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The development of an emergency sepsis care algorithm in Botswana

Le développement d'un algorithme de prise en charge d'urgence des états septiques au Botswana

Andrew Kestler [a,b,*], Amit Chandra [a], Karabo Thokwane [a], Ngaire Caruso [a], Miriam Haverkamp [c,d], Michelle Haas [c,d,e]

[a] *Princess Marina Hospital & Department of Emergency Medicine, University of Botswana, School of Medicine, Private Bag UB00713, Corner of Notwane and Mobuto Road, Gaborone, Botswana*
[b] *Department of Emergency Medicine, St. Paul's Hospital & University of British Columbia, Faculty of Medicine, 1081 Burrard Street, Vancouver, BC, Canada V6Z1Y6*
[c] *Princess Marina Hospital & Department of Medicine, University of Botswana, School of Medicine, Private Bag UB00713, Corner of Notwane and Mobuto Road Gaborone, Botswana*
[d] *Botswana-University of Pennsylvania Partnership, PO Box AC 157 ACH, Gaborone, Botswana*
[e] *Denver Health Medical Center, 777 Bannock Street, Denver, CO 80204, USA*

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Abstract *Introduction:* Sepsis is a common cause of morbidity and mortality in populations with a high prevalence of HIV, but the full package of early goal directed therapy (EGDT) for sepsis is not feasible in most low and middle-income countries. The objective was to develop emergency adult sepsis care guidelines for Botswana appropriate to available resources and local epidemiology in referral hospitals and in lower levels of care.
Methods: The individual components of guidelines from the Surviving Sepsis Campaign were compared with available resources for their applicability in a tertiary referral hospital in Botswana.

* Corresponding author at: Department of Emergency Medicine, St. Paul's Hospital & University of British Columbia, Faculty of Medicine, 1081 Burrard Street, Vancouver, BC, Canada V6Z1Y6. Tel.: +1 604 806 8480; fax: +1 604 806 8488.
E-mail address: andrew.kestler@ubc.ca (A. Kestler).

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Antibiotics were chosen based on the hospital antibiogram, national antibiotic guidelines, and the cost and availability of antibiotics. The preliminary algorithm was presented to emergency centre medical officers in a referral hospital for feasibility and acceptability of implementation. The referral hospital guideline was further modified as part of a National Guidelines Project for suitability to all levels of care.
Results: An acceptable and feasible sepsis algorithm was developed and implemented in a referral hospital in Botswana in accordance with the established hospital process. In turn, it served as the basis for the development of a national guideline.
Discussion: The principles of EGDT are adaptable to Botswana, and are likely to be adaptable to a variety of low- and middle-income countries on the basis of local resources and epidemiology. Further research is needed to study adherence and outcome related to the modified guidelines.

Abstract *Introduction:* Les états septiques sont une cause courante de morbidité et de mortalité dans les populations caractérisées par une forte prévalence de VIH, mais le protocole EGDT (early goal directed therapy) complet associé aux états septiques ne peut être suivi dans la plupart des pays à bas et moyens revenus. L'objectif était de développer des directives de prise en charge d'urgence des états septiques chez les adultes pour le Botswana, appropriées aux ressources disponibles et à l'épidémiologie locale dans les hôpitaux de référence et dans les systèmes de prise en charge de rang inférieur.
Méthodes: Les composantes individuelles des directives tirées de la campagne Surviving Sepsis ont été comparées aux ressources disponibles afin de déterminer dans quelle mesure ces directives pouvaient s'appliquer dans un hôpital tertiaire de référence au Botswana. Les antibiotiques ont été sélectionnés à partir de l'antibiogramme de l'hôpital, des directives nationales relatives aux antibiotiques et du coût et de la disponibilité des antibiotiques. L'algorithme préliminaire a été présenté aux responsables médicaux du service des urgences d'un hôpital de référence afin d'en évaluer la faisabilité et de déterminer s'il était possible de les mettre en œuvre. Les directives de l'hôpital de référence ont encore été modifiées dans le cadre du Projet de directives nationales afin d'en assurer l'adéquation à tous les niveaux de prise en charge.
Résultats: Un algorithme des états septiques acceptable et applicable a été développé et mis en œuvre dans un hôpital de référence au Botswana, conformément à la procédure hospitalière fixée. Celui-ci a ensuite servi de base à l'élaboration d'une directive nationale.
Discussion: Les principes des protocoles EGDT peuvent être adaptés au Botswana, et peuvent probablement être adaptés à un large éventail de pays à bas et moyens revenus en fonction de leurs ressources locales et de l'épidémiologie. Des études supplémentaires doivent être réalisées afin d'étudier dans quelle mesure les directives amendées sont respectées et les résultats qui en découlent.

