Evidence-based guidelines for supportive care of patients with Ebola virus disease

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Summary

The 2013-2016 Ebola virus disease (EVD) outbreak in West Africa was associated with unprecedented challenges in the provision of care to EVD patients, including lack of pre-existing isolation and treatment facilities, patients' reluctance to present for medical care due to fear of a high risk of mortality in treatment units, lack of effective Ebola virus-specific therapy and limitations in provision of supportive medical care. Case fatality rates (CFR) in West Africa were initially greater than 70% but over time decreased with increasing clinical and health system experience that included improvements in supportive care. To inform optimal care in a future EVD outbreak, we employed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to develop evidence-informed guidelines for the delivery of supportive care to patients admitted to Ebola treatment units.
[1,2]

Introduction

The 2013-2016 Ebola Virus Disease (EVD) outbreak in West Africa was associated with unprecedented challenges in the provision of care to EVD patients, including need for acute care that outstripped health worker numbers, lack of pre-existing treatment and isolation facilities, a lack of Ebola virus (EBOV)-specific treatments and, possibly, limitations in the provision of supportive medical care. [1,2]

The clinical manifestations of EVD include a febrile, multisystem illness, with a predominance of gastrointestinal symptoms and signs – nausea, vomiting, diarrhea and abdominal pain – that frequently lead to hypovolemia, metabolic acidosis, renal dysfunction, and multi-system organ dysfunction.[1-5]

With initial severe mismatches in care demand and system capacity, and reluctance to present for treatment, the initial risk of mortality was greater than 70%. Individualized clinical supportive care improved as community health and Ebola treatment units (ETUs) developed.[6] This care included better symptom control, laboratory-facilitated diagnosis of organ dysfunction, treatment of shock with enteral and parenteral fluids and electrolytes, and rapid diagnosis or empiric treatment of concomitant illness such as malaria and bacterial infections. Associated with these measures, case fatality rate (CFR) dropped to approximately 40% across the region, and fell further with increasing clinical and health system experience and capacity.[7]

These experiences suggested the need to develop an evidence-based approach to the supportive care of patients with EVD. Therefore, we developed evidence-informed guidelines for the delivery of supportive care to patients admitted to Ebola treatment units during a future outbreak using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[8]

Scope and definitions

These guidelines focus on the delivery of supportive care measures to patients in ETUs where health care resources are limited, a context typical in EVD outbreaks. The guidelines may be relevant to other infectious diseases with clinical syndromes similar to Ebola managed in isolation facilities (e.g. other hemorrhagic fever). The target audiences include health workers, governmental and non-governmental health agencies, public health organizations, local and clinical facility managers, and health policymakers at all levels.

Group composition and meeting

The multidisciplinary guidelines panel comprised 34 participants: 10 critical care physicians (2 specialized in pediatric care), 1 critical care nurse, 2 emergency medicine physicians, 2 general practice physicians, 5 infectious diseases physicians, 1 lawyer, 1 psychologist and bioethicist, 4 public health experts, 3 health research methodologists, 1 qualitative researcher, 1 EVD survivor, and 3 World Health Organization staff observers (see Appendix).

The panel met for two days in London, UK in August 2016 and voted on six recommendations. The panel finalized two additional recommendations during two follow-up teleconferences in October 2016. Voting panelists participated as individuals rather than as representatives of organizations of which they were members.

Formulating questions

The steering committee used data from a quantitative survey and structured interviews of health workers involved in the international response to the West African EVD outbreak to inform the questions addressed by these guidelines.

Search strategy and selection criteria

The complete systematic review appears in the appendix. Briefly, the search strategy for our systematic review of interventions for shock and shock-like syndromes in resource-limited settings included an extensive list of illnesses that share characteristics with EVD (shock, ebola, cholera, sepsis and other severe diarrheal illnesses) and was not limited to specific interventions. We searched the following databases from inception to February 2016: Medline, Medline In-Process, Embase, Cochrane Database of Systematic Reviews, Cochrane Central, African Index Medicus, PubMed (supplemental for non-Medline records).
Additional data to populate the evidence summary was acquired by a more targeted search of pre-MEDLINE and grey literature (e.g. medical history textbooks).

