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Outcomes of patients with severe infection in Uganda according to adherence to the World Health Organization's Integrated Management of Adolescent and Adult Illness fluid resuscitation guidelines

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ABSTRACT

Purpose: We determined outcomes in hospitalized patients in Uganda with World Health Organization's Integrated Management of Adolescent and Adult Illness (IMAI) defined septic shock (IMAI-shock) or severe respiratory distress without shock (IMAI-SRD) based on whether they received recommended fluid resuscitation according to IMAI guidelines.
Materials and methods: We performed a secondary analysis of a prospective cohort of adult septic patients in Uganda that included the volume of fluids patients received during the first 6 h of resuscitation. We used logistic regression to determine predictors of outcomes.
Results: We evaluated 122 patients with IMAI-shock and 32 patients with IMAI-SRD. For patients with IMAI-shock or IMAI-SRD, there was no difference in mortality between those that received IMAI recommended fluid volume and those that did not (30% vs 36%, $p = 0.788$; 22% vs 57%, $p = 0.08$). For patients with IMAI-shock, in-hospital mortality was associated with mid-upper arm circumference (adjusted odds ratio [aOR] 0.841, 95% confidence interval [CI] 0.722–0.979, $p = 0.026$) and ambulation (aOR 0.247, 95%CI 0.084–0.727, $p = 0.011$). We found no associations with in-hospital mortality for patients with IMAI-SRD.
Conclusion: IMAI recommended fluid resuscitation was not associated with better outcomes for patients with IMAI-shock or IMAI-SRD. Further studies are needed to optimize resuscitation for patients with severe infection in resource-limited settings such as Uganda.

1. Introduction

Critical illness including septic shock and severe respiratory distress is a leading cause of hospitalization and mortality in resource-limited settings such as most of sub-Saharan Africa (SSA). This burden includes 1.8–2.2 million cases of sepsis and 130–650 thousand cases of acute lung injury in SSA annually [1]. Despite this growing critically ill population, the capacity to diagnose, treat, and monitor these patients remains limited and there are few intensive care unit beds to manage them [2]. In that light, in 2011 the World Health Organization published the Integrated Management of Adolescent and Adult Illness (IMAI) District Clinician Manual as a resource to guide the management of many common severe illnesses in austere environments [3].

The manual provides recommendations for oxygen, antimicrobial therapy, and fluid administration as well as monitoring strategies for patients with septic shock (IMAI-shock) and severe respiratory distress without shock (IMAI-SRD) in the first 2, 2–6, and 6–24 h of resuscitation. These recommendations were derived by experts based on studies from high income settings, which may not be translatable to low income settings, and limited available evidence from austere environments [4]. However, fluid resuscitation studies of children and adults with severe infection in SSA have revealed the possible negative impact of high fluid volumes in these patients, particularly those with hypoxemic respiratory failure [5,6].

The IMAI guidelines for management of IMAI-shock and IMAI-SRD have not been evaluated in a real-world setting. Therefore, it is not clear that their broad implementation would lead to improved outcomes. Accordingly, in this study we aimed to determine whether adherence to IMAI fluid administration guidelines during the critical first 6 h of resuscitation would improve in-hospital mortality for patients

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with IMAI-shock or IMAI-SRD. Our hypothesis was that patients with IMAI-shock or IMAI-SRD that received IMAI recommended fluid volumes within the first six hours of admission would have improved in-hospital mortality compared to those that did not.

2. Materials and methods

2.1. Enrollment and definitions

We analyzed data from a previously published cohort of patients with severe sepsis admitted to Mbarara Regional Referral Hospital (MRRH) in Southwestern Uganda [7]. The hospital has an inpatient bed capacity of approximately 400 and serves as the main referral center for Southwestern Uganda including the neighboring parts of Rwanda and the Democratic Republic of Congo. Patients admitted with sepsis are initially evaluated in the medical emergency ward and then transferred to the general medical ward. The medical emergency ward has 8–10 beds and is staffed with 1 nurse, 2 intern doctors, 1 resident doctor and 1 attending physician. The hospital has a fully accredited microbiology and general medical laboratory.

