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

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The 2013–16 Ebola virus disease outbreak in west Africa was associated with unprecedented challenges in the provision of care to patients with Ebola virus disease, including absence of pre-existing isolation and treatment facilities, patients' reluctance to present for medical care, and limitations in the provision of supportive medical care. Case fatality rates in west Africa were initially greater than 70%, but decreased with improvements in supportive care. To inform optimal care in a future outbreak of Ebola virus disease, we employed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to develop evidence-based guidelines for the delivery of supportive care to patients admitted to Ebola treatment units. Key recommendations include administration of oral and, as necessary, intravenous hydration; systematic monitoring of vital signs and volume status; availability of key biochemical testing; adequate staffing ratios; and availability of analgesics, including opioids, for pain relief.

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Introduction

The 2013–16 Ebola virus disease outbreak in west Africa was associated with unprecedented challenges in the provision of care to patients with the disease, including a need for acute care that exceeded the number of health workers available, the absence of pre-existing treatment and isolation facilities, a dearth of treatments specific to Ebola virus, and, possibly, limitations in the provision of supportive medical care.[1,2]

Ebola virus disease is a febrile, multisystem illness, with a predominance of gastrointestinal symptoms and signs—namely nausea, vomiting, diarrhoea, and abdominal pain—that frequently lead to hypovolaemia, metabolic acidosis, renal dysfunction, and multi-system organ dysfunction.[1–5]

With initial severe mismatches between care demand and system capacity, and the reluctance of people to present for treatment, the initial risk of mortality was greater than 70%. Individualised clinical supportive care improved as community health and Ebola treatment units 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 empirical treatment of concomitant illnesses such as malaria and bacterial infections. Associated with these measures, the case fatality rate decreased to approximately 40% throughout west Africa, and declined further while clinical and health system experience and capacity increased.[6,7]

These experiences suggested the need to develop an evidence-based approach to the supportive care of patients with Ebola virus disease. 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 Ebola treatment units where health care resources are limited, a context typical in outbreaks of Ebola virus disease. The guidelines could be relevant to other infectious diseases with clinical syndromes similar to Ebola that are managed in isolation facilities (eg, other haemorrhagic fevers). The target audiences include health workers, governmental and non-governmental health agencies, public health organisations, local and clinical facility managers, and health policy makers at all levels.

Group composition and meeting

The multidisciplinary guidelines panel comprised 34 participants: ten critical care physicians (two specialists in paediatric care), one critical care nurse, two emergency medicine physicians, two general practice physicians, five infectious diseases physicians, one lawyer, one psychologist

Search strategy and selection criteria

We searched MEDLINE, MEDLINE In-Process, Embase, Cochrane Database of Systematic Reviews, Cochrane Central, African Index Medicus, and PubMed for papers published in any language between the first available date in each database and February, 2016. For our systematic scoping review of interventions for shock and shock-like syndromes in resource-limited settings, we included an extensive list of illnesses that share characteristics with Ebola virus disease (Ebola, shock, cholera, sepsis, and other severe diarrhoeal illnesses) and we did not limit the search to specific interventions. Additional data to populate the evidence summaries was acquired by a more targeted search of PreMEDLINE and grey literature (eg, medical history textbooks, literature that is not controlled by commercial publishers). The complete systematic scoping review appears in the appendix.

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and bioethicist, four public health experts, three health research methodologists, one qualitative researcher, one survivor of Ebola virus disease, and three WHO staff observers (appendix).

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

Formulating questions

The steering committee (FL, RAF, NKA, SM, GHG) used data from a quantitative survey and structured interviews of health workers involved in the international response to the west African Ebola virus disease outbreak to inform the questions addressed by these guidelines.

