

UPDATED  
GUIDELINE

Paediatric emergency  
triage, assessment  
and treatment

Care of critically ill children



World Health  
Organization



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# Paediatric emergency triage, assessment and treatment

Care of critically ill children

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# Abbreviations and acronyms

AVPU	Alert (A), responds to your Voice (V), responds to Pain (P), Unresponsive (U)
bw	body weight
CI	confidence interval
CNS	central nervous system
CT	computerized tomography
EEG	electroencephalography
ETAT	emergency triage, assessment and treatment
FEAST	fluid expansion as supportive therapy
FiO <sub>2</sub>	fraction of inspired oxygen
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HFNC	high-flow nasal cannula
IM	intramuscular
IV	intravenous
MCA	Maternal, Newborn, Child and Adolescent Health (WHO department of)
MRI	magnetic resonance imaging
PaO <sub>2</sub>	partial pressure of oxygen
PICO	population, intervention, control, outcome
RCT	randomized controlled trial
RR	relative risk
SpO <sub>2</sub>	peripheral capillary oxygen saturation

# Definitions

**Acute symptomatic seizure:** seizures that occur in close temporal relation to a brain insult such as trauma, infection or metabolic or structural abnormalities

**Coma:** unconscious state as defined on the AVPU scale: Alert (A), responds to your Voice (V), responds to Pain (P), Unresponsive (U)

**Convulsion:** see “Seizure”

**Critical illness:** any severe problem with the airway, breathing or circulation, or acute deterioration of conscious state; includes apnoea, upper airway obstruction, hypoxaemia, central cyanosis, severe respiratory distress, total inability to feed, shock, severe dehydration, active bleeding requiring transfusion, unconsciousness or seizures

**Cyanosis:** a bluish discoloration of skin and mucous membranes due to excessive concentration of reduced haemoglobin in the blood

**Emergency signs (as described in this guideline):**

- obstructed or absent breathing
- severe respiratory distress
- central cyanosis
- signs of shock (defined as cold extremities with capillary refill time > 3 s and weak, fast pulse)
- coma (or seriously reduced level of consciousness)
- seizures
- signs of severe dehydration in a child with diarrhoea with any two of the following signs: lethargy or unconsciousness, sunken eyes, very slow return of skin after pinching

**Febrile seizure:** a seizure occurring in childhood after 1 month of age associated with fever not caused by an infection of the central nervous system (CNS), without previous neonatal seizures or a previous unprovoked seizure and not meeting the criteria for other acute symptomatic seizures (International League against Epilepsy, 1993)

**Hyperoxaemia:** high blood oxygen tension or increased oxygen content of the blood

**Hypoxaemia:** abnormally low level of oxygen in the blood [peripheral capillary oxygen saturation (SpO<sub>2</sub>) < 90%]; more specifically, oxygen deficiency in arterial blood

**Hypoxia:** diminished availability of oxygen to body tissues

**Neonate:** an infant aged 0–28 days

**Seizure:** transient signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain with a clear start and finish (International League against Epilepsy, 2015). Seizures can present as a wide array of physical changes or changes in consciousness, of varying severity. For the purposes of this guideline, the term “seizure” is used to refer only to convulsive seizures and is equivalent to the term “convulsion”.

**Severe anaemia:** erythrocyte volume fraction (haematocrit) < 15 or haemoglobin < 5 g/dL

**Severe acute malnutrition:** in infants and children aged 6–59 months, weight-for-height  $< -3$  Z-score of the median of the WHO growth standards, or clinical signs of bilateral oedema of nutritional origin, even if other measures are above specified cut-off values (WHO, 2009a)

**Severe dehydration:** two or more of the following signs present: lethargy or unconsciousness, sunken eyes, unable to drink or drinks poorly, skin returns very slowly after pinching ( $\geq 2$  s)

**Severely impaired circulation:** cold extremities *or* a weak and fast pulse *or* capillary refill  $> 3$  s

**Shock:** cold extremities *with* capillary refill  $> 3$  s *and* a weak, fast pulse (all signs must be present)

**SpO<sub>2</sub>:** peripheral capillary oxygen saturation, usually measured with a transcutaneous monitor

Status epilepticus: a condition of abnormally prolonged seizures. For generalized convulsions, the operational definition is  $\geq 5$  min of continuous seizures or two or more discrete seizures without complete recovery of consciousness in between, with  $\geq 30$  min of seizure activity resulting in long-term neurological sequelae (International League Against Epilepsy, 2015).



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# Executive summary

Deaths of children in hospital often occur within the first 24 h of admission. Many of these deaths could be prevented if very sick children were identified and appropriate treatment started immediately upon their arrival at the health facility. This can be facilitated by rapid triage for all children presenting to hospital in order to determine whether any emergency or priority signs are present and providing appropriate emergency treatment. WHO therefore published guidelines and training materials for paediatric emergency triage, assessment and treatment (ETAT) in 2005 (WHO, 2005a). The guidelines and materials were destined mainly for low-resource settings and were adapted from the guidelines for Advanced Paediatric Life Support that are used in high-income countries (European Resuscitation Council, 2005). An abbreviated version was included in the first edition of the *Pocket book of hospital care for children* (WHO, 2005b). WHO paediatric ETAT guidelines aim to identify children presenting with airway obstruction and other breathing problems, circulatory impairment or shock, severely altered CNS function (coma or convulsive seizures) or severe dehydration, because it is these children who require urgent appropriate care to prevent death.

Since the first edition of the ETAT guidelines in 2005, new evidence has become available and a number of international guidelines have changed. The changes include recognition of the importance of cardiac pulmonary resuscitation in children, use of mask ventilation during resuscitation, new oxygen delivery methods, use of oxygen titration to limit the risk for hyperoxaemia, especially in preterm neonates, new anticonvulsant drugs and routes of administration, increased use of intraosseous access and fluid resuscitation approaches in circulatory shock.

In 2013, a WHO guideline development scoping group reviewed the paediatric ETAT guidelines and identified areas of care and specific recommendations that should be updated in light of the new evidence and international consensus (WHO, 2013a). Three priorities for the care of sick infants and children were identified: detection of hypoxaemia and use of oxygen therapy, fluid management of infants and children presenting with impaired circulation and management of seizures.

The recommendations in this publication complement or update guidance in published WHO ETAT materials. This guideline does not, therefore, reflect all WHO recommendations on paediatric ETAT but only those identified by the WHO guideline development group in 2013. Relevant standing recommendations are shown with the updated recommendations to put them in context. Other WHO recommendations will be addressed in future guideline reviews.

This updated guideline was prepared by a panel of international experts and informed by systematic reviews of evidence. It makes recommendations on:

- when to start and stop oxygen therapy; oxygen flow rates and humidification in severely ill children with emergency signs;
- which intravenous fluids, at what rate and for how long, should be used in the management of infants and children presenting with impaired circulation or shock; and
- anticonvulsant medicines for children with acute seizures when intravenous (IV) access is and is not available; second-line anticonvulsant medicines for children with established status

epilepticus; pharmacological interventions as prophylaxis to prevent recurrence of febrile seizures in children; and diagnostic tests that should be performed on infants and children presenting with seizures with altered consciousness.

