REVIEW PAPER

Surviving Sepsis in High HIV Prevalence Settings

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Sepsis, also known as septicaemia, is a systemic inflammatory response to severe infection. The most common case definition requires two or more systemic inflammatory response syndrome (SIRS) criteria in the presence of a presumed life-threatening infection (see Table 1). In its most severe forms, sepsis leads to multiple organ dysfunction, septic shock, and death. Sepsis affects adults and children and is a common diagnosis in medical, surgical, and obstetric patients. Thus, doctors of all specialties must be familiar with its signs, symptoms and treatment.

In sub-Saharan Africa, the problem of sepsis is compounded by the HIV/AIDS epidemic. In two Ugandan referral hospitals, 85% of patients admitted with sepsis were HIV positive[1]. Studies among AIDS patients on highly active antiretroviral therapy (HAART) in Sub-Saharan Africa identified bacterial sepsis as the cause of death in up to 19% of fatalities[2]. The true number is likely much higher, since this estimate doesn't include patients with sepsis due to tuberculosis or cryptococcal infection. Although control of the HIV epidemic must focus on prevention and early detection and treatment, acute infections manifesting as sepsis remain a major cause of morbidity and mortality. Optimal management of severe sepsis and septic shock is an important goal for Sub-Saharan Africa healthcare providers.

In 2001, a multinational advisory committee published evidence-based guidelines for the management of severe sepsis and septic shock under the title "The Surviving Sepsis Campaign"(SSC). In 2008, the committee updated these guidelines to reflect changes in the available evidence[3]. Many Western hospitals have incorporated portions of the guidelines into intensive care unit (ICU) protocols. In Sub-Saharan Africa, the use of these guidelines has been limited, due in part to limited resources but also to lack of awareness. Additionally, the validity of the Campaign's evidence-based recommendations for non-Western settings has not been fully explored. This article will review the surviving sepsis guidelines for adult sepsis management and focus on their applicability to Zambia and other countries with high HIV prevalence.

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Surviving Sepsis Campaign

SSC guidelines are separated into three broad areas: (1) initial resuscitation and infection management, (2) hemodynamic support and adjunctive therapy, and (3) other supportive therapy.

Initial resuscitation and infection management

Initial resuscitation encompasses care delivered in the first six hours after the recognition of sepsis. The guidelines recommend immediate resuscitation targeting goals of central venous pressure (CVP) of 8 – 12 mmHg, Mean Arterial Pressure (MAP) ≥65 mm Hg, urine output ≥0.5 mL/kg/hr, and central venous oxygen saturation (CVO_2) ≥ 70%. These recommendations were based on a study in the United States by Rivers et al that randomized pts to standard ICU care versus an early goal-directed therapy (EGDT) protocol[4]. All patients in the EGDT group had CVP and CVO_2 monitoring. They received IV fluids to reach CVP of 8-12 mm, then vasopressors, if necessary, to reach MAP≥65 mm. If CVO_2 was < 70%, then patients received dobutamine to improve cardiac contractility, and those with

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Table 1: Diagnostic criteria

Systemic Inflammatory Response Syndrome (SIRS)	Two or more of the following: - Core temperature > 38 C or < 36 C - Heart rate > 90 - Respiratory rate > 20 or PaCO2 < 32 mmHg or mechanical ventilation - White cell count > 12,000/mm^3 or < 4000/mm^3 or > 10% bandemia
Sepsis	Presence of SIRS and life-threatening infection
Severe Sepsis	Presence of sepsis and sepsis-induced organ dysfunction[26]: - Skin mottling - Decreased capillary refill - Urinary output < 0.5 mL/kg/hr - Serum lactic acid > 1 mmol/L - Change in mental status - Platelets < 100,000/mL - INR > 1.5 - Bilirubin > 70 mmol/L - ALI/ARDS - Cardiac dysfunction
Sepsis with hypotension	Sepsis and SBP <90 or MAP <70 mm Hg
Septic shock	Severe sepsis with: - MAP < 60 mm Hg after 40-60 mL/kg IV saline or - Need for vasopressors to maintain MAP>60
Refractory septic shock	Need for dopamine > 15 mcg/kg/minute to maintain MAP > 60

MAP = mean arterial pressure = (2xDBP + SBP)/3
DBP = diastolic blood pressure; SBP = systolic blood pressure
ALI = acute lung injury; ARDS = acute respiratory distress syndrome

hematocrit < 30% received red cell transfusion. The EGDT group had a 16% lower absolute risk of death compared with standard management (30.5% vs. 46.5%). Although the two groups received almost identical amounts of fluids over the first 72 hours (13.4 L vs. 13.3 L), the EGDT group received significantly more fluid in the first six hours (5.0 L vs. 3.5 L).