For the original study, we enrolled patients from the medical emergency ward where they or a guardian provided informed consent. We obtained vital signs and blood lactate measurements (Lactate plus, Nova Biomedical Corporation, Waltham, MA, USA) at admission and then six hours after resuscitation. All values were reported to the primary team. We recorded the volume of fluid each patient received over the first 6 h of resuscitation and followed them in hospital until their discharge or death. For this analysis, we selected patients meeting criteria for 1) IMAI-shock defined as suspected infection, systolic blood pressure (SBP) <90 mm Hg and at least 1 of the following: pulse >100 beats per minute, respiratory rate >24 breaths per minute, or temperature < 36 °C or >38 °C, or 2) IMAI-SRD defined as suspected pneumonia or acute lung injury without heart failure, respiratory rate >30 or SpO_2 <90, and SBP >90 mm Hg [4].

We determined whether patients in each group received fluid resuscitation according to IMAI recommendations during the first 6 h of resuscitation [3]. For patients with IMAI-shock, the guidelines recommend an initial 1 L fluid bolus of lactated ringers solution or normal saline followed by an infusion of 20 mL/kg/h up to 60 mL/kg within the first 2 h. At that point, if the SBP is >90 mm Hg, the fluids should continue at 2 mL/kg/h; if the SBP is ≤90 mm Hg, the fluids should continue at 5–10 mL/kg/h until 6 h of resuscitation is completed. Patients with IMAI-SRD should receive fluids at 1 mL/kg/h over the course of 6 h with no preceding bolus. We assumed 50–70 kg as the approximate average weight for patients based on a prior study of the association of nutritional status with mortality for patients admitted to MRRH [8]. We considered patients in the IMAI-shock group who received 2.4–6 L of fluid and patients in the IMAI-SRD group who received 0.3–0.5 L of fluid as adherent to IMAI fluid guidelines for the first 6 h of resuscitation.

2.2. Statistical analysis

We recorded data using Epi-Info (Centers for Disease Control, Atlanta, Ga, 2011) and used SPSS software (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, New York) for all analyses. We summarized patient characteristics as frequency with percentage for categorical variables and median with interquartile range (IQR) for continuous variables. We used the Chi-squared test for comparisons of proportions and the Mann-Whitney *U* test for comparisons of continuous variables. We determined relationships between clinical and laboratory variables and outcomes using logistic regression. For the logistic regression models, we adjusted for severity of illness a priori by including heart and respiratory rate, blood pressure, oxygen saturation, lactate concentration, and ambulatory status. Given the high prevalence of HIV in our study population, we also adjusted for chronic illness by including mid-upper arm circumference. We did not include predictor variables that were correlated with each other as defined by a Pearson correlation p value <0.05 (e.g. ambulatory status and Glasgow coma scale score). We considered a two-sided p value <0.05 significant for all statistical tests.

2.3. Ethical considerations

The study was approved by both the Faculty Ethics Review Committee and Institutional Ethical Review Committee of Mbarara University of Science and Technology, as well as the Institutional Review Board of the University of Virginia.

3. Results

3.1. Patient characteristics

We included 122 patients with IMAI-shock and 32 patients with IMAI-SRD. The demographics of both groups were similar with a median age of 35 and 31 years, respectively, and an equal proportion of male and female patients (Table 1). In the IMAI-shock group, the prevalence of HIV infection was 62% and the median (IQR) CD4+ T cell concentration was 66 (15–197) cells/μL. The median (IQR) mean arterial pressure (MAP) was 55 (43–67) mm Hg, the heart rate was 120 (106–140) beats/min, the respiratory rate was 33 (28–40) breaths/min, the temperature was 38 (36–39) °C, and the oxygen saturation was 91 (83–95) %. The median (IQR) lactate concentration at admission was 3.4 (2.2–5.6) mmol/L. In the IMAI-SRD group, the prevalence of HIV infection was 53% and the median (IQR) CD4+ T cell concentration was 44 (9–94) cells/μL. The median (IQR) MAP was 83 (74–92) mm Hg, the heart rate was 120 (107–140) beats/min, the respiratory rate was 39 (32–44) breaths/min, the temperature was 38 (37–39) °C, and the oxygen saturation was 93 (86–95) %. The median (IQR) lactate concentration at admission was 3.4 (1.9–5.7) mmol/L.

