Community-Acquired Pneumonia in Sub-Saharan Africa

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Abstract

Community-acquired pneumonia (CAP) in sub Saharan Africa is a common cause of adult hospitalisation and is associated with significant mortality. HIV prevalence in the region leads to differences in CAP epidemiology compared with most high-income settings: patients are younger, and co-infection with tuberculosis and opportunistic infections is common and difficult to diagnose. Resource limitations affect the availability of medical expertise, radiological and laboratory diagnostic services. These factors impact on key aspects of healthcare, including pathways of investigation, severity assessment and the selection of empirical antimicrobial therapy. This review summarises recent data from sub-Saharan Africa describing the burden, aetiology, risk factors and outcome of CAP. We describe the rational and context-appropriate approach to CAP diagnosis and management, including supportive therapy. Priorities for future research to inform strategies for CAP prevention and initial management are suggested.

Keywords

Community-acquired pneumonia; sub-Saharan Africa; tuberculosis; HIV

Introduction

Community-acquired pneumonia (CAP) is a common cause of morbidity and mortality in adults worldwide. Whilst the context of disease is different in high and low income countries, common questions arise, relating to prevention, antimicrobial choice, risk stratification and supportive therapy. In sub-Saharan Africa, key differences in clinical management include HIV-related co-infections (particularly tuberculosis), and limited resources with respect to healthcare workers, drugs and equipment. This review summarises recent data on the pneumonia burden, aetiology, risk factors and outcome from the region, and highlights areas for which data are scarce, and in which research is necessary.

Epidemiology

Burden

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.[1,2] In 2010, lower respiratory tract infection (LRTI) accounted for 2.8 million deaths and the loss of 115 million disability-adjusted life years.[2,3] In sub-Saharan Africa, estimates suggest 4 million episodes of pneumonia each year, resulting in 200,000 deaths.[4] Respiratory illness and infectious diseases are the commonest reason for adult hospitalisation in many countries in the region.[5,6] The annual incidence of LRTI in adults under 60 years is estimated at 10 episodes per 1000, but is several-fold higher in the elderly and in HIV infected individuals.[1]

Risk factors

In high income settings the dominant risk factors for CAP are: increasing age;[7,8] male sex;[8,9] comorbid illness, particularly COPD, congestive heart failure, cerebrovascular disease, dementia and diabetes;[10-15] and smoking.[16] These physiological and comorbid risks factors are likely to have similar associations with CAP in sub-Saharan Africa, but these risks are dwarfed by that associated with HIV infection: before antiretroviral therapy (ART), a 17 to 35 fold increase in disease[17,18] and 100 fold increase in pneumococcal bacteraemia compared with control populations.[19] Even on established ART, risks

remain elevated.[17,18] In CAP cohorts from the region, HIV prevalence of 50 to 75% is typical,[20-24] and advanced HIV infection is frequently complicated by CAP despite the widespread rollout of ART.[5]

Exposure to household air-pollution as a consequence of domestic combustion of biomass fuels for heating, lighting and cooking has been causally linked to childhood pneumonia. Adults may also be at risk from respiratory infections,[25,26] and this is the subject of current investigation.[27] Malnutrition and household crowding may further contribute to the burden of pneumonia in the region.[10,25,28] The combined effect of these risk factors mean that, in marked contrast to well-resourced settings, CAP cohorts in sub-Saharan Africa are dominated by relatively young, working age patients.[4,17,29,30]

Outcome

The mortality rate of CAP varies markedly with disease severity and treatment setting, ranging from <1% to nearly 50%.[31] Differences in patient demographics and comorbidity profile and clinical practice, particularly in terms of hospitalisation rate and intensive care referral, make direct comparison between cohorts difficult. Crude mortality rates of adults hospitalised with pneumonia in sub-Saharan Africa (7-14%) are comparable at to those reported from well-resourced settings, despite the average age of affected patients being much lower.[20,24,32-34]

CAP cohorts from sub-Saharan Africa typically report inpatient or 30-day mortality rates that may substantially underestimate total-pneumonia related mortality. In high-income countries, after apparent clinical resolution, survivors of CAP have an elevated risk of death for at least one year.[35,36] One third of hospitalised CAP patients die within one year of hospital discharge.[37] This excess mortality appears to be primarily driven by cardiovascular comorbidity.[38] There are no data on long-term mortality or symptomatic recovery following pneumonia in a sub-Saharan African setting.

