One in four die from acute infectious illness in an emergency department in Eastern Cape Province, South Africa

A Jenson,[1] MD, MPH; **A Rao,**[2] MSPH; **P Mda,**[3] MD; **B Cawe,**[4] MB ChB; **J Iruedo,**[5] MB ChB, MMed, FCFP; **T Dubula,**[6] MB ChB, FCP (SA); **D Stead,**[7] MB ChB, MPhil, FCP (SA), ID Cert (SA); **R Rothman,**[1] MD, PhD; **B Hansoti,**[8] MD, MB ChB, PhD

[1] *Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, Md., USA*
[2] *Johns Hopkins University Bloomberg School of Public Health, Baltimore, Md., USA*
[3] *Faculty of Health Sciences, Walter Sisulu University, Mthatha, South Africa*
[4] *Head of Family Medicine, Mthatha Regional Hospital, Mthatha, South Africa*
[5] *Department of Family Medicine, Mthatha Regional Hospital, Mthatha, South Africa*
[6] *Head of Internal Medicine, Nelson Mandela Academic Hospital, Mthatha, South Africa*
[7] *Director of Infectious Diseases, Frere and Cecilia Makiwane hospitals, East London, South Africa*
[8] *Department of International Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Md., USA*

Corresponding author: *A Jenson (alexander.jenson@gmail.com)*

Background. Despite the breadth of data supporting evidence-based practice for sepsis care in high-resource settings, there are relatively few data to guide the management of sepsis in low-resource settings, particularly in areas where HIV and tuberculosis (TB) are prevalent. Furthermore, few studies had broadened sepsis parameters to include all patients with acute infectious illness or followed patients up after hospital discharge. Understanding the epidemiology and outcomes of acute infections in a local context is the critical first step to developing locally informed targeted management strategies.

Objectives. To quantify and describe the incidence of and risk factors for mortality in a cohort of patients with undifferentiated acute infectious illnesses who presented to an emergency department (ED) in the Eastern Cape region of South Africa (SA).

Methods. In this prospective cohort study, patients with suspected acute infectious illness were enrolled at a district casualty ward in Mthatha, SA, between 1 July and 1 September 2017. Demographic data, interventions, diagnostic studies and disposition were prospectively collected during the initial encounter and during the hospital stay. Follow-up was conducted both in hospital and via phone interviews 30 days after the index visit.

Results. A total of 301 patients presented to the ED with acute infectious illness during the study period, of whom 54.8% had complete 30-day follow-up. Of the study population, only 5.7% had a complete set of vital signs (heart rate, respiratory rate, blood pressure and temperature) documented. Of the cohort, 51.8% had HIV and 32.9% active or treated TB; 25.2% of patients died within 30 days. Accounting for medical history, diagnosis and ED interventions, risk of mortality was independently associated with age (odds ratio (OR) 1.03; 95% confidence interval (CI) 1.00 - 1.06), HIV-positive status (OR 4.10; 95% CI 1.44 - 11.67) and Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score (OR 1.90; 95% CI 1.14 - 3.19) in an adjusted model. No ED interventions were protective for mortality, with intravenous fluid administration associated with increased 30-day mortality in this cohort (OR 3.65; 95% CI 1.38 - 9.62).

Conclusions. Among adults with suspected acute infectious illness in Mthatha, SA, 30-day mortality was concerningly high. Mortality was highest in patients with concomitant HIV infection. In particular, vital sign assessment to identify possible sepsis in this cohort is crucial, as it affects mortality to a meaningful extent, yet is often unavailable. Future research is needed on the management of sepsis in low-resource settings, particularly in HIV-positive individuals.

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Acute infectious illnesses, while a major cause of morbidity and mortality across the world, disproportionally affect low-resource settings. In fact, >80% of worldwide deaths from infectious diseases, and resulting sepsis, occur in low- and middle-income countries (LMICs).[1,2] Landmark studies for management of life-threatening infectious diseases and septic shock in the emergency department (ED) and intensive care unit (ICU) have largely been conducted and validated in high-income countries (HICs).[3] The three pillars of sepsis management are aggressive fluid resuscitation, early broad-spectrum antimicrobial agents and invasive monitoring.[1,4-7] Unfortunately these approaches are not always feasible in LMICs. Blood tests and physiological parameters such as lactic acid, central venous pressure and mixed venous oxygen saturation are logistically challenging and expensive in LMICs,[8] and ventilators to manage complications from aggressive fluid resuscitation are scarce.[8,9]