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 a 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,[9] the quality of supporting evidence, and underlying values and preferences. Following the GRADE framework,[10] we report our overall confidence in estimates of effect (ie, the quality of supporting evidence) using the ratings very low, low, moderate, or high. The confidence in effect estimates from randomised controlled trials starts as high, whereas confidence in the evidence from observational studies starts as low. Confidence ratings could be decreased if there was risk of bias,[11] imprecision,[12] inconsistency,[13] indirectness,[14] and likelihood of publication bias.[15] The rating of observational evidence could be increased 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, and the final assessments were achieved by consensus among voting panel members.

	Strong recommendations (we recommend)	Conditional recommendations (we suggest)
Patients	Most people in this situation will want the recommended course of action, and only a few will not	The majority of people in the situation would want the recommended course of action, but a substantial minority would not
Clinicians	Most patients should receive the recommended course of action	Different choices will be appropriate for different patients. Patients will need help to arrive at a management decision consistent with their values and preferences
Policy makers	The recommendation could be adopted as policy	There is a need for substantial debate and involvement of stakeholders

Table 1: **Strength of recommendations and their implications**

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 would choose a possibly effective intervention, even if evidentiary support is limited.[9]

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 Ebola virus transmission to health-care 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 wellbeing of patients and a lower value on very low and uncertain risk of Ebola virus transmission to the family. We placed a very high value on the reduction of pain suffered by patients with Ebola virus disease, and a lower value on potential negative perceptions associated with the use of specific medications, particularly opioids.

Other considerations

We discussed but did not make recommendations regarding resources, feasibility, and equity; recommendations for interventions considered routine in high-income countries; diagnosis and treatment of malaria; distinct susceptible populations; the limitations of making inferences from data collected in high-resource settings; and the importance of continuing clinical research during outbreaks of infectious diseases and, more generally, in low-income 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 are summarised in table 2.

(1) Oral rehydration

We strongly recommend, with moderate confidence, administering oral rehydration solution in an adequate amount rather than non-standardised rehydration

Indirect evidence gathered from other febrile gastrointestinal syndromes with relevance to Ebola—ie, cholera

Although the pathophysiology of Ebola virus and cholera infections differ, both often result in profuse diarrhoea 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 the fatality rate of severe cases in

a British prison from approximately 50% to 3%.[16] In the most severe cases, mortality approached 100% without rehydration, but less than 9% of those on oral rehydration therapy died.[16] In a before and after study of Bangladeshi refugees with cholera and cholera-like illness in India in 1971, the case fatality rate decreased from approximately 30% to 3·6% after the introduction of oral rehydration therapy.[17]

Human-to-human Ebola virus transmission

Ebola virus is transmitted by direct contact with blood or body fluids and possibly through direct skin contact with a person with symptomatic Ebola virus disease; airborne transmission has never been conclusively reported.[18] Ebola virus transmission risk is extremely low with proper infection prevention and control (IPC) practices, including appropriate personal protective equipment.[18–20] In 2007, 14 health workers were infected with Ebola virus in Uganda before an isolation ward with basic IPC was established, and none afterwards.[21] An unrecognised case of Ebola virus disease in South Africa had direct contact with over 300 health workers; only one was infected with Ebola virus.[18,22] Although more than 800 health workers were infected with Ebola virus

