

Treatment failure among children under 5 years hospitalized with pneumonia at the pediatric ward of Mbarara Regional Referral Hospital in Southwestern Uganda: a prospective observational study

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Abstract

Background: Pneumonia remains a significant global health concern, particularly for children in low- and middle-income countries. Despite advancements in medical care and the availability of effective medication, treatment failure still occurs.

Objective: This study evaluated the incidence, associated factors, and outcomes of treatment failure among children under 5 years with pneumonia.

Design: A prospective observational study.

Method: We conducted this study among children under 5 years hospitalized with pneumonia at the pediatric ward of Mbarara Regional Referral Hospital over a period of 3 months. We enrolled the participants in the study consecutively. Data was analyzed using SPSS software Version 27. Logistic regression was used to determine factors associated with treatment failure.

Results: A total of 216 children aged between 0 and 59 months were included in the study. The incidence of treatment failure after 48 h was 53 (24.5%). A total of 32 (60.4%) cases of treatment failure occurred early (between 48 and 72 h), while 21 (39.6%) occurred late (after 72 h). Distance of >5 km from the nearest health facility (adjusted odds ratio (AOR)=2.2, 95% CI: 1.1–4.4, p -value=0.029), severe acute malnutrition (AOR=6.2, 95% CI: 2.4–16.1, p -value < 0.001), and adverse drug reaction (AOR=6.9, 95% CI: 2.6–18.4, p -value < 0.001) were independent predictors of treatment failure. The outcomes of treatment failure included prolonged hospitalization, death, referral to a higher-level facility, and complications of pneumonia.

Conclusion: Our study identified a high incidence of treatment failure among children under 5 years in this setting. There is a need for early and accurate diagnosis, which includes culture and sensitivity tests, timely initiation of effective antibiotic therapy, active pharmacovigilance, and close monitoring of patients with acute malnutrition to reduce the likelihood of treatment failure.

Keywords: associated factors, children, pneumonia, treatment failure

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Introduction

Pneumonia refers to an acute lower respiratory tract infection that results in inflammation of the alveoli. Pneumonia is the primary cause of ill

health and death for children under the age of five worldwide, resulting in 17% overall mortality.¹ The global incidence of pediatric pneumonia is roughly 151 million cases per year. In low- and

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middle-income countries, 7%–13% of cases require hospitalization.² About 90%–95% of the deaths occur in underdeveloped countries, particularly sub-Saharan Africa and South Asia.³ Even though conjugate vaccines against *Streptococcus pneumoniae* (PCV) and *Haemophilus influenzae* type b (Hib) have made recent progress in prevention and care, pneumonia persists to be a major cause of morbidity and mortality.⁴

A 2020 meta-analysis and systematic review of studies from six countries in East Africa found the burden of pneumonia in children under 5 to be 34%. Use of wood as fuel, caring for a child while cooking, not getting immunized, and a child's past record of an acute respiratory tract infection were some of the predisposing factors for pneumonia reported.⁵ According to a study conducted in Bushenyi, Southwestern Uganda, pneumonia was found to affect 25.6% of children under the age of 5 and was responsible for 16% of infant deaths.⁶ Furthermore, estimates place the cost of treating pneumonia among children at the inpatient and outpatient settings per episode at \$62 and \$16, respectively. A previous study demonstrated that family members of patients with pneumonia bear a significant financial burden.⁷ Although pneumonia affects all age categories, the effects are more profound in children below 5 years as compared to others due to their underdeveloped immunity.⁸

The causative pathogens of infectious pneumonia include viruses, bacteria, and fungi. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common bacterial causes of community-acquired pneumonia (CAP). *Staphylococcus aureus* and *Pseudomonas aeruginosa* are known to mostly cause nosocomial infections. Other microorganisms less commonly involved include *Moraxella catarrhalis*, *M. pneumoniae*, and viruses (respiratory syncytial virus, influenza, and measles). *Mycobacterium tuberculosis* and *P. jiroveci* are known to cause pneumonia among children living with HIV.⁹

The identification of causative microorganisms of pneumonia in children has been made quite complex by the inability to obtain sufficient quantities of samples of blood and sputum cultures from the lower respiratory tract.¹⁰ The WHO has therefore recommended the use of clinical features primarily in the diagnosis of pneumonia with the

subsequent use of empirical antibiotics for treatment.^{11,12}

Oral antibiotics, amoxicillin at 40 mg/kg body weight every 12 h for 5 days, are recommended for the treatment of non-severe pneumonia in children who don't exhibit any danger signs of pneumonia, whereas intravenous antibiotics and supportive care are used to treat severe pneumonia.¹³ In Uganda, children younger than 5 who have severe pneumonia are first given an ampicillin injection at a rate of 50 mg/kg body weight or a benzylpenicillin injection at a rate of 50,000 IU/kg body weight every 6 h, along with gentamicin 7.5 mg/kg body weight once a day for 5–10 days.⁹

