THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Lamontagne F, Fowler RA, Adhikari NK, et al. Evidence-based guidelines for supportive care of patients with Ebola virus disease. *Lancet* 2017; published online Oct 17. http://dx.doi.org/10.1016/S0140-6736(17)31795-6.

Appendix

Guideline development

Scope and definitions

We considered the following issues beyond the scope of these guidelines: delivery of advanced organ support such as renal replacement therapy and mechanical ventilation. We also did not address issues of laboratory management, personal protective equipment and infection prevention and control protocols, management of other concurrent illnesses especially where accepted guidelines for care exist (e.g. malaria) and anti-Ebola virus-specific therapies under investigation.

General Procedure

The development of these guidelines adhered to standards for trustworthy guidelines, including those of the US Institute of Medicine,[1] World Health Organization (WHO), and Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[2] The Chair led a 90-minute session reviewing the essentials of the GRADE process[3] and subsequently provided clarifications of GRADE guidance during the meeting when required.

Preparatory work

The guidelines are embedded in a program of research initiated by a collaborative of healthcare professionals who worked in Ebola treatment units during the 2013-2016 outbreak, quantitative and qualitative researchers, guidelines and knowledge synthesis experts. The other components of this program of research include projects that were designed and conducted in preparation for the guidelines meeting. This preparatory work consisted of a 1) a systematic review, 2) qualitative interviews of clinicians, infection prevention and control experts, and public health officers who were active in the 2013-2016 Ebola epidemic, 3) a quantitative survey; and, 4) outreach to relevant stakeholders, which involved providing information on the guidelines to non-governmental organizations responsible for Ebola treatment units during the outbreak four months before the first meeting. We did not solicit participation or endorsement from organizations but rather solicited input on processes, including guidelines development group composition.

Group composition

Supported by the WHO, a **steering committee** of four members led the development of the guidelines. Specifically, the steering committee designed and conducted preparatory work, engaged potential meeting participants, coordinated the guidelines meeting and teleconferences, drafted the guidelines and incorporated

feedback from all participants and stakeholders. The **voting panel members** consisted of 21 meeting participants as well as the Chair of the panel. The steering committee identified candidate panellists based on its knowledge of international expertise in the area and by consulting relevant stakeholder organizations. Panel composition aimed to reflect the diversity of relevant perspectives. Specifically, we sought representation from

- Clinicians (i.e. physicians, nurses, physician assistants and nursing assistants) who cared for patients with Ebola virus disease (EVD) in West Africa and in Europe and the United States, irrespective of their affiliation;
- Decision-makers who influenced the delivery of care but did not work in Ebola treatment units, affiliated with national governments and their Ministries responsible for the delivery of health care, non-governmental organizations, or the WHO;
- Experts in international law and ethics;
- Methodological experts, particularly related to GRADE (among voting members, primarily the Chair).

Thirteen additional **non-voting panel members** attended the meeting and teleconferences and contributed their unique expertise or experience. Non-voting participants had the opportunity to contribute to the discussions without constraints (including views regarding the direction and strength of recommendations). The primary reason that these individuals did not participate as voting members is that they were identified late in the process. We were committed to following WHO procedures that include posting of *curricula vitae* for one month before the panel meeting. Non-voting participants included one EVD survivor, a nurse who worked in Ebola Treatment Units, WHO staff, a qualitative researcher who conducted interviews with health care providers during the 2014-2015 EVD outbreak and knowledge translation experts. The four members of the steering committee were also non-voting panel members.

Managing potential conflicts of interest

Before the panel meeting, every voting member completed a declaration of interest form and submitted a *curriculum vitae* to the WHO Epidemic Clinical Management Unit and reviewed the WHO Code of Conduct. WHO disclosed the names and brief biographies of potential panel members for public notice and comment (http://www.who.int/csr/disease/clinical-management/Biosketches.pdf). We did not identify any financial or intellectual conflicts relevant to Ebola supportive care.

