

Bacterial aetiology and outcome in children with severe pneumonia in Uganda

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Abstract

Background: Pneumonia is a major cause of morbidity and mortality in the 'under-5s' and in Uganda accounts for 10–30% of childhood deaths. Antibiotic resistance is increasing.

Objective: To describe the bacterial aetiology, antimicrobial sensitivity and outcome of severe pneumonia among children aged 2–59 months admitted to the Acute Care Unit, Mulago Hospital, Uganda.

Methods: A total of 157 children aged 2–59 months with symptoms of severe pneumonia according to WHO guidelines were recruited over a 4-month period in 2005/2006. Blood and induced sputum were obtained for culture, and chest radiographs were undertaken. Children were clinically classified as having severe or very severe pneumonia and were followed up for a maximum of 7 days.

Results: Bacteraemia was detected in 15.9% of patients with *Staphylococcus aureus* (36%) and *Streptococcus pneumoniae* (28%) were the organisms most commonly isolated. Bacteria were isolated from sputum in half of the children, the commonest organisms being *Streptococcus pneumoniae* (45.9%), *Haemophilus influenzae* (23.5%) and *Klebsiella* species (22.4%). *Staphylococcus aureus* had only 33.3% sensitivity to chloramphenicol and *H. influenzae* isolates were completely resistant. *S. pneumoniae* was sensitive to chloramphenicol in 87.4% of cases. The case fatality rate was 15.5%. Independent predictors of death were very severe pneumonia (OR 12.9, CI 2.5–65.8), hypoxaemia (SaO₂ <92%, OR 4.9, CI 1.2–19.5) and severe malnutrition (OR 16.5, CI 4.2–65.5).

Conclusion: *S. aureus*, *S. pneumoniae* and *H. influenzae* are common bacterial causes of severe pneumonia. Chloramphenicol, the current first-line antibiotic for treating severe pneumonia in Ugandan children, is useful in pneumonia caused by *S. pneumoniae* but other common bacteria show resistance. The presence of severe malnutrition, hypoxaemia and very severe pneumonia increase the risk of death and should be considered in case management protocols.

Introduction

Acute lower respiratory tract infections (ALRIs) among children under 5 years of age are a major cause of morbidity and mortality worldwide, particularly in low-income countries.^{1–3} Most deaths from

ALRIs are caused by severe pneumonia and 70% of them occur in low-income countries, especially in sub-Saharan Africa.^{2,4} In Uganda, ALRIs are the second major cause of morbidity after malaria and the leading cause of death among children under 5. Severe pneumonia accounts for 25–33% of admissions and contributes up to 30% of deaths on the general paediatric wards in Mulago Hospital.

In general, management of severe pneumonia is based on clinical and radiological

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findings without culture. This often requires expensive antibiotics, the cost of which must be met by the family. There is also widespread and rapidly developing resistance to commonly used antimicrobial agents, especially in HIV-infected children, which further compounds the problem.⁷⁻⁹ Understanding the spectrum of bacteria causing pneumonia is necessary for appropriate case management and effective use of limited health-care resources in low-income countries.

The aim of the study was to provide information on the bacterial causes of severe pneumonia, the sensitivity patterns of the isolates and the outcome in children aged 2-59 months.

Methods

A cross-sectional study design was used for recruitment and an unmatched cohort study design for follow-up.

Study area and subjects

The study was conducted in the Acute Care Unit and general paediatric wards of Mulago Hospital which is a district and national referral hospital serving an urban and peri-urban catchment population of two million. The hospital was selected as the study site because of its ability to handle laboratory and radiological diagnosis of pneumonia, facilities that are not readily available in rural Ugandan hospitals. The national and hospital recommendation for first-line treatment of severe pneumonia in children at the time of the study was parenteral chloramphenicol. Vaccination against *Haemophilus influenzae* type b was introduced nationally in 2004 and in 2006 national vaccine coverage was estimated to be 66%.¹⁰

The study comprised 157 children aged 2-59 months admitted to Mulago Hospital between December 2005 and March 2006. Children who fulfilled the WHO criteria for severe pneumonia were included.¹¹ Known

asthmatics and those with cardiac failure owing to heart disease or severe anaemia were excluded.

Study procedure

After obtaining informed consent, children had their peripheral oxygen saturation measured using a pulse oximeter before they were given oxygen. A history was taken and physical examination conducted by one of the research physicians. Blood samples were collected for full blood count, culture and an HIV test (DNA-PCR for children <18 mths and Rapid Test for those >18 mths) after counselling the parents/guardians. All except three children had chest radiographs which were read independently by two radiologists who were not blinded to the diagnosis. The chest radiographs were classified as normal or abnormal. Three children died before the radiographs could be done.