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	Recommendation	Population	Intervention	Comparator	Outcomes	Strength of recommendation	Confidence*	Comment
1	Oral rehydration	Patients with suspected, probable, or confirmed Ebola virus disease	Administration of oral rehydration solution in adequate amount	Non-standardised rehydration	Mortality; transmission of Ebola virus to health workers	Strongly in favour	Moderate	Rating increased because of large effect size
2	Parenteral administration of fluids	Patients with suspected, probable, or confirmed Ebola virus disease who are unable to drink or who have inadequate oral intake	Parenteral administration of fluids	No parenteral administration of fluids	Mortality; transmission of Ebola virus to health workers	Strongly in favour	Moderate	Rating increased because of large effect size
3	Systematic monitoring and charting of vital signs and volume status	Patients with suspected, probable, or confirmed Ebola virus disease	Systematic frequent monitoring and charting of vital signs and volume status, at least three times per day	No monitoring and charting	Mortality; transmission of Ebola virus to health workers	Strongly[2] in favour	Low	Rating decreased because of inconsistency and indirectness
4	Serum biochemistry	Patients with suspected, probable, or confirmed Ebola virus disease	Measurement and charting of serum biochemistry (eg, electrolytes, glucose, and blood gas) with correction of abnormalities when clinically necessary	No measurement or charting of serum biochemistry or correction of abnormalities	Mortality; transmission of Ebola virus to health workers	Strongly in favour	Low	NA
5	Staffing ratio	Patients with suspected, probable, or confirmed Ebola virus disease	Higher intensity clinician care of patients, with Ebola treatment unit ratio of ≥1 clinician at the bedside per 4 patients, including the following considerations: patient assessment ≥3 times per day, continuous (24 h per day) presence of personnel inside the Ebola treatment unit to allow prompt recognition of and reaction to acute changes in condition	Appreciably lower intensity clinician care, not including elements above	Mortality; transmission of Ebola virus to health workers	Strongly in favour	Moderate	Rating increased because of evidence of a dose-response in observational data
6	Communication with family and friends	Patients with suspected, probable, or confirmed Ebola virus disease	Facilitating communication with family and friends while isolated in the Ebola treatment unit	Not facilitating communication with family and friends while isolated in the Ebola treatment unit	Psychological distress; Ebola virus transmission to family and friends	Conditionally in favour	Low	NA
7	Analgesic therapy	Patients with suspected, probable, or confirmed Ebola virus disease who are in pain	Use of analgesic therapy sufficient to control pain, including parenteral opioids if necessary	No pain medication	Pain; adverse effects of analgesic medications	Strongly in favour	High	NA
8	Antibiotics	Patients with suspected, probable, or confirmed Ebola virus disease with high severity of illness	Prompt administration of broad-spectrum antibiotics	No administration of broad-spectrum antibiotics	Mortality; transmission of Ebola virus to health workers; adverse effects of antibiotics; antibiotic resistance	Strongly in favour	Moderate	Rating increased because of large effect but decreased for indirectness

NA=not applicable. *Confidence is based on the quality of the evidence for main outcome.

Table 2: **Clinical recommendations**

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See Online for appendix

during the 2013–16 west Africa outbreak, most transmissions occurred in situations without adequate IPC measures (eg, early in the outbreak, at non-Ebola treatment units where patients were not identified as having the disease, 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 this intervention will not constitute large incremental exposure.

Conclusion and remarks

Oral rehydration therapy probably reduces mortality and is unlikely to increase transmission of Ebola virus to health workers. This recommendation focuses on ensuring actual fluid intake rather than simply the delivery of an oral rehydration solution. Patients who are too young or ill to prepare and drink oral rehydration solution independently require active assistance from health-care providers. Adequacy of oral fluid intake refers to the volume that will prevent or correct signs of hypovolaemia and should be considered on an individual basis (see third recommendation).

(2) Parenteral administration of fluids

We strongly recommend, with moderate confidence, parenteral administration of fluids rather than no parenteral administration for patients who are unable to drink or whose volume losses are larger than oral volume intake

Low-income versus high-income countries

Early in the 2013–16 west African Ebola virus disease outbreak, systematic administration of intravenous fluids was uncommon and 1230 (70·8%) of 1737 patients with Ebola virus disease died,[19] compared with 5 (18·5%) of 27 patients with the disease who were treated with intravenous fluid rehydration in the USA and Europe (relative risk [RR] 0·26, 95% CI 0·12–0·58; risk difference [RD] –52.4%, 95% CI –62·3 to –29·7; p<0·0001).[23] Care in high-income countries included many interventions beyond those we recommend, and their relative contribution is uncertain. Nevertheless, parenteral fluids constitute a key component of the care that patients in high-income settings received.