This guideline is intended for use in low-resource settings where infants and children are likely to be managed by non-specialists. The aim is to provide clinical guidance to these health workers on managing infants and children presenting with signs of severe illness.

The recommendations were made by a WHO steering committee and a 21-member guideline development group (GDG) of experts. Additional experts provided technical support by conducting systematic reviews, drafting summaries of the evidence and preparing Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables. Each GDG member submitted a declaration of potential conflicts of interest (Annex 1); none were identified. An initial set of priorities was identified, and WHO commissioned independent institutions to conduct systematic reviews for each. Using these reviews, the WHO steering committee prepared an initial set of draft recommendations. Members of the group then reviewed and evaluated the quality of the evidence identified in the systematic reviews by the GRADE method ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)) and revised and finalized the recommendations. The final recommendations, which were submitted for approval by the WHO Guidelines Review Committee, are listed in Table 1.

The target readership of this guideline includes: national policy-makers in health ministries; programme managers working in child health, essential drugs and health worker training; health care providers, researchers and clinicians who manage sick children at various levels of health care; and development partners that provide financial or technical support for child health programmes.

TABLE 1

**Updated WHO recommendations on paediatric emergency triage, assessment and treatment (ETAT)**

<b>1. DETECTION OF HYPOXAEMIA AND USE OF OXYGEN THERAPY</b>			
<b>When to start and stop oxygen therapy for severely ill children with emergency signs</b>			
1.1	Pulse oximetry is recommended to determine the presence of hypoxaemia in all children with ETAT emergency signs. <sup>a</sup> When the child has only respiratory distress, oxygen supplementation is recommended at SpO <sub>2</sub> < 90%. Children presenting with other ETAT emergency signs with or without respiratory distress should receive oxygen therapy if their SpO <sub>2</sub> is < 94%.	<b>Strong</b>	<b>Very low</b>
1.2	Oxygen therapy can be stopped when the child no longer has ETAT emergency signs <sup>a</sup> and maintains an oxygen saturation of SpO <sub>2</sub> ≥ 90% in room air.	<b>Conditional</b>	<b>Very low</b>
<b>Oxygen flow rate and humidification in severely ill children with emergency signs</b>			
1.3	Severely ill children with signs of obstructed breathing, central cyanosis, severe respiratory distress, signs of shock or who are unconsciousness should receive oxygen initially by nasal prongs at a standard flow rate (0.5–1 L/min for neonates, 1–2 L/min for infants and 2–4 L/min for older children) or through an appropriately sized face mask (> 4 L/min) to reach an SpO <sub>2</sub> of ≥ 94%.	<b>Strong</b>	<b>Very low</b>
1.4	For standard flow oxygen therapy, humidification is not needed.	<b>Strong</b>	<b>Very low</b>
1.5	In an emergency setting, when a flow of > 4 L/min through nasal cannulae is required for more than 1–2 h, effective heated humidification should be added.	<b>Strong</b>	<b>Very low</b>

## 2. FLUID MANAGEMENT IN CHILDREN WITH SIGNS OF IMPAIRED CIRCULATION

### Children who are not in shock but have signs of circulatory impairment

2.1	Children with only one or two signs of impaired circulation – cold extremities <i>or</i> capillary refill > 3 s <i>or</i> a weak and fast pulse – but who do not have the full clinical features of shock, i.e. all three signs present together, should not receive any rapid infusion of fluids but should still receive maintenance fluids appropriate for their age and weight. <sup>b</sup>	Strong	High
2.2	In the absence of shock, rapid IV infusion of fluids may be particularly harmful to children who have severe febrile illness, severe pneumonia, severe malaria, meningitis, severe acute malnutrition, severe anaemia, congestive heart failure with pulmonary oedema, congenital heart disease, renal failure or diabetic ketoacidosis.	Strong	High
2.3	Children with any sign of impaired circulation, i.e. cold extremities or prolonged capillary refill or weak, fast pulse, should be prioritized for full assessment and treatment and reassessed within 1 h.	Strong	High

### Children who are in shock

2.4	Children who are in shock, i.e. who have <i>all</i> the following signs: cold extremities <i>with</i> capillary refill > 3 s <i>and</i> a weak and fast pulse, should receive IV fluids. <ul style="list-style-type: none"> <li>• They should be given 10–20 mL/kg body weight (bw) of isotonic crystalloid fluids over 30–60 min.</li> <li>• They should be fully assessed, an underlying diagnosis made, receive other relevant treatment and their condition monitored.</li> <li>• The child should be reassessed at the completion of infusion and during subsequent hours to check for any deterioration: <ul style="list-style-type: none"> <li>— If the child is still in shock, consider giving a further infusion of 10 mL/kg bw over 30 min.</li> <li>— If shock has resolved, provide fluids to maintain normal hydration status only (maintenance fluids).</li> </ul> </li> <li>• If, at any time, there are signs of fluid overload, cardiac failure or neurological deterioration, the infusion of fluids should be stopped, and no further IV infusion of fluids should be given until the signs resolve.</li> </ul>	Conditional	Low
2.5	Children in shock and with severe anaemia [erythrocyte volume fraction (haematocrit) < 15 or haemoglobin < 5 g/dL as defined by WHO <sup>b</sup> ] should receive a blood transfusion as early as possible and receive other IV fluids only to maintain normal hydration.	Strong	Low
2.6	Children with severe acute malnutrition <sup>c</sup> who are in shock should receive 10–15 mL/kg bw of IV fluids over the first hour. Children who improve after the initial infusion should receive only oral or nasogastric maintenance fluids. Any child who does not improve after 1 h should be given a blood transfusion (10 mL/kg bw slowly over at least 3 h) (WHO, 2013b).	Strong	Low

## 3. MANAGEMENT OF SEIZURES

### Choice of anticonvulsant medicines for children with acute seizures when IV access is not available

3.1	When IV access is not available for the control of acute seizures in children, non-parenteral routes of administration of benzodiazepines should be used. Options include rectal diazepam, oral or intranasal midazolam and rectal or intranasal lorazepam. Some benzodiazepines (lorazepam and midazolam) may be given intramuscularly; this requires additional expertise and expense. The preference may be guided by availability, expertise and social preference.	Strong	Low
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### Choice of anticonvulsant medicines for children with acute seizures when IV access is available

3.2	For children presenting with acute seizures where IV administration is available, IV diazepam or IV lorazepam should be used to terminate the seizure.	Conditional	Very low
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### Choice of second-line anticonvulsant medicines for children with established status epilepticus resistant to first-line benzodiazepines

3.3	In children with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, IV valproate, IV phenobarbital or IV phenytoin can be used, with appropriate monitoring. The choice of drug depends on local resources, including availability and facilities for monitoring. IV valproate is preferred to IV phenobarbital or IV phenytoin because of its superior benefit–risk profile. When IV infusion or monitoring is not feasible, intramuscular (IM) phenobarbital remains an option. Phenytoin and valproate must not be given intramuscularly.	<b>Conditional</b>	<b>Low</b>
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### Pharmacological interventions for prophylaxis of recurrence of febrile seizures