Beyond resource limitations, it also remains unclear how the different causes of acute infectious illness in LMICs impact on the effectiveness of interventions that were previously tested in HICs. Acute infectious illnesses in LMICs include fungal, viral and parasitic infections that are rare in HICs,[1,7,10,11] where most infectious disease mortality is the result of severe bacterial infections.[12] In addition, patients in LMICs frequently have comorbidities such as HIV, tuberculosis (TB) and malnutrition, which alter host immunity and change the course of infectious illness.[9-11,13]

There are few data on what sepsis management strategies are most effective in settings that do not have advanced diagnostics and monitoring, and do have a higher burden of comorbidities such as malnutrition, HIV and TB.[1] Only a few dedicated studies on sepsis management in LMICs have been conducted, and most of these data are conflicting. Recent randomised controlled trials of

early goal-directed therapy for children with sepsis in Kenya,[14,15] and adults with severe sepsis in Zambia,[9,13] were halted early owing to increased mortality and respiratory complications in patients receiving aggressive resuscitation. Conversely, the only study on interventions for acute infectious illness in an ED in South Africa (SA), a retrospective analysis in urban Cape Town, showed a reduction in mortality with early antimicrobials and aggressive fluid resuscitation.[2] All these studies were focused on patients who had a diagnosis of 'sepsis' (based on vital signs or laboratory data) and were in a hospital setting. No study to this point has broadened the scope of investigation beyond patients with signs of sepsis to all those with acute infectious illnesses and those who were possibly seen in and discharged from an outpatient care setting. This is concerning, given that the resources required to diagnose sepsis are not always available, and studies to date may therefore misrepresent the mortality related to acute infectious illness, as limited and incomplete vital sign collection in resource-limited settings may under-represent true sepsis. Furthermore, the risk of mismanagement is highest in patients who are discharged based on a limited evaluation, as opposed to those admitted to an ICU. Lastly, only tracking patients during their hospital stay excludes potentially sick patients who were discharged and later suffered complications.

Objectives

This study prospectively evaluated a cohort of patients with undifferentiated acute infectious illness who presented to a busy district-level ED in Mthatha, SA, with the goal of quantifying the effect of ED management strategies on 30-day mortality in order to locally inform sepsis management guidelines and identify risk factors for poor clinical outcomes.

Methods

Study design and setting

This prospective observational pragmatic cohort study was conducted in the ED of Mthatha Regional Hospital from 1 July to 1 September 2017. Mthatha Regional Hospital is located in the rural city of Mthatha in Eastern Cape Province and is a secondary care centre that serves an area >3 000 km^2 and ~500 000 people. The ED has only 8 beds and is staffed by family medicine doctors, none of whom have formal training in emergency medicine. During business hours (Monday to Friday, 09h00 - 17h00) there are up to 5 providers in the EC, while only 2 remain overnight. The ED provides care 24 hours a day. Patients who present for care are triaged using the South African Triage Scale (SATS)[16] (although the SATS requires a complete set of vital signs, our study found that this was infrequently done). The vast majority of patients are seen in the order they arrived, the exception being those in extremis (defined as a SATS designation of 'Emergency'). There is no electronic health record, and patient tracking is recorded in handwritten logbooks, independently in the EC and in each ward if the patient is admitted.

Recruitment and enrolment

Given incomplete vital sign collection, the study expanded the inclusion criteria to include all patients with presumed acute infectious illness, such as lower respiratory tract infection, meningitis or acute otitis media. All patients who presented for care during the study period, were identified by study staff or ED providers to have an acute infectious illness and were aged >18 years were eligible for enrolment. The treating provider would notify study staff of such patients, and the study staff would approach the patient or family for consent for enrolment. Study staff were present in the ED 7 days a week from 07h00 to 19h00. While doctors could identify potential cases 24 hours a day, participants were only approached to give consent for enrolment during these hours. Study staff were trained in good clinical practice, informed consent practice, and data collection.

Outcomes and data collection

Demographic data collected on each patient included medical history, presenting complaint, and initial vital signs (when recorded) at enrolment. If vital signs were incomplete, study staff did not collect these data themselves, but simply left the data field blank. During the patient's stay in the ED, data were collected on diagnostic tests and therapeutic interventions performed, including volume of fluid resuscitation, antibiotic administered (if any), and intervention timing. Eventual disposition and final diagnosis were also collected.

The Systemic Inflammatory Response Syndrome (SIRS) criteria and Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) were calculated based on presenting vital signs, when recorded. These definitions were based on the Surviving Sepsis Campaign.[17-19] If a particular vital sign was not recorded, it was presumed to be in the normal range. Hypotension was defined as a systolic blood pressure (SBP) <90 mmHg or a mean arterial pressure (MAP) <65 mmHg.