Aetiology

A huge number of microorganisms, including bacterial, viral and fungal pathogens, can cause CAP. In most high income countries, the vast majority of cases are caused by one of: *Streptococcus pneumoniae*; *Haemophilus influenzae; Mycoplasma pneumoniae; Chlamydophila pneumoniae*; respiratory viruses; *Legionella pneumophila; Staphylococcus aureus*; *Pseudomonas aeruginosa*; Gram-

negative enteric bacilli. There are important geographical variations in the aetiological profile of CAP. In areas of high incidence, *Mycobacterium tuberculosis* is common cause of acute CAP.[24,39,40] In South Africa and many regions in Asia, hypervirulent strains of *Klebsiella pneumoniae* are frequent isolates in severe CAP.[41,42] *Burkholderia pseudomalleii*, the causative agent of melioidosis, is endemic in certain regions in South-East Asia and may present as an acute pneumonic illness.[43,44] In sub-Saharan Africa the array of potential pathogens is broadened further still by high rates of HIV co-infection.[30]

Bacterial pathogens

Streptococcus pneumoniae

Streptococcus pneumoniae is consistently the most commonly identified pathogen amongst hospitalised patients with CAP globally, and in sub-Saharan Africa where it accounts for at least one-quarter of all cases.[45] Relatively insensitive diagnostic tests, compounded by high rates of prior antimicrobial use are likely to lead to substantial underestimation.[46] Scott *et al.* found evidence of pneumococcal infection in 46% of a large Kenyan CAP cohort using blood and urine antigen testing and culture of percutaneous transthoracic lung aspirates in addition to standard techniques.[24] Using the density of pneumococcal nasopharyngeal colonisation as a marker of pneumococcal disease in a South African CAP cohort increased diagnostic rates from 27% to 53%.[47]

Gram-negative bacteria

Gram-negative pathogens represent a significant minority of CAP in sub-Saharan Africa. *Klebsiella pneumoniae* – typically implicated as a cause of hospital-acquired pneumonia in well-resourced setting – is frequently seen in hospitalised CAP patients, accounting for up to 19% of CAP in high dependency settings in South Africa.[21,48-53]

Invasive *Salmonella* infection is the commonest cause of bacteraemic illness in many sub-Saharan African settings.[54] HIV-positive patients are susceptible to invasive infection with non-typhoidal salmonella species (*S. enteritidis* and *S. typhimurium*). CAP studies have reported *Salmonella* infections in 2-10% of patients.[24,55] It is unclear whether the pneumonic illness represents primary causation, or co-infection with an undetected co-pathogen,[56] although the therapeutic need for broader spectrum antibiotics is the same.

Atypical bacteria

The burden of adult pneumonia in sub-Saharan Africa caused by so-called atypical bacterial infections (including *Legionella* spp., *Mycoplasma pneumoniae* and *Chlamydophila* spp.) is poorly described. For *Mycoplasma* and *Chlamydophila*, the few available studies are largely based on serological assays using varying methods (e.g. ELISA, immunofluorescence, complement fixation) with incomplete sampling frames;[21,24,50,57,58] estimated prevalence ranged from 0-9% and 0-21%, respectively. For *Legionella*, studies that have in addition used a urinary antigen assay have estimated prevalence at 2-9%.[59,60] Under-ascertainment is possible however since the urinary antigen assay only reliably detects *L. pneumophila* serogroup 1 and considerable geographical variation in the predominance of particular *Legionella* species and serogroups has been reported.[61,62]

Influenza and other respiratory viruses

There are limited data from dedicated CAP cohorts describing the burden of viral pathogens in hospitalised patients using modern molecular diagnostic tests. Using serological testing Scott *et al.* identified a viral aetiology in 6% of a cohort of Kenyan patients, the majority of which were cases of influenza.[24] In a cohort of 51 Malawian patients with severe pneumonia, virus was identified by a multiplex PCR assay of bronchoalveolar lavage (BAL) specimens in 6% as the sole - and presumed causal - pathogen and in 16% as co-infection typically with bacterial or *Pneumocystis* pneumonia.[53] By comparison, a recent US CAP cohort found one or more viruses in 23% of patients, most frequently rhinovirus (9%), influenza (6%) and human metapneumovirus (4%).[63] Large scale community severe-acute respiratory illness (SARI) surveillance studies in sub-Saharan Africa have similarly highlighted a potentially much greater burden of circulating respiratory viral pathogens including influenza, rhinovirus, respiratory syncytial virus, human metapneumovirus and adenovirus.[64,65]