3.4	Prophylactic treatment with intermittent antipyretics, intermittent anticonvulsant medications (diazepam or clobazam) or continuous anticonvulsant medications (phenobarbital or valproate) should not be used for febrile seizures.	<b>Strong</b>	<b>Low</b>
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### Role of diagnostic tests in the management of seizures with altered consciousness, particularly when used by non-specialists in low- and middle-income countries

3.5	The following diagnostic tests should be performed in children with acute seizures or altered consciousness: <ul style="list-style-type: none"> <li>• blood glucose</li> <li>• blood sodium (in children with severe dehydration or diarrhoea)</li> <li>• lumbar puncture in febrile children with signs of meningitis</li> </ul>	<b>Strong</b>	<b>Very low</b>
3.6	Lumbar puncture should be considered for any infant or child who appears severely ill (e.g. high fever with altered consciousness or seizure) and with any of the following: <ul style="list-style-type: none"> <li>• age &lt; 18 months (especially &lt; 6 months);</li> <li>• complex febrile seizures (prolonged, focal or recurrent during the same febrile illness);</li> <li>• antimicrobials were given before assessment;</li> <li>• not vaccinated against Haemophilus influenzae type b or Streptococcus pneumoniae or with unknown immunization status.</li> </ul>	<b>Strong</b>	<b>Very low</b>
3.7	Lumbar puncture should be performed in infants and children only after all of the following clinical signs have been resolved: <ul style="list-style-type: none"> <li>• unresponsive or in coma (based on ETAT AVPU scale)</li> <li>• focal neurological signs</li> <li>• signs of brainstem herniation</li> <li>• signs of raised intracranial pressure</li> <li>• signs of respiratory compromise</li> <li>• ETAT signs of shock</li> <li>• infections in the skin overlying the site of the proposed lumbar puncture</li> <li>• evidence of a bleeding disorder</li> </ul>	<b>Strong</b>	<b>Very low</b>
3.8	Neuroimaging [ultrasound in young infants, computerized tomography (CT) or magnetic resonance imaging (MRI)] should be considered for children with altered consciousness or a new focal neurological deficit.	<b>Strong</b>	<b>Very low</b>

<sup>a</sup> Emergency signs described in the WHO ETAT guideline include:

- obstructed or absent breathing
- severe respiratory distress
- central cyanosis
- signs of shock, defined as cold extremities with capillary refill time > 3 s and a weak, fast pulse
- coma (or seriously reduced level of consciousness)
- seizures
- signs of severe dehydration in a child with diarrhoea with any two of these signs: lethargy or unconscious, sunken eyes, very slow return after pinching the skin.

<sup>b</sup> WHO (2013b)

<sup>c</sup> In infants and children aged 6–59 months, severe acute malnutrition is defined as weight-for-height < –3 Z-score of the median of the WHO growth standards or clinical signs of bilateral oedema of nutritional origin, even if other measures are above specified cut-off values (WHO, 2009a).



It is expected that individual countries will adapt the recommendations to suit their local social, health care resource and economic contexts. Countries are encouraged to hold discussions with relevant stakeholders before introducing the recommendations into national programmes. In 2019, WHO will constitute a new GDG to review the literature related to ETAT and update the recommendations as necessary.

### Scope and purpose of the guideline

The guideline provides recommendations on three areas of emergency paediatric care:

- detection of hypoxaemia and use of oxygen therapy for severely ill children with emergency signs;
- use of IV fluids in the management of infants and children presenting with severely impaired circulation or shock; and
- anticonvulsant medicines for children with acute seizures when IV access is and is not available; second-line anticonvulsant medicines for children with established status epilepticus; pharmacological interventions for use as prophylaxis to prevent recurrence of febrile seizures in children; and diagnostic tests that should be performed on infants and children presenting with seizures and/or altered consciousness.

The guideline informs national policy-makers in health ministries and local programme managers on what may be relevant for national policies and programmes, including essential drugs and training of health workers. It provides clinical guidance to health care providers, researchers and clinicians involved in the management of sick children at various levels of health care and updated information to development partners providing financial or technical support for child health programmes. It will also inform revisions of current WHO training and reference materials, such as the *Integrated management of childhood illness chart booklet* (WHO, 2014a) and the *Pocket book of hospital care for children: guidelines for the management of common illnesses* (WHO, 2013b).

The guideline is intended for use in low-resource settings, where infants and children presenting with signs of severe illness are likely to be managed by non-specialists. In these settings, care may be complicated by lack of diagnostic equipment and medical technology, insufficient human resources and a high work-load. Health workers in these settings commonly provide care for a wide range of conditions, using algorithmic approaches for clinical diagnostic and management decisions. It is important to note that this guideline is to be used by health care workers with appropriate training, supplied with the necessary equipment, job aids and medicines and with adequate supervision and oversight. Implementation of the guideline should be monitored to ensure that successes and challenges are identified and documented.

This guideline does not reflect all WHO recommendations on paediatric ETAT but only those prioritized by the WHO GDG (WHO, 2013a). Relevant standing recommendations are juxtaposed to updated recommendations to put them in context. Other WHO recommendations will be addressed in future guideline reviews.

# 1. Background

Deaths of children in hospital often occur within the first 24 h of admission. Many of these deaths could be prevented if very sick children were identified soon after their arrival in the health facility and appropriate treatment started immediately. This can be facilitated by rapid triage of all children arriving at a hospital to determine whether emergency or priority signs are present. WHO therefore published guidelines for paediatric ETAT and supportive training materials in 2005 (WHO, 2005a). The guidelines and materials were developed mainly for low-resource settings and were adapted from the guidelines for Advanced Paediatric Life Support that are used in high-income countries (European Resuscitation Council, 2005). An abbreviated version was included in the first edition of the *Pocket book of hospital care for children* (WHO, 2005b).

The WHO ETAT guidelines are used to identify children with the life-threatening conditions seen most frequently in developing countries. Thus, children presenting with the following signs should be treated as emergencies:

- obstructed or absent breathing,
- severe respiratory distress,
- central cyanosis,
- signs of shock (cold extremities with capillary refill time > 3 s and weak and fast pulse),
- coma (or seriously reduced level of consciousness),
- seizures or,
- in a child with diarrhoea, any two signs of severe dehydration signs: lethargy or unconsciousness, sunken eyes, very slow return of skin after pinching.

Children who present with these emergency signs are a heterogeneous group with a diverse range of clinical conditions and underlying pathophysiological processes. Nevertheless, the three commonest presentations are respiratory distress and hypoxaemia, severely impaired circulation or shock and seizures with altered consciousness.

Immediate treatment is begun when any emergency sign is identified (by assessment of Airway, Breathing and Circulation, ABC) until the end of the algorithm. Children who require prompt, full assessment and rapid treatment are then checked for priority signs. Children without emergency or priority signs are deemed “non-urgent” on completion of triage.

Hypoxaemia is a common, important complication in critically ill children and increases their risk for death. A range of hypoxaemic respiratory and non-respiratory conditions is associated with or accounts for the clinical presentation of children with ETAT emergency signs. Oxygen therapy has been strongly recommended as a therapeutic intervention to reduce mortality and morbidity from primary insults such as pneumonia shock or severe sepsis. Evidence for the use of oxygen in pneumonia comes from before-and-after field trials; no data are available from controlled trials to support the recommendations on use of oxygen in children with ETAT emergency signs. The current guidance is based on international resuscitation guidelines, observational data and pathophysiological principles. Current ETAT guidelines do not include oxygen saturation thresholds for starting or stopping oxygen; rather, the decision to give oxygen is based on clinical signs.