Infection management recommendations address diagnosis, antibiotics, and source control. The recommendations stress the culturing of potential infection sites prior to initiation of antibiotics and the prompt imaging of suspected anatomic foci. Broad-spectrum intravenous antibiotics should be started as early as possible. A study of septic shock patients by Kumar et al in Canadian ICUs found that patients who received effective antibiotics within the first hour of hypotension had a survival rate of 79.9%[5]. Survival rates decreased by 7.6% for each hour of delay up to six hours and continued to decrease with delays up to 3 days. Antibiotic selection should reflect local microbiologic patterns, if known. Antibiotics should generally be limited to 7 – 10 days unless otherwise indicated, and should be narrowed when susceptibilities are known. As early as possible, the medical team should identify the anatomic site of infection and determine if source control measures, including surgical drainage and catheter removal, are needed.

Hemodynamic Support and Adjunctive Therapy

Interventions for stabilizing hemodynamic status are separated into fluid therapy, vasopressors, inotropes, and steroids. Fluid therapy should begin with 1000 mL boluses of crystalloid fluids (e.g. normal saline) over 30 minutes while monitoring the hemodynamic response. Boluses should be repeated until CVP reaches at least 8 mm Hg. Based on the SAFE study in Australia, colloid and crystalloid fluids are considered equally effective methods of volume resuscitation[6]. In that study, 6997 intensive care patients were randomized to either 4% albumin or normal saline fluids. There were no differences in mortality (21% in both groups) or ICU or hospital lengths of stay.

If MAP remains below 65 mm Hg despite adequate fluid administration, vasopressors should be started. Norepinephrine or dopamine are the preferred vasopressors and should be administered through a central venous line. Low-dose dopamine (< 5 mcg/kg/min) should not be used for renal protection. A large randomized trial and meta-analysis showed no differences in renal function between those

receiving low-dose dopamine and placebo[7,8]. Dobutamine should be considered in septic patients with low cardiac output.

The recommendations regarding corticosteroid use in sepsis have changed over the years. A recent large trial of septic shock patients found no survival benefit from the use of hydrocortisone 50mg IV every six hours[9]. This study contrasted with an earlier one that only included septic shock patients with persistent hypotension despite fluids and vasopressors[10]. The earlier study showed a 10% absolute decrease in mortality in patients receiving steroids (53% vs. 63%). The guidelines conclude that corticosteroids be given only to septic shock patients whose blood pressure does not respond to fluid and vasopressor therapies.

Recombinant activated protein C is recommended for patients with sepsis-induced multi-organ failure and high risk of death (APACHE II score > 24). Currently, practical resource allocation in most Sub-Saharan countries precludes the availability of this therapy.

Other Supportive Therapies

Several other therapies should be considered for improved outcomes in septic patients. Red blood cell transfusion may be beneficial. However, a multicenter randomized trial in Canada showed no difference between target hemoglobins of 7.0-9.0 g/dL compared with 10.0-12.0 g/dL[11]. Mechanical ventilation, if available, should be used in patients with respiratory failure. In patients with Acute Lung Injury (ALI) or Acute Respiratory Distress (ARDS), tidal volumes should be set at 6 mL/kg of ideal body weight with plateau pressures of 30 cm H_20 or less. In an ARDSNET trial, this strategy reduced mortality from 40% to 31% compared with tidal volumes of 12 mL/kg[12]. DVT prophylaxis with heparin or low molecular weight heparin, and stress ulcer prophylaxis are recommended for all septic patients. Hemodialysis can be considered in appropriate patients with renal failure. If patients have hyperglycemia, an insulin drip or sliding scale may be used, but there is no benefit with tight (5-6 mmol/L) versus standard glucose control[13].