Tuberculosis

Traditional teaching has attuned clinicians to suspecting pulmonary tuberculosis (TB) in patients with prolonged symptoms - typically a cough for longer than 2 weeks - and this group has historically been the focus of TB diagnostic services in high burden settings.[66] In sub-Saharan Africa, TB is consistently reported as a cause of illness in patients presenting with CAP symptoms, signs and radiology, and with shorter duration of illness.[24,67] Overall *M. tuberculosis* is identified in 9 to 25% of CAP, with rates in

HIV-infected patients typically higher.[21,24,53,68] Microbiological testing of samples from bronchoscopy has identified similar proportions: CAP cohorts from Central African Republic, Senegal, South Africa and Malawi estimate rates from 13% to 29%.[21,51,53,68] In HIV co-infection, using rigorous TB diagnostic algorithms with intensive specimen collection, up to one-third of all HIV-positive acute medical in-patients are found to have TB in South Africa, Zambia and Malawi.[69-71] In post mortem series of HIV-infected medical in-patients as many as 62% have TB.[72]

Pneumocystis jirovecii pneumonia

In US and European cohorts, *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia (PCP) is the commonest opportunistic infection in individuals with advanced HIV.[73,74] Historically, the reported burden of HIV-related PCP in sub-Saharan Africa has been considerably lower,[75-77] although the causative protozoan is ubiquitous. These lower rates may be partly attributable to early mortality from more rapidly progressive infections. However, ascertainment bias is likely in the absence of sensitive diagnostic tests.[78,79] Difficulties of specimen collection from bronchoscopy are also likely to cause selection bias due to under-sampling of critically unwell patients.[79] When performed, bronchoscopy studies from African centres have demonstrated a considerable burden of PCP amongst HIV-infected patients with features of respiratory infection.[53,80-82] Amongst patients with CAP estimates of the burden of PCP vary considerably ranging from 2% in general hospital inpatient cohorts to 27% amongst patients admitted to high dependency unit.[51,53,68,83]

Approach to clinical assessment

Diagnosis

A number of conventions frequently define studies of respiratory infection: 1) the standardised definition of pneumonia typically requires radiological evidence of an infiltrate (e.g. on plain posteroanterior chest radiograph); 2) pneumonia is distinguished from acute bronchitis and infective exacerbations of COPD, where chest X-ray changes are not required for diagnosis; 3) pneumonia in immunocompromised patients is generally considered separately because of the broader spectrum of pathogens; 4) TB is differentiated from CAP rather than regarded as its cause. These conventions have

led CAP management guidelines in high income countries to restrict their scope to tightly defined presentations of CAP which do not fully represent the spectrum of disease elsewhere. This diagnostic framework for pneumonia needs to be re-considered in sub-Saharan African settings where the majority of CAP cases occur in HIV-positive (i.e. immunocompromised) individuals. Here, radiographic changes for certain pathogens may be atypical (e.g. the classical upper zone infiltration of tuberculosis is found less frequently).[84] Opportunistic pathogens such as *Pneumocystis* often have only subtle changes on plain chest radiography[85] which is inconsistently interpreted.[86,87] In many settings, chest radiography is not immediately available or these resources might be deliberately restricted for those failing to respond to treatment.[88,89] In community settings, the first level healthcare workers or lay-providers may not have been trained to perform chest auscultation.[88] World Health Organization (WHO) treatment guidelines for resource-limited settings therefore use a clinical definition of pneumonia of cough associated with two of fever/night sweats, tachypnoea or chest pain.[88,89]

Severity assessment

CAP guidelines recommend that initial management decisions, such as site of care and choice of antimicrobial, are guided by an objective assessment of disease severity made using a validated tool.[90,91] More than a dozen CAP severity assessment tools have been developed, but almost universally derive from patients in well-resourced settings without immunocompromise.[92,93] Given differences in demographics, comorbidity profile, and disease aetiology, extrapolation beyond these cohorts should be cautioned. Relevant data from sub-Saharan Africa are limited. In a small cohort of 88 patients from Nigeria, 30-day mortality rose with CURB65 and at a threshold score of 3 or more, reported sensitivity and specificity were 80% and 97%, respectively.[94] In a well-characterised cohort of 280 HIV-infected patients with radiographic CAP from South Africa, Albrich *et al.* found CURB65 was not a useful discriminator of in-hospital mortality for either all CAP patients or those with confirmed pneumococcal pneumonia.[22] Similarly, CRB65 (the abbreviated version of CURB65 that does not require laboratory urea measurement) showed only moderate discriminative capability (i.e. CRB65 ≥2: sensitivity 36%; specificity 81%; positive predictive value 30%; negative predictive value

85%; AUROC 0.65) for predicting inpatient mortality in a cohort of patients with clinically defined pneumonia from Malawi.