Formulating questions

The selection of clinical questions was based on information obtained from interviews and a survey of health care providers involved in the international response to the 2013-2016 EVD outbreak in West Africa. We chose interview and survey participants based on pre-specified criteria (including decision-makers,

clinicians, participants of different ages, gender, citizens of affected countries, members of non-governmental organizations, presence at different periods of the outbreak). We initially identified individuals known to the survey team and then used a snowball approach based on suggestions from initial participants. Research team members did not participate as interview participants. The individuals who participated in in-depth interviews also completed a quantitative survey. Respondents shared their opinions regarding barriers to and facilitators of effective supportive care in Ebola treatment units and suggested components of supportive care for adoption in future outbreaks. The steering committee used these reports to formulate eight clinical questions that were submitted to the guidelines panel before the first meeting. Specifically, we oriented the questions on the components of care that all respondents felt could potentially be considered quality standards. Discussions of the evidence summaries and the recommendations commenced only once the panel achieved consensus on each element of the questions (i.e. the patient population, intervention, comparator and outcomes). The panel considered outcomes important to patients (mortality, psychological well-being, pain) and family and health workers (risk of Ebola virus transmission).

Evidence review and summary

In collaboration with the steering committee, a knowledge synthesis expert recruited a team of qualified individuals to conduct a systematic review of interventions for shock and shock-like syndromes in resource-limited settings. The search strategy included an extensive list of illnesses that share certain characteristics with EVD and was not limited to specific interventions.

After formulating the clinical questions, we conducted a more targeted search, including grey literature (e.g. lay web browsers, medical history textbooks), and completed the evidence summary for each question.

In seeking evidence to inform recommendations, we stated *a priori* that systematic reviews were preferable to individual studies and that clinical trials were preferable to observational studies. We also prioritized evidence originating from studies focusing on patients with EVD rather than other illnesses, but we incorporated evidence from diseases with similar clinical manifestations and pathogenesis (e.g. cholera).

Assisted by the literature synthesis team, the knowledge synthesis expert prepared narrative summaries of the evidence for each clinical question, as well as a Summary of Findings tables. Following the GRADE framework,[4] we report our overall confidence in estimates of effect 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,[5] imprecision,[6] inconsistency,[7] indirectness,[8] and likelihood of publication bias.[9] 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.

Voting on recommendations

Voting on recommendations was by secret ballot. For a strong recommendation we required 80% of votes in favour. A smaller proportion in favour of a strong recommendation would result in a conditional recommendation. After a first vote, if there was a lack of consensus (defined as only one voter in disagreement from a denominator of 21) discussion resumed and another vote was taken.

Drafting and review of the guidelines document

The steering committee drafted the guidelines, which were reviewed and edited by all panel members.

Funding

A grant from the Canadian Institutes of Health Research provided the funds for this initiative. The funder had no role in the design, development and drafting of the guidelines. WHO paid for travel costs for staff members to participate in the face-to-face meeting.

External review

We have submitted the draft guidelines to the CDC and to the WHO for external review. The objective was to gather feedback on the draft recommendations, assess their applicability and to seek input on dissemination. Both organisations have approved the submission of this manuscript and provided feedback that we incorporated in the manuscript and approved by the panel.

Other considerations

Resources, implementation, feasibility and equity

In determining the strength and direction of recommendations, guidelines panels may consider the availability of resources required for their application. Because these guidelines specifically address the delivery of care in resource-limited settings, the panel discussed the advantages and disadvantages of considering resource availability (e.g. access, logistical feasibility) and cost in formulating recommendations.

The panel considered the following arguments in favour of considering resource issues: 1) the opportunity cost of investing resources to respond to an acute sporadic illness while more benefit might be derived from addressing other major

health problems (e.g. HIV, malaria, lower respiratory tract infection, diarrhoea); 2) the potential deterrent effect (and legal consequences) on non-governmental organizations, who are often the first to respond to outbreaks, of strong recommendations for interventions that would be challenging to implement; 3) the health risks associated with interventions administered in settings lacking monitoring capacity.

The panel considered the following reasons not to consider resource issues: 1) the concern that adapting medical guidelines to the resources available in a given geographical area would perpetuate disparities that facilitated the outbreak; 2) the panel's perspective that its mandate did not include making recommendations based on resource allocation in previous or future outbreak settings.