HIV-positive patient representation in studies

Nearly all of the studies cited in the Surviving Sepsis Campaign were conducted in North America, Europe, or Australia, where HIV prevalences are < 1%. Thus most of these studies included very few HIV positive patients. Additionally, many studies used HIV infection or low CD4 count as exclusion criteria. Table 2 gives patient characteristics of studies mentioned in the previous sections.

Table 2: HIV patient inclusion in sepsis studies

Treatment	Study	Location	Diagnosis	HIV & patient inclusion
Early goal-directed therapy	Rivers, et al[4]	United States	Severe sepsis	Immunosuppression excluded 3% of pts HIV+
Antibiotics < 1hr	Kumar, et al[5]	Canada	Septic shock	1.4% AIDS 15% on immunosuppressive tx
Albumin vs. Crystalloids	SAFE[6]	Australia/ NZ	ICU pts, 18% sepsis	Not excluded, number not specified
Steroids	CORTICUS[9]	Europe and Israel	Septic shock	Immunosuppression excluded
	Annane, et al[10]	France	Refractory septic shock	AIDS excluded
Activated Protein C	PROWESS[15]	Worldwide	Severe sepsis	Excluded CD4 < 50
Goal Hb	Hebert, et al[11]	Canada	ICU pts, 6% sepsis	Not excluded, number not specified
Low tidal volumes	ARDSNET[12]	United States	ARDS, 26% sepsis	Not excluded, number not specified
Insulin	COIITSS[13]	France	Septic shock	Not excluded, number not specified

The lack of HIV-positive patient representation may limit the generalizability of some findings. For example, anaemia is very common among HIV-infected patients, and the causes and chronicity of anaemia differ in HIV-positive versus HIV-negative African patients[14]. It is unclear how these variables may impact on hemoglobin goals for transfusion. Similarly, HIV-positive patients were excluded from CORTICUS and the corticosteroid trial by Annane[9,10]. Even in the absence of sepsis, HIV-positive patients are predisposed to adrenal insufficiency from tuberculosis, opportunistic infections, or HIV itself. Baseline adrenal insufficiency and immunosuppression may alter the risk-benefit ratio of empiric corticosteroids for septic shock.

Researchers have begun to investigate sepsis management strategies in HIV positive patients. However, most of the studies have been limited by their observational designs. In Uganda, Jacob et al followed 382 patients admitted with sepsis and SBP less than 100 mm Hg[1]. Eighty-five percent of patients were HIV positive with a median CD4 count of 52 cells/mm3. The main objectives of the study were to identify clinical predictors of mortality and to describe the management and epidemiology of sepsis in this setting. Only 12% of patients received at least 1500 mLs of fluid within the first six hours. Those who received fluids within one hour of enrollment actually had a higher mortality rate than those who did not (64% vs. 49%). Early (< 1 hour) administration of antibiotics was not associated with improved outcomes. The authors attributed the results to the heterogeneous usage of antibiotics and the possibility that sicker patients with poorer prognosis were triaged to receive antibiotics and fluids earlier than less sick patients.

HIV-specific considerations

Bacterial and mycobacterial etiologies

Infective etiologies in HIV positive patients and in high-HIV prevalence regions differ from those reported in the SSC studies. Among SSC studies that reported microbiology results, blood cultures were positive in 30-36% of cases and a causative organism was identified from some culture site in 66-76%[5,15]. The most common pathogens were *Escherichia coli* (16-22% of positive cultures), *Staphylococcus aureus* (15%), and *Streptococcus pneumoniae* (8-12%).

In contrast, studies of bloodstream infections in sub-Saharan Africa have found low prevalence of E.coli or Staph aureus. Instead, *Mycobacterium tuberculosis* (TB) and non-typhi salmonella species have been the predominant pathogens, particularly in HIV positive patients (see table 3)[1,16-19]. In four studies that reported results by HIV serostatus, 16% of all HIV positive febrile patients had TB mycobacteremia[16-19]. These accounted for 45% of all positive blood cultures. An additional 26% of positive cultures grew salmonella species. Overall, HIV positive patients were nearly three times as likely to have positive blood cultures (37% vs. 13%). With the exception of one study in Uganda, disseminated nontuberculous mycobacteria have not been routinely detected.