Several authors have attempted to derive tools better suited for use in sub-Saharan African populations. Birkhamshaw *et al.* reported that a novel severity score, termed SWAT-Bp, based on the presence of male sex, wasting, inability to stand, pyrexia/hypothermia and low blood pressure outperformed CRB65 in predicting in-hospital mortality (SWAT-Bp ≥3: sensitivity 84%; specificity 77%; positive predictive value 45%; negative predictive value 96%; AUROC 0.65).[23] In a cohort of HIV-infected patients from Uganda with cough for greater than two weeks and clinically suspected pneumonia, Koss *et al.* suggested an alternative severity-assessment tool based on tachycardia, tachypnoea, hypoxaemia and low CD4 count.[95] These small studies demonstrate that there is considerable potential for improving severity assessment, and that tools should be revalidated when adopted in new settings.

Establishing aetiological diagnosis

General considerations

Aetiological confirmation of CAP is challenging. Even in a recent prospective cohort study in the US that used extensive testing and multiple assays, pathogens where identified in only 38%.[63] In routine clinical practice the proportion is much lower.[96] In well-resourced settings, CAP guidelines recommend that selection of empirical antimicrobial therapy is based on severity assessment, and modified by risk factors for resistant organisms.[90,91,97] Concordance with antimicrobial treatment guidelines is associated with improved outcome,[98] and the use of antigen testing (for *S. pneumonia*e and *L. pneumophila)* for early targeted (pathogen-directed) antimicrobial treatment has so far failed to demonstrate significant benefit to patient management or clinical outcome.[99] In many sub-Saharan African settings, however, to give adequate antimicrobial cover for all likely pathogens empirical CAP therapy would often have to include treatment for both TB and PCP. A pathogen-directed approach, at least to the level of distinguishing bacterial pneumonia from TB and PCP is likely to be beneficial.[100] However, the laboratory infrastructure to support diagnostic microbiological in many sub-Saharan African settings is weak or limited.[89] Bacteriological culture or molecular techniques that form the mainstay of CAP diagnostics in well-resourced settings are often lacking and may not be sustainable

outside of referral hospital or research laboratories: point-of-care or rapid diagnostic tests have great potential in these settings.

Streptococcus pneumoniae

The Alere BinaxNOW *Streptococcus pneumoniae* antigen card is a lateral flow assay that detects pneumococcal antigens in urine requiring minimal laboratory infrastructure.[101] In adults in well-resourced settings, it may be used to diagnose pneumococcal CAP with reasonable accuracy (overall sensitivity and specificity 74% and 97%, respectively), but in children lacks specificity due to high rates of pneumococcal nasopharyngeal colonisation.[102,103] In low-resource sub-Saharan African settings, pneumococcal nasopharyngeal colonisation is common in adults also. The limited available data indicate that specificity of BinaxNOW *S. pneumoniae* assay in adults is not affected by nasopharyngeal colonisation,[104] but the impact of concurrent HIV infection and pneumococcal colonisation has not been analysed. When used in CAP studies in sub-Saharan Africa, it increases the proportion of cases attributable to *S. pneumonia*.[47,105] The practical value of a test that confirms pneumococcal aetiology in this setting is uncertain: recommended empirical CAP therapy always includes anti-pneumococcal cover and in this setting a positive result would not obviate the need to exclude co-infections such as TB.[106,107]

Tuberculosis

Until recently, smear microscopy and chest radiography were the mainstay investigations for the acute diagnosis of TB but both had poor sensitivity, particularly in concurrent HIV infection.[108,109] The automated Cepheid Xpert MTB/RIF platform can identify *Mycobacterium tuberculosis* and common rifampicin resistance genotypes from unprocessed sputum specimens in less than two hours.[110] Since 2010, this platform has been rolled-out to many low- and middle-income countries where it is frequently the central pillar of TB diagnostics.[111] Compared to the gold-standard diagnostic test of sputum culture, Xpert MTB/RIF has an overall sensitivity of 88% and specificity of 98%.[112] In HIV-associated TB, the sensitivity of Xpert MTB/RIF is estimated at 84%.[110]