African relevance

- Sepsis is a top cause of death for HIV positive Africans.
- Simple measures within reach of LMICs can improve sepsis care.
- More sepsis research is now focusing on improving care in LMICs.

What's new?

- International sepsis guideline revisions have made them more accessible to LMICs.
- International guidelines can be rationally adapted to local resources and conditions.
- Local variability in pathogens requires tailoring antibiotic choices for sepsis.

Introduction

It is well known that sepsis is a leader in HIV-related mortality in Africa in the era of highly active anti-retroviral therapy.[1] Botswana is a high-burden HIV country, with an HIV prevalence of 17.6% in the general population, and a peak of 40.6% in the 40–44 age group.[2] The estimated HIV prevalence of patients admitted to the medical ward at Princess Marina Hospital (PMH) in Gaborone ranges between 50% and 66% (personal communications Haas M and Haverkamp M, 2009 & 2012 data, Botswana-University of Pennsylvania Partnership). In the same ward, a 2009 cross-sectional survey of patients showed sepsis constituted 1.6% of all admissions. Though this survey data could not generate sepsis-specific and HIV-associated mortality rates, it did reveal an overall mortality rate of 20%, with a leading admission diagnosis of pneumonia (Haas M, personal communication). In Botswana, data from the central statistics office indicate that unspecified ''septicaemia'' was

the cause in 3.3% of inpatient deaths in 2008.[3] A 3-month audit of 2010 PMH EC data revealed that 3.3% of adult EC patients were admitted to the ward with temperature and heart rate criteria consistent with sepsis (Kestler A, personal communication). This EC audit data and the authors' personal experience suggest that sepsis is under-diagnosed and under-recorded in Botswana, particularly in HIV-infected adults presenting for emergency care. The desire to improve sepsis recognition provided an additional impetus for sepsis algorithm development.

Rivers' original study[4] and subsequent follow up research has shown that Early Goal-Directed Therapy (EGDT) and associated interventions outlined in guidelines from the Surviving Sepsis Campaign (SSC)[5,6] improve sepsis survival. It is likely that septic patients in Botswana do not yet routinely receive EGDT, as the concepts of EGDT were not commonly emphasized until recently.

Several authors have considered the challenge and necessity of adapting EGDT to low- and middle-income countries (LMICs) with high burdens of sepsis.[7–10] One group conducted a comprehensive and useful systematic review of EGDT components in LMICs.[9] With the exception of one group in Thailand, few authors have described the process of adapting EGDT to a specific LMIC, its resources, and its epidemiology.[11] This paper will describe our efforts to develop sepsis algorithms for Botswana, specifically focusing on adults and on acute management (typically within the first 6 h of care). Our descriptive paper focuses primarily on the process of algorithm development in the Methods section. Because the prevalence of paediatric HIV is low relative to that of adults in Botswana[2], and because children may have different fluid resuscitation needs in sepsis[12], a separate paediatric sepsis guideline is currently being developed and will not be discussed here.