Treatment failure is a medical condition where the body doesn't respond properly to antibiotic treatment and the pneumonia symptoms don't go away or get worse after 48 h of treatment. It often requires a change of therapy.¹⁴ Although the response to therapy among most children is very good, with most of them achieving treatment success, pneumonia remains the primary cause of death for children under five, with treatment failure accounting for the majority of these deaths.¹⁵ Treatment failure still remains a bigger challenge globally, especially in developing countries like Uganda in sub-Saharan Africa.¹⁶

Treatment failure has been widely studied in developed states and a few African countries but there are no similar studies about treatment failure and the associated risk factors in Uganda. High proportions of treatment failure have been reported in some Sub-Saharan African countries like 50.4% in Tanzania¹⁷ and 46.7% in Malawi.⁴ These differences could be explained by variations in participant characteristics and health care practices. The possible explanations for treatment failure in our setting remained unknown.

Therefore, the aim of this study was to determine the incidence, associated factors, and outcomes of treatment failure among children under 5 years with pneumonia admitted at the Pediatric ward of Mbarara Regional Referral Hospital (MRRH).

Methods

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplemental Material).¹⁸

Study design and setting

A prospective observational study was conducted among children under 5 years hospitalized with a clinical diagnosis of pneumonia at the pediatric ward of MRRH from May to August 2024. Mbarara Regional Referral Hospital is a government-owned tertiary and teaching hospital and the largest referral facility in southwestern Uganda. The hospital provides care to about 4 million residents from 13 districts of southwestern Uganda. The pediatrics unit has a bed capacity of 82 with an average monthly admission of 400 patients. The Pediatric Department of MRRH is a specialized unit that provides medical care to children from birth up to 15 years of age generally and above 15 years for children with chronic illnesses from childhood, such as sickle cell and diabetes mellitus, among others. The unit is staffed by pediatricians, senior housing officers, intern doctors, nursing professionals, and other healthcare professionals who specialize in the care of children. The department offers a range of services, including emergency care, inpatient care, outpatient care, and specialized care for children with chronic illnesses. Acute care, critical care, high dependency, nutrition, and neonatal units are among those that make up the ward. The study included children admitted to all children's units.

Study participants

We included all children under 5 years admitted to the pediatric ward during the study period with a clinical diagnosis of pneumonia, receiving antibiotic treatment for pneumonia, and whose caretakers provided written informed consent to participate in the study. The study excluded participants who received referrals to other health facilities within 48 h of admission and those with incomplete medical records.

Sample size

The sample size of the study was determined using Fisher's formula,¹⁹ taking into account the estimated proportion of treatment failure at 15%²⁰ at a 95% confidence interval, with a 5% margin of error, and an additional 10% for lack of response. The estimated proportion was obtained from a prospective cohort study done in a similar setting in Malawi, which determined a 15% treatment failure to antibiotics in children with pneumonia.²⁰ The total calculated sample size was 216 participants. A consecutive sampling technique

was used to enroll the participants in the study until the required sample size was obtained.

Data collection tools and procedures

After obtaining informed consent from the patient's caretakers, trained research assistants and the principal investigator used a structured interviewer-administered questionnaire to collect data on the socio-demographics and patient-related variables of patients who satisfied the study's inclusion criteria. The questionnaire was developed after a comprehensive review of literature and consultations with a pediatrician and a clinical pharmacist on the study team. The tool was pretested among 10 participants to ensure its validity and coherence. The data from the pretest were not considered in the final analysis of this study but rather used to refine the data collection tool. In this study, pneumonia was diagnosed clinically by the pediatric residents on duty, and it was considered when a child had at least two features of either cough or difficulty in breathing plus any of the following features: rapid breathing, oxygen saturation <90% on pulse oximetry or central cyanosis, lower chest indrawing, severe respiratory distress, chest auscultation signs (crackles, decreased breath sounds, abnormal vocal resonance), general danger signs of pneumonia (inability to breastfeed or drink, lethargy, reduced level of consciousness, convulsions).¹⁴ Respiratory distress was shown by signs of more work being done to breathe, like tachypnea, subcostal recessions, intercostal recessions, tracheal tug, head bobbing, and nasal flaring. Tachypnea was adjusted for age, which included ≥ 60 breaths/min in a child aged < 2 months, ≥ 50 breaths/min in a child aged 2–11 months, and ≥ 40 breaths/min in a child aged 1–5 years. The pediatric residents on duty initiated antibiotics and supportive care for the children admitted with pneumonia. Baseline clinical assessment, chest radiograph, complete blood count results, and any other investigations done were recorded whenever available upon enrolment. We conducted the patient's vital signs and physical examination once every 24 h.

The patients' medical records were looked at every day to review factors related to their diseases (like the type and severity of their pneumonia and any other illnesses they had) and their medications (like dosage, drug interactions, and not following their treatment plan).

Active pharmacovigilance was used to obtain information on adverse drug reactions daily. The Naranjo ADR scale was then used to assess for causality.²¹ The possible drug–drug interactions were checked using Lexicomp’s Interaction checker. The appropriateness of regimen and dosage of medications was evaluated using Uganda Clinical Guidelines 2022, the British National Formulary for Children (2023–2024) version and Up to Date.