The recently developed Alere Determine TB LAM Ag is a point-of-care test assay that detects the mycobacterial cell wall glycopeptide lipoarabinomannan (LAM) in urine, and provides an incremental increase in sensitivity over sputum smear microscopy alone.[113,114] Diagnostic yield is higher in the

most highly immunocompromised patients and those with features of severe disease (e.g. anaemia, elevated CRP) at greatest risk of death, where it probably represents diagnosis of disseminated TB disease.[115-117] Use of the test to guide initiation of anti-tuberculous is associated with a 17% relative reduction in mortality compared to standard diagnostic strategy.[118]

Pneumocystis jirovecii

Definitive diagnosis of PCP relies on detection of *Pneumocystis* either by microscopy or molecular techniques in bronchoalveolar lavage fluid or induced sputum. The current availability of PCR assays with improved sensitivity may permit the use of more readily obtained non-invasive specimens such as expectorated sputum[119] or nasopharyngeal aspirates,[120] where *Pneumocystis* organisms are present in lower concentrations. Although there is currently no analogue of the Xpert MTB/RIF for PCP that permits rapid detection of DNA in unprocessed clinical specimens. An alternative strategy is based on detection of the fungal cell wall component 1-3-β-D-glucan in serum.[121] Several studies have indicated that serum 1-3-β-D-glucan has excellent (>95%) sensitivity and reasonable specificity (84-86%) for detecting PCP in patients with both HIV and other forms of immunocompromise.[122,123] However, currently available assays are based on photometric methods that require considerable manual processing and dedicated equipment that would preclude use in many low-resource setting clinical laboratories.

Alternative approaches

In the absence of a confirmed microbiological diagnosis, radiographic and laboratory indices are sometimes used to infer aetiology and guide therapy in routine clinical practice.[124] There are well described associations of aetiology with radiographic appearance: upper lobe consolidation, cavitation, unilateral pleural effusion and lymphadenopathy are associated with TB;[125] diffuse bilateral fine or ground glass shadowing is typical of PCP.[81,126] However, these associations are not strong enough to discriminate to impact clinical practice and chest radiograph features vary with immune status in HIV-infected patients.[84]

In HIV-positive patients, the sequence of pulmonary complications parallels the depletion of CD4 cells; bacterial pneumonia and TB become more common from early in the disease course when CD4 counts are well-preserved, whilst PCP and other opportunistic pathogens are generally only seen

when CD4 counts fall below 200 cells/mL.[30,127] However, in acute illness, CD4 counts may fall substantially,[128,129] and therefore cannot accurately infer the stage of HIV illness or inform the likely spectrum of pathogens during an episode of pneumonia.

Inflammatory biomarkers such as procalcitonin (PCT) or C-reactive protein (CRP) are increasingly being used in well-resourced settings to guide the management of respiratory infection.[130] Combining PCT or CRP measurements with clinical assessment improves accuracy for diagnosing radiographic CAP.[131] Total antibacterial exposure and median duration of therapy may be safely reduced without compromising clinical outcomes using PCT-guided algorithms.[132] In a sub-Saharan African setting, limited data suggest that PCT may be useful in distinguishing bacterial pneumonia from other causes. PCT levels in bacterial CAP are approximately 5 times higher that for TB and 19 times higher that for PCP.[73,83,133]

Antimicrobial therapy

General considerations

Initial antimicrobial therapy in CAP is almost always empirical, and should be based on severity.[90,91,97] In severe CAP, broad-spectrum antimicrobials are used to give immediate cover for all probable pathogens. These include *Staphylococcus aureus*, Gram-negative enteric bacteria, *Legionella pneumophila* and in some cases *Pseudomonas aeruginosa*. Extended microbiological investigations are promoted as a method of early rationalisation of treatment.[130]

In high-income countries, mild disease is usually treated with narrower spectrum agents, although there is significant variation in recommendations for cover of “atypical” organisms. Using this approach, therapy is broadened in the event of clinical failure.

Adopting similar approaches in many sub-Saharan African settings presents difficulties. By default, a “step-up” approach is taken where by clinical non-response on broad-spectrum antibacterials results in sequential addition of other agents, such as antimycobacterials and antifungals. This limits the use of expensive and complex treatment, but may miss the opportunity for early gains from aggressive therapy.