The panel ultimately decided that for the eight interventions discussed in these guidelines, resource availability would not bear on the recommendations. The panel recognized that a more in-depth discussion of the effectiveness, safety, feasibility, and cost-effectiveness of more advanced life-sustaining therapies, such as dialysis, mechanical ventilation and advanced laboratory facilities in resource-limited settings was needed but beyond the scope of this guideline.

Recommendations for interventions considered routine in high-income countries

The recommendations represent the standard of care in most high-income settings where some (e.g. medical records) are mandated by law or regulation. The practices in high income settings do not necessarily translate into adoption in low income settings: this was certainly the case in the EVD outbreak. Therefore, these recommendations are necessary to guide care in settings such as those of the EVD epidemic.

Malaria

The panel acknowledged that 1) the 2013-2016 West African Ebola outbreak occurred in a malaria-endemic zone, 2) patients with confirmed EVD are also at risk for malaria, 3) early clinical manifestations of malaria and EVD often cannot be readily distinguished, 4) usual systems in place to diagnose and treat malaria may fail during an EVD outbreak, and 5) some deaths during the recent outbreak may have been due to unrecognized and untreated malaria.[10] Accordingly, identifying and treating malaria should be a very high priority during an EVD outbreak. Rather than making recommendations addressing this issue, however, we anticipate that readers of these guidelines will consult the relevant WHO guidance.[11]

Vulnerable populations

Clinical management of pregnant women, very young children, and older adults posed special challenges during the 2013-2016 EVD outbreak and CFRs were high.[12,13] In pregnancy, both EBOV virus-infected and uninfected women suffer consequences. Maternal hemorrhage is a leading cause of mortality in child-bearing women in resource-limited settings. During an EVD outbreak, concerns regarding

infection transmission led to interruptions of usual obstetric care.[14] Decreased healthcare utilization for children under 5 was also reported.[15] Young children as well as older adults are particularly vulnerable when clinical management relies heavily on self-administration of oral rehydration solution. While the target population for these guidelines consists of all suspect, probable, and confirmed cases of EVD, additional research is required to fully address the needs of these more vulnerable populations.

Observational data from high-resource settings

The small number of EVD patients treated in high-resource settings received several of the interventions recommended in these guidelines, usually simultaneously. In many cases, experimental therapies and advanced life-sustaining therapies were also administered. Use of these interventions was not controlled and so their relative contribution remains uncertain. Observational data that emerged from high-resource settings constitute direct evidence suggesting that large mortality reductions can be achieved. However, these data provide indirect evidence for these guidelines focused on supportive care in resource-limited settings. Nevertheless, the interventions we recommend constitute key elements of care delivered in high-resource settings.

Further clinical research during outbreaks of infectious diseases and in low and middle-income countries

The dearth of evidence directly relevant to the questions addressed by these guidelines underscores the need for high-quality research in this context. The panel encourages research focused on operationalization of the current recommendations, and addressing the many unresolved related questions. Various organizations have proposed a research agenda for EVD, which is the object of a continuing dialogue (https://www.iddo.org/data-platforms/ebola/research).[16]

Dissemination

The final document will be broadly disseminated in open-access format, in one or more peer-reviewed journals, presented at relevant conferences, and posted on the appropriate websites. In addition, in keeping with recent recommendations on data sharing,[17] the steering committee will encourage other organizations to disseminate, and/or endorse it, whether or not they choose to make modifications beforehand.

Updating

Although we do not anticipate that new data will emerge in the foreseeable future that would change our recommendations, we will consider revisions to our guidelines pending new evidence.

Systematic review

Introduction

To inform the guideline, we performed a scoping review. The goals of the review were to 1) obtain the best estimates of effectiveness for key interventions in patients with shock and shock-like syndromes, including Ebola virus disease (EVD) in resource-limited settings and 2) identify evidence-based interventions to help prioritize the questions that the guideline would address.

Anticipating that the quality of direct evidence for most or all interventions for EVD in resource-limited settings would be low or very low, we broadened the scope of the review to include sepsis and septic shock from any cause in resource-limited settings. All of the interventions identified were presented to the guideline panel who decided whether or not to make a recommendation on each of them. The guideline panel also had the opportunity to identify priority interventions that were not identified in the scoping review. For all interventions prioritized by the guideline panel and where the quality of evidence was low or very low from the scoping review, we also searched for the best possible indirect evidence. Indirect evidence could be indirect for the intervention, location, and/or population, but was judged to be at least possibly applicable by the guideline panel.