Severe pneumonia was defined as having a cough or difficult breathing, tachypnoea and chest in-drawing and very severe pneumonia referred to those who had cyanosis and/or inability to feed in addition to signs of severe pneumonia.¹¹ Bacterial pneumonia was defined as any child in whom bacteria were isolated from blood or sputum.

Laboratory methods

Sputum induction was undertaken by a nurse physiotherapist and one of the research doctors. Children were pre-medicated with 200 µg of salbutamol, using an ultrasonic nebuliser, to prevent bronchoconstriction. They were then given 3-5 ml of nebulised hypertonic saline (3%). A 10-gauge nasal catheter attached to a foot-operated suction machine was passed through the nose into the nasopharynx and at least 2 ml of sputum obtained. Samples were placed into universal containers and transported within 1 hour to the Department of Microbiology laboratory in

Makerere University for gram and Ziehl-Neelsen (ZN) staining.

Culture and sensitivity for blood and sputum was done using the disc diffusion method.

Slides for gram and ZN staining were prepared according to standard methods.¹²

The sputum samples were then inoculated onto blood, chocolate and McConkey agar. Blood and Chocolate plates were incubated at 35–37°C in 5% carbon dioxide for 18–24 hours. McConkey plates were incubated without carbon dioxide for 18–24 hours.

Antibiotic sensitivity/resistance was determined by reading the zone of inhibition around the discs using calipers and interpreted according to the Clinical and Laboratory Standards Institute.¹²

Management of patients

The children were managed according to the WHO standard case management protocol for severe pneumonia using intravenous chloramphenicol.¹⁰ In those who failed to improve within 48 hours, this was changed to IV ceftriaxone. Children suspected clinically and/or radiologically of having *Pneumocystis jiroveci* pneumonia were given IV cotrimoxazole in addition. Malnourished children were transferred to the hospital's Nutrition Unit and managed as per standard protocol which included a combination of parenteral ampicillin and gentamicin.¹³

Where the organisms cultured were sensitive to antibiotics different from those prescribed, the attending doctors were informed and the necessary changes effected.

Children with hypoxemia ($\text{SaO}_2 < 92\%$) were given oxygen by nasal cannula at a rate of 1–3 L/min.¹⁴ Those unable to feed orally were fed via a nasogastric tube on milk, porridge or locally available soups provided by the caretakers.

The clinical course was monitored until discharge, death or for a maximum of 7 days, whichever came first. Parameters

monitored included temperature, respiratory rate, ability to feed, grunting, chest indrawing and SaO_2 level.

Main outcome measures were clinical improvement, complications and death.

Statistical analysis

Data were entered using the EpiInfo 6.4 computer software package and analysed using SPSS. Children were categorised as being positive or negative for bacterial pneumonia for univariate and bivariate analysis. Differences between these two groups were analysed using the χ^2 test. Differences in progression of disease between children with bacterial and non-bacterial pneumonia were compared. A logistic regression model was used to determine independent risk factors for poor outcome.

Results

Background characteristics of the study subjects

A total of 157 children aged 2–59 months admitted to the acute care unit with severe pneumonia were recruited. Fifty-five (35%) were classified as having very severe pneumonia. The mean (SD) age was 15.4 (9.7) months. Eighty-seven (55.4%) were aged <12 months. Forty-eight (30.6%) were HIV-infected. Twenty-two (14.3%) caretakers had written evidence that the child had received *H. influenza* type b vaccination. Seventy-eight (49.7%) patients reported having used an antibiotic before admission.

Causative bacterial organisms

Bacteria were isolated from the blood of 25 (15.9%) children, 14 (56%) of whom were aged 2–12 months (Table 1). The commonest organism isolated was *Staphylococcus aureus* (nine children), representing 36% of blood isolates. Six of these children were under 2 years of age and five had severe malnutrition. The second commonest

organism was *Streptococcus pneumoniae* (seven children, 28% of isolates). *Salmonella enteritidis* (four), *Klebsiella* spp (three) and *H. influenzae* (two) were also isolated from blood.

Bacteria were isolated from sputa in 85 (54%) children, 61 of whom were aged 2–12 months (Table 1). *S. pneumoniae* was the organism most commonly isolated from sputum in 39 children (45.9% of isolates), followed by *H. influenzae* (23.5%), *Klebsiella* spp (22.4%), *Escherichia coli* (15.3%) and others. Mixed infections were present in 28% of the isolates from sputum but in none from blood. Organisms were isolated from blood and sputa in 21 (24.7%) children. All the children with *S. aureus* in their blood had it in the sputum also.