Circulatory impairment can be the consequence of several pathophysiological conditions: those associated with reduced circulating intravascular volume, such as dehydration after diarrhoea or severe haemorrhage; those associated with vasodilatation, including sepsis and anaphylaxis; and conditions associated with reduced cardiac output, such as heart failure. More than one type of pathophysiology may be involved in the same clinical case of circulatory impairment, and different processes may be involved at different stages of the illness. For example, a case of sepsis may evolve over hours or days from vasodilatation to reduced cardiac output and may be associated with reduced circulating blood volume because of vomiting, diarrhoea or reduced fluid intake. Very severe circulatory impairment is referred to as “shock” and results in reduced oxygen delivery to tissues (hypoxia) and cellular damage. The effects of shock are initially reversible but may rapidly become irreversible, resulting in multi-organ failure and death. Rapid, aggressive fluid resuscitation has been the cornerstone of management of hypovolaemic and septic shock; however, a large trial conducted in several low-resource settings in Africa of the management of children with fever and signs of impaired perfusion concluded that fluid boluses were potentially harmful to children with signs of circulatory impairment including shock (Maitland et al., 2011). In high-resource settings, adverse effects are increasingly being documented after administration of excessive fluids in resuscitation. These effects are usually detected by intensive monitoring and managed with ventilatory support, inotropic drugs and diuretics, whereas such intensive mitigation of the adverse effects of excess fluid is not a realistic option in many low-resource settings.

Seizures with altered consciousness are common in children and may be followed by death or long-term neurocognitive sequelae. Febrile seizures are the most common seizures in childhood, occurring on average in 4% of children. They are often classified as simple or complex febrile seizures, depending on their characteristics. While there is some evidence that features of both simple and complex febrile seizures are associated with intracranial pathology (Hesdorffer et al., 2008), the vast majority are not. Nevertheless, recurrent or prolonged febrile seizures may slightly increase the risk for longer-term epilepsy and neurocognitive impairment. Seizures associated with CNS infections or other brain injury are common in low- and middle-income countries, where the incidence of infections is higher than in high-income countries. Differentiating between febrile seizures and seizures associated with CNS infections or other brain injury is important, as the treatment and prognoses are quite different.

### Objective of the guidelines

Since the first edition of the ETAT guidelines in 2005 (WHO, 2005a), new evidence has become available and a number of international guidelines have changed. The changes include use of mask ventilation during resuscitation, new oxygen delivery methods, use of oxygen titration to limit the risk for hyperoxaemia, fluid resuscitation approaches in circulatory shock and new anticonvulsant drugs and routes of their administration.

In order to reduce mortality among infants and children presenting with critical danger signs that require immediate management, WHO reviewed the guidelines on emergency triage, assessment and treatment to provide updated guidance in three areas of clinical care: oxygen therapy for critically ill children, fluid management in critically ill infants and children and management of children presenting with seizures and altered consciousness.

### Target readership

The target readership of this guideline includes national policy-makers in health ministries; programme managers working in child health, essential drugs and health worker training; health care providers, researchers and clinicians who manage sick children at various levels of health care; and development partners that give financial and/or technical support for child health programmes.

## Population of interest

The guideline addresses the management of critically ill infants and children presenting to health facilities in low-resource settings with emergency signs, namely:

- airway or breathing problems, defined as obstructed or absent breathing, central cyanosis or severe respiratory distress: Is the child breathing? Is the airway obstructed? Is the child blue (central cyanosis)? Does the child have severe respiratory distress?
- signs of circulation impairment, defined as cold hands or capillary refill > 3 s or weak with rapid pulse
- signs of seizure or coma, defined as not alert, does not respond to voice or painful stimulus (AVPU) or is convulsing now
- signs of severe dehydration, defined as the presence of diarrhoea or another dehydrating condition such as vomiting or insufficient fluid intake due to e.g. malaise and fever, with any of the three signs: lethargic or unconscious, sunken eyes, pinched skin returns very slowly (> 2 s).

## Clinical priorities for review

In order to identify the priorities for the guideline update, the WHO department of Maternal, Newborn, Child and Adolescent Health (MCA) convened a meeting of international experts in March 2013 to review the areas of critical care and identify clinical questions that warranted a review and synthesis of the evidence and updating of the guideline. (See list of experts in Acknowledgements.) The experts reviewed the ETAT guidelines and prioritized 74 areas of emergency paediatric care on the basis of defined criteria; the areas were then scored and ranked according to whether:

- there was controversy or uncertainty regarding this area of care or a gap in WHO guidance;
- there was recent evidence relevant to WHO recommendations that might warrant a change in the recommendations; or
- new interventions have become available that could be used in following WHO guidelines.

The three most highly ranked areas were optimal management of airway and breathing, including oxygen delivery; circulatory impairment and shock; and management of seizures with altered consciousness. In consultation with the international experts, questions were formulated for each clinical area, with the relevant population, intervention, comparison and outcome (PICO), and used as the basis for systematic reviews (Table 2). For each question, outcomes deemed to be either “critical” or “important” were identified.

TABLE 2

### Questions to be addressed in systematic reviews of the evidence

Question 1	For infants and children presenting with emergency signs (as described in ETAT guidelines <sup>a</sup> ), at what oxygen saturation is oxygen therapy effective as compared with not giving oxygen in preventing morbidity and mortality?	Importance
Population	Infants and children ≤ 59 months presenting with emergency signs (as described in WHO ETAT guidelines <sup>a</sup> )	
Intervention	Starting oxygen therapy at a threshold oxygen saturation	
Comparison	Not giving oxygen	
Outcome	<ul style="list-style-type: none"><li>• Mortality</li><li>• Morbidity</li></ul>	Critical Important

<b>Question 2</b>	<b>For infants and children presenting with emergency signs (as described in ETAT guidelines<sup>a</sup>), at what oxygen saturation will stopping oxygen therapy as compared with continuing oxygen have no effect on morbidity or mortality?</b>	<b>Importance</b>
<b>Population</b>	Infants and children ≤ 59 months presenting with emergency signs (as described in WHO ETAT guidelines <sup>a</sup> )	
<b>Intervention</b>	Stopping oxygen therapy in hypoxaemic children at a threshold oxygen saturation	
<b>Comparison</b>	Continuing oxygen	
<b>Outcome</b>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Morbidity</li> </ul>	Critical Important

<b>Question 3</b>	<b>What flow rate for nasal delivery of oxygen restores normal oxygen saturation and/or the best clinical outcome in infants and children presenting with respiratory distress or other emergency signs (as described in WHO ETAT guidelines<sup>a</sup>)?</b>	<b>Importance</b>
<b>Population</b>	Infants and children ≤ 59 months (excluding premature infants) presenting with emergency signs due to respiratory distress (as described in WHO ETAT guidelines <sup>a</sup> )	
<b>Intervention</b>	Nasal delivery of oxygen at different flow rates	
<b>Comparison</b>	Among flow rates	
<b>Outcome</b>	Oxygen saturation (SpO <sub>2</sub> ) or partial pressure of oxygen (PaO <sub>2</sub> )	Important