The evidence summary followed the GRADE framework,[9] in which confidence in evidence is rated "very low," "low," "moderate" or "high". Confidence based on randomized controlled trials begins as high; confidence from observational studies begins as low. Confidence can be rated down for risk of bias,[10] imprecision,[11] inconsistency,[12] indirectness,[13] and publication bias.[14] Observational evidence can be rated up for a large magnitude of association, a dose-response gradient or if all unaccounted confounders would increase confidence in estimates of effect.

Formulating recommendations

The panel voted on the direction and the strength (strong or conditional) of each recommendation. Voting on recommendations was by secret ballot. For a strong recommendation we required 80% of votes in favour and smaller proportion in favour of a strong recommendation would result in a conditional recommendation. In making recommendations, the panel considered the magnitude of benefits and harms[15], the quality of supporting evidence, and underlying values and preferences. Following the GRADE framework,[9] we report our overall confidence in estimates of effect (i.e. the quality of supporting evidence) using the ratings "very low," "low," "moderate" or "high". The confidence in effect estimates from randomized controlled trials begins as high, while confidence in the evidence from observational studies begins as low. Confidence can be rated down for risk of bias,[10] imprecision,[11] inconsistency,[12] indirectness,[13] and likelihood of publication bias.[14] Observational evidence can be rated up in the presence of a large

magnitude of association, a dose-response gradient or if all unaccounted confounders increase confidence in estimates of effect. The steering committee suggested confidence ratings for each evidence summary; the final assessments were achieved by consensus among voting panel members.

Table 1 presents interpretations of strong and conditional recommendations from the perspectives of patients, clinicians and policy-makers.[8] We restricted strong recommendations when evidence was of low or very low quality to situations of very high mortality in which almost all informed individuals will choose a possibly effective intervention, even if evidentiary support is limited.[15]

Values and preferences

We specified the following value and preference judgments that informed the recommendations: we placed a very high value on uncertain, substantial mortality reduction associated with any of the interventions and a lower value on very uncertain increase in EBOV transmission to healthcare providers; we placed a much lower value on rare complications of antibiotic therapy than on uncertain mortality benefit associated with antibiotic administration; we placed a high value on uncertain improvement in psychological well-being of patients and a lower value on very low and uncertain risk of EBOV transmission to the family; we placed a very high value on the reduction of pain suffered by EVD patients and a lower value on potential negative perceptions associated with the use of specific medications, in particular opioids.

Other considerations

We discussed, but did not make recommendations regarding 1) resources, feasibility and equity, 2) recommendations for interventions considered routine in high-income countries, 3) diagnosis and treatment of malaria, 4) distinct vulnerable populations, 5) the limitations of making inferences from data collected in high-resource settings, and 6) the importance of continuing clinical research during outbreaks of infectious diseases and, more generally, in low and middle-income countries. A description of the group consensus on these issues appears in the appendix.

Recommendations

The clinical questions, strength of each recommendation and confidence in the underlying evidence appear in Table 2.

1. We recommend (strong) administering oral rehydration solution in an adequate amount over non-standardized rehydration (moderate confidence).