Through this iterative process, we summarize the best available evidence that informed each of the eight recommendations.

Methods

Registration

The scoping review and meta-analysis is registered with PROSPERO: CRD42016038772.

Eligibility criteria

We included any observational or experimental comparative study of an intervention in patients with severe sepsis, septic shock, or severe diarrhoea in patients being treated in resource-limited settings. Specifically, we included studies of patients with septic shock, shock (other types), sepsis, EVD, severe diarrheal illness, severe malaria, severe dengue, and severe cholera. We intended to include any intervention, whether implemented at the patient level (e.g. fluid resuscitation) or at a higher level (e.g. healthcare worker staff scheduling).

The guideline panel reviewed all of the interventions identified in the scoping review. They considered whether the interventions were a priority for patients with EVD and whether making recommendations about the specific interventions would be helpful.

When using indirect evidence, we included any study type, including randomised controlled trials (RCTs) and comparative observational studies. We excluded case series and case studies unless there was a similar comparison group. There were no language restrictions.

Information sources

For the systematic search of interventions for sepsis, shock, and severe diarrhoea, we searched Medline, Medline in-process, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central, African Index Medicus, and PubMed (supplemental for non-Medline records) with the help of a clinical services librarian. The search was from database conception to February 24, 2016. We used a combination of MeSH and keywords for sepsis AND low-income settings. The search did not include any terms for specific interventions. The study design search filter was developed using a combination of the sensitive strategies for Therapy (RCTs), or systematic reviews, or the cohort, case-control, case series, and case study strategy. The full report of this systematic review will be published separately.

Five members of the guideline leadership committee also independently searched Google Scholar, PubMed, and through informal channels for studies informing the eight specific questions that the guideline panel requested. This was complemented by a systematic search performed by a clinical services librarian for studies specific to EVD.

Search

The complete search strategy for Medline is included below. The search strategy for other databases was similar.

Database: Ovid MEDLINE(R) <1946 to February Week 2 2016>
Search Strategy:
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1 [shock, ebola, sepsis and similar diseases] (0)
2 shock/ (16421)
3 multiple organ failure/ (9171)
4 shock, cardiogenic/ (6781)
5 shock, hemorrhagic/ (10395)
6 shock, traumatic/ (4281)
7 exp systemic inflammatory response syndrome/ (103693)
8 shock.mp. (172885)
9 hypoperfusion*.mp. (7882)
10 hypo-perfusion*.mp. (94)
11 (circulat* adj2 fail*).mp. (2228)
12 (circulat* adj2 collaps*).mp. (911)
13 (cardiovascular adj2 collaps*).mp. (1362)
14 (Multiple Organ? adj2 Dysfunction*).mp. (2784)
15 (Multiple Organ? adj2 Failure*).mp. (12621)
16 MODS.tw. (1318)
17 Crush Syndrome?.mp. (1108)
18 (Inflammatory Response Syndrome* adj2 Systemic).mp. (5997)
19 toxic forward failure.mp. (0)
20 exp sepsis/ (100467)
21 sepsis.mp. (90788)
22 (septic adj2 disease).mp. (235)
23 urosepsis.mp. (756)
24 blood poisoning?.mp. (13)
25 Septic?emia?.mp. (17559)