To better understand Botswana's level of resources for sepsis care, it is worth noting that it is a middle-income country with approximately 2 million people on a land mass comparable to that of France. Transport from a primary hospital or clinic to a referral hospital may take 8 h or more, not including potential delays in obtaining an ambulance. There are 28 hospitals in the "public sector" of which 2 are tertiary referral centres, 1 is a psychiatric hospital, and 2 are mining hospitals operated in collaboration with the government as district hospitals.[13] An independent audit of trauma care resources in these hospitals identified gaps in equipment and skills needed for respiratory and circulatory support of critical patients.[14] In the two referral hospitals, intensive care unit (ICU) space is extremely limited and typically reserved for patients deemed to have few comorbid conditions and predicted to have short-ICU stays. Severe sepsis and septic shock, which often occur in patients with advanced HIV/AIDS, are therefore usually treated outside of the ICU. The healthcare work force consists of nurses predominantly from Botswana and generalist doctors predominantly from outside Botswana. Specialist doctors work in the referral hospitals and a few of the larger district hospitals. Healthcare worker turnover in public emergency care is high for a variety of reasons; including annual Ministry of Health staff rotations, short-term expatriate contracts, and departure for the private sector.

Methods

The initial setting for algorithm development was the Emergency Centre (EC) of Princess Marina Hospital (PMH), a 567-bed public tertiary hospital in Gaborone, the capital of Botswana. The EC sees around 30,000 patients per year, with a 44% admission rate and with a preponderance of adults with non-traumatic complaints.

As a starting point for algorithm development, we focused on the resuscitation bundle of the 2008 SSC guidelines. The SSC resuscitation bundle, intended for the first 6 h of care, incorporates EGDT, and additionally includes the relevant cultures and appropriate antibiotics within 1 h of presentation.[5] The SSC management bundle, intended primarily for ICU care after the first 6 h, was felt to include many components deemed inappropriate in LMICs: peak pressure management in ventilated patients, drotrecogin alfa, and tight glucose control. It is worth noting that some components of the original SSC bundles, such as drotrecogin alfa[15] and tight glucose control[16] have subsequently been shown to have no benefit even in well-resourced countries, and have been removed from the 2012 SSC guidelines[6]

The first step considered the challenge of sepsis recognition. As other authors[9] have noted, not all of the SSC diagnostic criteria[5] are practical in LMICs. C-reactive protein and serum lactate measurements, for example, are possible through the referral hospital laboratory, but are rarely available in real-time for clinical decision-making. We therefore chose criteria from SSC that would be immediately available at the bedside (Box A, Fig. 1).

Further investigations (Box B, Fig. 1) were selected based on commonly available tests and epidemiology. Our HIV testing recommendation is consistent with national guidelines advocating annual testing for previously sero-negative adults, sooner in individuals presenting with clinical signs of advanced immunosuppression or a history of a recent high-risk exposure. Testing for malaria is not universally recommended in Southern Botswana unless in the setting of an outbreak or in the context of a fever in a returned traveller from an endemic area. In Botswana, malaria transmission is seasonal and largely confined to the northern areas of the country.

The core of the algorithm focuses on early fluid resuscitation and early antibiotic therapy. While various therapeutic measures are combined in SSC bundles, studies have found independent survival benefit of individual measures, notably early antibiotics[17] and early aggressive fluid resuscitation.[18] These are relatively simple interventions that can be realistically implemented in low resource settings. Our algorithm chose crystalloid over colloid as evidence fails to show a clear benefit of higher-cost colloid fluids[19] and even suggests that colloid may lead to worse outcomes in sepsis.[20]

The selection of algorithm empiric antibiotics was based on PMH microbiology reports, on a preliminary draft of revised national antibiotic guidelines,[21] on the availability of common antibiotics, and on cost considerations. For example, vancomycin was included for sepsis of unknown source and for sepsis from skin and soft-tissue infections (SSTIs) because MRSA was found to cause 44% of *Staphylococcus aureus* bacteraemia[22] and 22% of *S. aureus*-related SSTIs.[23] Because of vancomycin's limited availability, we suggested clindamycin as an alternative