<b>Question 4</b>	<b>Does humidified high-flow oxygen therapy result in better oxygen saturation or better clinical outcomes than non-humidified standard-flow oxygen therapy in infants and children presenting with respiratory distress or other emergency signs (as described in WHO ETAT guidelines<sup>a</sup>)?</b>	<b>Importance</b>
<b>Population</b>	Infants and children ≤ 59 months (excluding premature infants) presenting with emergency signs due to respiratory distress (as described in WHO ETAT guidelines <sup>a</sup> )	
<b>Intervention</b>	Heated humidified high-flow nasal cannula (HFNC) oxygen therapy	
<b>Comparison</b>	Non-humidified low-flow nasal cannula oxygen therapy	
<b>Outcome</b>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Morbidity</li> </ul>	Critical Important

<b>Question 5</b>	<b>In infants and children presenting with emergency signs (as described in WHO ETAT guidelines<sup>a</sup>), which clinical signs or disease markers or combination of signs or other markers indicate severely impaired circulation and the need for intravenous fluids?</b>	<b>Importance</b>
<b>Population</b>	<p>Critically ill infants &lt; 12 months of age and children aged 12–59 months with signs of impaired circulatory perfusion (defined as the presence of one or more of the following signs: systolic blood pressure &lt; 50 mm Hg or &lt; 70 mm Hg for infants &lt; 12 months and &lt; 60 mm Hg or &lt; 75 mm Hg for children &gt; 12 months, capillary refill time ≥ 2 s, cold extremities, severe tachycardia &gt; 180 beats per min for infants &lt; 12 months and &gt; 160 beats per min for children &gt; 12 months of age) <i>but excluding haemorrhage</i>, stratified by:</p> <ul style="list-style-type: none"> <li>• fulfilling or not fulfilling WHO criteria for shock (i.e. cold extremities <i>with</i> capillary refill time &gt; 3 s <i>and</i> weak and fast pulse),</li> <li>• presence or absence of severe dehydration and</li> <li>• presence or absence of severe acute malnutrition</li> </ul>	

<b>Question 5</b>	<b>Continued</b>	
<b>Intervention</b>	Isotonic fluids at normal maintenance rates in the first hour of resuscitation, with no additional IV bolus or rapid continuous infusion of isotonic fluids	
<b>Comparison</b>	Isotonic fluids at normal maintenance rates in the first hour of resuscitation, with additional IV boluses or rapid continuous infusions of isotonic fluids up to 60 mL/kg bw	
<b>Outcome</b>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Measures of physiological function (blood pressure, presence or strength of pulse, capillary refill time (&lt; 2 s), urine output)</li> </ul>	Critical Important

<b>Question 6</b>	<b>In infants and children with severely impaired circulation, which intravenous fluids, at what rate and for how long are associated with the lowest risk for mortality?</b>	<b>Importance</b>
<b>Population</b>	<p>Critically ill infants &lt; 12 months and children aged 12–59 months with signs of impaired circulatory perfusion (defined as the presence of one or more of the following signs: systolic blood pressure &lt; 50 mm Hg or &lt; 70 mm Hg for infants &lt; 12 months and &lt; 60 mm Hg or &lt; 75 mm Hg for children &gt; 12 months), capillary refill time ≥ 2 s, cold extremities, severe tachycardia (&gt; 180 beats per min for infants &lt; 12 months and &gt; 160 beats per min for children &gt; 12 months of age) <i>but excluding haemorrhage</i>, stratified by:</p> <ul style="list-style-type: none"> <li>• fulfilling or not fulfilling WHO criteria for shock (i.e. cold extremities <i>with</i> capillary refill time &gt; 3 s <i>and</i> fast and weak pulse),</li> <li>• presence or absence of severe dehydration and</li> <li>• presence or absence of severe acute malnutrition</li> </ul>	
<b>Intervention</b>	Isotonic fluids at normal maintenance rates in the first hour of resuscitation, with additional IV boluses or rapid continuous infusions of isotonic fluids at no more than 20 mL/kg bw	
<b>Comparison</b>	Isotonic fluids at normal maintenance rates in the first hour of resuscitation, with additional IV boluses or rapid continuous infusions of isotonic fluids up to 60 mL/kg bw	
<b>Outcome</b>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Measures of physiological function (blood pressure, presence or strength of pulse, capillary refill time &lt; 2 s, urine output)</li> </ul>	Critical Important

<b>Question 7</b>	<b>For children with acute convulsive seizures in first-level care or in the community (with no IV access), which antiepileptic medicines are the most beneficial or harmful for the specified outcomes?</b>	<b>Importance</b>
<b>Population</b>	Children with acute convulsive seizures with no IV access	
<b>Intervention</b>	<p>Anti-epileptic medications by non-IV routes:</p> <ul style="list-style-type: none"> <li>• diazepam (rectal, IM)</li> <li>• midazolam (intranasal, IM, oral)</li> <li>• lorazepam (intranasal, oral, rectal, IM)</li> <li>• paraldehyde (IM, rectal)</li> </ul>	
<b>Comparison</b>	<p>IV benzodiazepines (diazepam, lorazepam)</p> <ul style="list-style-type: none"> <li>• benzodiazepines by other routes</li> </ul>	
<b>Outcome</b>	<p>Seizure cessation (within 10 min)</p> <ul style="list-style-type: none"> <li>• adverse effects: respiratory complications requiring ventilation or intubation</li> </ul>	Critical Critical

<b>Question 8</b>	<b>For children with acute convulsive seizures where IV access is available, which first-line anticonvulsant medications should be used to abort seizures?</b>	<b>Importance</b>
<b>Population</b>	Children presenting with acute convulsive seizures where IV access is available	
<b>Intervention</b>	<ul style="list-style-type: none"> <li>• IV diazepam</li> <li>• IV lorazepam</li> <li>• IV midazolam</li> <li>• IV phenobarbital</li> <li>• IV phenytoin</li> </ul>	
<b>Comparison</b>	Among interventions	
<b>Outcome</b>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Non-cessation of seizures</li> <li>• Requirement for ventilatory support</li> </ul>	Critical Critical Critical

<b>Question 9</b>	<b>In children with established status epilepticus, i.e. seizures persisting after treatment with the first-line agent (benzodiazepine-resistant status epilepticus), which antiepileptic drugs are associated with better clinical outcomes (seizure cessation and fewer adverse effects)?</b>	<b>Importance</b>
<b>Population</b>	Children presenting with established status epilepticus, i.e. seizures persisting after treatment with the first-line agent (benzodiazepine-resistant status epilepticus)	
<b>Intervention</b>	<ul style="list-style-type: none"> <li>• IV phenobarbital</li> <li>• IV valproate</li> <li>• IV phenytoin</li> <li>• IM phenobarbital</li> </ul>	
<b>Comparison</b>	Among interventions	
<b>Outcome</b>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Cessation of seizures</li> <li>• Adverse effects</li> <li>• Recurrence of seizures within 24 h</li> </ul>	Critical Critical Critical Important