Time series of single outbreaks

The Hastings Police Training Centre clinic in Freetown, Sierra Leone, reported a decreasing case fatality rate 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 month *vs* third month RR 0·49, 95% CI 0·38–0·64; RD -24·3%, 95% CI –29·7 to –17·3; p<0·0001). Similarly, the case fatality rate across west Africa was greater than 70% between January and March, 2014, and decreased to less than 40% between July and September, 2015.[6,7] This decrease coincided with increased efforts towards improved supportive care, including parenteral fluid therapy when necessary. During the 1995 Ebola outbreak in Democratic Republic of Congo, 231 (79·1%) of 292 people died before intravenous fluids were available, and 14 (56·0%) of 25 people died after fluids were introduced (RR 0·71, 95% CI 0·50–1·00; 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 case fatality rates in these analyses.

Case series of hypovolaemic shock

Intravenous fluid resuscitation was first studied clinically during World War 2, and 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 case fatality rate from hypovolaemic shock.[26] However, original reports of the military case series are not readily available. On the basis of these initial reports, intravenous fluid resuscitation became standard of care for hypovolaemic 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 Ebola virus transmission

See evidence summary for the first recommendation. Additional use of open-bore needles, which are used during venous cannulation to administer parenteral fluids, potentially increases the risk of Ebola virus transmission. Although deep needle-stick injuries are probably a high risk for Ebola virus transmission,[28] they remain infrequent events when precautions are taken, such as using needles with safety features.[29]

Conclusion and remarks

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. Options for parenteral fluid administration include peripheral and central intravenous[30,31] or intraosseous routes.[32] Enteral fluids via nasogastric tube could be an acceptable alternative for selected patients (eg, children with difficult intravenous access with adequate gastrointestinal motility, mild to moderate volume depletion, and tolerance of a nasogastric tube), and with sufficient provider technical skill. Results from a three-arm randomised clinical trial comparing albumin fluid boluses, saline solution boluses, or no boluses in 3141 children younger than 12 years 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 relevant to patients with Ebola virus disease because few patients in this trial (<10%) suffered from volume depletion, patients with gastroenteritis-like syndromes were excluded, patients in both study arms received

maintenance intravenous fluids, which we recommend, and because we did not address the issue of fluid boluses.

(3) Systematic monitoring and charting of vital signs and volume status

In all patients with Ebola virus disease, we strongly recommend, with low confidence, systematically monitoring and charting of vital signs and volume status rather than no systematic monitoring or charting.

Hypovolaemia in adults

A systematic review of hypovolaemia in adults identified several diagnostically helpful clinical signs.[34] A pulse increment of 30 beats per min or more, or severe dizziness when standing up from lying down, are highly sensitive (0·97, 95% CI 0·91–1·0) and specific (0·98, 0·97–0·99) physical findings for severe hypovolaemia, defined as acute blood volume loss of more than 600 mL. Supine tachycardia (pulse >100 beats per min; specificity 0·96, 95% CI 0·88–0·99) and supine hypotension (systolic blood pressure <95 mm Hg; specificity 0·97, 0·90–1·0) are helpful to confirm hypovolaemia. Stool output can be measured reliably and can guide rehydration requirements: in a case series, all 41 patients with severe cholera, who received intravenous rehydration in a 1:1 ratio with stool output volume, survived.[27]

Hypovolaemia in children

A systematic review of hypovolaemia 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 1·7–9·8], likelihood ratio negative test 0·57 [0·39–0·82]). A prospective cohort study[36] found that the 12-point DHAKA score, combining mental status, respiration, skin pinch, and the presence of tears, might improve detection of hypovolaemia (appendix).