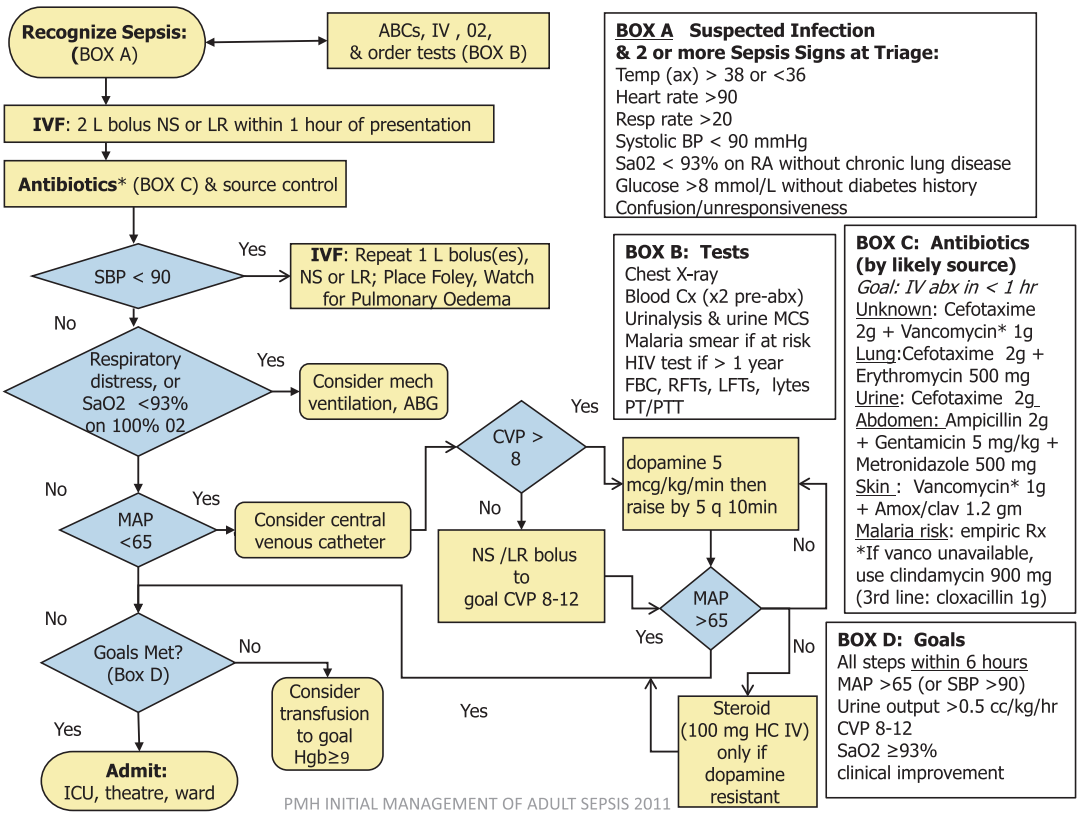

Fig. 1 Princess Marina Hospital Emergency Centre adult sepsis guideline 2011. NS, normal saline; LR, lactated Ringer's; IV, intravenous; SaO_2, oxygen saturation; RA, room air; FBC, full blood count; RFTs, renal function tests; LFTs, liver function tests; lytes, electrolytes; PT/PTT, prothrombin time/partial thromboplastin time; Cx, culture; MCS, microbial culture and sensitivity; abx, antibiotics; CVP, central venous pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; Hgb, haemoglobin; amox/clav, amoxicillin/clavulanate; PMH, Princess Marina Hospital.