<b>Question 10</b>	<b>Which prophylactic pharmacological interventions will prevent recurrence of febrile seizures, and what are the benefits and harm in specific outcomes?</b>	<b>Importance</b>
<b>Population</b>	Children with febrile seizures	
<b>Intervention</b>	<ul style="list-style-type: none"> <li>• Intermittent antipyretic treatment (physical methods, ibuprofen, paracetamol, diclofenac)</li> <li>• Intermittent anticonvulsant treatment (intermittent diazepam, clobazam)</li> <li>• Continuous anticonvulsant treatment (phenobarbital, valproate)</li> </ul>	
<b>Comparison</b>	Active comparator drug or placebo	
<b>Outcome</b>	<ul style="list-style-type: none"> <li>• Prevention of recurrence of febrile seizure</li> <li>• Prevention of epilepsy</li> <li>• Adverse effects</li> </ul>	Critical Important Important

<b>Question 11</b>	<b>What is the role of diagnostic tests in the management of seizures and altered consciousness, particularly when used by non-specialists in low- and middle-income countries?</b>	<b>Importance</b>
<b>Population</b>	Children presenting with seizures or altered consciousness in low-resource settings where they are likely to be managed by non-specialists	
<b>Intervention</b>	Diagnostic tests	
<b>Comparison</b>	Not applicable	
<b>Outcome</b>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Admission to hospital</li> <li>• Length of stay in hospital</li> <li>• Cost</li> <li>• Neurocognitive sequelae</li> </ul>	Critical Important Important Important Important

- <sup>a</sup> Emergency signs described in the WHO ETAT guideline include:
- Obstructed or absent breathing
  - Severe respiratory distress
  - Central cyanosis
  - Signs of shock, defined as cold extremities with capillary refill time > 3 s and weak and fast pulse
  - Coma (or seriously reduced level of consciousness)
  - Seizures
  - Signs of severe dehydration in a child with diarrhoea with any two of the following signs: lethargy or unconscious, sunken eyes, very slow return of skin after pinching.

A background paper on the physiology of shock and fluid management was commissioned and reviewed as part of guideline preparation.



## 2. Methods

The steps outlined in the *WHO handbook for guideline development* (WHO, 2012a) were followed: (i) identification of priority clinical questions and outcomes; (ii) retrieval of evidence; (iii) assessment of the quality of evidence and synthesis of the findings; (iv) formulation of recommendations, including future research priorities; and (v) planning for dissemination, implementation, impact evaluation and updating of the guideline.

The GRADE method was used to prepare tables of evidence from up-to-date systematic reviews of publications on the selected topics. The GDG comprised content experts, methodologists and representatives of potential stakeholder groups. Some of the experts participated in a WHO technical consultation held in Geneva in March 2013 to draft questions for the systematic reviews and guideline update.

The full GDG met in Geneva on 30 September–2 October 2014 to review and discuss the evidence, draft the recommendations and agree on their strength, taking into consideration desirable and undesirable effects of this intervention, the quality (confidence in estimates of effect) of the evidence, values and preferences related to the intervention and outcomes and contextual factors in different settings.

An additional group of external experts and stakeholders reviewed the draft recommendations. All members of the GDG submitted declarations of interest before each meeting and made verbal declarations of interest at the beginning of each meeting (Annex 1).

### Evidence retrieval, assessment and synthesis

Evidence on the priority questions was retrieved according to the standard in the *WHO Handbook for guideline development* (WHO, 2012a). The reviewers are listed in the Acknowledgements. A protocol was designed for each systematic review, which included the search terms and strategy; the populations, interventions, comparators and outcomes were used to define the inclusion and exclusion criteria. The search strategy for each priority question was agreed upon in discussions between the steering group and the lead investigators of each review. Medline and EMBASE databases were used to identify peer-reviewed publications, and the Cochrane Central Register of Controlled Trials, the International Standard Randomised Controlled Trial Number Register and ClinicalTrials.gov were searched for on-going studies. Each review includes a flow diagram of the numbers of studies excluded and included. The quality of the evidence for each priority question was assessed by the GRADE method ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)) and was graded as high, moderate, low or very low according to the definitions in the *WHO Handbook for guideline development* (WHO, 2012a). GRADE tables were prepared with the GRADE profiler software (GRADEPro), when appropriate. The reviews and the background document on the physiology of shock and fluid management are available on file and will be published. They consist of the following.

Systematic reviews and GRADE tables related to the detection of hypoxaemia and use of oxygen therapy:

- *Oxygen therapy in children presenting with emergency signs as per ETAT guidelines: a systematic review*
- *A systematic review of emergency oxygen therapy management in critically ill children: flow rate and humidification*

Systematic reviews, GRADE tables and a background paper related to fluid management in critically ill children:

- *Fluid resuscitation of critically ill children aged 2 to 59 months with impaired circulation*
- *Signs of severe circulatory impairment in children*
- *Physiological basis for the administration of intravenous fluids to children with shock*

Systematic reviews and GRADE tables related to the management of seizures with altered consciousness:

- *Treatment of acute convulsive seizures in children in first level care or in the community (when no IV access is available)*
- *First line treatment of acute convulsive seizures in children where intravenous administration is available*
- *Treatment in established status epilepticus, i.e. seizures persisting after the first line agent (benzodiazepine-resistant status epilepticus)*
- *Prophylaxis to prevent recurrence of febrile seizures*
- *The role of diagnostic tests in children with seizures and altered consciousness*

On the basis of the reviews, the WHO steering committee proposed initial draft recommendations.

### WHO steering committee

A steering committee with members from the WHO departments of MCA, Mental Health and Substance Abuse, Neglected Tropical Diseases, Service Delivery and Safety and the Global Malaria Programme oversaw the guideline review. WHO staff are listed in the Acknowledgements.

### Guideline development group

WHO convened the 21-member GDG, with regional representation, consisting of internationally recognized experts in content and methodology, who are listed in the Acknowledgements. The task of the group was to review and evaluate the quality of the evidence identified in the systematic reviews with the GRADE method (described below) and to revise and finalize the guideline recommendations.

### External peer review

The external peer review group was asked to review the recommendations drafted by the GDG to ensure that there were no important omissions, contradictions or inconsistencies with scientific evidence or programmatic feasibility and to assist in clarifying the language, especially in relation to implementation and how policy-makers and programme staff might read them. The external reviewers were advised that no additional recommendations would be considered. The list of peer reviewers, from various countries and disciplines, and their affiliations is provided in the Acknowledgements.

### Management of conflicts of interest

All members of the GDG were required to sign and submit a declaration of interests before participating in meetings. The steering group reviewed the declarations before the GDG meeting to identify any conflict that might preclude or limit participation, such as personal financial interests, business interests, investments, financial support for research or intellectual property interests for themselves or immediate family members that might prejudice or be seen to prejudice their contributions to the

meeting. The interests declared are listed in Annex 1. No conflicts of interest were identified that were considered prejudicial, and all members of the GDG participated fully.