Patients were monitored daily for 7 days or until discharge (whichever was shorter), and treatment outcomes were documented at discharge or on day 7 of follow-up for patients who were still on the ward. Treatment failure was identified by the PI and the research team, and the diagnosis of treatment failure was confirmed by the pediatrician on duty, who was able to rule out all other differential diagnoses. This was then followed by a change of therapy to an alternative antibiotic regimen as recommended in the guidelines and agreed upon by the clinicians and research team.

Study variables

Dependent variable. The primary outcome of this study was treatment failure, defined as the inability to improve or exacerbation of at least two clinical features of pneumonia, such as rapid breathing, oxygen saturation <90% on pulse oximetry, or features of central cyanosis, chest indrawing, and chest auscultation signs (crackles, decreased breath sounds, abnormal breath sounds) after 48 h but within 72 h for early treatment failure and after 72 h to 7 days (late treatment failure) while the patient was receiving treatment.

The secondary outcomes of the study included the consequences of treatment failure, such as prolonged hospitalization, death, referral to a higher-level facility, and complications of pneumonia (respiratory failure, sepsis, meningitis, pleural effusion, and empyema).

Independent variables. These included patient-related factors (age, gender, vaccination status, socio-economic status, pre-hospital use, and distance to health facility), medication-related factors (dosage, compliance, ADR, and drug–drug interactions), and disease-related factors (severity of pneumonia, type of pneumonia, comorbid conditions, and nutrition status).

Data analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS), version 27 (SPSS Inc., Cary, NC, USA). The sociodemographic and clinical characteristics of the study participants were presented using descriptive statistics such as median, frequencies, and percentages. The incidence and outcomes of treatment failure were reported in percentages. Univariate logistic regression was used to determine the association between independent and dependent variables; variables with a p -value <0.25 were adopted for multivariate analysis, and variables with a p -value <0.05 were considered statistically significant.

Results

During the study period, a total of 216 children aged 0–59 months were enrolled and included in the final analysis.

Demographic and clinical characteristics of the study participants

Most of the participants in this study were male (122, 56.5%) with a median age of 10 (3.3–18.0) months. About 157 (72.7%) of the children had normal nutritional status, and 145 (67.2%) completed pneumococcal conjugate/Haemophilus type b conjugate vaccination. The majority of the participants (130, 60.2%) reported use of antibiotics before admission. Only 102 (47.2%) participants reported use of unknown herbal medications in the last 2 weeks before admission. About 82 (38.1%) of the participants reside more than 5 km from the nearest health facility (Table 1).

Most of the patient admissions, 204 (94.4%), were as a result of community-acquired pneumonia. Most of the children, 191 (88.4%), had severe pneumonia. Almost all the children, 206 (95.6%), presented with cough, 177 (81.9%) had difficulty in breathing, 163 (75.5%) were febrile, and 128 (59.3%) experienced tachypnea (Figure 1).

In terms of comorbid conditions, there were 14 (6.5%) children with congenital heart disease, 11 (5.1%) were HIV exposed, 8 (3.7%) with Down syndrome, 7 (3.2%) had pulmonary tuberculosis, and only 4 (1.9%) were living with HIV as chronic comorbidities (Figure 2).

Table 1. Demographic and clinical characteristics of children under 5 years diagnosed with pneumonia at the Pediatric Ward of Mbarara Regional Referral Hospital.

Characteristic	Category	Frequency	Percentage
Age of the child, median (IQR) 10 (3.3–18.0) months	0 to <1 years	134	62.0
	1–5 years	82	38.0
Gender of the child	Male	122	56.5
	Female	94	43.5
Occupation of caretaker	Formal employment	24	11.1
	Self-employment	30	13.9
	Housewife	40	18.5
	Subsistence farmer	122	56.5
Education level of caretaker	No formal education	33	15.3
	Primary	99	45.8
	Secondary	62	28.7
	Tertiary	22	10.2
Exclusive breastfeeding	No	59	27.3
	Yes	157	72.7
Fully vaccinated against PCV/Hib	No	71	32.9
	Yes	145	67.2
Pre-hospital antibiotic use	No	86	39.8
	Yes	130	60.2
Herbal medicine use in the past 2 weeks	No	114	52.8
	Yes	102	47.2
Income status of the caretaker	≤62 USD	53	24.5
	>62 USD	163	75.5
Distance from nearest health facility	<5 km	133	61.9
	>5 km	82	38.1
Nutritional status of the patient	Normal	157	72.7
	Mild malnutrition	7	3.2
	Moderate malnutrition	28	13.0
	Severe malnutrition	24	11.1
Hib, Haemophilus Influenza Type b; PCV, pneumococcal conjugate vaccine.			

