half of deaths that occur in the three months following an episode of CAP are directly attributable to pneumonia.[29] The risk of death in CAP patients remains elevated for at least one year compared to individuals hospitalised for other conditions, with much of the excess mortality risk being related to decompensation of underlying cardiovascular disease. [30] Neither the nature of mortality following CAP (i.e. pneumonia related or non-pneumonia related) nor the impact of CAP on long term survival is described in low-income countries.

4 Pneumonia aetiology

Initial antimicrobial therapy for CAP is almost always empirical; selecting an appropriate regimen therefore requires knowledge of the spectrum of organisms implicated in CAP locally. The differences in climate, geography and social conditions between high-income countries in temperate regions and low-income countries in tropical regions are likely to influence the prevailing aetiological profile of CAP.[31]

4.1 Streptococcus pneumoniae

For most low-income countries, *Streptococcus pneumoniae* is amongst the commonest cause of CAP, typically identified in around one-quarter of all cases.[16, 32, 33] The true burden of disease may however be considerably higher since most aetiological studies employ only relatively insensitive diagnostic modalities (e.g. sputum Gram stain and culture).[34] Reduced *in vitro* susceptibility to both β-lactams and macrolides is widespread in *S. pneumoniae* isolates and very common in sub-Saharan Africa and Southeast Asia.[35, 36]

4.2 Atypical bacterial pathogens

There are limited data on the burden so-called atypical bacterial infections (i.e. *Legionella* spp., *Mycoplasma pneumoniae*, *Chlamydophila* spp.) in low-income countries. Recent CAP cohorts from Kenya and South Africa identified legionellosis by commercial urinary antigen test in 9% and 2% of patients, respectively.[37, 38] Geographical variations in the prevailing species and serogroups of *Legionella* may reduce the effective sensitivity of urinary antigen testing which is specific for *L. pneumophila* serogroup 1.[39] In a recent CAP cohort from rural Thailand, legionellosis was identified in 5% of patients and all cases were caused by *L. longbeachae*.[40]

The apparent burden of *Mycoplasma* and *Chlamydophila* infection depends on the diagnostic assays used. The few available African studies are largely based on serological assays (e.g. ELISA, immunofluorescence, complement fixation).[13, 16, 41] A high prevalence of *Mycoplasma pneumoniae* with high rates of macrolide resistance has been observed in some middle-income Asian countries,[32] but data from low-income countries are lacking.

4.3 Gram-negative bacteria

The burden, spectrum and relative predominance of Gram-negative pathogens in CAP varies considerably by geographic region. *Haemophilus influenzae* remains a common cause of CAP and the prevalence of β-lactam resistance is increasing.[35] In South Africa and some Asian countries *Klebsiella pneumoniae* is a common cause of severe bacteraemic CAP, in some cohorts displacing *S. pneumoniae* as the commonest bacterial cause.[42, 43] *Acinetobacter baumannii* – typically associated with noscomial pneumonia in high-income countries – has also been identified in as a cause of severe CAP in tropical settings.[44] *Burkholderia pseudomallei*, the causative agent of melioidosis, is endemic in much of Southeast Asia, and commonly presents as an acute pneumonic illness.[45]

4.4 Tuberculosis

The global burden of TB rests disproportionately heavily on low-income countries. TB incidence in the WHO African and Southeast Asian regions is 275 and 246 cases per 100,000, respectively and 86% of global TB deaths occur in these regions.[4] Whilst TB case finding programmes have largely focused on individuals with prolonged respiratory symptoms (usually cough for more than two weeks),[46] TB is a frequent

cause of acute CAP in high burden settings. In a prospective cohort from Cambodia, TB was the commonest cause of acute pneumonia amongst older children and adults, accounting for a 26% of all radiographic pneumonia and 55% of cavitatory pneumonia.[33] Similarly in sub-Saharan Africa, in CAP cohorts where systematic testing has been performed, up to 25% of all adult CAP is attributable to TB.[13, 16, 24]

4.5 Respiratory viruses

The increasing availability of sensitive molecular diagnostic tests has highlighted the high prevalence of respiratory viruses amongst CAP in high-income countries.[5, 26] Community surveillance of severe-acute respiratory illness in sub-Saharan Africa has demonstrated the high burden of circulating respiratory viral pathogens including influenza, rhinovirus, respiratory syncytial virus and adenovirus.[12] Influenza, in particular, is a common cause of hospitalised LRTI.[12] The seasonality that characterises transmission in temperate climates is often not evident in tropical settings. The weak public health and diagnostic laboratory infrastructure, and the close proximity of human populations to animal reservoirs, present in many low-income settings renders them vulnerable to the emergence and propagation of novel respiratory pathogens.