### Grading the quality of the evidence

The GDG used the GRADE method to evaluate the quality of the evidence. This method is widely used for characterizing the quality of evidence and distinguishes between the quality of evidence and the strength of recommendations (WHO, 2012a). The Cochrane Collaboration and WHO have adopted GRADE as a standard approach for preparing systematic reviews and recommendations for clinical practice guidelines. GRADE tables summarize the details of the studies reviewed, including outcomes, limitations (risk of bias), possible inconsistency, indirectness, imprecision and other factors that might affect the quality of evidence. GDG members used this information to define the overall quality of evidence as “very low”, “low”, “moderate” or “high”, as defined in Table 3.

TABLE 3  
Definitions of quality of evidence in the GRADE method

QUALITY	DEFINITION	IMPLICATION
<b>High</b>	The GDG is highly confident that the true effect lies close to the estimate of the effect.	Further research is very unlikely to change confidence in the estimate of effect.
<b>Moderate</b>	The GDG is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
<b>Low</b>	The GDG has limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
<b>Very low</b>	The GDG has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.	The estimate of effect is very uncertain.

In general, evidence based on randomized controlled trials (RCTs) is considered to be of high quality and evidence from observational studies to be of low quality. These initial ratings may be adjusted by the following factors:

- study limitations or considerations of risk for bias, such as concealment, blinding, type of analysis;
- consistency, namely whether the results of different studies are similar and the effect is in the same direction;
- directness, namely whether the population, intervention or comparator is the same as that addressed by the clinical question;
- imprecision, namely whether the data are for a large or a small population and the breadth of confidence intervals; and
- reporting or publication bias, namely whether the underlying beneficial or harmful effect is systematically underestimated or overestimated due to selective publication of studies or selective reporting of outcomes.

Other considerations, such as dose–response gradients, direction of plausible bias and magnitude of effect, can also change the grade of non-randomized studies.

### Decision-making

The WHO steering committee in Geneva convened a GDG meeting on 30 September–2 October 2014, at which each member of the GDG was given electronic versions of the systematic reviews.

The steering committee presented a synthesis of the evidence, the GRADE tables and the wording of each draft recommendation. Decision-making tables were drafted with the benefits and risks of each intervention from a public health perspective; values, preferences and acceptability to programme managers and policy-makers, health care providers and patients; and the feasibility of implementation (including resources required for national programmes in resource-limited countries and other settings). The cost of the options available to health care workers in different settings was not formally assessed because of lack of primary data in the literature or elsewhere, but the cost and resource implications were considered in a general discussion, in which comments were restricted to personal experiences and extrapolations from general considerations of programme costs.

Each member was asked to review the material and to comment independently and suggest revisions to the proposed guidance and decision-making tables. They were asked to rank the overall quality of evidence by the GRADE method (independently of the rating in the synthesis of the evidence), the benefit–harm balance, values that should be considered in making a recommendation and the applicability of the proposed recommendations to the populations for whom they are intended. Finally, they were asked to assess the strength of the recommendation on the basis of the criteria in Table 4.

TABLE 4  
**Criteria for assessing the strength of recommendations**

STRENGTH	RATIONALE
<b>Strong</b>	The GDG is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. With strong recommendations, the guideline indicates that, in most situations, the recommendation can be adopted as policy.
<b>Conditional</b>	The GDG concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects; however, the recommendation is applicable to only a specific group, population or setting, or new evidence may change the risk–benefit balance, or the benefits may not warrant the cost or resource requirements in all settings. Recommendations are made conditionally when there is uncertainty about the benefits and risks, values and preferences, feasibility and acceptability and cost, or if local adaptation involves a wider variety of values and preferences, or when the resources required make the intervention suitable for some but not other locations. There must therefore be substantial debate and involvement of stakeholders before such a recommendation can be adopted as policy.
<b>No recommendation</b>	Further research is required before any recommendation can be made.

The GDG finalized the recommendations by consensus, defined as general agreement of the GDG members. After each participant expressed an opinion and made suggestions on the recommendation, the chairperson and steering committee summarized the opinion of the GDG and presented it to the group members to gauge the degree of consensus and any differences. The chairpersons of the GDG facilitated discussions among members until consensus was reached on the wording of the recommendation, the quality of evidence and the strength of the recommendation.

WHO staff did not express personal opinions on data, language, the strength of recommendations or the quality of evidence during the discussions; they limited themselves to expressing the principles and guidelines for WHO decision-making.

The GDG reached consensus on all the recommendations after revisions of the text. Some recommendations, especially those on fluid management of ill children presenting with shock (all three signs of circulatory impairment) required significant revisions to achieve consensus.

The steering committee then circulated the draft recommendations to external peer reviewers, who made suggestions to improve the document. The steering committee reviewed the suggestions with the Chair and Co-chair of the GDG, and clarifications on which there was full consensus were incorporated into the guideline. Only one external reviewer returned a conflicting view; the points raised were discussed at the GDG meeting, which agreed on the final recommendations after taking them into account. The literature and justifications submitted by this reviewer were fully considered by the steering committee and GDG chairs.

No new recommendations were considered in this round of comments, and the final version was approved by the GDG.

# 3. Evidence and recommendations

## 3.1 Detection of hypoxaemia and use of oxygen therapy

### Background

Hypoxaemia is a common, important complication of critical illness in childhood that may increase their risk for mortality. It is observed in a variety of diseases – both respiratory and non-respiratory (Duke et al., 2002). Acute respiratory conditions, particularly severe pneumonia, bronchiolitis and asthma, are associated with hypoxaemia. Non-respiratory causes of hypoxaemia include malaria, severe sepsis, seizures, coma and severe anaemia (DeBruin et al., 1992; Subhi et al., 2009; Chisti et al., 2012). In acute CNS disorders, such as meningitis, encephalitis, status epilepticus and trauma, hypoxaemia may occur because of reduced respiratory drive, apnoea or lung conditions such as pulmonary aspiration or co-existent pneumonia. As each of these conditions may be associated with ETAT emergency signs, hypoxaemia should be considered when assessing and managing children with these signs.

Oxygen therapy has long been used to relieve symptoms associated with hypoxaemia (Binger, 1928) and is commonly recommended as a therapeutic intervention to reduce morbidity and mortality from pneumonia, shock or severe sepsis. When severe, hypoxaemia leads to poor oxygen delivery to tissues and anaerobic respiration and is associated with pulmonary arterial vasoconstriction and hypertension. Tissue hypoxia leads to death. In observational studies of effectiveness, a reduced risk for mortality was found when improved oxygen systems, including monitoring with pulse oximetry, were introduced into hospitals (Duke et al., 2008). Conducting a placebo-controlled RCT in critically ill children or adults to demonstrate the benefit of oxygen would generally be deemed unethical. Oxygen therapy for hypoxaemia is widely accepted, as reflected in many international guidelines, including the Advanced Paediatric Life Support (Mackway-Jones et al., 2005), Advanced Pediatric Life Support (Fuchs et al., 2007) and WHO ETAT training materials, on the grounds that the probable benefits are greater than any possible associated harm.