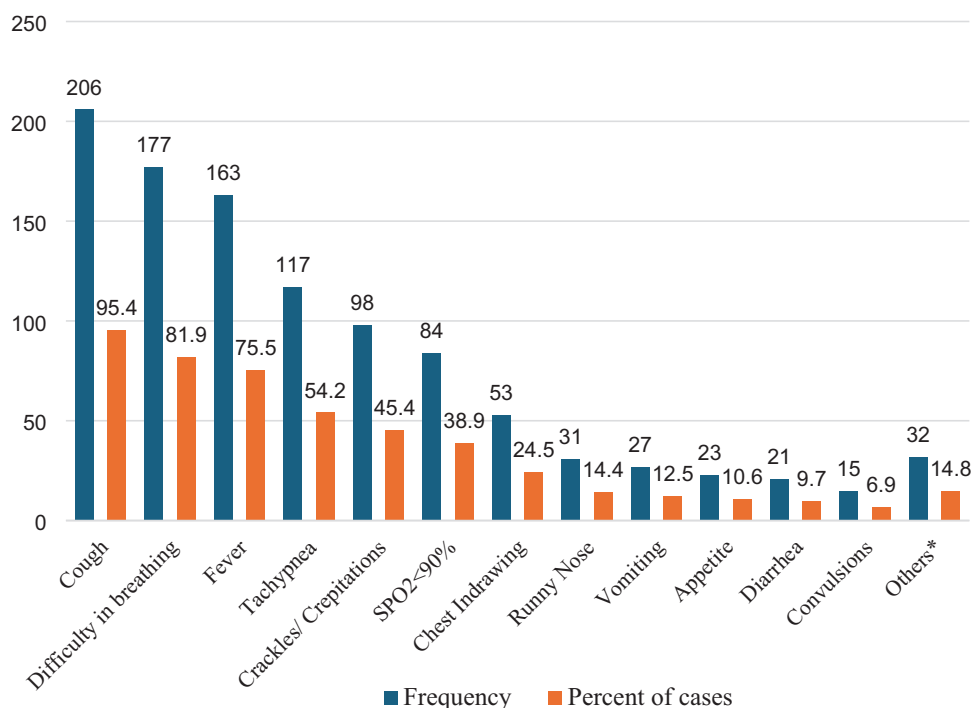


Figure 1. Presenting complaints of children under 5 years diagnosed with pneumonia at the Pediatric Ward of Mbarara Regional Referral Hospital.

*Respiratory distress (11), Chest pain (4), Body swelling (3), Grunting (3), Loss of consciousness (2), Oral thrush (2), Night sweats (1), Excessive crying (1), Hypoglycemia (1), Joint pain (1), Pleural effusion (1), Head nodding (1), Tachycardia (1).

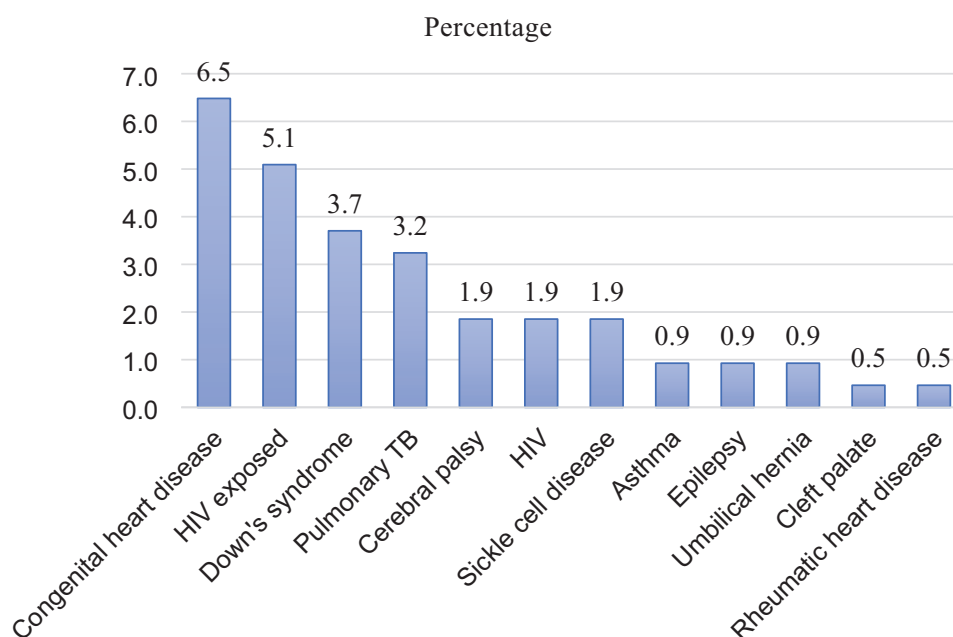


Figure 2. Chronic comorbid conditions among children under 5 years diagnosed with pneumonia at the Pediatric Ward of Mbarara Regional Referral Hospital.

Table 2. Adverse drug reactions experienced by the study participants.