Each patient was prospectively followed up during their admission or discharge. The primary study outcome was 30-day mortality. Secondary outcomes included requirement for admission and time to death. Patients were tracked during their admission for changes in diagnosis and clinical status (alive v. dead) during hospitalisation. In addition, each patient or patient family member was contacted by a study staff member 30 days after presentation, and data were collected on subsequent visits to the hospital, clinical status at 30 days, and date of death if the patient had died. The study staff performing follow-up phone calls were blinded to the initial presentation and the ED interventions.

Sample size and data analysis

Previous studies on outcomes of acute infectious illness in low-resource settings estimated a 15% 30-day mortality. The necessary power for a mortality estimate of 15%, with 5% precision, 95% confidence and a power of 0.8, required 196 patients to be enrolled. Data were analysed using a descriptive statistical approach using Stata v.12 (StataCorp, USA). Descriptive statistics were generated for specific demographic covariates, ED diagnoses and ED interventions.

To analyse the effect of demographic covariates and ED interventions on mortality, multiple logistic regressions with forward stepwise elimination were used. For specific univariate comparisons on rates of mortality in groups receiving antibiotics, HIV tests, and intravenous (IV) fluids in the ED, two-tailed *t*-tests were used. In addition, Cox proportional hazards and survival analyses were performed to analyse the effect of demographics and interventions on time to death. These models included age, gender, past medical history, qSOFA score, ED interventions, disposition and ED diagnosis in the model, preselected prior to study implementation.

Ethical considerations

The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board (ref. no. IRB00135764), the University of Cape Town Human Research Ethics Committee, and the Walter Sisulu University Human Research Ethics Committee (ref. no. 013/2017). Written consent was obtained for all participants who enrolled in the study, or from the patient's next of kin if they were unable to consent at the time of enrolment. Written consent was conducted in English or isiXhosa, with a translator present at all times if there was a language discrepancy between study staff and participant.

Results

Of the 4 623 patients who presented to the ED during the study period, 710 (15.4%) were suspected of having an acute infectious illness, of whom 310 (43.6%) were approached by study staff and enrolled (Fig. 1). It is notable that of the 710 patients who were diagnosed with an infectious illness, 28 were not approached because they were paediatric, and 372 patients were missed for enrolment. For the 372 who were missed, only limited data were available for ED log books. The average age for missed patients was 46.6 years (average age for enrolled patients 46.5 years), 50.7% (*n*=189) were male (41.5% of enrolled patients were male), and 1.8% (*n*=7) died in the ED. Of the patients who were not enrolled but were eligible, 54.0% (*n*=201) were eventually discharged from the ED, many before daytime hours resumed for enrolment.

Demographics

Baseline demographics were collected on all patients enrolled in the study (Table 1). The majority of the patients were between 31 and 50 years old (35.6%) and most were

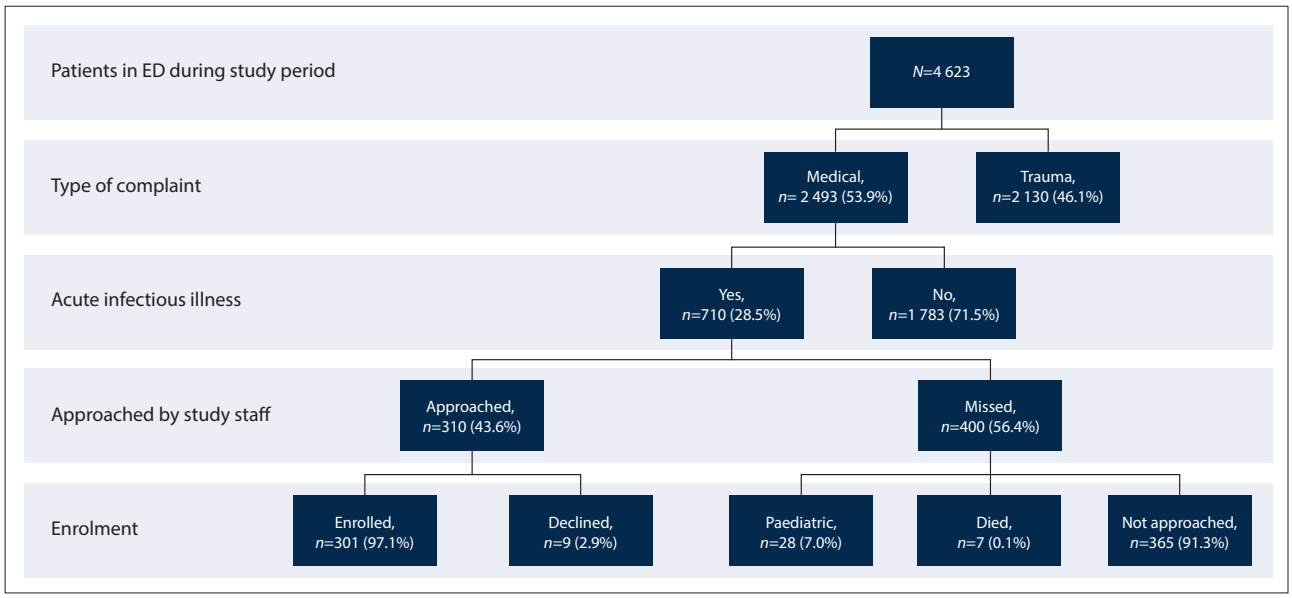

Fig. 1. Study enrolment procedure. (ED = emergency department.)