Indirect evidence gathered from other febrile gastro-intestinal syndromes with relevance to Ebola - Cholera: Although the pathophysiology of EBOV and cholera infections differ, both often result in profuse diarrheoa leading to intravascular volume depletion, hypotension, organ hypoperfusion and, in severe cases, shock. The first case series of oral rehydration therapy for cholera reported a reduction in CFR of severe cases in a British prison from approximately 50% to 3%.[16] In the most severe cases, mortality approached 100% without rehydration, but <9% died with oral rehydration therapy.[16] In a before-after study among Bangladeshi refugees with cholera and cholera-like illness in India in 1971, the CFR fell from approximately 30% to 3.6% after introduction of oral rehydration therapy.[17]

Human-to-human EBOV transmission: Ebola virus is transmitted through direct contact with blood or body fluids and possibly through direct skin contact of a person with symptomatic EVD; airborne transmission has never been conclusively reported.[18] EBOV transmission risk is extremely low with proper infection prevention and control (IPC) practices including appropriate personal protective equipment (PPE).[18-20] In 2007, 14 health workers were infected with EBOV in Uganda before an isolation ward with basic IPC was established, and none afterwards.[21] An unrecognized case of EVD in South Africa had direct contact with over 300 health workers; only one was infected with EBOV.[18,22] Although over 800 health workers were infected with EBOV during the 2013-2016 West Africa outbreak, most transmissions occurred in situations without adequate IPC measures (e.g. early in the outbreak, at non-Ebola treatment units where patients were not identified as having EVD, when IPC practices were infrequently or improperly applied, or in the community).[18] Our recommendations apply to contexts in which health workers will use appropriate IPC practices and will have contact with patients for reasons other than encouraging oral intake. Therefore the intervention will not constitute large incremental exposure.

Conclusion: Oral rehydration therapy probably reduces mortality and is unlikely to increase transmission of EBOV to health workers.

Remark: This recommendation focuses on ensuring actual fluid intake rather than simply the delivery of oral rehydration solution. Patients who are too young or sick to prepare and drink oral rehydration solution independently require active assistance from healthcare providers. Adequacy of oral fluid intake refers to the volume that will prevent or correct signs of hypovolemia and should be considered on an individual basis (see recommendation 3).

2. We recommend (strong) parenteral administration of fluids over no parenteral administration for patients unable to drink or whose volume losses are larger than oral volume intake (moderate confidence).

Low- versus high-income countries: Early in the 2013-2016 West African EVD outbreak, systematic administration of intravenous fluids was uncommon and 1230/1737 (70.8%) EVD patients died,[19] compared with 5/27 (18.5%) EVD patients treated with intravenous fluid rehydration in the United States and Europe (relative risk [RR] 0.26, 95% confidence interval [CI]0.12 to 0.58; risk difference [RD]-52.4%, 95% CI -29.7% to -62.3%; *P*<0.0001).[23] Given that care in high-income countries encompassed many other interventions, this provides indirect supportive evidence for parenteral fluids.

Time-series from single outbreaks: The Hastings Police Training Centre clinic in Freetown, Sierra Leone reported a decreasing CFR over time from 47.7% (n=151) in the first month, to 31.7% (n=126) in the second month, to 23.4% (n=304) in the third month[24] (first versus last time period RR 0.49, 95% CI 0.38 to 0.64; risk difference -24.3%, 95% CI -17.3% to -29.7%; *P*<0.0001). Similarly, the CFR across West Africa was greater than 70% between January and March 2014, and decreased to less than 40% between July and September 2015.[7] This coincided with increased efforts towards improved supportive care, including parenteral fluid therapy when necessary. During the 1995 Zaire (now Democratic Republic of Congo) Ebola outbreak, 231 of 292 (79.1%) died before intravenous fluids were available and 14 of 25 (56.0%) after they were introduced (RR 0.71, 95% CI 0.50 to 1.00; RD -23.1%, 95% CI -39.7% to +0.6%; *P*=0.055).[25] Improved access to parenteral therapy represents one potential explanation for lower CFRs in these analyses.