Table 1
Patient characteristics.

	IMAI-shock, $N = 122$	IMAI-SRD, $N = 32$
Age (years), median (IQR)	35 (26–45)	31 (25–57)
Female, n (%)	61 (50)	15 (48)
HIV+, n (%)	76 (62)	17 (53)
CD4+ T-cell concentration (cells/μL), median (IQR)	66 (15–197)	44 (9–94)
WHO stage, median (IQR)	4 (3–4)	4 (3–4)
SBP (mm Hg), median (IQR)	80 (60–80)	110 (100–125)
DBP (mm Hg), median (IQR)	45 (30–60)	70 (60–70)
MAP (mm Hg), median (IQR)	55 (43–67)	83 (74–92)
Heart rate (bpm), median (IQR)	120 (106–140)	120 (107–140)
Respiratory rate (brpm), median (IQR)	33 (28–40)	39 (32–44)
Temperature (°C), median (IQR)	38 (36–39)	38 (37–39)
O_2 saturation (%), median (IQR)	91 (83–95)	93 (86–95)
GCS, median (IQR)	15 (15–15)	14 (10–15)
MUAC (cm), median (IQR)	21 (19–24)	23 (21–26)
WBC (K cells/μL), median (IQR)	7 (4–12)	7 (5–17)
Hemoglobin (g/dL), median (IQR)	11 (8–13)	11 (4–14)
Platelets (K cells/μL), median (IQR)	166 (98–297)	96 (53–241)
Glucose	92 (8–131)	123 (13–156)
Lactate (mmol/L), median (IQR)	3.4 (2.2–5.6)	3.4 (1.9–5.7)
Antibiotics given, n (%)	105 (88)	29 (94)
Oxygen given, n (%)	6 (5)	7 (23)
Blood given, n (%)	13 (11)	8 (27)
Total fluids (cc), n (%)	1500 (1000–2000)	1000 (500–1500)

Bpm = beats/min, brpm = breaths/min, CD = cluster designation, DBP = diastolic blood pressure, GCS = Glasgow coma scale, HIV = human immunodeficiency virus, IQR = interquartile range, MAP = mean arterial pressure, MUAC = mid-upper arm circumference, SBP = systolic blood pressure, WBC = white blood cell, WHO = World Health Organization.

3.2. Fluid resuscitation

Patients with IMAI-shock that did ($N = 28$) or did not ($N = 94$) receive IMAI recommended fluid resuscitation were similar at baseline with the exception of lower oxygen saturation (86 vs 93%, $p = 0.004$), SBP (55 vs 80 mm Hg, $p = 0.019$), DBP (33 vs 50 mm Hg, $p = 0.001$), and MAP (46 vs 58 mm Hg, $p = 0.004$) in the group that received IMAI recommended fluids (Table 2). After 6 h of resuscitation, the group that received IMAI recommended fluids received a greater volume of fluids than those that did not (3 vs 1.5 L). This group also had increased lactate clearance compared to the group that did not receive IMAI recommended fluids (34 vs 19%, $p = 0.003$). There was no difference in the number of patients that developed IMAI-SRD after 6 h of resuscitation between patients with IMAI-shock that did or did not receive IMAI recommended fluid administration (21 vs 20%, $p = 0.95$). In the adjusted analysis, mean arterial pressure was independently associated with receipt of IMAI recommended fluids (adjusted odds ratio [aOR] 0.978, 95% confidence interval [CI] 0.957–0.999, $p = 0.048$). For patients with IMAI-SRD, except for the volume of fluids received (0.5 L vs 1 L), there were no clinical or laboratory differences at baseline or at 6 h between those who did ($N = 9$) or did not ($N = 23$) receive IMAI recommended fluid resuscitation (Table 3). Due to the small number of patients with IMAI-SRD, we did not perform an adjusted analysis of predictors of receiving IMAI recommended fluids for this group of patients.