26 Bacter?emia?.mp. (32205)
27 bacill?emia?.mp. (59)
28 meningococc?emia?.mp. (727)
29 Hemorrhagic Fever, Ebola/ (2417)
30 ebola.mp. (3565)
31 (H?emorrhagic adj2 fever?).mp. (10709)
32 exp dengue/ (8598)
33 dengue?.mp. (13130)
34 Aden fever?.mp. (1)
35 bouquet fever?.mp. (0)
36 Breakbone Fever?.mp. (6)
37 Break-Bone Fever?.mp. (5)
38 dandy fever?.mp. (0)
39 solar fever?.mp. (0)
40 Cholera?.mp. (28148)
41 Cholera/ (7732)
42 exp Dysentery/ (13569)
43 dysentery.mp. (14996)
44 dysenteria?.mp. (2639)
45 diarrh?eal illness*.mp. (1139)
46 diarrh?eal disease?.mp. (4467)
47 (severe adj2 diarrh?ea*).mp. (3083)
48 amoebic colopath*.mp. (0)
49 dehydration/ (11351)
50 dehydrated.mp. (6028)
51 dehydration.mp. (27040)
52 hypovolemia/ (1249)
53 (intravascular volume adj2 deplet*).mp. (128)
54 hypovol?emia*.mp. (4908)
55 hypo-vol?emia*.mp. (2)
56 hypovol?emic*.mp. (3515)
57 hypo-vol?emic*.mp. (6)
58 (fluid adj2 deplet*).mp. (228)
59 hypohydration.mp. (282)
60 hypo-hydration.mp. (3)
61 hypohydrated.mp. (129)
62 hypo-hydrated.mp. (3)
63 or/2-62 (422563)
64 [resource limited settings] (0)
65 Developing Countries/ (65061)
66 (developing adj2 countr*).mp. (97736)
67 (developing adj2 nation?).mp. (1718)
68 (less-developed adj2 countr*).mp. (1009)
69 (less-developed adj2 nation?).mp. (53)
70 (under-developed adj2 countr*).mp. (71)
71 (underdeveloped adj2 countr*).mp. (710)
72 (under-developed adj2 nation?).mp. (2)
73 (underdeveloped adj2 nation?).mp. (60)
74 (least-developed adj2 countr*).mp. (168)
75 (least-developed adj2 nation?).mp. (10)
76 third-world.mp. (2657)
77 (resource? adj2 limited).mp. (10639)
78 resource-challenged.mp. (49)
79 (resource? adj2 constrained).mp. (1038)
80 resource-poor.mp. (3033)
81 (low?? adj2 income adj2 countr*).mp. (3476)

82 (low?? adj2 income adj2 nation?).mp. (55)
83 afghanistan.mp. (4310)
84 afghan?.tw,kw. (700)
85 benin.mp. (2680)
86 Dahomey.mp. (65)
87 burkina faso.mp. (2955)
88 Upper Volta.mp. (256)
89 burundi.mp. (734)
90 Urundi.mp. (109)
91 cambodia?.mp. (3221)
92 Khmer Republic.mp. (3)
93 Kampuchea.mp. (48)
94 central african republic.mp. (892)
95 Ubangi-Shari.mp. (2)
96 chad.mp. (918)
97 comoros.mp. (321)
98 Comoro Islands.mp. (41)
99 Mayotte.mp. (183)
100 Comores.mp. (52)
101 zaire.mp. (1870)
102 belgian congo.mp. (338)
103 (congo adj2 democratic republic).mp. (843)
104 katanga.mp. (78)
105 eritrea?.mp. (407)
106 ethiopia?.mp. (9233)
107 gambia?.mp. (6548)
108 french guinea.mp. (13)
109 (republic adj2 guinea).mp. (115)
110 haiti??.mp. (3189)
111 north korea?.mp. (237)
112 (Democratic adj2 Republic adj2 Korea).mp. (158)
113 "Democratic People's Republic of Korea"/ (122)
114 liberia?.mp. (1195)
115 madagascar.mp. (3530)
116 Malagasy Republic.mp. (14)
117 malawi??.mp. (4458)
118 Nyasaland.mp. (43)
119 mali.mp. (2753)
120 Portuguese East Africa.mp. (14)
121 mozambique.mp. (2287)
122 nepal.mp. (6504)
123 nepalese.mp. (837)
124 niger.mp. (9663)
125 rwanda?.mp. (2073)
126 Ruanda?.mp. (130)
127 sierra leone.mp. (1255)
128 somalia?.mp. (1612)
129 sudan.mp. (6862)
130 tanzania?.mp. (9908)
131 Zanzibar.mp. (350)
132 Tanganyika.mp. (401)
133 togo.mp. (1154)
134 Togolese.mp. (96)
135 uganda?.mp. (10270)
136 zimbabwe.mp. (5753)
137 rhodesia.mp. (597)