Case series of hypovolemic shock: Intravenous fluid resuscitation was first studied clinically during World War II: the survival of many soldiers was attributed to the administration of colloids and blood transfusions.[26] Intravenous crystalloid solution was introduced during the Vietnam War and associated to a reduction in CFR from hypovolemic shock.[26] However, original reports of the military case series are not readily available. Based on these initial reports, intravenous fluid resuscitation became standard of care for hypovolemic shock.[26] All 140 patients with cholera and hypotension survived in a case series of patients treated with intravenous fluid in India in 1965.[27]

Human-to-human EBOV transmission: See evidence summary accompanying recommendation 1. Additional use of open-bore needles used during venous cannulation to administer parenteral fluids potentially increases the risk of EBOV transmission . Although deep needlestick injuries are probably a high risk for EBOV transmission[28], these remain infrequent events when precautions are taken, such as using needles with safety features.[29]

Conclusion: Parenteral administration of fluids probably reduces mortality in patients who are unable to drink or who have inadequate oral intake to keep up with current volume losses.

Remark: Options for parenteral fluid administration include peripheral and central intravenous[30,31] or intraosseous routes.[32] Enteral fluids via nasogastric tube may be an acceptable alternative for selected patients (e.g. children with difficult intravenous access with adequate gastrointestinal motility, mild-moderate volume depletion, and tolerance of a nasogastric tube) and with sufficient provider technical skill. A three-arm randomized clinical trial comparing albumin fluid boluses, saline solution boluses or no boluses in 3141 children less than 12 years old with severe febrile illness and impaired perfusion showed better survival among patients who were treated without fluid boluses.[33] We did not consider data

from this trial as relevant to patients with EVD because few patients in this trial suffered from dehydration (less than 10%), gastroenteritis-like syndromes were systematically excluded, and because patients in both study arms received maintenance intravenous fluids, *which is encompassed in the current recommendation*. While there was consensus on the superiority of parenteral fluid administration of fluids over no parenteral administration when patients are unable to drink or whose volume losses are larger than oral volume intake, we acknowledge the lack of reliable data to guide the titration or cessation of parenteral fluid administration.

3. In all patients with EVD, we recommend (strong) systematically monitoring and charting of vital signs and volume status over no systematic monitoring or charting (low confidence).

Hypovolemia in adults: A systematic review of hypovolemia in adults identified several diagnostically helpful clinical signs.[34] A pulse increment of ≥30 beats/min or severe dizziness when standing from lying is highly sensitive (0.97, 95% CI 0.91 to 1.0) and specific (0.98, 95% CI 0.97 to 0.99) for severe hypovolemia, defined as acute blood volume loss >600mL. Supine tachycardia (pulse >100 beats/min; specificity 0.96, 95% CI 0.88 to 99) and supine hypotension (systolic blood pressure <95mmHg; specificity 0.97, 95% CI 0.90 to 1.0) are helpful to confirm hypovolemia. Stool output can be measured reliably and guide rehydration requirements: in a case series, all 41 patients with severe cholera survived who received intravenous rehydration in a 1:1 ratio with stool output volume.[27]

Hypovolemia in children: A systematic review of hypovolemia in children identified helpful clinical signs.[35] Prolonged capillary refill was the most reliable predictor of volume depletion (likelihood ratio positive test 4.1 [95% CI 1.7 to 9.8], likelihood ratio negative test 0.57 [95% CI 0.39 to 0.82]). A prospective cohort study found that the 12-point DHAKA score (see Appendix) combining mental status, respiration, skin pinch and the presence of tears may improve detection of hypovolemia.[36]

Early warning scores in adults; Two cluster-randomised control trials have examined the effects of medical outreach and early warning systems. In the first, 23 hospitals were randomised; there was no significant effect (adjusted odds ratio [OR] for composite outcome of cardiac arrest, unexpected death, or unplanned ICU admission 0.98; 95% CI 0.83 to 1.16).[37] The second trial randomised 16 hospital wards and found that the intervention reduced hospital mortality (adjusted OR 0.52; 95% CI 0.32 to 0.85).[38] A meta-analysis was not possible due to heterogeneity.[39] A systematic review included 4 before-after studies of variable quality:[40] 3 of these studies suggested that using an early warning score improves outcomes.