3.3. Mortality

The overall in-hospital mortality was 32% for patients with IMAI-shock and 45% for patients with IMAI-SRD. There was no difference in in-hospital mortality between patients who did or did not receive IMAI recommended fluids for IMAI-shock (30% vs 36%, $p = 0.788$) or for IMAI-SRD (22% vs 57%, $p = 0.080$). For patients with IMAI-shock, in the adjusted analysis, in-hospital mortality was independently associated with mid-upper arm circumference (aOR 0.841, 95%CI 0.722–0.979, $p = 0.026$) and ambulation (aOR 0.247, 95%CI 0.084–0.727, $p = 0.011$; Table 4). Due to the small number of patients with IMAI-SRD, we did not perform an adjusted analysis of predictors of mortality for this group of patients.

4. Discussion

Despite the high mortality rates associated with severe infections in resource-limited settings, best treatment practices in these environments remain unknown. We evaluated the outcomes of patients with severe infections in Uganda according to whether or not they received IMAI recommended fluid resuscitation. For patients with IMAI-shock, the majority of our patients, we found that adherence to IMAI fluid resuscitation guidelines was associated with admission blood pressure. However, after adjusting for severe and chronic illness, adherence to IMAI guidelines was not associated with in-hospital mortality. Instead, in-hospital mortality was more closely associated with wasting and ability to ambulate.

It is possible that clinicians made decisions related to fluid resuscitation based on perceived severity of illness [7,9]. In a prior study conducted at the same site in Uganda, patients with severe sepsis and an admission CRB-65 score ≥3 received an average of 1 L more of fluid compared to patients with a CRB-65 score of 1 or 2 [9]. In our study, patients with IMAI-shock that received IMAI recommended fluid volumes had a lower mean arterial blood pressure and oxygen saturation at admission than those that did not but there was no difference in these values after 6 h of resuscitation. There was also increased lactate clearance in patients that received IMAI recommended fluids compared to those that did not. Taken together, these findings suggest that patients that received IMAI recommended fluid volumes were more severely ill at admission with decreased end-organ perfusion that was recognized by clinicians and improved with resuscitation.

Patients with IMAI-SRD received less fluid than patients with IMAI-shock perhaps indicating that clinicians were concerned about worsening pulmonary edema and causing respiratory failure. This is a legitimate concern given the findings of the FEAST trial which found that fluid boluses significantly increased 48-hour mortality in critically ill African children with infection and impaired perfusion [6]. Furthermore, a study of early goal-directed therapy in adults with severe sepsis in Zambia had to be stopped due to a high (100%) mortality in patients with hypoxemic respiratory failure in the intervention arm [5]. These patients received 2.8 vs 1.6 L of fluid for controls over the first 6 h of resuscitation. However, in our study, patients with IMAI-shock who received IMAI recommended fluids of approximately 3 L were not more likely to develop severe respiratory distress at the end of 6 h of resuscitation.

Despite improvements in blood pressure and lactate concentration over the first 6 h of resuscitation in patients with IMAI-shock, there was no difference in in-hospital mortality between patients that did or did not receive IMAI recommended fluid resuscitation. Patients with IMAI-shock were more likely to die if they were wasted with a reduced mid-upper arm circumference and less likely to die if they were ambulatory at admission. Wasting is a known risk factor for in-hospital mortality for hospitalized patients in SSA, particularly for those with HIV-infection [8]. In a recent study from Uganda, patients that were able to ambulate at admission had a 60-day mortality of 5% compared to 25% if they had an unstable gait, or 50% if they were bedridden [10]. Similarly, poor Karnofsky Performance Scale scores were a significant risk

Table 2
Patient characteristics of patients with IMAI-shock at baseline ($T = 0$) and 6 h after resuscitation ($T = 6$) according to whether they did (IMAI fluids +) or did not (IMAI fluids −) receive IMAI recommended fluid resuscitation.