5 Pneumonia in the context of HIV

Respiratory infections are a leading cause of morbidity and mortality in patients living with HIV.[47] The sequence of pulmonary complications of HIV-infection parallels the depletion of CD4 cells.[48] Bacterial pneumonia and TB are common even when CD4 counts are well preserved whilst opportunistic infections, of which *Pneumocystis jirovecii* pneumonia (PCP) is most common, are generally only seen when CD4 counts

fall below 200 cells/mL. Most studies of HIV-associated respiratory infections have focused on specific aetiologies rather than systematically describing the full spectrum of pathogens and therefore there is no consensus on the optimal diagnostic algorithm.[47] In high-income settings, pneumonia in HIV-infected patients is usually regarded separately to CAP in other patients; management is individualised and there is often early recourse to invasive investigation. In high burden settings where up to three-quarters of all hospitalised CAP patients are HIV-positive, the challenge for local CAP guidelines is to provide appropriate recommendations for this complicated group of patients using only basic diagnostic facilities.

The profile of HIV-associated pulmonary infections varies considerably by region. [47, 49] In high-income countries, bacterial infection, in particular *Streptococcus pneumoniae*, is the commonest cause of CAP in HIV-positive adults overall, whilst PCP is the commonest opportunistic infection in those with advanced disease.[50] Globally, TB is the most important HIV-associated opportunistic infection and is the leading cause of HIV-associated mortality.[4] *Mycobacterium tuberculosis* is frequently amongst the most commonly identified organism in CAP cohorts from sub-Saharan Africa and high TB burden settings in Southeast Asia.[13, 24, 33] In certain regions of South Africa, 42% of all hospitalised HIV-positive patients with cough have microbiologically-confirmed TB.[51] Historically the burden of PCP in low-income settings was thought to be low,[52] but recent bronchoscopy studies from African and Asian centres have reported PCP prevalence amongst HIV-infected patients with pneumonia of 18 to 44%.[22, 53, 54]

Other less common causes of pneumonia may be regionally important. Invasive nontyphoidal Salmonella infection is the commonest causes of bacteraemic illness in

HIV-positive patients in sub-Saharan Africa and up to 10% present with an apparent pneumonic presentation.[55] Endemic fungi are common in HIV-infected patients living in high burden regions.[47] *Penicillium marneffei*, the causative agent of penicilliosis, is endemic throughout much of Southeast Asia and often presents as an acute severe pneumonic illness that is clinically indistinguishable from other causes of CAP.[31] Cryptococcosis and histoplasmosis also each account for more than 10% of acute pneumonic presentations in HIV-infected patients in endemic areas.[31, 56] Non-infective complications of HIV (e.g. pulmonary Kaposi's sarcoma) may masquerade as infections and should be consider in the differential diagnosis of acute pneumonic illnesses.[22, 47]

6 Healthcare system context

CAP management guidelines developed in high-income countries assume levels of resource in terms of the availability of drugs, equipment, laboratory diagnostics and personnel that are absent in most low-income settings.[57] In low-income countries healthcare services are typically organised in a three-tiered system consisting of community health centres, district hospitals and regional central hospitals. In community facilities - where the majority of patients are managed - initial assessment is made by first level health care workers who may, for example, not have been trained to perform chest auscultation.[58] Diagnostic tests are typically limited to point-of-care HIV and malaria antigens tests, and sputum smear microscopy for acid-fast bacilli (AFB). District hospitals are largely staffed by non-medically-qualified general multipurpose practitioners such as clinical officers or senior nurses who may lack expertise in the management of complicated immunosuppressed patients.[58] Whilst usually available, chest radiography might be delayed or deliberately restricted for

patients with clinical pneumonia who fail to respond to treatment. Specialist physician input and laboratory facilities for bacterial and mycobacterial culture and *Pneumocystis* diagnostics are often only available at regional or central hospitals.[58]

Whilst the World Health Organization (WHO) list of essential medicines includes all of the antimicrobial agents commonly used to treat CAP in high-income settings, many healthcare facilities in low-income countries – particularly at community level – experience regular and prolonged stock outs.[59] Equipment for supportive management of patients is also often lacking or deficient.[57] Fewer than half of all healthcare facilities in sub-Saharan Africa have uninterrupted access to an oxygen source and one-quarter have no access at all.[60] Even where facilities and resources exist, however, transportation costs, user fees for diagnostics or treatment and loss of earnings for carers may impose substantial financial barriers that prevent equitable access to healthcare provision.