Early warning scores in children: The Paediatric Early Warning Score (PEWS) score identified children at risk of cardiac arrest (area under the receiver operating characteristics curve 0.87, 95% CI 0.85 to 0.89) in a case-control study of 2074 individuals evaluated at 4 hospitals.[41]

Human-to-human EBOV transmission: See evidence summary accompanying recommendation 1.

Conclusion: Monitoring and documentation of vital signs to detect hypovolemia and early warning signs of poor outcomes might reduce mortality and is unlikely to increase transmission of EBOV to health workers.

Remark: 'Vital signs' refer to components of the physical examination that can ascertain volume status (i.e. heart rate, blood pressure, gastro-intestinal fluid loss, urine output, and, in children, capillary refill, skin pinch and tears), as well as mental status, respiratory rate, oxygen saturation and temperature. This recommendation neither specifies which method should be used to quantify gastro-intestinal losses and urine output (e.g. collection in buckets or catheters), nor the threshold for applying specific interventions. The panel believed these specific decisions should be made by clinicians exercising their clinical judgement after considering, case-by-case, all context-specific benefits and risks.[42,43]

4. We recommend (strong) that provision for serum biochemistry be available, that testing be conducted as deemed desirable by the attending clinicians, that results be charted, and the interventions in response to results be implemented according clinicians' judgment (low confidence).

Observational study of EVD: In a cohort study of 150 EVD patients in Sierra Leone, serum potassium and acid-base disturbances were associated with increased risk of death:[44] 3/69 (4%) survivors and 10/28 (36%) non-survivors had a potassium measurement >5.1mmol/L (P<0.001 after adjusting for severe acute kidney injury). Low total CO_2 (38.8%, n=18), hyponatremia (31.8%, n=113), hypokalemia (19.6%, n=97), and hyperkalemia (13.4%, n=97) were common in patients with EVD; [44] all are independent predictors of mortality.[35-39] Although all are surrogate markers for risk of death – mostly from cardiac arrhythmias or brain oedema – reversal of electrolyte derangements may mitigate the risk.

Low- versus high-income countries: See evidence summary accompanying recommendation 2. In the United States and Europe, clinical management systematically included close monitoring and correction of biochemical abnormalities.[23]

Human-to-human EBOV transmission: Blood sampling, transport and laboratory testing carries some risk of EBOV transmission. As mentioned in the evidence summary accompanying question 2, the absolute risk is small and can be mitigated by the proper IPC practices and equipment, including needles with safety features. Moreover, virologic testing for Ebola diagnosis already requires blood sampling from infected patients. Therefore, measurement of serum electrolytes is possibly associated with a small incremental risk of EBOV transmission.

Conclusion: Measuring and charting serum biochemistry with clinically relevant correction of abnormalities may reduce mortality. This intervention may result in a small increase in the risk for EBOV transmission to health workers.

Remark: Whenever possible, biochemistry tests should be consolidated with EBOV testing and blood sampled via an existing intravenous line or needles with safety features to minimise the risk of needlestick injury. In addition to the expected survival benefits associated with treatment of severe biochemical abnormalities, the intervention could reduce iatrogenic

deaths caused by inappropriate administration of electrolytes (e.g. potassium in acute renal failure),[44] and brain oedema associated with rapid correction of hypernatremia with hypotonic solutions.

5. We recommend (strong) Ebola treatment unit staffing ratio of ≥1 clinician to 4 patients, including the following considerations: patient assessment ≥3 times per day and continuous (24h per day) monitoring of patients to allow prompt recognition of and reaction to acute changes in condition (moderate confidence).

Observational data in high-income countries: A meta-analysis of 5 observational studies found that an increase by one nurse full-time equivalent per patient-day was associated with a reduced risk of death in intensive care units (odds ratio 0.91, 95% CI 0.86 to 0.96). There was a clear dose-response relationship.[45]

Low- versus high-income countries: See evidence summary accompanying recommendation 2. In the United States and Europe, patients were treated in units with a nurse:patient ratio of 1:1 or more and continuous monitoring.[23]

Human-to-human Ebola virus transmission: See evidence summary accompanying recommendation 1. Increasing the clinician:patient ratio probably increases health worker time in contact with patients. However, higher clinician:patient ratios may also prevent fatigue, especially working in full PPE for extended periods, thereby preventing IPC mistakes. However, no published data has addressed this issue.