Adverse drug	Drugs responsible	Frequency	Percentage	Naranjo rating scale
Vomiting	Ceftriaxone, ampicillin, gentamicin	14	58.3	Possible
Itchy skin rash	Ceftriaxone, benzylpenicillin, ampicillin	4	16.7	Probable
Vomiting/itchy skin rash	Ceftriaxone, ampicillin	3	12.5	Probable
Diarrhea/itchy skin rash	Ampicillin	2	8.3	Possible
Diarrhea	Ampicillin	1	4.2	Probable

Naranjo ADR scale = 1–4 (possible), 5–8 (probable).
ADR, adverse drug reaction.

Twenty-four of the 216 study participants (11.11%) experienced adverse drug reactions. The ADRs included vomiting 17 (70.8%), itchy body skin rash 9 (37.5%), and diarrhea 3 (12.5%). Ceftriaxone and ampicillin were responsible for most of the ADRs (Table 2).

Incidence proportion of treatment failure

Out of the 216 children admitted with pneumonia, 163 (75.5%) had successful treatment outcomes, whereas 53 (24.5%) (95% CI: 19.2–30.8) experienced treatment failure after 48 h. Of the 53 treatment failure cases, 32 (60.4%) had early treatment failure (within 48 to 72 h), and 21/53 (39.6%) experienced late failure (after 72 h) up to 1 week from the time of treatment initiation. Out of the 53 participants who experienced treatment failure, 48 (90.6%) were switched to alternative antibiotics, and 5 (9.4%) died before they could be shifted to the next line of antibiotics. The majority (44, 83.0%) of the participants had prolonged hospitalization of more than 7 days, 8 (15.1%) died, and 1 (1.9%) was referred to a higher-level facility for further management of a co-existing congenital heart disease. More than half (28, 52.8%) of the patients who experienced treatment failure incurred different complications: meningitis (8, 28.6%), sepsis (7, 25.0%), pleural effusion (5, 17.9%), empyema (5, 17.9%), respiratory failure (2, 7.1%), and pneumothorax (1, 3.6%).

Antibiotics used at initiation of treatment for pneumonia

The most commonly prescribed antibiotic combinations for the management of pneumonia were ampicillin and gentamicin (75/216, 34.7%)

and benzylpenicillin plus gentamicin (73/216, 33.8%) (Table 3).

Antibiotics used following treatment failure

The most commonly used antibiotics upon treatment failure were ceftriaxone (37.5%), ampicillin/cloxacillin (10.4%), and ceftriaxone with benzylpenicillin (10.4%) (Table 4).

Factors associated with treatment failure

The association of independent variables with treatment failure was investigated using both univariate and multivariate logistic regression techniques. At univariate logistic regression analysis, associations between each independent variable and treatment failure were determined by crude odds ratio (COR). Associations with a *p*-value <0.25 and clinical significance were considered for multivariate analysis to adjust for potential confounders in order to obtain the adjusted odds ratio (AOR).

At univariate analysis, distance from health facility > 5 km (COR=2.2, 95% CI: 1.2–4.2, *p*-value=0.012), severe pneumonia (COR=2.6, 95% CI: 0.7–9.1, *p*-value=0.134), mild/moderate malnutrition (COR=2.8, 95% CI: 1.3–6.3, *p*-value=0.011), severe malnutrition (COR=5.7, 95% CI: 2.3–14, *p*-value=<0.001), male gender (COR=1.7, 95% CI: 0.9–3.2, *p*-value=0.108), and adverse drug reaction (COR=5.5, 95% CI: 2.2–13.3, *p*-value=<0.001) were included in multiple logistic regression.

After adjusting for potential confounders, the following factors were predictive of treatment failure among children admitted with pneumonia;

Table 3. Treatment failure rates for each regimen of antibiotics used to treat pneumonia at admission.

Antibiotics	Frequency of use	Frequency of treatment failure	Percent of treatment failure
Ampicillin + gentamicin	75	25	33.3
Benzylpenicillin + gentamicin	73	10	13.7
Ampicillin/cloxacillin + gentamicin	13	5	38.5
Ceftriaxone + benzylpenicillin	21	4	19.0
Ceftriaxone	10	1	10.0
Ceftriaxone + gentamicin	2	1	50.0
Ampicillin/cloxacillin	3	2	66.7
Benzyl penicillin	1	0	0.0
Ceftriaxone + metronidazole	2	0	0.0
Benzyl penicillin + ampicillin/ cloxacillin + gentamicin	2	0	0.0
Ceftriaxone + ampicillin/cloxacillin	8	3	37.5
Ceftriaxone + azithromycin	1	0	0.0
Ampicillin + ceftriaxone	1	1	100.0
Ampicillin + gentamicin + metronidazole	1	0	0.0
Ampicillin/cloxacillin + benzylpenicillin	1	0	0.0
Ampicillin/cloxacillin + metronidazole	1	1	100.0
Benzyl penicillin + metronidazole	1	0	0.0

distance from the nearest health facility > 5 km (AOR=2.2, 95% CI: 1.1–4.4, p -value=0.029) compared to those within 5 km of the facility, severe acute malnutrition (AOR=6.2, 95% CI: 2.4–16.1, p -value=<0.001) compared to normal nutrition status and participants with adverse drug reaction (AOR=6.9, 95% CI: 2.6–18.4, p -value=<0.001) compared to those without ADRs, were determined to be statistically significant predictors (p -value<0.05) of treatment failure among children under 5 years with pneumonia admitted at MRRH (Table 5). Therefore, living at a distance >5 km from the nearest health facility, severe acute malnutrition, and the presence of adverse drug reactions increased the odds of treatment failure by 2.2, 6.2, and 6.9 times, respectively.