These constraints define the scope of clinical practice in low-income settings. Clinical management guidelines concerning initial assessment, aetiological diagnostics and therapeutic options all must be adapted accordingly.[58]

7 Diagnosis and assessment

The three main components of the initial assessment of a patient presenting with suspected pneumonia are: confirmation of the diagnosis of pneumonia; assessment of disease severity; and identification of the causal pathogen. The approach taken to each of these tasks must be adapted in light of the differences in the profile of CAP and the available resources.

7.1 Defining and diagnosing pneumonia

The widely accepted diagnostic standard for pneumonia is the presence of a presumed new lung parenchymal infiltrate on a plain chest radiograph in the context of a compatible clinical presentation.[61, 62] Recent studies of computerised tomography scanning for patients presenting with suspected CAP have revealed the intrinsic limitations of plain chest radiography to accurately identify consolidation.[63] These limitations are accentuated for immunocompromised patients where the radiographic features of infection may be subtle or atypical.[64] Poor quality of film production coupled with interpretation by junior clinicians with limited radiological training may further compromise the accuracy of plain radiography.

On a practical level, chest radiography might not be immediately available in many low-income settings. Currently, WHO advocates a syndromic approach in community settings in which pneumonia is diagnosed on the basis of the combination of cough or breathing difficulties with two of fever, tachypnoea or chest pain are present.[58] The accuracy of this clinical case definition for radiographic pneumonia has not been systematically evaluated.

Thoracic ultrasound is an attractive alternative approach for pneumonia diagnosis well suited to use in resource-limited settings. Compared to conventional chest radiography, it does not require expensive radiation-proof facilities or a consistent supply of developer reagents. Portable, battery-operated devices suitable for use in community facilities with intermittent electrical power supply are available at increasingly affordable prices. With skilled operators, thoracic ultrasound has comparable specificity and superior sensitivity to chest radiography to detect lung

consolidations.[65] Following focused training, the technique can be performed by non-specialist clinicians with reasonable accuracy.[66] Preliminary data also indicate potential utility in HIV populations.[67]

7.2 Assessing disease severity

CAP management guidelines from high-income countries recommend that management decisions about the setting of patient care and initial antimicrobial choice are based on an objective assessment of disease severity made using a validated tool.[61, 62] CAP severity assessment tools in current use have almost universally been derived in populations of non-immunocompromised patients in high-income settings. It should not be assumed these tools perform accurately in CAP populations from low-income countries with very different demographic, comorbidity and aetiological profiles.

The widely used CURB65 score estimates the risk of 30-day mortality in CAP patients based on the presence of confusion, urea >7 mmol/L, respiratory rate ≥30/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤60 mmHg and age ≥65 years. The derivation cohorts from the UK, New Zealand and Netherlands, however, specifically excluded individuals with either HIV or confirmed TB.[68] CURB65 has been extensively validated in numerous high-income countries and has consistently shown good prognostic performance (area under receiving operating characteristic curve (AUROC) of 0.80).[69] Its relative simplicity compared to other tools such as the pneumonia severity index (PSI) make it attractive for use in low-income settings. However, the available studies of its accuracy in these populations yield mixed results. In a cohort of 280 HIV-infected CAP patients from South Africa, CURB65 score did not

correlate with in-hospital mortality for either all CAP overall or specifically pneumococcal pneumonia.[14] Similarly, CRB65 (the abbreviated version of CURB65 that does not require laboratory urea measurement) showed only moderate discriminate ability (AUROC: 0.65) for predicting in-patient mortality in a cohort of predominantly HIV-positive patients with clinically defined pneumonia in Malawi.[15] In a hospitalised CAP cohort from Pakistan, however, CURB65 performed accurately with an AUROC of 0.86.[70]

Several studies have attempted to derive alternative locally adapted tools. In a cohort from Malawi, Birkhamshaw *et al.* derived the SWAT-Bp score (based on male sex, wasting, inability to stand, pyrexia/hypothermia and low blood pressure) that outperformed CRB65 for the prediction of in-patient mortality.[15] In a cohort of HIV-infected patients with suspected pneumonia in Uganda, Koss *et al.* derived a tool based on tachycardia, tachypnoea, hypoxaemia and low CD4 count.[25] Whilst neither of these novel tools has been adequately validated, these studies serve to indicate that there is considerable potential to improve disease severity assessment in low-income countries by using alternative tools.