Table 1. Demographics on presentation stratified by follow-up

Variable	Incomplete follow-up (*N*=136), *n* (%)	Complete follow-up (*N*=165), *n* (%)	Total (*N*=301), *n* (%)
Age (years)			
18 - 30	36 (26.5)	39 (23.6)	75 (24.9)
31 - 50	46 (33.8)	61 (37.0)	107 (35.6)
51 - 70	35 (25.7)	39 (23.6)	74 (24.6)
≥71	19 (14.0)	26 (15.8)	45 (15.0)
Sex			
Male	49 (36.0)	76 (46.1)	125 (41.5)
Female	87 (64.0)	89 (53.9)	176 (58.5)
Vital signs			
HR ≤100 bpm	63 (46.3)	76 (46.1)	139 (46.2)
HR >100 bpm	42 (30.9)	53 (32.1)	95 (31.6)
Hypotensive	19 (14.0)	19 (11.5)	38 (12.6)
Non-hypotensive	96 (70.6)	116 (70.3)	212 (70.4)
Altered mental status	15 (11.0)	31 (18.8)	46 (16.7)
qSOFA ≥2	15 (11.0)	20 (12.1)	35 (11.6)
SIRS ≥2	39 (28.7)	54 (32.7)	93 (30.9)
Past medical history			
HTN	21 (15.4)	21 (12.7)	42 (14.0)
DM	11 (8.1)	10 (6.1)	21 (7.0)
CAD	1 (0.7)	0	1 (0.3)
COPD	5 (3.7)	4 (2.4)	9 (3.0)
HIV	63 (46.6)	96 (56.8)	156 (51.8)
TB	42 (30.9)	44 (26.7)	86 (28.6)

HR = heart rate; qSOFA = Quick Sequential (Sepsis-Related) Organ Failure Assessment; SIRS = Systemic Inflammatory Response Syndrome; HTN = hypertension; DM = diabetes mellitus; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; TB = tuberculosis.

female (58.5%). At presentation, 30.9% of patients (*n*=93) were septic according to SIRS criteria (SIRS ≥2), and 11.6% (*n*=35) had a qSOFA score of at least two criteria, corresponding to high mortality. However, only 12.6% of patients (*n*=38) were hypotensive (SBP <90 or MAP <65) on presentation. HIV was either reported or subsequently diagnosed in 51.8% of patients (*n*=156), and 28.6% (*n*=86) reported a history of previous or active TB. Of those with known 30-day clinical status (*n*=165), 25.5% (*n*=42) died within 30 days of the index visit.

ED management

The ED management data divided by final outcome (death, alive or lost to follow-up) are presented in Table 2. While in the ED, only 5.7% of the enrolled patients (*n*=17) had a full set of vital signs (temperature, respiratory rate, heart rate and blood pressure) recorded in the chart; 65.1% (*n*=196) had a chest radiograph and 23.7% (*n*=71) had an HIV test. Sixteen new diagnoses of HIV were made in the ED, representing 22.5% of HIV tests performed and 5.3% of the cohort (Table 2). Patients who died were less likely to have received an HIV test compared with those still alive at 30 days, but this was not significant (14.6% v. 27.6%; *p*=0.094%) (Table 2).

The majority of patients (86.0%; *n*=259) received antibiotics while in the ED, of whom 62.8% (*n*=163) received ceftriaxone as monotherapy and 21.2% (*n*=55) received ceftriaxone and another antibiotic. There was no significant difference in mortality based on antibiotic prescription practices in the ED (Table 2; *p*=0.431 for comparison of mortality between groups by antibiotic administration). Of note, no patients received coverage for *Mycobacterium tuberculosis* or *Pneumocystis jirovecii* within the first 24 hours after presentation.

Overall, IV fluids were used sparingly; 39.2% of patients (*n*=118) did not receive any fluids in the first 6 hours, and 51.1% (*n*=153) received 1 L of fluids. Only 10% of patients (*n*=30) received >1 L of fluids in the first 6 hours. In the subset of patients who eventually died, a larger proportion received 1 L of fluids or >1 L of fluids (66.7% and 14.3%, respectively) compared with patients who survived the follow-up period (44.7% and 8.1%, respectively) (*p*=0.002 when comparing 1 L with no fluids, *p*=0.015 when comparing >1 L with no fluids). Among those who died, rates of IV fluid administration were similar among those who died within 2 days (86.7%) and those who died between 2 and 30 days (77.8%) (*p*=0.494).