	IMAI fluids (+) $N = 28$ $T = 0$	IMAI fluids (−) $N = 94$ $T = 0$	p	IMAI fluids (+) $N = 28$ $T = 6$	IMAI fluids (−) $N = 94$ $T = 6$	p
Temperature (°C), median (IQR)	37 (35–39)	38 (37–39)	0.085	37 (36–38)	38 (37–38)	0.105
Heart rate (bpm), median (IQR)	125 (113–140)	120 (105–140)	0.649	108 (96–128)	112 (100–120)	0.939
Respiratory rate (brpm), median (IQR)	36 (28–44)	32 (26–40)	0.643	28 (22–35)	28 (24–32)	0.687
O_2 saturation (%), median (IQR)	86 (67–94)	93 (86–96)	0.004	94 (86–96)	93 (88–96)	0.863
Lactate (mmol/L), median (IQR)	4.6 (2.3–7.3)	3.3 (2.2–4.8)	0.083	2.6 (1.6–4.1)	2.8 (1.7–4.1)	0.746
SBP (mm Hg), median (IQR)	55 (0–82)	80 (70–81)	0.019	90 (70–100)	90 (82–100)	0.121
DBP (mm Hg), median (IQR)	33 (0–43)	50 (40–60)	0.001	50 (40–60)	60 (50–70)	0.031
MAP (mm Hg), median (IQR)	46 (0–57)	58 (50–67)	0.004	62 (50–77)	70 (62–78)	0.063
≥10 mm Hg increase SBP, n (%)	–	–	–	19 (68)	69 (74)	0.509
≥10 mm Hg increase DBP, n (%)	–	–	–	15 (58)	50 (55)	0.804
≥10 mm Hg increase MAP, n (%)	–	–	–	15 (58)	51 (56)	0.881
≥10 brpm decrease in respiration rate, n (%)	–	–	–	7 (25)	17 (19)	0.483
≥10 bpm decrease in heart rate, n (%)	–	–	–	15 (60)	49 (56)	0.743
Lactate clearance, median (IQR)	–	–	–	34 (20–54)	19 (−7–36)	0.003

Bpm = beats/min, brpm = breaths/min, DBP = diastolic blood pressure, IQR = interquartile range, MAP = mean arterial pressure, SBP = systolic blood pressure.

Table 3
Patient characteristics of patients with IMAI-SRD at baseline ($T = 0$) and 6 h after resuscitation ($T = 6$) according to whether they did (IMAI fluids +) or did not (IMAI fluids −) receive IMAI recommended fluid resuscitation.

	IMAI fluids (+) $N = 9$ $T = 0$	IMAI fluids (−) $N = 23$ $T = 0$	p	IMAI fluids (+) $N = 9$ $T = 6$	IMAI fluids (−) $N = 23$ $T = 6$	p
Temperature (°C), median (IQR)	38 (37–40)	38 (37–39)	0.592	38 (37–39)	38 (37–38)	0.183
Heart rate (bpm), median (IQR)	126 (111–138)	118 (101–140)	0.593	112 (107–120)	113 (94–121)	0.651
Respiratory rate (brpm), median (IQR)	40 (28–44)	36 (32–44)	0.934	32 (20–40)	28 (27–36)	0.749
O_2 saturation (%), median (IQR)	92 (86–95)	93 (86–95)	0.869	90 (83–95)	94 (88–96)	0.213
Lactate (mmol/L), median (IQR)	2.5 (2.0–4.1)	4.1 (1.8–6.1)	0.433	2.2 (1.2–4.8)	2.1 (1.4–4.1)	0.869
SBP (mm Hg), median (IQR)	120 (110–130)	110 (100–122)	0.157	110 (100–112)	108 (100–120)	0.902
DBP (mm Hg), median (IQR)	70 (50–70)	70 (60–75)	0.742	70 (55–80)	70 (58–80)	0.773
MAP (mm Hg), median (IQR)	85 (76–87)	83 (73–93)	0.869	83 (73–91)	80 (71–89)	0.805
≥10 mm Hg increase SBP, n (%)	–	–	–	9 (100)	3 (13)	0.255
≥10 mm Hg increase DBP, n (%)	–	–	–	4 (44)	6 (26)	0.314
≥10 mm Hg increase MAP, n (%)	–	–	–	1 (11)	3 (13)	0.882
≥10 brpm decrease in respiration rate, n (%)	–	–	–	3 (33)	9 (41)	0.694
≥10 bpm decrease in heart rate, n (%)	–	–	–	3 (33)	13 (59)	0.193
Lactate clearance, median (IQR)	–	–	–	27 (−10–40)	21 (15–56)	0.681