7.3 Determining microbial aetiology

7.3.1 General considerations

Initial antimicrobial therapy for CAP is almost invariably empirical. Determining the microbial aetiology of disease not only allows targeted therapy with the resultant benefits of optimised clinical efficacy and reduced promotion of antimicrobial resistance, but also provides valuable local surveillance data on the temporal trends in CAP pathogens.[61] CAP management guidelines in high-income countries recommend

that both empirical antimicrobial therapy and the extent of investigation to determine microbial aetiology are based on severity assessment.[61, 62] Patients with severe disease initially receive the broadest spectrum treatment to cover all likely pathogens and in tandem undergo the most extensive investigation to maximise the chance of later targeting therapy. In reality, however, identifying the causal pathogen in CAP is challenging: even with extensive investigation in the context of research studies it is only achieved in around 50%, and in clinical practice the proportion is much lower.[5, 26]

The resource constraints of low-income settings demand that only investigations likely to result in a direct and substantial impact on patient management will be sustained. For example, the practical clinical value of a test to confirm pneumococcal aetiology is uncertain. All empirical CAP treatment regimens include antipneumococcal treatment and in low-income settings with high HIV burden, a positive result would not necessarily remove the need for continued investigation to exclude co-infections.[71] The utility and cost effectiveness of different diagnostic modalities will also vary by region and context. Whilst blood cultures are an expensive and usually fairly insensitive diagnostic modality in CAP,[61] in a Southeast Asian setting, for example, with high rates of bacteraemic Gram-negative disease, the facility might be valuable.[33, 43] Diagnostic tests for use in community-level facilities must require minimal staff training and laboratory infrastructure to perform.[72] As a complementary strategy to strengthening diagnostics at an individual patient-level, maintaining infection surveillance programmes based in centres that can support more extensive diagnostics (e.g. research facilities), may provide additional, valuable information on local trends in prevailing pathogens to inform national treatment guidelines.

7.3.2 Tuberculosis diagnostics

Until recently, the acute diagnosis of TB relied solely on smear microscopy and chest radiography. The single-most important advance in TB diagnostics in recent years is the development of the automated Cepheid Xpert MTB/RIF platform that can identify *M. tuberculosis* in an unprocessed sputum specimen in less than 2 hours. With an overall sensitivity of 88% compared to sputum culture, it offers an incremental increase in sensitivity over smear microscopy of approximately 30%.[73] In a pragmatic clinical trial, Xpert MTB/RIF testing was used effectively by nurses in primary care healthcare facilities resulting in increased rates of same-day TB diagnosis and treatment initiation compared to a smear-microscopy approach.[74] Trials of a new battery operated platform (GeneXpert Omni) using next generation Xpert MTB/RIF Ultra cartridges with reported sensitivity approaching that of TB culture are currently underway.[75, 76]

New urine-based diagnostics may help to meet the challenge posed by patients with suspected TB who are unable to produce a sputum specimen. The TB Alere Determine TB LAM Ag is a point-of-care test assay that detects the mycobacterial cell wall glycopeptide lipoarabinomannan (LAM) in urine. Whilst overall, its sensitivity for HIV-associated TB is only moderate (44%), it does provide improved diagnostic yield over sputum smear microscopy alone and is most sensitive in patients with severe disease at greatest risk of death (e.g. highly immunocompromised, anaemia, elevated CRP).[77]

7.3.3 *Pneumocystis jirovecii* pneumonia diagnostics

Until recently, the definitive diagnosis of PCP required the microcscopic examination of bronchial lavage or induced sputum specimens for the direct visualisation of

Pneumocystis organisms.[78] The need for both bronchoscopy and an experienced microscopist precluded its use in many low-resource settings, hence the historically low-rate of reported PCP in low-income settings.[52] New molecular quantitative PCR tests have improved sensitivity such that analysis of more easily obtained upper respiratory tract specimens (e.g. oral wash, nasopharyngeal aspirate) may be sufficiently accurate.[79] Recently developed assays that detect circulating fungal cell wall components (e.g. 1-3-β-D-glucan) in serum have shown excellent sensitivity for detecting PCP in patients with HIV.[80] However neither of these two new modalities is as yet available in a format that could feasibly be applied in a resource-limited setting and new diagnostic options are urgently needed.