The majority of patients (52.5%; *n*=158) were diagnosed with a respiratory infection, followed by TB or possible TB (23.6%; *n*=71), possible meningitis (10.3%; *n*=31) or abdominal infection (9.6%; *n*=29).

Of patients enrolled, 24.9% (*n*=76) were initially discharged, 36.5% (*n*=110) were admitted, and 36.9% (*n*=111) were 'observed' in the ED, with eventual disposition pending test results and clinical course. Of those who died, the majority (53.7%; *n*=22) were admitted, although 9.8% (*n*=4) of patients who died were initially discharged from the ED after the index visit. Of enrolled patients, 7.3% (*n*=3) died while in the EC.

Table 2. ED patient care stratified by follow-up and outcome

Variable	Incomplete follow-up (*N*=136), *n* (%)	Complete follow-up		Total (*N*=301), *n* (%)
		Alive (*N*=123), *n* (%)	Dead (*N*=42), *n* (%)	
Full vital signs recorded (temp, RR, HR, BP)	5 (3.7)	9 (7.3)	3 (7.1)	17 (5.7)
Work-up				
Chest radiograph	86 (63.2)	85 (69.1)	25 (59.5)	196 (65.1)
Lumbar puncture	18 (14.6)	18 (14.6)	4 (9.8)	40 (13.3)
HIV test	31 (22.8)	34 (27.6)	6 (14.6)	71 (23.7)
TB test	33 (24.3)	30 (24.4)	10 (23.8)	73 (24.3)
Interventions				
Blood transfusion	13 (9.6)	5 (4.1)	5 (11.9)	23 (7.6)
Antibiotics in the ED	116 (85.2)	105 (85.4)	38 (90.2)	257 (86.0)
Oxygen in the ED	18 (13.3)	21 (17.2)	13 (31.0)	52 (17.4)
Fluids				
No fluids at 6 hours	58 (42.6)	58 (47.2)	8 (19.0)	118 (39.2)
1 L at 6 hours	64 (47.1)	55 (44.7)	28 (66.7)	153 (51.1)
>1 L at 6 hours	14 (10.3)	10 (8.1)	6 (14.3)	30 (10.0)
No blood drawn	50 (36.8)	53 (43.1)	14 (33.3)	117 (38.9)
Diagnosis (at least 1)				
Lung infection	69 (50.7)	68 (55.3)	21 (50.0)	158 (52.5)
Abdominal infection	15 (11.8)	8 (6.5)	5 (11.9)	29 (9.6)
Meningitis	13 (9.6)	13 (10.6)	5 (11.9)	31 (10.3)
Urinary tract infection	6 (4.4)	3 (2.4)	0 (0)	9 (3.0)
TB/possible TB	28 (20.6)	33 (26.8)	10 (23.8)	71 (23.6)
Fever of unknown origin	2 (1.5)	1 (0.8)	3 (7.1)	6 (2.0)
Disposition				
Discharge	33 (24.3)	39 (31.7)	4 (9.8)	76 (24.9)
Admit/transfer	33 (24.3)	38 (30.9)	22 (53.7)	110 (36.5)
Observe	53 (39.0)	46 (37.4)	12 (29.3)	111 (36.9)
Died	0	0	3 (7.3)	3 (1.0)

ED = emergency department; temp = temperature; RR = respiratory rate; HR = heart rate; BP = blood pressure; TB = tuberculosis.

Predictors of mortality

Multiple demographic and therapeutic factors were associated with 30-day mortality on follow-up (Table 3). In univariate analysis, age (odds ratio (OR) 1.03; 95% confidence interval (CI) 1.01 - 1.06), HIV (OR 4.10; 95% CI 1.52 - 11.01), qSOFA score (OR 1.99; 95% CI 1.22 - 3.24), and IV fluids (per litre) (OR 2.17; 95% CI 1.15 - 4.07) all positively predicted mortality. In a multivariate regression, age (OR 1.03; 95% CI 1.01 - 1.06), HIV (OR 4.10; 95% CI 1.44 - 11.67), qSOFA score (OR 1.90; 95% CI 1.14 - 3.19) and IV fluid therapy (OR 3.65; 95% CI 1.38 - 9.62) remained significantly associated with mortality, while lung infection (OR 0.41; 95% CI 0.17 - 0.99) was protective against mortality. Of note, an initial decision to admit the patient, while trending towards increasing mortality, was not significantly predictive in the model (OR 2.47; 95% CI 0.80 - 7.64).