138 Afghanistan/ (2515)
139 Benin/ (1129)
140 Burkina Faso/ (2379)
141 Burundi/ (554)
142 Cambodia/ (2369)
143 Central African Republic/ (642)
144 Chad/ (582)
145 Comoros/ (221)
146 "Democratic Republic of the Congo"/ (3191)
147 Eritrea/ (230)
148 africa, central/ (1103)
149 africa, eastern/ (3609)
150 africa, western/ (4782)
151 Ethiopia/ (7759)
152 Gambia/ (2121)
153 Guinea/ (663)
154 Guinea-Bissau/ (768)
155 Haiti/ (2473)
156 Liberia/ (855)
157 Madagascar/ (2550)
158 Malawi/ (3495)
159 Mali/ (1852)
160 Mozambique/ (1591)
161 Nepal/ (5459)
162 Niger/ (940)
163 Rwanda/ (1620)
164 Sierra Leone/ (926)
165 Somalia/ (1217)
166 Sudan/ (4061)
167 Tanzania/ (8312)
168 Togo/ (867)
169 Uganda/ (8447)
170 Zimbabwe/ (4862)
171 or/65-168 (208448)
172 63 and 171 (9074)
173 animals/ not (animals/ and humans/) (4154861)
174 172 not 173 (8516)
175 [study design filters for systematic review, RCTs from Brian Haynes et al, and , cohort, case-control, case series, and case study from BMJ clinical evidence] (0)
176 clinical trial.mp. (599447)
177 clinical trial.pt. (496612)
178 random:.mp. (912717)
179 tu.xs. (3714661)
180 search:.tw. (247252)
181 meta analysis.mp,pt. (87487)
182 review.pt. (2007715)
183 di.xs. (4731489)
184 associated.tw. (2367255)
185 exp Cohort Studies/ (1493921)
186 cohort$.tw. (298086)
187 controlled clinical trial.pt. (90055)
188 Epidemiologic Methods/ (30052)
189 limit 188 to yr=1971-1988 (9380)
190 exp case-control studies/ (754581)
191 (case$ and control$).tw. (332332)
192 (case$ and series).tw. (122456)

193 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 189 or 190 or 191 or 192 (10762694)
194 174 and 193 (5441)

Study selection and data collection process
Two people independently screened each title and abstract for possible inclusion. If either felt that the study might meet eligibility criteria, then two people independently screened the full text for inclusion. Disagreements were resolved through discussion and if necessary by a third person.

Two people independently abstracted data into a standardized form and disagreements were solved by consensus. The reviewers also provided a narrative summary of key results for patient important outcomes.

Data items
We collected information on each study about disease, setting, total number of patients, age and gender distribution, and proportion with malaria and/or HIV co-morbidity. The effect estimate of each intervention on all patient-important outcomes was abstracted as relative and absolute risk differences.

Risk of bias in individual studies
We used modified Cochrane risk of bias tools for RCTs, cohort studies, and case-control studies. The Cochrane tool was modified to include “probably high risk” and “probably low risk” categories instead of the single “unclear” category. Disagreements were resolved by consensus.

Summary measures
All results are reported as absolute risk differences whenever possible, and narratively in other circumstances.

Synthesis of results
We planned to use DerSimonian and Laird random-effects meta-analysis to pool relative effects wherever possible and appropriate. We report the relative effects in the measures that were originally reported in the studies. When multiple analyses of the same outcome were presented, we opted for the most adjusted analysis unless the model was overfit (which we defined as less than ten events per variable included). If dichotomous data was available, then we calculated risk ratios. We calculated the absolute effect (usually risk difference) using the baseline risk and relative effect measure. When data could not be pooled, we reported results narratively.

Risk of bias across studies
We use the GRADE framework to assess certainty in the evidence.[4] We included and presented the information with the highest certainty. If two sources of evidence provided similar certainty in an outcome, then we report both.