since it provides reasonable MRSA coverage. Trimethoprim–sulfamethoxazole was not included as an alternative because of its low effectiveness against MRSA in Botswana,[22] likely due to its frequent use in the population as prophylaxis for HIV positive patients. If no parenteral drug was available to cover potential MRSA sepsis in SSTI, we still recommended MSSA coverage with cloxacillin. Since guideline writing, newer laboratory data suggest lower MRSA rates than initially calculated, and thus further supports adequacy of cloxacillin as a second line in SSTI-related sepsis and for *S. aureus* coverage in sepsis of unknown source (Haas M, personal communication). Other antibiotic recommendations were based on pathogens identified as common causes of bacteraemia regionally.[21,24]

Some advanced sepsis care components were adopted from SSC guidelines on a "consider" basis, because they were determined not to be fully implementable or not to have a clearly demonstrated stand-alone survival benefit in sepsis.[17] The insertion of a central venous catheter for central venous pressure monitoring and vasopressor administration, or the initiation of mechanical ventilation would only be possible on an occasional basis at our referral centre. As an elective measure, we included transfusion to the upper limit of suggested haemoglobin in the 2008 SSC guidelines, even though it is above the Botswana recommended transfusion haemoglobin threshold of <7 g/dL. Blood products remain in short supply in Botswana and our recommendation was to continue judicious use when available and appropriate in patients with sepsis. Of interest, the 2012 SSC guidelines subsequently adopted 7 g/dL as their new threshold for transfusion, for a goal of 7–9 g/dL, while leaving the option to transfuse to a higher level in cases of on-going myocardial ischaemia and other special circumstances. With regard to steroids, the group took the position that steroids are rarely indicated, reserved for cases of vasopressor-resistant shock or suspected adrenal insufficiency.[9] Additionally, the algorithm development group was concerned about steroids masking symptoms of tuberculosis and leading to delayed diagnosis in Botswana, where the background incidence of tuberculosis is 550/100,000.[25]The criteria for monitoring response (Fig. 1, Box D) to therapy were chosen based on the SSC guidelines but adapted for feasibility of bedside monitoring in Botswana. The monitoring of central venous pressure (CVP) was included as an option because depending on staffing levels, staff experience, and patient volume, it is occasionally feasible.

The referral hospital algorithm draft was presented in staff meetings of EC medical officers (general practitioners working in the EC) and at hospital grand rounds for comment and for clarification of wording before finalization.

In a second phase of algorithm development, the Botswana National Guidelines Committee used the referral hospital sepsis algorithm as a starting point for the development of national

guideline. The sepsis subcommittee removed all invasive measures from the algorithm, as these would not be feasible in primary and secondary hospitals. The transfusion threshold was modified to conform to national guidelines regarding transfusion for all conditions (active bleeding excluded). The antibiotic recommendations were harmonized with the finalized National Antimicrobial Guidelines.[21] Some differences between the referral hospital guideline and the national guideline reflect newer susceptibility data, concerns over adverse effects, and drug availability. Cloxacillin is not directly mentioned as an alternative for SSTIs, though readers are referred to the National Antimicrobial Guidelines for additional choices.

Recent susceptibility patterns supported keeping cefotaxime for gram-negative coverage. Cefotaxime also covers non-typhoidal salmonella, which, though rarely isolated in blood cultures in Botswana, is a common cause of bacteraemia in Africa, particularly in HIV-infected individuals.[24] Aminoglycosides were not recommended because B-lactams in combination with aminoglycosides are associated with increased toxicity in patients with sepsis.[26] Fluoroquinolones were not recommended for gram-negative coverage as they may lead to delays in diagnosis of tuberculosis.[27] In addition to antimicrobial recommendations, the national guideline committee added additional wording on the optimal setting of care and on transfers to guide general practitioners in smaller hospitals.

Results

The process of algorithm development generated a referral hospital algorithm (Fig. 1) that was felt to be practical and applicable to a referral hospital EC in Botswana. The algorithm was disseminated according to established hospital policy, which included presentation to and incorporation of feedback from EC staff, inclusion in an easily accessible guideline binder in the doctor work area, and filing with the hospital committee monitoring quality improvement initiatives.