Survival analysis

When modelled as a survival function (Fig. 2A), HIV status significantly predicted time to 30-day mortality. This was retained in a multivariate Cox proportional hazard model (hazard = 7.58; 95% CI 1.91 - 29.99; $p<0.01$). The majority of this discrepancy in death occurred after day 7 (Fig. 2A), when the proportion of HIV-positive patients still living continued to decline, while deaths in HIV-negative patients plateaued. In addition, while the overall administration of IV fluids was associated with mortality (Fig. 2B) ($p=0.045$), the difference between 1 L of IV fluid and >1 L of IV fluid was not associated with mortality (Fig. 2B).

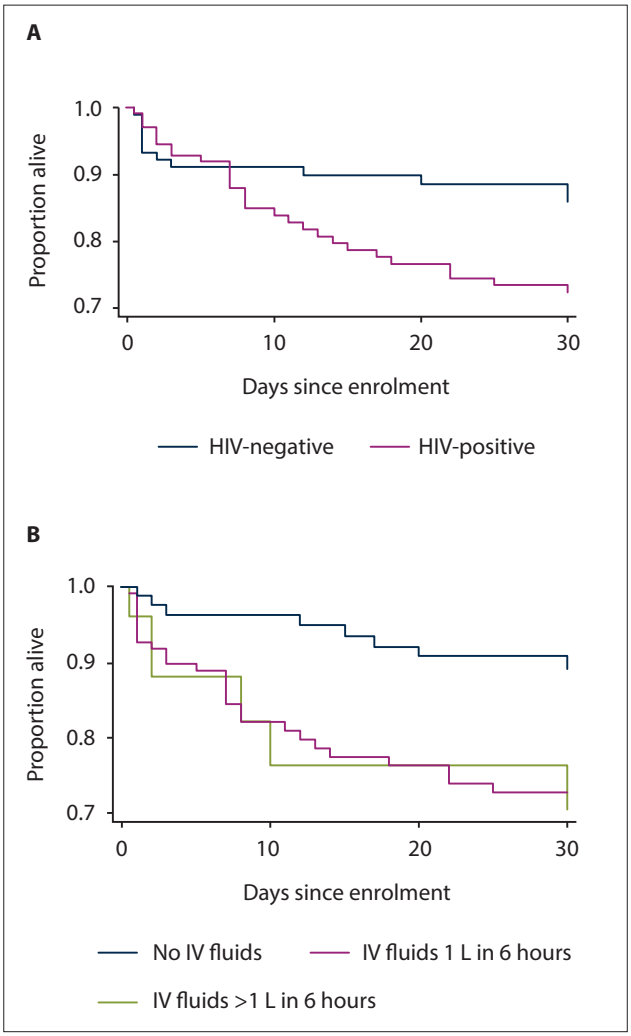

Fig. 2. 30-day survival according to HIV status (A, significant by Cox proportional hazards model) and IV fluids received in 6 hours (B, difference between no IV fluids and any IV fluids significant by Cox proportional hazards model). (IV = intravenous.)

Discussion

This study is the first of its kind to collect prospective data on management of and 30-day mortality associated with acute infectious illness in the emergency setting in sub-Saharan Africa. We show that over a quarter of these patients died within 30 days of their index visit to the ED. The only other comparable study in SA, conducted in urban Cape Town, only followed up patients with sepsis or septic shock, and demonstrated 34% mortality for the total cohort, but only 17% mortality for the sepsis (i.e. without hypotension) cohort.[2] Our study was conducted in a rural resource-limited setting, and demonstrates that acute infectious illness, independent of concomitant sepsis or septic shock, represents a potentially life-threatening condition. In addition, following up patients to a full 30 days, including post-discharge phone calls, demonstrated that a surprisingly high proportion of discharged patients (9.8%) and observed patients (29.3%) died by 30 days. This cohort probably represents individuals who were thought to be clinically stable for discharge yet had high sepsis-related mortality. Furthermore, the study indicates that infectious illness is a potential touchstone for patient engagement and post-discharge follow-up, as mortality remains high regardless of disposition.