Drug sensitivity

S. aureus, the most common isolate from blood, was sensitive to erythromycin in 77.8% and to chloramphenicol in 33.3%. Six (66.7%) were sensitive to gentamicin. *S. pneumoniae* isolates from blood showed no resistance to chloramphenicol and erythromycin whereas 28 (6%) were resistant to ampicillin. The two isolates of *H. influenzae* from blood were resistant to both chloramphenicol and ampicillin and one was sensitive to erythromycin. Gram-negative organisms isolated from blood (*S. enteritidis* and *Klebsiella* spp) were sensitive to ciprofloxacin, amoxicillin-clavulanic acid

(augmentin) and gentamicin. All organisms isolated from blood, except one *Klebsiella* spp isolate, were sensitive to ceftriaxone.

The most common isolate from sputum, *S. pneumoniae*, was sensitive to ampicillin, erythromycin and chloramphenicol in 76.9%, 97.4% and 87.2% of cases, respectively. *H. influenzae* type b isolates showed complete resistance to chloramphenicol. All isolates showed high susceptibility to ceftriaxone and ciprofloxacin. Resistance of *E. coli* to gentamicin was more common in malnourished children (83.3%) (Fig. 1).

Factors associated with bacterial pneumonia

Bacterial pneumonia refers to cases where bacteria were isolated from either sputum and/or blood. Factors significantly associated with bacterial pneumonia by multivariate analysis were severe malnutrition and consolidation on chest radiograph (Table 2).

Outcome of children with severe pneumonia

Of the 157 children, 24 (15.3%) died and, of these, 66.7% had bacterial pneumonia. Three children (1.9%) developed complications: two had empyema and one had pneumothorax. The remaining 82.8% showed clinical improvement. Twenty-three (14.6%) children stayed in hospital for more than 7 days, either because of clinical

TABLE 1. Bacteria isolated from children with severe pneumonia.

Organism	Blood total=25, n (%)	Sputum total=85, n (%)	Blood & sputum total=21, n (%)
<i>Streptococcus pneumoniae</i>	7 (28.0)	39 (45.9)	7 (33.3)
<i>Haemophilus influenzae</i>	2 (8.0)	20 (23.5)	2 (9.5)
<i>Staphylococcus aureus</i>	9 (36.0)	9 (10.6)	9 (42.9)
<i>Klebsiella</i> spp	3 (12.0)	19 (22.4)	2 (9.5)
<i>Moraxella catarrhalis</i>	0	4 (4.7)	0
<i>Escherichia coli</i>	0	13 (15.3)	0
<i>Salmonella enteritidis</i>	4 (16.0)	1 (1.2)	1 (4.8)
<i>Pseudomonas aeruginosa</i>	0	3 (3.5)	0
Others*	0	6 (7.1)	0

* *Citrobacter*, *Streptococcus pyogenes*, *Proteus vulgaris*.