Discussion

In this study, about a quarter of the participants (24.5%) experienced treatment failure. More than half (60.4%) had early treatment failure occurring within 48–72 h of treatment initiation, while 39.6% had late treatment failure, occurring after 72 h up to 1 week from the time of initiation of antibiotics. The findings of this study are similar to the 20% reported in Kenya,²² 15% in Malawi,²⁰ 20.4% in India,¹⁵ and 17% in the Philippines.³ The findings are, however, significantly lower than the 46.7% and 50.4% reported in Malawi⁴ and Tanzania¹⁷ respectively. This difference could be attributed to the fact that these studies were limited to first-line antibiotics for pneumonia, while our study included patients on all types of antibiotics for pneumonia. Another

Table 4. Antibiotics used upon treatment failure in children under 5 years.

Antibiotics	Frequency	Percentage
Ceftriaxone	18	37.5
Ampicillin/cloxacillin	5	10.4
Ampicillin/cloxacillin/ +gentamicin	3	6.3
Ceftriaxone + benzylpenicillin	5	10.4
Benzyl penicillin + gentamicin	4	8.3
Benzyl penicillin	3	6.3
Ampicillin + gentamicin	1	2.1
Gentamicin + metronidazole	1	2.1
Benzyl penicillin + ceftriaxone + azithromycin	1	2.1
Vancomycin + metronidazole + acyclovir	1	2.1
Meropenem + vancomycin + azithromycin	1	2.1
Benzyl penicillin + azithromycin	1	2.1
Ceftriaxone + meropenem + ampicillin/cloxacillin	1	2.1
Gentamicin	1	2.1
Benzyl penicillin + gentamicin + azithromycin	1	2.1
Benzyl penicillin + metronidazole	1	2.1

possible explanation could be the higher prevalence of HIV and SAM among patients in these studies compared to our study, as HIV and SAM have been shown to greatly predict treatment failure in pneumonia. On the other hand, the incidence of treatment failure observed in the current study is much higher than the 11.11% reported in India.²³ This discrepancy could be attributed to the differences in the timing of treatment failure as well as the exclusion of patients with co-morbidities from the Indian study as compared to our study. The possible reasons for the observed proportion of treatment failure in this study could be due to a combination of patient factors, pathogen characteristics, and treatment-related issues such as inappropriate antibiotic therapy, delayed initiation of therapy, antibiotic resistance, severe pneumonia, co-infections with viruses and other bacteria, chronic illnesses, delayed or incorrect diagnosis, very young age, and malnutrition.

This study identified severe acute malnutrition, a distance >5 km from the nearest health facility, and adverse drug reactions as the independent predictors of treatment failure. This study demonstrated that children with SAM had 6.2 greater odds of treatment failure than children without malnutrition. This is consistent with the findings of other studies.^{3,4,15,17}

Children with SAM frequently exhibit non-specific features of pneumonia due to their dysfunctional immune system, which may delay initiation of therapy with parenteral antibiotics, ultimately leading to the progression of the disease.²⁴ Additionally, gram-negative bacteria account for most bacterial infections linked to severe pneumonia or bacteremia in children suffering from severe acute malnutrition; as a result, the antibiotics used in the treatment of pneumonia in these patients do not sufficiently cover the bacteria involved, leading to a higher risk of antibiotic

Table 5. Univariate and multivariate analysis of factors associated with treatment failure among children under 5 years with pneumonia hospitalized at the pediatric ward of MRRH.