WHO and African treatment guidelines

The WHO Integrated Management of Adolescent and Adult Illness (IMAI) guidelines were devised to provide general recommendations for disease management in resource-limited settings and improve healthcare at facility level.[88,89]

For those with severe pneumonia, IMAI guidelines recommend ceftriaxone (or ampicillin and gentamicin) plus a macrolide.[89] South African guidelines suggest the use of gentamicin (or another aminoglycoside) in view of the high frequency of CAP due to Gram-negative bacilli, especially *Klebsiella.*[124] In high TB burden settings, the WHO approach to severe CAP is to first trial broad spectrum antibacterials, and introduce empirical TB treatment at 3 days where improvement is not evident.[134] This approach misses 20% of patients with retrospectively culture-proven TB and risks delaying treatment in a group of patients with a high risk of early death.[135] Early empirical TB for high-risk patients is the focus of current research.[136,137]

For HIV-positive patients, IMAI guidelines recommend that high dose co-trimoxazole for treatment of PCP is added for all patients with severe pneumonia.[89] South African guidelines modify this recommendation, advising empirical PCP treatment where the chest radiograph is suggestive (i.e. bilateral infiltrates).[124] Antimicrobial guidelines in other sub-Saharan African countries also differ. In Malawi an initial regimen of ceftriaxone or a combination of penicillin plus chloramphenicol is recommended. A macrolide, gentamicin and consideration of PCP treatment are advised for patients not improving at 48 hours.[138]

For non-severe pneumonia, IMAI recommends monotherapy with oral amoxicillin. South African guidelines differ, recommending that atypical cover in the form of a macrolide or doxycycline is also used for all patients. For elderly patients or those with comorbid illness, these recommend that amoxicillin is replaced by co-amoxiclav or a cephalosporin to provide broader antimicrobial cover.[124] In South African guidelines, macrolide monotherapy is avoided because of concerns about resistance in *S. pneumoniae.*[139] In view of their potent anti-tuberculous activity, fluoroquinolones should be used with caution in high TB-burden settings, since empirical use of may lead to delayed diagnosis of TB and a higher risk of subsequently developing fluoroquinolone-resistant TB.[140,141]

Supportive management

Supportive therapy for pneumonia in adults in sub-Saharan Africa is driven by consensus guidelines.

Intravenous fluids

Respiratory infection accounts for more than half of sepsis.[142] For patients manifesting sepsis in high resource settings, early goal directed therapy (EGDT) has been the dominant recent theme. Aggressive fluid management and goal-orientated therapy have become accepted practice due to positive findings from early landmark studies,[143] and are supported by meta-analysis showing mortality reductions (OR 0.64; 95% CI: 0.43-0.96).[144]

Data from sub-Saharan Africa on early supportive management of sepsis are scarce. In a "before and after" Ugandan study of adults, headline mortality reduced from 45 to 33% over 2 years after the employment of dedicated medical officers to oversee early sepsis treatment. Median intravenous fluid administered in the first 6 hours increased from 500ml to 3000ml[145] but there was no dose response above 1000ml. In a Zambian randomised controlled trial of a simplified EGDT protocol, the volume of intravenous fluid administered was greater in the intervention group (2800 mL *vs.* 1600 mL), but this group encompassed people with normal blood pressure.[146] This trial was stopped early because of high overall in-hospital mortality (62.4%), particularly in patients with hypoxaemic respiratory failure.

The paediatric FEAST study similarly demonstrated higher mortality in septic children treated with aggressive fluid resuscitation.[147] Bolus fluids were associated with early improvements in shock, but later increased risks of cardiovascular collapse and mortality.[148]

Recommendations for fluid therapy in adults in sub-Saharan Africa are therefore fraught with uncertainty. Maintenance fluids should be prescribed to those who cannot maintain oral intake. Boluses totalling more than 20ml/kg should be used with caution, particularly in settings lacking critical care facilities.

Oxygen

Hypoxia is an independent predictor of mortality in adults with sepsis and pneumonia.[95,149] During admission to a hospital in Kigali, Rwanda, 12% required oxygen, as defined by resting saturations

(SpO_2) of less than 90% on air) at some point.[150] Of those whose SpO_2 did not increase with therapy, mortality was increased, but small numbers made the confidence margins wide.

Programmatic interventions in children based on improved oxygen supply using concentrators have been associated with a 35% reduction in mortality (in Papua New Guinea),[151] and paediatric studies of oxygen therapy for pneumonia are numerous, although commonly have no comparison or control group.[152] The randomised controlled COAST trial (ISRCTN15622505) is currently investigating, in Africa, high flow oxygen compared with standard therapy.