7.3.4 Alternative approaches to inferring aetiology

CAP guidelines from high-income settings advise that neither clinical nor radiological features are sufficiently characteristic to distinguish between pneumonia caused by *S. pneumoniae* and atypical bacterial pathogens.[61] In low-income settings with high HIV-burden, however, the pertinent clinical question is often to differentiate bacterial pneumonia from mycobacterial or *Pneumocystis* pneumonia. Clinical prediction tools based on radiological appearance (i.e. diffuse *vs.* focal infiltrates; presence of mediastinal lymphadenopathy) and clinical features (i.e. presence of hypoxaemia) have been developed and form the basis of some treatment guidelines despite not being widely validated.[54, 81] In practice there is considerable overlap in the pattern of radiological features seen in patients with PCP and bacterial pneumonia.[82] In HIV the radiographic features of TB become more variable with increasing degrees of immunocompromise.[83] Whilst standardised reporting tools and computer-aided

systems both reduce the inter-observer variability of interpretation, the inherent limitations of the modality still apply.[84, 85] Depending upon the local epidemiology, Gram-negative pathogens may be an equally likely cause of cavitatory pneumonia as TB.[33]

Inflammatory biomarkers (e.g. PCT, CRP) have been shown to distinguish bacterial from viral pathogens with reasonable accuracy in high-income settings and in children in sub-Saharan Africa. In adults with radiographic CAP, PCT levels in bacterial CAP are approximately 5 times higher that for TB and 19 times higher that for PCP.[50, 53] As yet there are no data examining the ability of inflammatory biomarkers to safely define antimicrobial therapy in Africa.

8 Antimicrobial therapy

8.1 General considerations

Antimicrobial therapy for CAP is generally defined by national or regional guidelines. In resourced-limited settings, both the cost of the drug and the broader implications of the treatment regimen in terms of the impact of dosing frequency on nursing time need to be considered. As a common indication for antimicrobials, ecological impact and likelihood of promoting antimicrobial resistance should be considered.[35] Continued efforts to improve antimicrobial stewardship are needed: a recent survey from Viet Nam found that intravenous antibiotics were used in 93% of hospitalised CAP patients regardless of the apparent severity of disease.[86] Fluoroquinolones have potent anti-tuberculous activity and in high TB-burden settings their empirical use may

lead to both delayed diagnosis of TB and an increased risk of fluoroquinolone-resistance.[87]

8.2 Severity-stratified antimicrobial selection

In high-income settings, antimicrobial selection is rationally stratified by disease severity and concordance with guidelines is associated with improved outcome.[88] In severe disease where the deleterious consequences of delayed appropriate treatment are potentially greatest, broad-spectrum therapy is used to give immediate cover for all probable pathogens including *Legionella* spp., *Staphylococcus aureus*, Gram-negative enteric bacteria and in some cases *Pseudomonas*. Adopting a similar approach in many low-income countries would present difficulties – particularly in high HIV and TB burden settings - since empirical therapy for all probable pathogens would often have to be broadened to include cover for TB, PCP and in some settings, drug resistant Gram-negative enteric bacteria and endemic mycoses. A "step-up" approach is typically adopted, whereby non-response on broad-spectrum antibacterials prompts sequential addition of other agents, such as antimycobacterials and antifungals. This avoids the routine use of complex, expensive and potentially toxic treatments, but may miss the opportunity for early gains from aggressive therapy.[89]

The WHO Integrated Management of Adolescent and Adult Illness (IMAI) guidelines were devised to provide general recommendations for disease management in low-income countries, particularly for clinicians working in community- or district-level healthcare facilities.[58] For severe pneumonia, IMAI guidelines recommend ceftriaxone plus a macrolide.[58] An aminoglycoside may be routinely added in regions with a high burden of CAP due to resistant Gram-negative pathogens.[81] For HIV-positive patients,

high dose co-trimoxazole for treatment of PCP is added for all patients,[58] although some national guidelines restrict empirical PCP treatment to patients with a suggestive chest radiograph or lack of clinical response at 48 hours.[81]