Table 3 Studies of bloodstream infections in patients with fever

	Patients	Positive Culture	TB	NTBM	NTS	SP	GN	SA
	n (%)	n (%)	n (% of positive cultures by HIV status)					
Malawi								
Peters, et al[15]				2†			9†	1†
HIV+	291 (83)	118 (41)	55(47)		44 (37)	13 (11)		
HIV-	61 (17)	10 (16)	2 (20)		2 (20)	3 (30)		
Archibald[16]								
HIV+	173 (74)	62 (36)	20 (32)	4(6)	12 (19)	21(34)	4 (6)	0
HIV-	60 (26)	8 (13)	0	0	1 (13)	4(50)	2 (25)	0
Tanzania								
Archibald[17]								
HIV+	282 (55)	118 (42)	57 (48)	0	23(19)‡	6 (5)	14(12)	5 (4)
HIV-	235 (45)	27 (11)	3 (11)	1 (3)	7 (26)	5 (19)	8 (30)	8 (30)
Uganda								
Jacobs, et al[1] ^	381	72(19)	25**	30**	20†	6†	5†	12†
HIV+	320 (85)*		†	†				
HIV-	57 (15)							
Ssali, et al[18]								
HIV+	227 (76)	61 (27)	28 (46)	2 (3)	13 (21)‡	11(18)	5 (8)	0
HIV-	72 (24)	11 (15)	0	0	0	4(36)	3 (27)	2 (18)

CN – *Cryptococcus neoformans;* GN – gram negative bacteriae other than salmonella; NTBM – Nontuberculous mycobacteria; NTS – nontyphoid salmonella species; SA – *Staphylococcus aureus;* SP – *Streptococcus pneumonia;* TB – *Mycobacteria tuberculosis*

† Results not available by HIV status
‡ All salmonella species, including typhi
^ Indication for culturing was sepsis. Only 58% of pts had fever on admission.
*only 377 patients tested for HIV
**out of 249 pts tested for mycobacterial blood cultures

Sepsis tuberculosa gravissima, or severe sepsis due to TB, can progress to multiorgan failure and septic shock. Zahar described 99 pts with pulmonary TB treated in two French ICU's, 60% of whom were HIV positive[20]. Significant predictors of mortality were symptom onset more than one month before treatment initiation, number of organ failures, serum albumin < 20 g/L, and number of involved lung lobes on chest x-ray.

Other infections

Physicians caring for HIV positive septic patients must consider other opportunistic infections (OI) as potential causes of sepsis. Cryptococcal meningitis has been identified as the cause of death in up to 20% of AIDS patients on HAART in sub-Saharan Africa and should be suspected in HIV positive patients with sepsis and headache[2]. *Toxoplasma gondii* may be an underdiagnosed etiology of sepsis among HIV postive patients. In one French study, 8 (29%) of 28 HIV+ pts with septic shock had OI as etiologic agent[21]. Four patients had Toxoplasma gondii, 2 had crypto neoformans, one had aspergillus, and one had CMV sepsis. A study of HIV positive patients in Cote d'Ivoire attributed 10% of deaths to toxoplasmosis[22]. In addition to the commonly known neurologic manifestations, toxo can cause myocarditis, pneumonitis, adrenalitis, and gastrointestinal disease.

Most African autopsy studies have found *Pneumocystis jiroveci* (PCP) in less than 10% of AIDS fatalities, but a bronchoscopy study in Zimbabwe detected PCP in 8 of 37 (22%) HIV positive patients with cough, weight loss, fever, and dyspnoea[23]. Therefore, PCP should also be suspected in septic patients with pulmonary complaints. Cytomegalovirus (CMV) disease has diffuse systemic manifestations and can result in severe sepsis. CMV has been relatively uncommon in Africa, but it was identified as the cause of death in 4% of AIDS inpatients in one Kenyan study[22].

Although malaria is not an opportunistic infection, high-prevalence regions overlap those of HIV. Clinically, malaria shares many features of bacterial sepsis, including fever, tachycardia, anemia, confusion, and multiorgan failure. Thus, in endemic regions, the diagnosis of malaria should always be considered among septic patients. In several African studies, rates of malaria treatment failure have been consistently higher among HIV positive patients, particularly in adults and those with low CD4 counts[24]. Consequently, malaria-infected patients with HIV co-infection should be subject to closer monitoring and follow-up.