Results
Study selection (PRIMSA diagram)

Study characteristics
The scoping systematic review identified 17 studies, reported in 18 publications that met inclusion criteria. The interventions were categorized into eight interventions, including standardized care bundles,[18,19] fluid resuscitation,[20-22] different types of intravenous fluid resuscitations (e.g. albumin vs. saline),[20,21,23] pre-hospital resuscitation,[24] intensity of clinical monitoring,[25,26] outreach monitoring in neonates,[27-29] anti-diarrheal medications,[30-32] and corticosteroids.[33,34]

The panel considered whether making a recommendation for each of these interventions was a priority. Three interventions (fluid resuscitation, route of fluid resuscitation, and intensity of clinical monitoring) were identified as priorities. The other interventions we not felt to be as important for making formal recommendations.[35,36]

How the systematic review informed the guideline:
Recommendation 1: fluid resuscitation vs. no fluid resuscitation
There was no direct evidence for rehydration versus no rehydration identified through the regular search strategy, however the grey literature search identified two before-after case series, both of which showed a large reduction in mortality in patients with severe cholera and cholera-like syndromes.[37,38]

Recommendation 2: parenteral vs. oral fluids
We identified three studies, including two RCTs that evaluated intravenous (IV) bolus resuscitation vs. less aggressive resuscitation.[20-22] The two RCTs enrolled children living in Kenya, Tanzania, and Uganda with impaired perfusion and evidence of end-organ dysfunction. There was a high prevalence of malaria (approximately 60%) and most children with severe diarrhoea were excluded. For these reasons, the panel felt that these RCTs were not applicable to patients with EVD (see main text).

Recommendation 3: intensity of clinical monitoring
The scoping review identified two observational studies that compared more frequent to less frequent monitoring of vital signs.[25,26] One study compared patients with sepsis in Uganda who had blood pressure monitoring more than once per day to those who had blood pressure monitoring one time per day.[25] The study found that patients who had more frequent vital sign monitoring were more like to die than those who had less frequent vital sign monitoring: odds ratio 2.50 95% CI 1.39 to 4.48. The study did not however adjust for key confounders including severity of illness and therefore inferences about the effect of vital signs monitoring on mortality could not be made. The other study evaluated patients with sepsis in Colombia and found that patients who were admitted directly to an intensive care unit were less likely to die than patients who were admitted first to an intermediate

care unit: odds ratio 0.83 95% CI 0.70 to 0.98.[26] The study was at low risk of bias overall except that it too did not control for confounders.

Recommendation 4: Laboratory biochemistry availability
The scoping review did not identify any studies to directly inform this recommendation.

Recommendation 5: Healthcare worker to patient ratio
The scoping review did not identify any studies to directly inform this recommendation.

Recommendation 6: Patient isolation precautions
The scoping review did not identify any studies to directly inform this recommendation.