Variable	Category	Treatment failure		COR (95% CI)	p Value	AOR (95% CI)	p Value
		No n (%)	Yes n (%)				
Age of the child	0 to <1 years	101 (75.4)	33 (24.6)	1.0 (0.5–1.9)	0.969		
	1–5 years	62 (75.6)	20 (24.4)	1			
Occupation of the caretaker*	Formal employment	21 (87.5)	3 (12.5)	1			
	Self-employed	25 (83.3)	5 (16.7)	1.4 (0.3–6.6)	0.669		
	Housewife	30 (75.0)	10 (25.0)	2.3 (0.6–9.5)	0.237		
	Subsistence farmer	87 (71.3)	35 (28.7)	2.8 (0.8–10.0)	0.111		
Monthly income of caretaker	≤62 USD	43 (81.1)	10 (18.9)	1			
	>62 USD	120 (73.6)	43 (26.4)	1.5 (0.7–3.3)	0.272		
Distance from nearest health facility*	<5 km	108 (81.2)	25 (18.8)	1		1	
	>5 km	54 (65.9)	28 (34.1)	2.2 (1.2–4.2)	0.012	2.2 (1.1–4.4)	0.029
Gender of the child*	Male	87 (71.3)	35 (28.7)	1.7 (0.9–3.2)	0.108	1.9 (0.9–4.0)	0.078
	Female	76 (80.9)	18 (19.1)	1		1	
Education level of caretaker*	None	24 (72.7)	9 (27.3)	1.0 (0.3–3.4)	1.000		
	Primary	70 (70.7)	29 (29.3)	1.1 (0.4–3.1)	0.850		
	Secondary	53 (85.5)	9 (14.5)	0.5 (0.1–1.5)	0.186		
	Tertiary	16 (72.7)	6 (27.3)	1			
Fully vaccinated PCV/ Hib*	No	50 (70.4)	21 (29.6)	1.5 (0.8–2.8)	0.230		
	Yes	113 (77.9)	32 (22.1)	1			
Pre-hospital antibiotic use in last 4 weeks	No	66 (76.7)	20 (23.3)	1			
	Yes	97 (74.6)	33 (25.4)	1.1 (0.6–2.1)	0.722		
Herbal use in last 2 weeks	No	88 (77.2)	26 (22.8)	1			
	Yes	75 (73.5)	27 (26.5)	1.2 (0.7–2.3)	0.532		
Severity of pneumonia*	Non-severe	22 (88.0)	3 (12.0)	1		1	
	Severe	141 (73.8)	50 (26.2)	2.6 (0.7–9.1)	0.134	2.2 (0.5–9.9)	0.274

(Continued)

Table 5. (Continued)

Variable	Category	Treatment failure		COR (95% CI)	<i>p</i> Value	AOR (95% CI)	<i>p</i> Value
		No <i>n</i> (%)	Yes <i>n</i> (%)				
Chronic comorbidity	No	124 (75.2)	41 (24.8)	1.1 (0.5–2.2)	0.848		
	Yes	39 (76.5)	12 (23.5)	1			
Nutritional status of patient*	Normal	130 (82.8)	27 (17.2)	1		1	
	Mild/moderate malnutrition	22 (62.9)	13 (37.1)	2.8 (1.3–6.3)	0.011	2.2 (0.9–5.4)	0.066
	Severe malnutrition	11 (45.8)	13 (54.2)	5.7 (2.3–14.0)	<0.001	6.2 (2.4–16.1)	<0.001
Acute comorbidity	No	78 (74.3)	27 (25.7)	1.1 (0.6–2.1)	0.696		
	Yes	85 (76.6)	26 (23.4)	1			
ADR present*	No	153 (79.7)	39 (20.3)	1		1	
	Yes	10 (41.7)	14 (58.3)	5.5 (2.2–13.3)	<0.001	6.9 (2.6–18.4)	<0.001

*Factors considered for multivariate analysis; **Bold:** Statistically significant.

ADR, adverse drug reaction; AOR, adjusted odds ratio; COR, crude odds ratio; Hib, Haemophilus Influenza Type b; PCV, pneumococcal conjugate vaccine.

treatment failure.²⁴ Furthermore, the weakened immune defense and delayed clinical response to treatment in malnourished children make it harder for them to overcome infections. Finally, SAM can significantly affect the pharmacokinetics of antibiotics and other treatments, potentially leading to reduced efficacy and safety concerns.

Children who lived more than 5 km away from the closest health facility were 2.2 times more likely to experience treatment failure than children who lived <5 km away. This finding is consistent with the findings of a previous study.⁴ According to WHO, a health facility is considered accessible if it is located within 5 km of the population it serves.²⁵ Residing at a distance of more than 5 km from the nearest health facility limits access to health care due to socio-economic challenges such as financial constraints and poor transport systems, thereby causing delays in receiving treatment with the ultimate risk of treatment failure and poor outcomes. It has also been discovered that children who reside further from the nearest health facilities have higher levels of SAM, which has been demonstrated to significantly predict treatment failure in pneumonia.⁴

Communities living far from health facilities are often poorer and more marginalized, which further exacerbates the risk of malnutrition. Limited access to healthcare compounds other issues like food insecurity, poor water and sanitation, and inadequate housing, all of which contribute to malnutrition.

Our study results show that adverse drug reactions (11.11%) were a significant predictor of treatment failure among children under five. Compared to children without ADRs, those who experienced ADRs had a 6.9-fold increased risk of treatment failure. This finding is similar to a study conducted in Malawi.²⁶

Antibiotics such as ceftriaxone and ampicillin were the main cause of the adverse drug reactions, which included vomiting (17, 70.8%), itchy skin rashes (9, 37.5%), and diarrhea (3, 12.5%). Several factors were responsible for the observed rate of ADRs in this study. The young age of the participants is known to be associated with an increased risk of ADRs because of their underdeveloped body organs and systems. Children may not adequately handle the absorption,

distribution, metabolism, and excretion of drugs in the body when compared to older individuals. Drug-drug interactions (7.4%), which were also observed among the study participants, could have contributed notably to the ADRs. The lack of an active pharmacovigilance system at the ward as well as the genetic predisposition of some of the children could have also been responsible for the ADRs. ADRs can lead to discontinuation of treatment and switching to an alternative medication, which might be less effective or result in dose reduction as a way of managing the ADR, thereby lowering the final concentration of antibiotics in the body needed to treat pneumonia.²⁷ Furthermore, some ADRs have been shown to weaken the child's immunity, making it difficult for the body to fight infections. ADRs might require prolonged hospitalization, leading to exposure to hospital-acquired infections, which are usually resistant to treatment with subsequent treatment failure.²⁸