In the absence of randomised controlled trial evidence in adults, British Thoracic Society guidelines suggest to maintain SpO_2 between 94% and 98%.[153] Oxygen supply and delivery infrastructure is inadequate in many healthcare facilities across sub-Saharan Africa.[154] In the absence of piped oxygen infrastructure, low-flow (around 5 L/min) mains-powered oxygen concentrators are the mainstay of oxygen provision, although cylinders may be preferable in specific situations.[155] Descriptions of performance and robustness of oxygen concentrator models have been published,[156] but data on their effectiveness for correcting hypoxia in acutely ill adults or improving outcomes is lacking.

Ventilatory support

The lack of adequately staffed critical care units means that invasive positive pressure ventilation (IPPV) is confined mostly to regional centres in Africa. There is a lack of evidence surrounding the cost-effectiveness of highly resource-intensive therapies such as IPPV. Meta-analysis of non-invasive ventilation in pneumonia in high resource settings has not demonstrated any mortality benefit, but did show a reduction in intubation rates.[157]

Steroids

Meta-analysis of trials of adjunct corticosteroids in CAP has not shown any mortality benefit, but demonstrated a reduction in hospital stays and ARDS rates in high resource settings.[158] As a result of corticosteroid treatment, the largest trial (from Switzerland) reported an 8% absolute increase in the number of patients requiring insulin treatment for hyperglycaemia.[159] In resource limited settings with high rates of HIV, corticosteroids may also be indicated for severe PCP. However, there is no

evidence supporting their use in pneumonia, and only one trial investigated this, in the setting of ITU in South Africa.[160]

Prevention

The opportunities for CAP prevention in sub-Saharan Africa are substantial. Antiretroviral therapy (ART) markedly reduces the risk of pneumonia and early initiation improves survival.[161,162] The rapid roll-out of ART in sub-Saharan Africa has been a huge public health success with more than 9.1 million started on treatment,[163] but the challenges of timely HIV diagnosis and prompt initiation of ART remain. Average CD4 cell counts at presentation and ART initiation are low at 251 and 152 cells/mm^3 respectively.[164] The recent shift of WHO policy to universal ART for all HIV-infected patients regardless of CD4 count may be beneficial.[165]

Co-trimoxazole preventative therapy (CPT) continues to reduce the risk of hospitalisation and pneumonia after ART initiation.[166] Isoniazid preventative therapy (IPT) also provides an additive benefit over ART, reducing incident TB cases by as much as 43% in high burden settings,[167,168] but to date has been widely underutilised in sub-Saharan Africa. A single fixed-dose pill combining both co-trimoxazole and isoniazid is currently in development.[169]

The 13-valent pneumococcal conjugate vaccine (PCV) has proven effectiveness to protect against invasive pneumococcal disease (IPD) in HIV-infected patients[170] and pneumococcal pneumonia in elderly adults.[171] In the US and UK, infant vaccination has indirect positive effects on disease in adult populations.[172,173] Universal infant PCV has recently been introduced in many countries across sub-Saharan Africa. The extent of indirect effects, particularly in HIV-infected adults, is as yet unclear and needs careful study to determine whether the burden of residual vaccine-serotype disease warrants additional targeted vaccination programmes.

Research priorities

Epidemiology

The burden of pneumococcal disease and TB is consistently demonstrated in CAP cohorts from across sub-Saharan Africa. Rates of PCP, however, are much more variably estimated: 27% in critically unwell patients in Malawi,[53] 39% in those with non-responsive pulmonary symptoms attending for bronchoscopy in Uganda[82] whilst other, less selected, cohorts have much lower rates.[75,76,174] With the advent of sensitive molecular diagnostic tests that can be performed on nasopharyngeal aspirates specimens that may be safely obtained in even hypoxic patients, the true burden of PCP in acute CAP cohorts should be definitively established.[120,175] Further aetiological studies to define the burden of atypical bacterial infection (i.e. *Legionella* spp., *Mycoplasma pneumoniae*, *Chlamydophila* spp.) and hence the need for atypical antimicrobial cover in empirical CAP therapy should also be undertaken. With improved molecular-based diagnostics, increasing proportions of patients are recognised to have infection with respiratory viruses.[63] Their relevance to the aetiology of CAP, both as primary cause and co-pathogen with other organisms, should be investigated.

Few centres are able to offer diagnostic microbiology services, but there is ample evidence from those that do that antimicrobial resistance is a key issue [52,139,176]. Surveillance studies are warranted to determine resistance patterns, and to direct national antibiotic recommendations.