In turn, the referral hospital algorithm served as the basis for the Botswana National Guidelines Project to develop a national sepsis guideline. Currently, the national sepsis algorithm draft (Fig. 2, online data supplement) is under review at the national level and is awaiting approval within the next 12 months.

Discussion

To our knowledge, the process of adapting international sepsis guidelines to a specific LMIC has not been previously described in detail. Though the available resources and the regional epidemiology would alter the algorithm recommendations on a country-by-country basis, we hope the process described will assist guideline developers in other LMICs. Even within the African continent, the relatively scant microbiological data show the epidemiology of blood stream infections and resistance patterns to vary significantly.[24] It is also known that emergency care and critical care resources differ widely from location to location in Africa.[28]

As guideline development is an iterative process, it is likely that the national guideline will affect subsequent versions of the referral hospital algorithm in Botswana. The antibiotic recommendations and transfusion threshold will likely be harmonized with the national guideline and the 2012 SSC guidelines.[6] Though the 2012 SSC guidelines strongly recommend norepinephrine over dopamine despite a small incremental benefit,[29] the referral hospital guideline will likely continue to include dopamine, in line with WHO recommendations.[30]

The World Health Organization (WHO) has issued a sepsis management algorithm for low resource settings. The WHO algorithm is similar to the referral hospital and national guidelines from Botswana, with a few minor differences: use of a goal Sp02 of 90% instead of 93%; use of jugular venous distension to monitor fluid status; use of vasopressors peripherally when central access is not available, and use of epinephrine or dopamine as vasopressors of choice because of their widespread availability.[30]

Additional technological innovations may also transform the process of monitoring response to sepsis treatment in high-income countries and LMICs alike. Several authors have presented evidence that measuring lactate clearance can be substituted for the invasive monitoring of central venous oxygen saturation.[18,31,32] Point of care lactate testing has already been studied with promising results in Uganda.[33] Depending on resource availability, EC bedside ultrasound measurement of inferior vena cava diameter variation may substitute for CVP monitoring.[34,35] Finally, in addition to evolving microbial resistance patterns influencing future algorithms, growing evidence for a high burden of tuberculosis-related sepsis in HIV-infected patients living in high incidence areas[24,36] may call for further algorithm modification.

Current and future challenges lie in implementing, monitoring, and demonstrating effectiveness of sepsis care measures in LMICs. Adherence to sepsis guidelines has proved difficult in all settings regardless of the level of available resources.[37–40] In Botswana, personal experience in the referral hospital EC suggests that medical officers are increasingly including sepsis in their differential diagnoses and frequently accessing the guideline binder where the algorithms for sepsis and other conditions are located. Barriers to algorithm implementation and guideline adherence in the referral hospital EC include wide variation in the education and training of medical officers, nursing staff shortages, supply stock-outs and key equipment malfunction.

The EC medical officers turn over frequently, arrive in the centre with a wide range of attitudes and knowledge regarding sepsis, and often have a limited appreciation for the importance of early aggressive management with fluids and antibiotics. In the context of challenging nurse-to-patient ratios (e.g., 1 nurse to 12 EC patients), the nursing staff understandably resists guidelines calling for more intensive nurse monitoring. Nursing staff limitations may therefore contribute to delays in the cornerstone sepsis care elements of administering fluids and antibiotics, even when doctors order timely algorithmic care. In terms of investigations, shortage of laboratory supplies and again staff limitations contribute to lower than desired rates of blood cultures, coagulation test, and pregnancy tests in septic EC patients. Though available in limited supply elsewhere in the hospital, vancomycin remains unavailable in the EC. Because the malfunction of an individual piece of equipment (laboratory, information technology, radiology) or the stock-out of an individual supply item (oxygen, intravenous fluids, catheters, and antibiotics) occurs with some frequency, the combined chance of at least one component missing is sufficiently high to lower sepsis algorithm adherence in the EC.