The outcomes of treatment failure reported in this study included prolonged hospitalization (83%), death (15.1%), complications of pneumonia such as meningitis (28.6%), sepsis (25.0%), pleural effusion (17.9%), empyema (17.9%), respiratory failure (7.1%), and pneumothorax (3.6%) and referral to a higher-level facility (1.9%). These findings tally with those from Spanish and Indian hospitals.^{15,29} Lengthier stays in hospitals and complications of pneumonia contribute to an increase in the daily health care costs and loss of productivity of the caretaker, with some households experiencing catastrophic health care expenditures.³⁰ The 15.1% mortality reported in this study is similar to previous studies done in Spain (25%), India (24%), and 21% in Bangladesh,^{15,24,29} but higher compared to studies done in Tanzania (4.8%), Malawi (7.6%) and Kenya (6%).^{4,17,22} The low death rate in the previous studies could be attributed to the different healthcare practices, with some of the studies conducted in settings with better access to diagnostic equipment, medication, and stringent guidelines for the management of pneumonia and its complications. This enables early detection and timely management, thereby averting death.

The current study had some limitations. First, the study was single-centered, and it employed a consecutive sampling method; both of these may limit the generalizability of the findings to a broader population. Moreover, the lack of culture

and sensitivity and other diagnostic tests to confirm bacterial pneumonia may affect the interpretation of response to antibiotic therapy and its subsequent identification as a treatment failure. Recall bias and poor medical recording may contribute to inaccurate or incomplete medication history and vaccination information. Similarly, limited time of follow-up on patients who were discharged in <7 days of the follow-up period might make it difficult to observe outcomes like late treatment failure.

Conclusion

The findings of this study indicate that treatment failure is still a big challenge among children under 5 years with pneumonia, and the risk of failure was predicted by severe acute malnutrition, adverse drug reactions, and a distance >5 km from the nearest health facility, with outcomes like prolonged hospitalization, death, referral to a higher-level facility, and complications of pneumonia. There is a need for early and accurate diagnosis, including culture and sensitivity tests, timely initiation of effective antibiotic therapy, active pharmacovigilance, and close monitoring of patients with acute malnutrition to reduce the likelihood of treatment failure. Furthermore, clinical pharmacy services should be embraced as part of patient care to diagnose, prevent, and manage medication-related problems on the wards, such as adverse drug reactions, drug interactions, medication errors, and promotion of rational use of medicines as a way of preventing treatment failure among children under five.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of Mbarara University of Science and Technology with IRB number: MUST-2024-1413. The hospital director of MRRH provided administrative clearance to conduct the study. Written informed consent was obtained from caretakers of each child before being enrolled into the study. The informed consent tool was translated into the local language Runyankole for caretakers who were unable to read and write English. The study participants' caregivers were then read the translated consent, and they used their thumbprints to indicate their agreement. Literate

family members and caregivers actively participated as witnesses to further assure the accuracy of the consent procedure, attesting to the accuracy of the consent document read aloud to the illiterate caretakers. The Mbarara University of Science and Technology's Research and Ethics Committee gave their approval to this process.

Consent for publication

Not applicable.

Author contributions

Laura Bacia: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft.

Stanslas Avaga: Data curation; Formal analysis; Writing – review & editing.

Simon Ngbape Ndrusini: Data curation; Methodology; Writing – review & editing.

Caroline Nakate: Data curation; Methodology; Writing – review & editing.

Abdu Damale: Data curation; Methodology; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data set and data collection tools used in this study are available upon reasonable request from the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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Appendix

Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ADR	Adverse Drug Reaction

AOR	Adjusted odds ratio	HIV	Human Immunodeficiency Virus
CAP	Community Acquired Pneumonia	ICU	Intensive Care Unit
CBC	Complete Blood Count	MAM	Moderate Acute Malnutrition
COPD	Chronic Obstructive Pulmonary Disease	MoH	Ministry of Health
COR	Crude odds ratio	MRRH	Mbarara Regional Referral Hospital
CRP	C-Reactive Protein	MUST	Mbarara University of Science and Technology
DDI	Drug–drug Interactions	PCT	Procalcitonin
DDRFD	Drug Dose Route Frequency Duration	PI	Principal Investigator
DRP	Drug-Related Problems	REC	Research Ethics Committee
FRC	Faculty Research Committee	SAM	Severe Acute Malnutrition
HDU	High Dependency Unit	TB	Tuberculosis
Hib	Haemophilus Influenza Type b	WHO	World Health Organization

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