In addition to evaluating the total burden of acute infectious illness at this rural district hospital, this study reaffirms the relationship between sepsis indicators, most notably qSOFA, and mortality. Unsurprisingly in a population with presumed infectious illness, qSOFA positively predicted 30-day mortality linearly, even in adjusted analysis, with each qSOFA point nearly doubling 30-day mortality (Table 3). This reproduces similar studies evaluating patients with acute infectious illness across the globe, including multicentre observational studies in high-resource settings.[20] In low-resource settings, other studies have demonstrated the usefulness of qSOFA in acute infectious illness, both in patients with fever or leukocytosis in Gabon[21] and in patients with HIV and sepsis in Rwanda.[22] The utility of qSOFA lies in the ease of data collection, as it relies only on a sphygmomanometer and direct observation to measure blood pressure, altered mental status and respiratory rate.[20,22] Notably, mortality was concerningly high in patients with low qSOFA in our study setting, i.e. 23% of patients with a SIRS score of 0 - 1 and 14% of patients with a qSOFA score of 0 during their initial EC evaluation died within 30 days.

More importantly, it is worth noting that only 5% of patients had requisite vital signs collected to identify the components of sepsis, making formal sepsis identification an under-estimate of the true prevalence of sepsis in this population. For the purpose of analysis, missing data were presumed to be normal. However, these incomplete data are a real-world demonstration of the difficulty for physicians to assess short-term mortality in this cohort with missing information. Previous studies in sub-Saharan Africa have focused only on patients with sepsis, severe sepsis and septic shock, and only on in-hospital mortality.[2,5,9,13,23] Our data demonstrate that we must expand this scope, as many of the patients in our study did not meet 'sepsis' criteria yet still died from acute infectious illness. Furthermore, we anticipate that inadequate vital sign collection makes identifying cases of sepsis difficult.

Of all possible factors associated with 30-day mortality both in a survival (Fig. 2) and linear regression (Table 3) model, HIV was

Table 3. Predictors of 30-day mortality in patients with acute infectious illness

	Univariate		Adjusted (stepwise selection)*	
Variables	**OR**	**95% CI**	**OR**	**95% CI**
Demographics				
Age	**1.03**	**1.01 - 1.06**	**1.03**	**1.00 - 1.06**
Gender	0.82	0.38 - 1.79	0.65	0.38 - 1.79
HIV (Hx or new)	**4.10**	**1.52 - 11.01**	**4.10**	**1.44 - 11.67**
Hx of TB	0.94	0.42 - 2.11	0.94	0.42 - 2.11
qSOFA score	**1.99**	**1.22 - 3.24**	**1.90**	**1.14 - 3.19**
Therapeutics				
IV fluids (per L) within 6 hours	**2.17**	**1.15 - 4.07**	**3.65**	**1.38 - 9.62**
Blood transfusion	3.33	0.83 - 13.39		
Oxygen in ED	2.18	0.90 - 5.31	**2.32**	**0.84 - 6.40**
Antibiotic in ED	1.18	0.35 - 3.97		
Diagnosis				
Lung infection	0.66	0.30 - 1.41	**0.41**	**0.17 - 0.99**
Abdominal infection	1.56	0.44 - 5.59		
Meningitis	1.29	0.80 - 7.64		
Admission				
Admit to ICU or floor	2.64	0.90 - 7.72	2.47	0.80 - 7.64

OR = odds ratio; CI = confidence interval; Hx = history of; qSOFA = Quick Sequential (Sepsis-Related) Organ Failure Assessment; IV = intravenous; ED = emergency department; ICU = intensive care unit; AIC = Akaike information criterion.
*Stepwise selection model by AIC with demographic covariates locked.
Bold font signifies $p<0.05$ for OR >1.0.

most strongly associated with mortality. In our cohort, mortality for HIV-positive patients presenting with acute infectious illness was >31%. This is similar to other data on inpatient mortality in an HIV-positive cohort,[2,9,13,23] but our study included patients who were discharged showing extremely high mortality rates. Studies on sepsis, severe sepsis and septic shock conducted in sub-Saharan Africa have shown non-significant associations with HIV and mortality.[2,9,13,23] However, those cohorts had larger proportions of patients who were HIV-positive (~80% as opposed to ~50% in our population). In addition, our study followed up patients to 30 days, and the majority of the difference in HIV-associated infectious illness mortality was after 7 days in our data (Fig. 2). This discrepancy in time to follow-up shows that more studies need to evaluate the effect of HIV and infectious illness on mortality after discharge, and prospectively follow up patients to 30 days after the index visit. Future studies also need to evaluate the efficacy of antiretroviral therapy (ART) in this population to reduce this mortality, and the utility of these HIV therapies in preventing infectious illness mortality in the acute setting.