Antiretrovirals in acute sepsis

There is limited data regarding when to continue antiretroviral therapy in patients admitted to the hospital with sepsis. If the patient has had a positive clinical or virologic response on antiretroviral therapy (ART), then it is reasonable to continue. Sepsis- or drug-induced organ damage (hepato- or nephrotoxicity, anaemia, lactic acidosis) may necessitate stopping or changing drug regimens.

Recent guidelines have recommended earlier initiation of ART in naïve patients during acute opportunistic infection. An American study by Zolopa et al showed a 9.9% absolute risk reduction for death or AIDS progression with early ART initiation[25]. However, even in the early start group, acute opportunistic or bacterial infections were treated for a median of 12 days before ART was begun. Stabilization of the patient and initial evaluation and treatment of acute infections should precede initiation of ART. When ART is initiated in hospital, patients should be monitored for signs of immune reconstitution inflammatory syndrome (IRIS) such as fevers or paradoxical worsening of symptoms.

RECOMMENDATIONS

Table 4 gives a summary of recommendations for managing sepsis in Sub-Saharan Africa. Although this approach is not evidence-based, if central venous oxygen saturation and pressure are not measurable, goal-directed therapy can be altered to allow the use of clinical parameters such as jugular venous pulsation and urine output. Where available, vasopressors should be used for hypotension refractory to fluids. In medical facilities where blood cultures are not available, priority should be given to early imaging and to obtaining gram stains of sputum, cerebrospinal fluid, and pus swabs. Ciprofloxacin or third-generation cephalosporins should be used when salmonella infection is suspected. If available, third-generation cephalosporins are also appropriate for empiric treatment of severe pneumonia or bacterial meningitis. Tuberculosis and opportunistic infections such as toxoplasma, cryptococcus, penumocystis, and cytomegalovirus should be suspected and treated if signs and symptoms are suggestive. If possible, mycobacterial blood cultures should be sent in every HIV positive patient with fever. Consider administering corticosteroids to patients with

Table 4: Recommendations for management of severe sepsis and septic shock

Recommendation	Considerations
Aggressive fluid resuscitation One litre in first 30 minutes Repeat every 30-60 minutes	- Most patients require 3-5L in 1st 6 hours - Monitor CVP (goal: 8-12 mm Hg) or JVP (0 to 3 cm above sternal notch) - Monitor urine output (goal: >0.5mL/kg/hr)
Vasopressors (if available) if pt still hypotensive after fluid challenge	- Target MAP ?65 - Start dopamine at 5 mcg/kg/min
Obtain appropriate cultures and gram stains: Blood cultures (if available), sputum gram stain & culture; sputum AFB stain; urine dipstick, microscopy, and culture; deep pus swabs	- Obtain prior to antibiotics if possible - Mycobacterial blood culture in HIV+ pts (if available)
Broad-spectrum antimicrobials	- Tailor empiric treatment to cover potential pathogens based on regional patterns and HIV status/CD4 count
Corticosteroids if patient still hypotensive after fluids and vasopressors, or if suspect HIV- or TB-related adrenal insufficiency	- Ensure that all suspected pathogens are treated
Blood transfusion if Hb < 7	- Goal Hb 7-9
Mechanical ventilation (if available) for patients in respiratory failure	- Set tidal volume at 5-7 mL/kg ideal body weight
Heparin 5000 Int Units SQ TID for DVT prophylaxis	- In all severe sepsis pts, if resources allow, unless contraindicate
H2 blocker or proton pump inhibitor for GI prophylaxis	- In all severe sepsis pts, if resources allow - Weigh risks (pneumonia) and benefits in mechanically ventilated patients

refractory septic shock, particularly those with high suspicion for TB adrenalitis. However, all suspected pathogens should be treated empirically if starting corticosteroids, and hydrocortisone doses should not exceed 50mg four times a day when used for this indication.

CONCLUSION

Severe sepsis is a common condition that more frequently affects immunocompromised patients. Although much has been written about severe sepsis and septic shock, very few studies have examined these processes in HIV positive patients. The Surviving Sepsis Campaign provides an important framework for sepsis management that can be adjusted to account for HIV- and region-specific concerns. Further research is needed to identify best practices in the management of severe sepsis and septic shock in resource-limited and high HIV prevalence settings.

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