Early warning scores in adults

Two cluster-randomised controlled trials have examined the effects of medical outreach and early-warning systems. In the first,[37] 23 hospitals were randomly assigned to continue functioning as usual or to introduce a medical emergency team system. There was no significant effect on the composite outcome of cardiac arrest, unexpected death, or unplanned ICU admission (adjusted odds ratio [OR] for composite outcome 0–98, 95% CI 0·83–1·16).[37] The second trial[38] involved 16 hospital wards and found that the introduction of a critical care outreach service reduced in-hospital mortality (adjusted OR 0·52, 0·32–0·85).[39] A meta-analysis was not possible due to heterogeneity.[38] A systematic review included four before and after studies of variable quality, in the UK and Australia.[40] Results from three of these studies suggested that using an early warning score improves outcomes.

Early warning scores in children

The Paediatric Early Warning Score was used in a case-control study of 2074 children who were evaluated in four hospitals, to identify those at risk of cardiac arrest (area under the receiver operating characteristics curve 0·87, 95% CI 0·85–0·89).[41]

Human-to-human Ebola virus transmission

See evidence summary for the first recommendation.

Conclusion and remarks

Monitoring and documentation of vital signs to detect hypovolaemia and early warning signs of poor outcomes might reduce mortality and are unlikely to increase transmission of Ebola virus to health workers.

Vital signs are components of the physical examination that can ascertain volume status (ie, heart rate, blood pressure, gastrointestinal fluid loss, urine output, and, in children, capillary refill, skin pinch, and tears), as well as mental status, respiratory rate, oxygen saturation, and temperature. A detailed discussion of specific aspects of the management of fluid depletion is beyond the scope of these guidelines. These specific decisions should be made by clinicians exercising their clinical judgment after considering, case by case, all context-specific benefits and risks.[42,43] Clinicians seeking such guidance can, however, consult several useful sources.[44,45]

(4) Serum biochemistry

We strongly recommend, with low confidence, that provision for serum biochemistry be made available, that testing be done as deemed desirable by the attending clinicians, that results be charted, and that interventions in response to the results be implemented according to clinicians' judgment.

Observational study of Ebola virus disease

In a cohort study[46] of 150 patients with Ebola virus disease in Sierra Leone, serum potassium and acid-base disturbances were associated with increased risk of death. Three (4%) of 69 survivors and ten (36%) of 28 non-survivors had a potassium measurement greater than 5·1 mmol/L ($p<0·001$ after adjusting for severe acute kidney injury). In patients with Ebola virus disease, low total carbon dioxide (7 [39%] of 18), hyponatraemia (36 [32%] of 113), hypokalaemia (19 [20%] of 97), and hyperkalaemia (13 [13%] of 97) were common in patients with Ebola virus disease;[46] all are independent predictors of mortality.[47–51] Although all of these factors are surrogate markers for risk of death—mostly from cardiac arrhythmias or brain oedema—reversal of electrolyte derangements might mitigate the risk.

Low-income versus high-income countries

See evidence summary for the second recommendation. In the USA and Europe, clinical management systematically

included close monitoring and correction of biochemical abnormalities.[23]

Human-to-human Ebola virus transmission

Blood sampling, transport, and laboratory testing carries some risk of Ebola virus transmission. As mentioned previously, the absolute risk of transmission is small and can be mitigated by proper IPC practices and equipment, including needles with safety features. Moreover, virological testing for Ebola diagnosis already requires blood sampling from infected patients. Therefore, the measurement of serum electrolytes is possibly associated with a small incremental risk of Ebola virus transmission.

Conclusion and remarks

Measuring and charting serum biochemistry with a clinically relevant correction of abnormalities might reduce mortality. This intervention could result in a small increase in the risk for Ebola virus transmission to health workers. Whenever possible, biochemistry tests should be consolidated with Ebola virus testing and with blood sampled via an existing intravenous line or needles with safety features to minimise the risk of needle-stick 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 (eg, potassium in acute renal failure),[46] and brain oedema associated with rapid correction of hypernatraemia with hypotonic solutions.