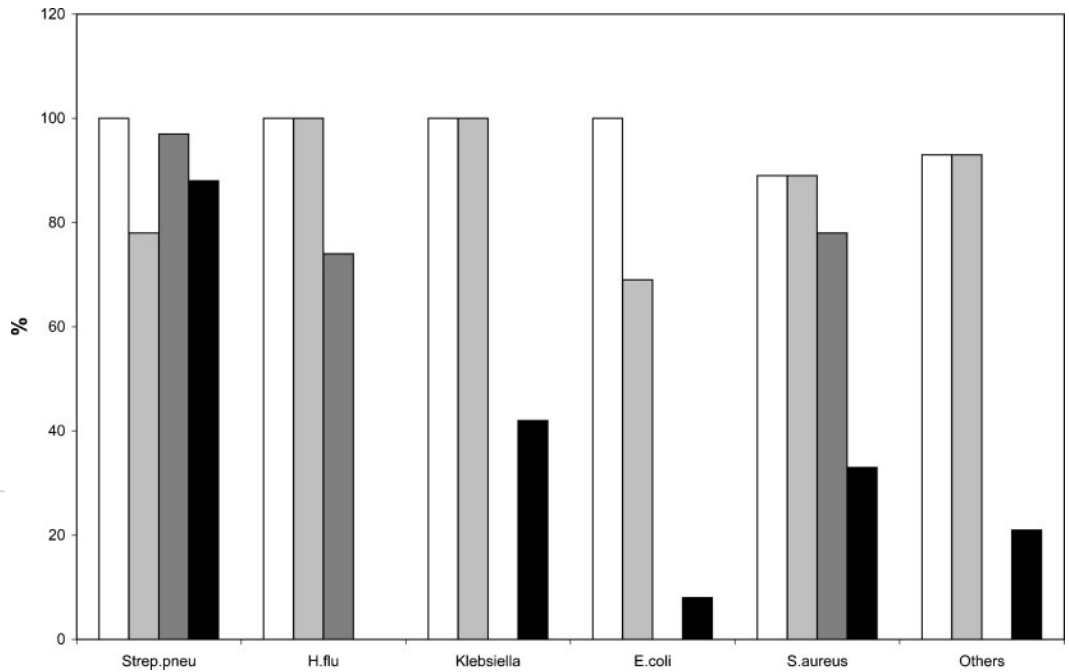


FIG. 1. Antimicrobial sensitivity of organisms isolated from sputum. (Others, *S. enteritidis*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*; □ ceftriax, ceftriaxone; ■ cipro, ciprofloxacin; ■ erythro, erythromycin; ■ chlora, chloramphenicol.)

complications or because they were severely malnourished and required further treatment.

Factors associated with death/survival among children admitted with severe pneumonia

By bivariate analysis, cyanosis, grunting, low SaO₂ (<92%), severe malnutrition, HIV infection and very severe pneumonia were significantly associated with death in children with severe pneumonia (Table 3).

However, by multivariate analysis, the independent predictors of death, were severe malnutrition, low SaO₂ (<92%) and very severe pneumonia.

Comparison of disease progression between children with bacterial and non-bacterial pneumonia

Respiratory rate was likely to take longer to normalise and chest indrawing to resolve in children with bacterial pneumonia than in

TABLE 2. *Factors associated with bacterial pneumonia (n=89/157).*

Variable	Total	Bacteria detected, n (%)	OR (95% CI)	p-value
Aged 2–12 mths	87	51 (58.6)	1.19 (0.63–2.25)	0.6
Temp. >37.5°C	41	21 (51.2)	1.35 (0.66–2.76)	0.4
Oxygen saturation <92%	62	32 (51.7)	0.71 (0.37–1.36)	0.2
Severe malnutrition	40	31 (77.5)	3.50 (1.53–8.00)	0.002*
HIV infection	48	31 (62.5)	1.41 (0.71–2.83)	0.3
Pneumonic consolidation	25	21 (84.0)	4.80 (1.58–14.94)	0.004†

* χ^2 test; † Fisher's exact test; OR, odds ratio; CI, confidence interval.

those without ($p=0.03$ and 0.05 , respectively, by the log-rank test). Patients with bacterial pneumonia were likely to die earlier than those with non-bacterial pneumonia ($p=0.05$). There was no statistical difference regarding time to normal oxygen saturation, time to stop grunting and time to disappearance of cyanosis.

Discussion

This study demonstrates (i) that *S. aureus* is an important invasive pathogen in severe pneumonia, alongside *S. pneumoniae*, (ii) that there is limited sensitivity of *S. aureus* and *H. influenzae* to chloramphenicol even though it is the recommended first-line antibiotic for treatment of severe pneumonia in children,¹¹ and (iii) that children who presented with severe malnutrition, $\text{SaO}_2 < 92\%$ or who were classified as having very severe pneumonia were more likely to die than those without these symptoms.

Studies undertaken in various low-income countries have found *S. pneumoniae* to be the commonest isolate from blood as well as sputum in children with severe pneumonia.^{15,18,19} The reason why the most common isolate in this study was *S. aureus* might be because the majority of children with bacteraemia were severely malnourished and *S. aureus* bacteraemia is commonly associated with malnutrition.¹⁶ In South

Africa, staphylococcal pneumonia was found to be more common in sputa of immunosuppressed patients.¹⁹ However, in the current study, HIV infection was not a risk factor for *S. aureus* bacteraemia. Other organisms isolated from blood were *H. influenzae* type b, *Klebsiella* spp and *S. enteritidis* and these findings are similar to those of other series.^{2,15,18}

The commonest isolate from the sputum was *S. pneumoniae*, accounting for 45.9% of cases. This is similar to other studies in low-income countries such as Papua New Guinea where *S. pneumoniae* was isolated from 52% of children with severe pneumonia.²⁰ Similar studies have shown that *S. pneumoniae* contributes 50–70% of bacterial isolates from children with severe pneumonia.^{15,17}

H. influenzae type b was the second most common isolate from sputum (23.5%), despite the fact that Ugandan children are now routinely immunised against Hib as part of the pentavalent vaccine. However, we were unable to ascertain accurately the proportion of children who had actually received the Hib vaccine because only 14.3% had documented evidence of having received the pentavalent vaccine. It is also possible that *H. influenzae* was isolated from sputum as part of the normal pharyngeal flora since the sputum was suctioned from the nasopharynx after induction.