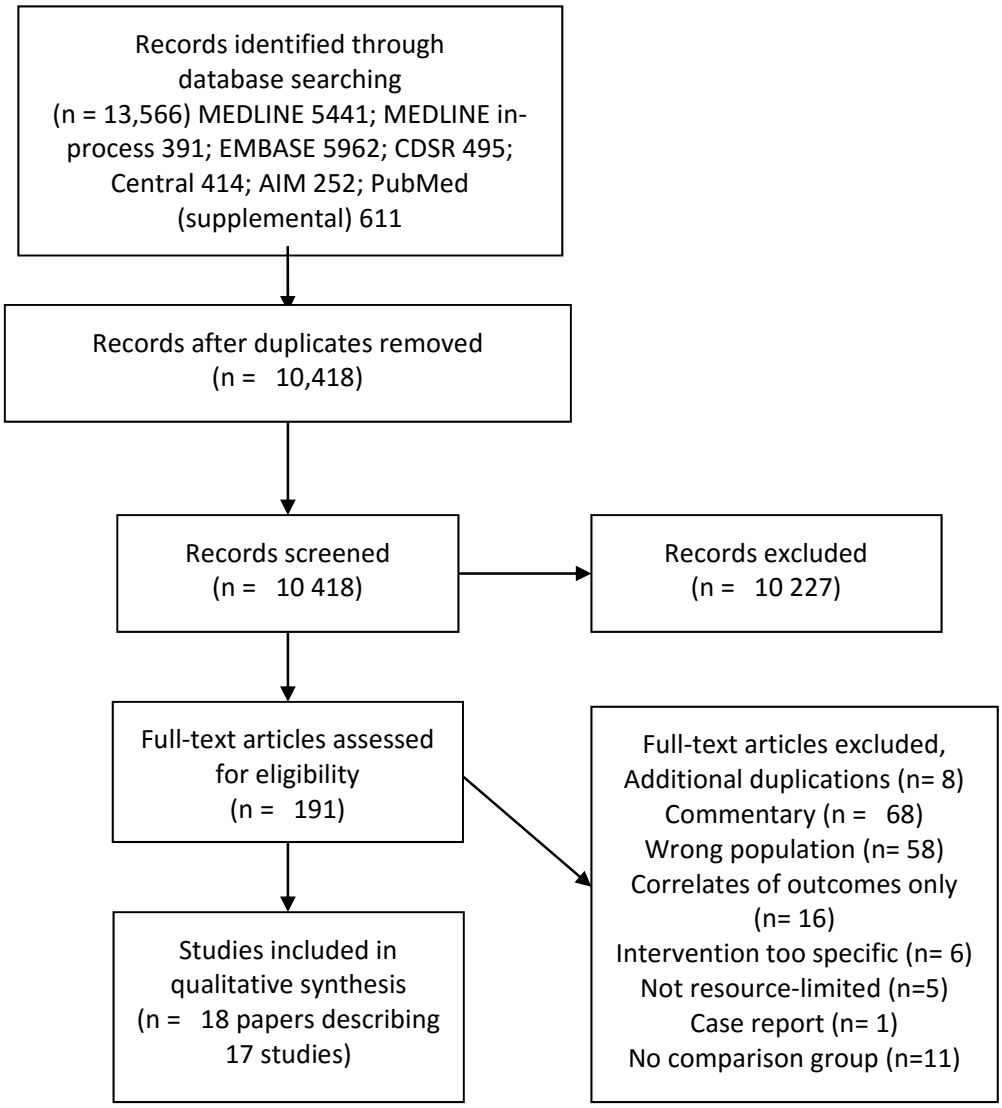
Recommendation 7: Analgesia
The scoping review did not identify any studies to directly inform this recommendation.

Recommendation 8: Antibiotic administration
The scoping review did not identify any studies to directly inform this recommendation.

Discussion

Our scoping systematic review identified 17 comparative studies of eight categories of interventions in patients with shock and shock-like syndromes receiving medical care in resource-limited settings. Three of the eight interventions were judged to align with the priorities in our guideline and be applicable to patients with EVD. Overall, there was only low or very low quality evidence identified in the systematic review, thus necessitating an informal review for additional evidence from indirect sources to inform the recommendations. Research in resource-limited settings on interventions for shock and shock-like syndromes including EVD is needed to directly inform guidelines applicable to low-resource settings.

PRISMA Flow Diagram
2627 duplicates



Panel members

Name	Profession	Affiliations	Country of residence (main)
Adachi, Takuya	Infectious Disease Physician	Toshima Hospital	Japan
Adhikari, Neill	Critical Care Medicine Physician	Sunnybrook Health Sciences Centre University of Toronto	Canada
Bausch, Daniel G.	Technical Lead Associate Professor Internal Medicine - Infectious Diseases Physician	Epidemic Clinical Management Unit Pandemic and Epidemic Diseases World Health organization Tulane School of Public Health and Tropical Medicine	Switzerland
Benhadj, Lynda	Research professional assistant with expertise in qualitative design	Centre de recherche – Hôpital Charles-Le Moyne Université de Sherbrooke	Canada
Brett-Major, David	Internal Medicine – Infectious Diseases Physician	U.S. Military HIV Research Program, Henry M. Jackson Foundation	United States
Clément, Christophe	Physician	Polyclinique Bordeaux Nord Aquitaine	France
Crozier, Ian	Infectious Diseases Physician	Infectious Diseases Institute College of Health Sciences Makerere University	Uganda
Edwin, Ama	Physician Clinical Psychologist Bioethicist	Korle Bu Teaching Hospital Ghana Health Service Ethical Review Committee	Ghana
Elkarsany, Mubarak Mustafa	Clinical microbiologist	Karary University	Sudan
Fischer II, William A.	Critical Care - Infectious Diseases Physician	The University of North Carolina at Chapel Hill	United States of America
Fletcher, Tom E.	Wellcome Trust/MoD Research Fellow	Liverpool School of Tropical Medicine	United Kingdom
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