Conclusion: higher clinician-to-patient ratios probably reduce mortality; the direction of effect, if any, on the risk of EBOV transmission is unknown.

Remark: The term clinician encompasses nurses, clinical officers and physicians. In practice, clinicians work with a partner or team in the isolation zone in order to ensure adherence to appropriate IPC practices. The minimum recommended clinician:patient ratio is an average (e.g. could vary within ETUs based on clinical severity). The clinical contact time likely influences care more than staffing ratios per se. Monitoring of patients may be facilitated by ETU design and technology.[46] Non-clinician health workers may reinforce clinical staff (e.g. to assist in oral rehydration solution administration).

6. We suggest (conditional) facilitating communication with family and friends for patients admitted to the treatment unit with suspect, probable or confirmed Ebola virus disease (low confidence).

Psychological distress: Four studies found that hospitalized patients who were isolated had higher depression and anxiety scores than those that were not isolated, while one study did not.[47] Other impacts on psychological well-being included anger/hostility, fear, and loneliness.[47] In West Africa, community distress over unknown activities in ETUs generated resistance, on occasions ranging from denying healthcare worker access to violent opposition.[48]

Human-to-human EBOV transmission: Risk of EBOV transmission to visitors is zero under strict isolation. The risk is probably extremely low if contact is allowed across a sufficient distance or a barrier to prevent droplet spread.

Conclusion: Facilitating communication of isolated patients with family and friends, including enabling the use of cell phones or the internet, might reduce psychological distress and can be achieved without increasing the risk of EBOV transmission. Closer contact situations, including burials,[49] may be safe if appropriate IPC practices, such as use of physical barriers, are employed.

7. We recommend (strong) analgesic therapy, including parenteral opioids, if necessary to reduce pain (high confidence).

Pain: Analgesic medications are beneficial for acute pain in almost all scenarios. For example, all opioid analgesics tested in a network meta-analysis of randomized trials improved pain scores compared to placebo.[50] A review of morphine for post-surgical analgesia found a large, immediate, and dose-dependent effect on pain after administration compared to placebo.[51]

Adverse effects: Analgesic medications may be associated with adverse effects, some of them serious, but evidence of the magnitude of risk applicable to the clinical management of patients admitted to ETUs is unavailable. This recommendation assumes that the risk of serious adverse effects can be minimized through good clinical practice.

Human-to-human EBOV transmission: See evidence summary accompanying recommendation 2.

Conclusion: Analgesic therapy reduces pain.

Remark: Assessing whether or not non-steroidal anti-inflammatory analgesics (in particular those that inhibit cyclooxygenase-1/ COX1) should be avoided because of anti-platelet effects or risks of acute kidney injury in the setting of Ebola virus disease was not possible with the available evidence. This recommendation is contingent upon uniform understanding of the objectives and techniques of palliative care, and education may be required to address any negative views of opioids held by health workers.[52]

8. We recommend (strong) prompt administration of broad-spectrum antibiotics to patients with suspect, probable, or confirmed EVD and high severity of illness (moderate confidence).