(5) Staffing ratio

We strongly recommend, with moderate confidence, an Ebola treatment unit staffing ratio of at least one clinician to four patients, including the following considerations—patient assessment at least 3 times per day and continuous (24 h per day) monitoring of patients to allow prompt recognition of and reaction to acute changes in condition.

Observational data in high-income countries

A meta-analysis[52] of five 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 (OR 0·91, 95% CI 0·86–0·96). There was a clear dose-response relationship.

Low-income versus high-income countries

See evidence summary for the second recommendation. In the USA and Europe, patients were treated in units with a nurse:patient ratio of 1:1 or more and had continuous monitoring.[23]

Human-to-human Ebola virus transmission

See evidence summary for the first recommendation. Increasing the clinician-to-patient ratio probably increases the contact time between health workers and patients. However, increased clinician:patient ratios could also prevent fatigue, especially when working in full personal protective equipment for extended periods, thereby preventing IPC mistakes. However, no published data has addressed this issue.

Conclusion and remarks

Increased clinician-to-patient ratios probably reduce mortality. The direction of effect, if any, on the risk of Ebola virus transmission is unknown. The term clinician encompasses nurses, clinical officers, and physicians. In practice, clinicians work with a partner or team in the isolation zone to ensure adherence to appropriate IPC practices. The minimum recommended clinician:patient ratio is an average (eg, could vary within Ebola treatment units on the basis of clinical severity). The clinical contact time likely influences care more than staffing ratios per se. Monitoring of patients can be facilitated by Ebola treatment unit design and technology.[53] Non-clinician health workers can support clinical staff (eg, to assist in administration of oral rehydration solution).

(6) Communication with family and friends

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

Psychological distress

Results from four studies showed that patients admitted to hospital who were isolated had higher depression and anxiety scores than those who were not isolated, whereas one study did not.[54] Other effects on psychological wellbeing included anger or hostility, fear, and loneliness.[54] In west Africa, community distress about unknown activities in Ebola treatment units generated resistance, on occasions ranging from denying health-care workers access to communities to violent opposition to the Ebola response.[55]

Human-to-human Ebola virus transmission

Risk of Ebola virus 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 and remarks

Facilitating the 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 Ebola virus transmission. Closer contact situations, including burials,[56] can be safe if appropriate IPC practices, such as use of physical barriers, are employed.

(7) Analgesic therapy

We strongly recommend, with high confidence, the use of analgesic therapy, including parenteral opioids, if necessary to reduce pain.

Pain

Analgesic medications are beneficial for acute pain in almost all scenarios. For example, all opioid analgesics tested in a network meta-analysis of randomised trials improved pain scores, compared with placebo.[57] A review[58] of morphine for post-surgical analgesia found a large, immediate, and dose-dependent effect on pain after administration compared with placebo.

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 Ebola treatment units is unavailable. This recommendation assumes that the risk of serious adverse effects can be minimised through good clinical practice.

Human-to-human Ebola virus transmission

See evidence summary for the second recommendation.

Conclusion and remarks

Analgesic therapy reduces pain. With the available evidence, it was not possible to assess whether non-steroidal anti-inflammatory analgesics (particularly those that inhibit cyclooxygenase-1) should be avoided because of anti-platelet effects or risks of acute kidney injury in the setting of Ebola virus disease. Satisfactory implementation of this recommendation will probably require the education of local health workers, family members, and communities to address negative views of opioids.[59]

(8) Antibiotics

We strongly recommend, with moderate confidence, prompt administration of broad-spectrum antibiotics to patients with suspect, probable, or confirmed Ebola virus disease and high severity of illness.