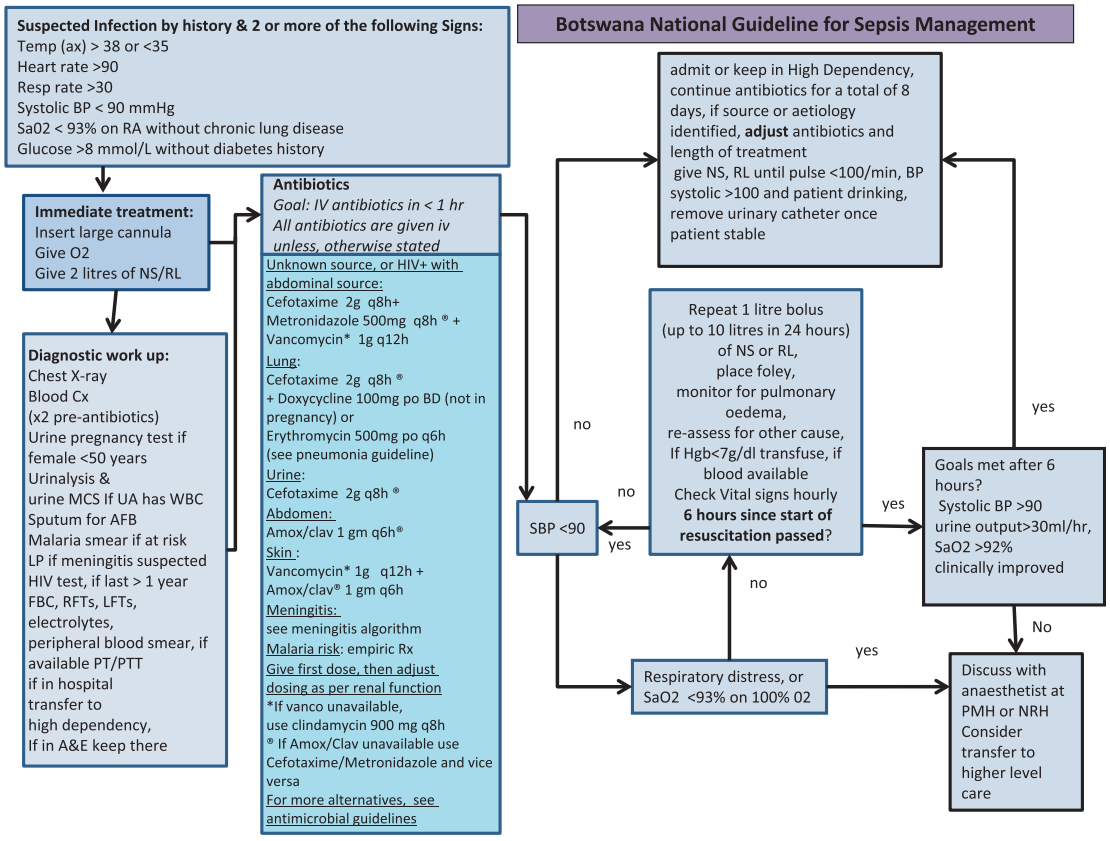

Fig. 2 Botswana National sepsis guideline. NS, normal saline; RL, Ringer's lactate; SaO_2, oxygen saturation; RA, room air; AFB, acid fast bacilli; LP, Lumbar puncture; FBC, full blood count; RFTs, renal function tests; LFTs, liver function tests; Cx, culture; MCS, microbial culture and sensitivity; IV, intravenous; BP, blood pressure; Hgb, haemoglobin; amox/clav, amoxicillin/clavulanate; A&E, accident & emergency; PMH, Princess Marina Hospital; NRH, Nyangabwe Referral Hospital (Francistown).