Mortality: Multiple time series and randomized clinical trials conducted between 1930 and 1950 consistently show that antimicrobials reduce mortality associated with bacterial infections. [53,54]

Antibiotic-related complications: In a multicentre prospective cohort study of 4143 patients, the overall incidence of healthcare–associated *C. difficile* infection was 28.1 cases per 10 000 patient-days.[55] The odds ratio of *C. difficile* infection for antibiotics was 5.25 (95% CI 2.2 to 12.8). In a retrospective cohort study of 34 298 adult inpatients in a large acute care teaching

hospital, the overall incidence of *C. difficile* infection was 5.95 per 10,000 patient-days.[56] Each 10% increase in ward-level antibiotic exposure (measured in days of antibiotic therapy per 100 patient-days) was associated with a 2.1 per 10,000 ($P < .001$) increased incidence in *C. difficile.* In a longitudinal cohort study of 110 656 older adults residing in nursing homes, the risk of allergic reactions varied from 0% in low antibiotic exposure homes to 0.1% high antibiotic exposure homes.[57]

Antibiotic resistance: Antibiotic use may increase antibiotic resistance. However, the volume of antibiotic use associated with this recommendation in managing patients during an EVD outbreak likely represents a negligible increase in overall use of antibiotics and is therefore unlikely to have a significant impact on resistance.

Human-to-human EBOV transmission: See evidence summary accompanying recommendation 2.

Conclusion: Prompt administration of antibiotics probably reduces mortality among patients with bacterial infections. This might result in a small increase in antibiotic-related complications and risk of EBOV transmission to health workers.

Remark: Patients with suspect, probable, or confirmed EVD and high severity of illness may be ill due to EBOV infection, bacterial infection, malaria, other infectious illnesses, or some combination. WHO provides guidance for investigation and management of malaria.[58] This recommendation addresses the possibility of bacterial infection as a primary or concurrent cause of illness where microbiology laboratory infrastructure is lacking. The rationale is that where ruling out bacterial infections is not possible, the consequence of not treating undiagnosed bacterial infections would likely lead to serious incremental morbidity and mortality.[59] In situations where microbiologic analyses are available, consideration should be given to obtaining cultures (blood, urine, respiratory, etc. as relevant) before initiating antibiotics if this can be achieved without delaying therapy. This would plausibly reduce the duration of initiated broad-spectrum antibiotics, considering that bacterial co-infection may affect a minority of patients.[60] In all cases, patients should be reassessed 48 hours after initiation to determine whether antibiotics are still necessary (based upon clinical condition and culture results, if available). In adults, clinicians can infer high severity of illness from early warning scores discussed for recommendation In African patients under 15 years old who are hospitalized for a febrile illness, the prevalence of bacteremia is high and therefore we recommend prompt antibiotics regardless of illness severity.[61] Critically ill patients will generally receive intravenous antibiotics, but clinicians could choose to administer oral antibiotics after considering bioavailability and likelihood of absorption (i.e. no vomiting).

Conclusion

First-hand accounts of the care that was delivered during the 2013-2016 West African outbreak provided impetus for these guidelines that address interventions considered routine in many contexts.[62]

Indirectness considerably limits the quality of the evidence that informed these recommendations. One of the reasons for this dearth of evidence is that during more than 40 years, after 18 outbreaks and more than 30 000 reported EVD cases, clinical descriptions were mostly limited to the presenting signs and symptoms for a very small proportion of all cases (i.e. unrepresentative sample).[63] Applying these recommendations may not only improve outcomes but enable data collection that will inform future practice.

Contributors

FL, RF, NKA, SM, and GHG contributed to the conception and design of the study. FL, RF, NKA, SM, DMBM, MJ, TMU, CV, SLN, WAF, TEF, ACL, PR, DGB, SG, AH, SS, RS, MCL, RK, PN, MJS, AE, AAH, STJ, MME, TA, LB, CC, IC, AG, SJH and GHG contributed to the search strategy, data extraction, interpretation of the data, and formulation of the recommendations. FL, RF, NKA, SM, and GHG drafted the report. DMBM, MJ, TMU, CV, SLN, WAF, TEF, ACL, PR, DGB, SG, AH, SS, RS, MCL, RK, PN, MJS, AE, AAH, STJ, MME, TA, LB, CC, IC, AG and SJH critically revised the report. All authors approved the final version.

Declaration of interests

We declare no competing interests.

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