Bpm = beats/min, brpm = breaths/min, DBP = diastolic blood pressure, IQR = interquartile range, MAP = mean arterial pressure, SBP = systolic blood pressure.

factor for mortality in a prior study of patients with severe sepsis in Uganda [11].

The etiology of excess mortality in patients with severe infection in SSA is likely multifactorial and may reduce the effectiveness of fluid resuscitation strategies including the IMAI fluid resuscitation guidelines. First, there is a high prevalence of HIV infection and immunosuppression which predisposes patients to severe infection and critical illness [5,12]. Second, the etiologies of infection are not easily recognized due to limited diagnostic resources. For example, many patients with severe sepsis are infected with *Mycobacterium tuberculosis* which is not frequently diagnosed or treated at presentation and is associated with a high mortality [5,13]. Third, monitoring of critically ill patients in resource-limited settings is sporadic and therefore opportunities to further resuscitate patients after admission to the general ward may be missed [9,14]. Equally, if not more importantly, given the problems with over-resuscitation identified in the FEAST and Zambia sepsis studies, respiratory distress due to pulmonary edema requiring diuresis may also go unrecognized. Finally, even if acute decompensation is recognized and appropriately treated, critically ill patients may still die if they do not have access to an intensive care unit level of support including mechanical ventilation and vasopressor administration [2].

Our study had several limitations. Notably, we recorded the volume of fluids administered to patients with severe infection over the first 6 h of resuscitation which are generally considered the most crucial time period in sepsis therapy and analyzed outcomes accordingly [15]. Therefore, it is possible that patients that received IMAI recommended fluids for the full 24 h may have had better, or based on the FEAST and Zambia sepsis studies, worse outcomes. Our analyses were dependent on a convenience sample of patients that met IMAI-shock and IMAI-SRD criteria and may have been underpowered; therefore, future prospective randomized studies of IMAI fluid resuscitation guidelines should be considered. There may also have been unmeasured confounders that influenced patient outcomes. For example, radiologic and microbiologic diagnostic maneuvers are limited at MRRH and therefore the influence of source control and underlying infection, e.g. tuberculosis, on response to IMAI recommended fluid is not known. Nonetheless, we have shown that fluid resuscitation of patients with severe infection in Uganda is likely sub-optimal and that further study and refinement of IMAI fluid resuscitation guidelines are needed.

Table 4
Multivariate analysis of clinical predictors for in-hospital mortality for patients with IMAI-shock.

	Adjusted odds ratio	95% confidence interval	p
Mean arterial pressure (mm Hg)	0.992	0.971–1.014	0.472
Heart rate (bpm)	1.002	0.979–1.024	0.892
Respiratory rate (brpm)	0.989	0.943–1.037	0.653
Oxygen saturation (%)	0.998	0.973–1.023	0.857
Mid-upper arm circumference (cm)	0.841	0.722–0.979	0.026
Ambulatory	0.247	0.084–0.727	0.011
IMAI recommended fluids (L)	1.251	0.359–4.362	0.725

Bpm = beats/min, brpm = breaths/min, IMAI = Integrated Management of Adolescent and Adult Illness.

5. Conclusion

IMAI guidelines for fluid resuscitation of patients with severe infection in resource-limited settings have not been previously evaluated. We found that there were no differences in outcomes for patients that did or did not receive IMAI recommended fluids for either IMAI-shock or IMAI-SRD. Instead, in-hospital mortality was associated with wasting and ambulatory status at admission. Further prospective studies of IMAI and other fluid resuscitation protocols are needed to better understand the optimal resuscitation and monitoring strategy for severely septic patients in resource-limited settings.

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