Early presentation and pre-hospital care

Maximising recognition of illness at the individual level is the key to all healthcare delivery. For children with pneumonia, guardian awareness of the features of illness is low.[177] However, long-established community level interventions, such as Integrated Management of Childhood Illness (IMCI), enhance many aspects of pre-hospital treatment and probably reduce mortality from acute illness.[178,179]

In adult pneumonia, care seeking is geographically variable, and within one active surveillance programme in rural Thailand, adults were reported to have lower rates of hospital attendance than children.[180] The IMAI guidelines described above are increasingly forming the basis for primary care delivery in resource-limited settings, although evidence of efficacy is mostly unpublished.[181] IMAI, and other national programmes for triage should be evaluated for their protocols to diagnose pneumonia, and to identify those patients who need onward referral.

Initial triage and treatment

Triage systems have been associated with decreased mortality in unselected children in sub-Saharan Africa.[182] Analogous systems for adults have been developed for low-resource settings (e.g. Cape Triage Score[183]), but even these presuppose significant medical knowledge. Simpler, perhaps non-compound measures of physiological derangement might be effective. The benefit of formalising systems for patient flow, and prioritising the critically unwell should be the subject of further implementation research.

Diagnostics

In skilled hands in the emergency department, thoracic ultrasound has a high accuracy for pneumonia diagnosis (94% sensitivity and 96% specificity).[184] Protocols for interpretation have not been validated in resource-limited settings, although ultrasound is becoming increasingly available and has been shown to be useful in diagnosing ARDS in a Rwandan ICU study.[185] However, there are minimal data on how chest ultrasound is being otherwise used. The potential benefits, including cost-effectiveness analysis of training should be undertaken.

Antimicrobial chemotherapy

The optimal antimicrobial regimen for the treatment of CAP in the high TB burden, HIV-prevalent settings that characterise much of sub-Saharan Africa is unknown. As for CAP cohorts across the world, selection of the initial regimen will almost always be empirical and there are several key therapeutic questions. Firstly, given the high prevalence of TB in patients presenting clinically as acute CAP,[21,24,53,67] there is potential for earlier TB treatment to improve outcomes. Strategies of empirical TB treatment in groups at high risk of early mortality compared to the systematic use of near-patient diagnostics in pneumonia patients should be further evaluated. Secondly, for HIV-positive patients who are critically unwell, co-initiation of PCP and antibacterial treatment in individuals should be evaluated. New highly sensitive molecular tests discussed above could be trialled in tandem as a "rule-out" diagnostic and basis for de-escalation of therapy.[120,175] Thirdly, the routine use of macrolides for the treatment of severe CAP both for their activity against atypical bacteria and as dual

therapy in pneumococcal pneumonia should be evaluated. The impact of any antimicrobial intervention on rates of antimicrobial resistance should be closely monitored.

Adjuvant treatment

Fluids

Clinical measurement of fluid balance in critical care settings is subjective and difficult.[146] Consensus guidelines on sepsis have been limited by a lack of objective definition of "adequate fluid resuscitation." Careful analysis of cardiovascular and respiratory outcomes of fluid resuscitation should be undertaken. In the light of FEAST,[147] an analogous trial of conservative *vs.* bolus fluid therapy in adults where there are no intensive care unit (ICU) facilities may be warranted.

Oxygen

Pragmatic recommendations from the WHO to use oxygen concentrators are based on the cost benefit over the most available alternative – cylinders.[186] Step-wedge interventions of oxygen concentrators to healthcare centre who currently have insufficient oxygen capacity would be very welcome. These could incorporate other health systems improvements, and could directly inform policy.

Non-invasive ventilation

Non-invasive ventilation (NIV) has no established mortality benefit in CAP in any setting.[187] However, endpoints in these trials are determined in the contexts of functioning ICU (with intubation as a "treatment failure"). Where IPPV is not available, NIV might find a niche, but the authors are not aware of any centres providing this.

Follow-up

Little is known of longer-term outcomes following CAP in resource-limited settings, or if the adverse cardiovascular outcomes seen in Western cohorts are applicable: this should be examined given the higher rates of cardiovascular disease in HIV.[188,189]

Conclusion

Community acquired pneumonia in sub-Saharan Africa has strong similarities in disease aetiology and treatment to high-income countries. This review has highlighted areas of divergence, including high rates of immunocompromised, low rates of clinical and laboratory support for patient management, investigation, and an absence of region-specific information on aetiology and the optimal treatment regime. International guidelines, such as IMAI, have been consciously devised with these difficulties in mind. The knowledge gaps offer potential for major gains in mortality, and research should be tailored to regional populations and regional resource limitations.

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