Mortality

Multiple time series and randomised clinical trials done between 1930 and 1950 consistently show that antimicrobials reduce mortality associated with bacterial infections.[60,61]

Antibiotic-related complications

In a multicentre prospective cohort study of 4143 patients, the overall incidence of healthcare-associated *Clostridium difficile* infection was 28·1 cases per 10 000 patient-days.[62] The OR of *C difficile* infection for antibiotics was 5·25 (95% CI 2·2–12·8). 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.[63] 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 ($p<0·001$) increased incidence in *C difficile*. In a longitudinal cohort study of 110 656 adults aged 66 years or older who resided in nursing homes, the risk of allergic reactions to antibiotics varied from 0% in homes with low antibiotic exposure to 0·1% in homes with high antibiotic exposure.[64]

Antibiotic resistance

Antibiotic use can increase antibiotic resistance. However, the degree of antibiotic use we recommend for the management of patients during an Ebola virus disease outbreak probably represents a negligible increase in the overall use of antibiotics, and it is therefore unlikely to have a significant effect on antibiotic resistance.

Human-to-human Ebola virus transmission

See evidence summary for recommendation 2.

Conclusion and remarks

Prompt administration of antibiotics probably reduces mortality among patients with bacterial infections. Antibiotic administration might result in a small increase in antibiotic-related complications and risk of Ebola virus transmission to health workers. Patients with suspect, probable, or confirmed Ebola virus disease and high severity of illness might be ill because of Ebola virus infection, bacterial infection, malaria, other infectious illnesses, or a combination of these infections. WHO provides guidance for the investigation and management of malaria.[65] This eighth recommendation addresses the possibility of bacterial infection as a primary or concurrent cause of illness when microbiology laboratory infrastructure is insufficient. The rationale is that when ruling out bacterial infections is not possible, the consequence of not treating undiagnosed bacterial infections would probably lead to serious incremental morbidity and mortality.[66] In situations when microbiological analyses are available, consideration should be given to obtaining cultures (eg, blood, urine, or respiratory, as relevant) before initiating antibiotics if this can be achieved without delaying therapy. This approach would plausibly reduce the duration of initiated broad-spectrum antibiotics, considering that bacterial co-infection might affect a minority of patients.[67] In all cases, patients should be reassessed 48 h after initiation of treatment to determine whether antibiotics are still necessary (on the basis of 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 younger than 15 years who are admitted to hospital for a febrile illness, the prevalence of bacteraemia is high and therefore we recommend prompt use of antibiotics, regardless of illness severity.[68] Critically ill patients will generally receive intravenous antibiotics, but clinicians could choose to administer oral antibiotics after considering bioavailability and likelihood of absorption (ie, if there is no vomiting).

Conclusion

First-hand accounts of the care that was delivered during the 2013–16 west African outbreak of Ebola virus disease provided impetus for these guidelines, which address interventions that are otherwise considered routine.[69]

Indirectness considerably limits the quality of the evidence that informed these recommendations. One of the reasons for this dearth of evidence is that during the past 40 years, after 18 outbreaks and more than 30 000 reported cases of Ebola virus disease, clinical descriptions were mostly limited to the presenting signs and symptoms for a very small proportion of all cases (ie, this was an unrepresentative sample).[23] Applying these recommendations could not only improve outcomes but enable data collection that will inform future practice.

Contributors

The steering committee (FL, RAF, SM, and GHG) contributed to the conception and design of the study. FL, RAF, NKA, SM, DMBM, MJ, TMU, CV, SLN, WAF, TEF, ACL, PR, DGB, SG, AH, SS, RAS, M-CL, 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, RAF, NKA, SM, and GHG drafted the report. DMB-M, MJ, TMU, CV, SLN, WAF, TEF, ACL, PR, DGB, SG, AH, SS, RAS, M-CL, RK, PN, MJS, AE, AAH, STJ, MME, TA, LB, CC, IC, AG, and SJH revised the report. All authors approved the final version.

Declaration of interests

STJ is a senior medical adviser for Shift Labs. SLN, RAS, and GHG are members of the GRADE Working Group. SLN has published numerous papers related to GRADE, and her career benefited from this relationship. TEF and SJH have been consultants to WHO. All other authors declare no competing interests.

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