In SA, studies of the association between HIV, acute infectious illness and mortality have largely been limited to the surgical sepsis literature,[24,25] which demonstrated a positive relationship between HIV infection and in-hospital mortality. The present study demonstrates the increasing need to view the ED as a feasible and necessary location for HIV counselling and testing.[26] Given the significant impact of mortality in the setting of acute infection, knowing a patient's HIV status is an essential element in adequate treatment, disposition and follow-up for the ED provider in this population. Moreover, the ED can be a possible link to ART initiation and aggressive HIV management.[26]

This study fits into a current active debate regarding appropriate fluid administration in HIV-prevalent sub-Saharan Africa. Previous studies in children in Kenya[14,15] and adults in Zambia[9,13] have questioned the applicability of aggressive fluid resuscitation in this context, as overloading septic patients with fluid could worsen respiratory status. Our data (Table 3, Fig. 2B) demonstrate a positive association between fluid administration and mortality in an observational cohort. Even in our population, when subdividing the population by time of death (mortality within 2 days compared with mortality after 2 days), mortality was associated with ED IV fluid resuscitation in both groups, and there was no significant difference in IV fluid administration between the group that died early and those who died later.

That said, the longer follow-up of our population (30-day mortality rather than in-hospital mortality) made our positive association less clinically relevant, as emergency IV fluid resuscitation is less relevant to long-term mortality as time extends from the ED visit. In examining Fig. 2B, the association between IVF and death is most significant in the first 10 days after ED presentation, and attenuates as time goes on. In this association between IV fluid in the ED and 30-day mortality, we are probably also measuring the significant confounder of severity of illness. Sicker patients are more likely to receive IV fluid, blood transfusions and oxygen in the ED, all of which had positive univariate associations with mortality. These may simply be markers of severity of illness rather than independent factors predicting mortality. More research is needed to prospectively evaluate the utility of fluids in the HIV-prevalent SA context, preferably in a resource mix of urban and rural settings.

This study raises several questions that require further investigation. Prospective randomised studies are required in the SA context to evaluate the relationship between IV fluid resuscitation and mortality in septic patients. In addition, more studies are required in varied practice settings to validate our result of 30-day mortality for all acute infectious illness. Studies to this point have focused on in-hospital mortality and the septic subset, but our data suggest that future studies should expand their scope to all presentations of acute infectious diseases, and should include 30-day and not simply in-hospital mortality.

Study limitations

While this study adds an essential component to the literature on infectious illness management in SA, there are notable limitations.

First, as it was a prospective cohort study, one can only infer associations with the outcome of interest (mortality). Second, owing to budget constraints this was a largely convenience sample that relied on provider identification of suspected acute infectious illness and daylight-hours enrolment (Fig. 1). As a result, 372 of a possible 700 patients were missed during the enrolment phase, either because they were not identified by providers or presented when a study worker was not present. Of those 372, 7 died in the ED (1.8%), which was similar to the mortality rate for enrolled patients (1.0%). That said, the average age of the two groups was similar (46.5 years v. 47.3 years in the enrolled v. missed groups). A larger proportion of the missed groups were eventually discharged, as they were discharged overnight before a study staff member could approach them, and were therefore missed. This may have caused an over-estimate of mortality in this population, as more ill patients were enrolled because they were still present when study staff returned during daylight hours.

In addition, owing to resource constraints in the Eastern Cape (unreliable phone coverage and infrastructure, etc.), follow-up of patients was very difficult, and almost 50% of patients were lost to follow-up during the 30-day period. This is similar to other studies in the developing world and is a major reason why most studies use in-hospital mortality as an outcome. We considered that the benefit of true mortality even after hospital discharge was an essential missing component of the literature, and this study provides valuable data despite this limitation. As a result of this proportion of patients who were lost to follow-up, mortality may in fact have been under-estimated, as patients who die are difficult to locate for follow-up. Conversely, patients who die in hospital have a known outcome and will be included in the data. Finally, vital sign collection was almost universally incomplete. This skewed the interpretation of contributors of mortality, but presented a real-world representation of the challenges of caring for patients with incomplete data at the time of care.

Conclusions

Our study, the first of its kind to evaluate 30-day mortality in adult patients presenting to an ED with presumed acute infectious illness, demonstrated 25% 30-day mortality for this cohort. Concomitant HIV infection (present in 52% of this cohort) significantly increased the odds of mortality and represents a potential point of contact for urgent linkage to ART in this population. In addition, treatment with IV fluids was associated with increased mortality, particularly early in the disease course, but was probably confounded by severity of illness. More research is needed to evaluate this association in a prospective controlled fashion. In studying acute infectious illness in an emergency context, we must expand our scope from simply severe sepsis and septic shock, as these data demonstrate that mortality remains high for all patients presenting with acute infectious illness. Infectious illness, particularly in an HIV-positive patient in this setting, represents a significant threat to life, and must be treated as such.

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Author contributions. AJ conceived the original idea. AJ, BH, DS and RR designed the protocol. AJ, AR, PM, BC, JI and TD co-ordinated the study and data collection. AJ and AR carried out analysis of data. AJ and BH prepared the manuscript.

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