In high TB burden settings, the WHO approach to patients with severe CAP and negative AFB sputum smears is to first trial broad spectrum antibacterials and if no improvement after 3-5 days start TB treatment.[46 58] The optimal clinical indicators to define non-response are unclear. This approach misses 20% of patients with retrospectively culture-proven TB and risks delaying treatment in patients with a high risk of early death.[74]

9 Supportive management

Severe pneumonia is often complicated by sepsis – a dysregulated host response to infection resulting in organ dysfunction. The key components of sepsis management are adequate antimicrobial treatment, source control where relevant, and supportive treatment. In high-income settings, a protocolised approach is typically used in which intravenous fluids are rapidly administered to correct abnormal physiology such as low blood pressure and is associated with reduced mortality.[90] In keeping with this approach, the WHO IMAI recommends early aggressive intravenous fluids to rapidly correct abnormal physiology,[58] but the only comparative trial of fluid resuscitation approaches in sepsis in a low-income setting was stopped early due to high mortality.[91] Rapid fluid administration may be complicated by acute respiratory distress syndrome that in the absence of an intensive care unit may lead to an irretrievable deterioration.

Further clinical trials are needed to determine whether an aggressive or conservative approach to intravenous fluid administration in sepsis in these settings is preferable.

Hypoxaemia is a common complication of pneumonia and is independently associated with mortality.[25] Supplemental oxygen provision in low-income settings is inadequate: fewer than half of health care facilities in sub-Saharan Africa have uninterrupted access to an oxygen source,[60] and in those that do demand invariably outstrips supply.[92] This is further compounded by the limited availability of pulse oximetry, such that the scant oxygen resources that are present may be inappropriately used in dyspnoeic but non-hypoxaemic patients.[93] In the absence of a piped-oxygen infrastructure, oxygen concentrators are often the mainstay of oxygen provision in many low-income settings; their effectiveness for correcting hypoxaemia in acutely ill adults has not been demonstrated. Whilst the use of non-invasive ventilation in CAP is not supported in high-income countries,[94] in settings where invasive ventilation is not available it is possible it might fill a niche role.

10 Pneumonia prevention

Strategies for pneumonia prevention should to also be adapted to the local disease profile to achieve maximal benefit. In high-income countries, pneumonia prevention strategies focus predominantly on pneumococcal and influenza vaccination of high-risk groups and smoking cessation.[61] Whilst pneumococcal conjugate vaccine (PCV) is known to be effective in HIV-positive patients,[95] it remains to be seen whether the significant reductions in vaccine-serotype pneumococcal disease observed in adults in high-income countries following the introduction of universal infant immunisation with

PCV are replicated in high HIV burden settings.[96] HIV-infected adults remain an important reservoir for carriage of pneumococci even after several years of ART and apparent immune reconstitution.[97] ART, however, markedly reduces the risk of pneumonia in HIV-infected patients and early initiation improves survival.[11] The rapid roll-out of ART in sub-Saharan Africa has been a huge public health success with more than 12.1 million started on treatment,[3] but continued efforts are needed to minimise patient dropout at each stage of the care cascade from initially seeking HIV testing services to HIV diagnosis and linkage to ART programmes and then treatment initiation and continued adherence.[98] Co-trimoxazole preventative therapy continues to reduce the risk of hospitalisation and pneumonia after ART initiation.[99] Isoniazid preventative therapy also provides an additive benefit over ART, reducing incident TB cases by as much as 43% in high burden settings,[100] but to date has been widely underutilised in sub-Saharan Africa.

11 Conclusions

The approach to the assessment and management of CAP must be tailored to local settings. This review has highlighted that not only does CAP differ markedly between high- and low-income countries in terms of its epidemiology and aetiology (see Box 1), most notably with regard to the burdens of HIV and TB, but also in the healthcare system context in which it is managed. There is urgent need for improved access for basic medical equipment for supportive management and innovations in rapid diagnostics both to correctly diagnose pneumonia and to identify the aetiological agent. Further research is needed to address key knowledge gaps in disease severity

assessment and region-specific aetiological patterns to inform optimal empirical treatment strategies with the potential for major reductions in mortality (see Box 2).

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