Concerns for the national guideline implementation mirror those of the referral hospital, with the added challenge of coordinating and disseminating an algorithm to numerous, widely dispersed facilities. On the plus side, the harmonization of sepsis algorithms and care across several levels of facilities provides an opportunity for better-coordinated and more appropriate referrals.

Provided high-levels of adherence to referral hospital and national guidelines (which focus on the initial period of care) are achieved, the concern remains that septic patients will not be monitored closely enough in subsequent care. As mentioned above, most septic patients are managed on general wards because of the scarcity of ICU beds in Botswana. That said, a recent study from Uganda, in which all patients were managed on general wards after the initial 6 h of aggressive management, gives one reason to be optimistic about improving sepsis care in LMICs without easy access to ICU beds.[41]

Measuring outcomes of sepsis interventions in LMICs is possible within the context of a study environment with dedicated study resources.[11,41] However, the challenge grows considerably for operational research on the impact of everyday sepsis care interventions on non-study outcomes. Botswana and many other LMICs currently lack resources to undertake outcomes-based research although general surveillance of causes of death occurs through recording of admission diagnoses and death at the Central Statistics Office. On the basis of personal experiences, we surmise that sepsis is underdiagnosed, under-recorded, and under-estimated as a cause of HIV-related morbidity and mortality. Strengthening inputs into current monitoring processes, including basic epidemiologic data on sepsis in Botswana, are greatly needed to inform guideline development at a national level. Future guideline implementation strategies should include identifying resources for surveillance and clinical outcome evaluation that are tailored to the setting. Finally, ensuring that external partners and in-country academic institutions have a firm understanding of research priorities and that they provide support in these key areas remains critically important.

At a bare minimum, we feel confident that the process of sepsis algorithm development and early dissemination has improved sepsis awareness and knowledge. This knowledge and attitude may itself be a basis for future research. Recognizing and addressing the guideline implementation barriers mentioned above may generate improved levels of adherence, which too may be monitored operationally. As for outcomes monitoring, it is hoped that external support for the National Guidelines Project in Botswana will facilitate operational research on a pilot basis. In Botswana, a new information technology system planned for referral hospitals may improve data capture of sepsis cases.

Appendix A. Short answer questions

Test your understanding of the contents of this case report (answers can be found at the end of the regular features section).

1. Regarding sepsis in Sub-Saharan Africa, choose the best answer:
   a. Sepsis is a common cause of HIV-related mortality.
   b. Severe malaria is easily distinguished from sepsis syndromes.
   c. The same antibiotics may be used throughout Sub-Saharan Africa for empiric sepsis coverage.
   d. Steroids are easily available, and therefore should be routinely used in sepsis care.
   e. All of the above are true.
2. Regarding sepsis treatment in lower and middle-income countries (LMICs).
   a. Most effective treatments for sepsis are beyond the reach of LMICs.
   b. Colloids are preferable to crystalloids in fluid resuscitation.
   c. Improvements in sepsis care require intensive care units with advanced ventilators and monitoring equipment.
   d. Drotrecogin alfa, tight glucose control and early transfusion to a haemoglobin >10 g/dL are cornerstones of current sepsis treatment.
   e. The most important components of sepsis treatment, namely early recognition, followed by timely fluids and antibiotics, are within the reach of LMICs.
3. Regarding the use and development of guidelines:
   a. Healthcare professionals in LMICs should not compromise, and only implement state-of-the art guidelines when all components are possible.
   b. Local resources and epidemiology should not influence the process of guideline development.
   c. Guidelines should be modified on a regular basis based on evolving evidence and on-going monitoring of guideline use and outcomes.
   d. Stakeholder participation in guideline development is not necessary as long as one has conducted a careful review of the evidence base.
   e. High-income countries regularly attain near perfect adherence to sepsis guidelines.

Conflict of interest

All authors state they have no conflicts of interest to report.

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