Only 33.3% of *S. aureus* isolates were sensitive to chloramphenicol. It is of even

TABLE 3. Factors associated with death ($n=24$) of children with severe pneumonia ($n=157$).

Variable	Total	Died, n (%)	OR (95% CI)	p -value
Aged 2–12 mths	87	14 (16.1)	1.15 (0.48–2.78)	0.7
Bacteria in blood	25	7 (28.0)	2.63 (0.96–7.23)	0.05
Bacteria in sputa	86	13 (15.1)	1.03 (0.43–2.46)	0.9
Cyanosis	21	7 (33.3)	3.50 (1.24–9.90)	0.01*
Grunting respiration	80	19 (23.8)	4.49 (1.58–12.72)	0.003*
Oxygen saturation $< 92\%$	62	18 (27.7)	6.07 (2.25–16.36)	$< 0.0001^*$
Severe malnutrition	40	18 (45.0)	15.14 (5.40–42.44)	$< 0.0001^*$
Very severe pneumonia	55	22 (40.0)	33.30 (7.44–149.4)	$< 0.0001^\dagger$
HIV infection	48	14 (29.2)	4.08 (1.66–10.05)	$< 0.001^*$
Immunisation up-to-date	89	10 (11.2)	2.05 (0.85–4.95)	0.1

* χ^2 test; † Fisher's exact test.

more concern that *H. influenza* isolates showed no sensitivity to chloramphenicol. The blood and sputum isolates of *S. pneumoniae* showed less resistance to chloramphenicol, which compares with studies from other parts of Africa. In Senegal, resistance of streptococcus to penicillin and chloramphenicol was 14% and 9%, respectively.²¹ Other studies have also shown intermediate resistance of *S. pneumoniae* to penicillin, but it did not necessarily affect their effectiveness.^{22,23} These findings indicate that chloramphenicol and ampicillin may still be of value in treating severe pneumonia in children in low-income settings. However, considering that bacterial culture is rarely undertaken in severe pneumonia, the high resistance to chloramphenicol of other organisms causing invasive pneumonia is worrying. A greater number of organisms were sensitive to ceftriaxone, ciprofloxacin and amoxicillin-clavulanic acid, but they are expensive and affordable to few in low-income settings.

Gram-negative organisms were resistant to gentamicin in fairly high proportions (50%), yet this is the drug commonly used to target gram-negative organisms when given empirically.¹³ Resistance of *E. coli* to gentamicin was more common in malnourished children (83.3%). These findings are similar to those of other studies which have documented that resistance to antibiotics is more common in children under 2 years as well as malnourished children.²⁴ Thus, malnourished children with severe pneumonia should preferably be treated with other antibiotics such as ceftriaxone and amoxicillin-clavulanic acid other than gentamicin.

The case fatality rate of 15.3% is similar to that in other studies of children with severe pneumonia.^{6,18,25} Studies in Mulago Hospital have found a case fatality rate ranging between 12% and 24%⁶ whereas those from other African countries show case fatality rates as high as 30%. It is therefore important to strengthen preventive and case management protocols for severe pneumonia to reduce such high case fatality.

The antibiotic policy for severe pneumonia needs to be revised.

The clinical factors associated with death were cyanosis, grunting respiration, peripheral oxygen saturation <92%, severe malnutrition, HIV infection and very severe pneumonia, similar to other studies.^{15,19,26,28,29}

The following are some limitations of the study. The likelihood of isolating bacteria might have been reduced in children who received antibiotics before presentation at hospital. It is also possible that isolates from induced sputum might represent the normal naso-pharyngeal flora and are therefore not necessarily responsible for the severe pneumonia. Furthermore, we were unable to isolate atypical bacteria (e.g. mycoplasma pneumonia and chlamydia pneumoniae) and perform advanced serotyping of some of the isolates which could have strengthened the epidemiology and pathogenicity of the study.

S. aureus, *S. pneumoniae* and *H. influenzae* are common causative organisms in severe pneumonia. Chloramphenicol, the current first-line antibiotic for treating severe pneumonia in Ugandan children, is useful in pneumonia caused by *S. pneumoniae*, but other common bacteria show resistance. Presence of severe malnutrition, hypoxaemia and very severe pneumonia indicate increased risk of death and need to be considered in case management protocols to help reduce the unacceptably high case-fatality rates.

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