Current WHO ETAT guidelines recommend giving oxygen therapy on the basis of clinical signs, and the recommendations in the WHO *Pocket book of hospital care for children* (WHO, 2013b) suggest a single uniform target of 90% oxygen saturation to start oxygen and  $\geq 90\%$  as a therapeutic aim. Few data are available, however, except for the neonatal population, on the level of oxygen saturation that should be achieved in sick children with immediately life-threatening problems and the saturation at which it is safe to cease oxygen therapy. Clinical signs of hypoxaemia are insensitive (Alario et al., 1995; Duke et al., 2002; Lodha et al., 2004; Laman et al., 2005), and a recent meta-analysis showed that neither single nor combined symptoms and signs are effective in predicting hypoxaemia among young children with acute respiratory tract infections (Zhang et al., 2011). Current international resuscitation guidance depends on physiological and mechanistic evidence and expert consensus on a safe approach to oxygen therapy.

Noninvasive measurement of oxygen saturation ( $SpO_2$ ) by pulse oximetry is often the most practical and easily applicable intervention for use in most settings. There is growing use of pulse oximeters in developing countries because of increased availability, lower cost and evidence of benefit. As a

result, oxygen saturation could become an effective routine component of triage and assessments for detecting hypoxaemia in low-resource settings. Normal and abnormal values vary, however, by altitude: a lower SpO<sub>2</sub> value (88–90%) is regarded as normal at high altitude, while an SpO<sub>2</sub> of 94–96% is regarded as normal at sea level. In facilities where the PaO<sub>2</sub> in blood can be measured by invasive arterial blood sampling, a value of < 7.3 kPa (range, 6–8 kPa) is used to indicate the requirement for oxygen therapy; in the same settings, an SpO<sub>2</sub> < 90% is used as an indicator for oxygen therapy. While some thresholds for starting oxygen therapy have been established on the basis of pathophysiology and experience, there is no empirical evidence on when to stop oxygen or when additional supportive care is needed.

### 3.1.1 When to start and stop oxygen therapy in severely ill children with ETAT emergency signs

**Question 1. For infants and children presenting with emergency signs (as described in ETAT guidelines), at what oxygen saturation is oxygen therapy effective as compared with not giving oxygen in preventing morbidity and mortality?**

*(Oxygen therapy in children presenting with emergency signs as per ETAT guidelines: a systematic review)*

#### Summary of evidence on when to start and stop oxygen therapy

No studies or systematic reviews were identified in which morbidity and mortality outcomes were compared for different target saturation levels in a population of children with ETAT emergency signs.

- Five pre–post observational studies were identified in which the outcomes of using different saturation targets for oxygen therapy were included.
- Duke et al. (2002) compared the outcomes of 703 prospectively enrolled children in Papua New Guinea (1600 m above sea level) with severe or very severe pneumonia who received oxygen if their SpO<sub>2</sub> was < 85% as measured by pulse oximetry with those of 258 children who received oxygen on the basis of clinical signs (primarily cyanosis). The mortality rate was 6.5% (46/703) among the prospectively enrolled children and 10% (26/258) in the comparison children, giving a mortality risk ratio of 0.65 [95% confidence interval (CI), 0.41–1.02; two-sided Fisher exact test,  $p = 0.07$ ].
- Duke et al. (2008) prospectively studied 11 291 children in Papua New Guinea (0–1800 m) admitted for pneumonia, of whom 7161 received oxygen on the basis of clinical signs (primarily cyanosis) and 4130 children who received oxygen if their SpO<sub>2</sub> was < 90% by pulse oximetry. The mortality rate was 4.97% (356/7161) in the children who received oxygen on the basis of clinical signs and 3.22% (133/4130) in those who received oxygen on the basis of pulse oximetry. The risk for death of a child with pneumonia was 35% lower in the group receiving oxygen on the basis of SpO<sub>2</sub> < 90% (risk ratio, 0.65; 95% CI, 0.52–0.78;  $p < 0.0001$ ).
- Singhi et al. (2012) enrolled 58 children with chest indrawing pneumonia and normoxaemia (SpO<sub>2</sub> > 90%), who were randomly assigned to receive supplemental oxygen (nasal prongs, 1–2 L/min) ( $n = 29$ ) or room air ( $n = 29$ ). Hypoxaemia later developed in 31 patients (53%), with no significant difference between the two arms (relative risk [RR], 0.61; 95% CI, 0.36–1.04). The patients with and without hypoxaemia were similar, except for a lower SpO<sub>2</sub> on enrolment, but they took longer to recover from tachypnoea ( $p = 0.05$ ), chest indrawing ( $p = 0.05$ ) and fever, indicating that they had more severe disease. Early oxygen therapy did not alter the course of disease.
- Webb et al. (2012) assessed clinical treatment failure rates in 568 children in Kenya with severe and very severe pneumonia. They reported that children with mild hypoxaemia (SpO<sub>2</sub>, 90–95%) had worse outcomes than those with higher saturation but did not provide details.
- West et al. (1999) reported the long-term survival of 190 children in The Gambia who were admitted to hospital for severe pneumonia. Of these, 83 were hypoxaemic (SpO<sub>2</sub> < 90%) and were treated

with oxygen, and 107 were not. On follow-up 4 years later, 62% were traced. Eight of the children with hypoxaemia and four of those who had not had hypoxaemia had died, giving mortality rates of 4.8 and 2.2 deaths per 100 child-years of follow-up, respectively, which were not statistically significantly different ( $p = 0.2$ ).

No studies of the use of different threshold oxygen saturation as a basis for stopping oxygen therapy were identified in children presenting with ETAT emergency signs.

### Additional evidence not included in the GRADE table

In the absence of clinical trials of different oxygen saturation thresholds, understanding the physiological principles that regulate oxygen delivery in the body during critical illness may help to define a rational, safe approach to oxygen therapy in children with emergency signs. Critically ill children are at increased risk for hypoxia due to both increased tissue oxygen demand and impaired oxygen delivery. Conditions that cause or are associated with ETAT emergency signs, such as obstructed or absent breathing, severe respiratory distress, central cyanosis, shock (cold extremities with capillary refill time > 3 s and weak and fast pulse), low or unmeasurable blood pressure, coma (or seriously reduced level of consciousness) are associated with hypoxaemia, tissue hypoxia and (sometimes) increased tissue oxygen requirements. A child presenting with ETAT emergency signs may have a combination of impaired oxygen delivery due to the underlying disease and existing comorbid conditions, such as severe anaemia, malnutrition or cardiac failure. These children will be less capable of withstanding moderately low oxygen than children with only lung disease.

Most international guidelines for resuscitation advocate use of higher target oxygen saturation thresholds in children who are severely unwell. This recommendation is based mainly on expert opinion, in view of the absence of controlled trials on this subject. The following table summarizes national and international guidelines on the use of oxygen during and after resuscitation.

GUIDELINE	OXYGEN SATURATION TARGET
Resuscitation Council (United Kingdom) (2010)	100% oxygen should be used for initial resuscitation. After the return of spontaneous circulation, inspired oxygen should be titrated, by pulse oximetry, to achieve an oxygen saturation of 94–98%.
European Resuscitation Council: Paediatric Advanced Life Support (Nolan et al., 2010a)	Give oxygen at the highest concentration (100%)* during initial resuscitation. Once circulation is restored, give sufficient oxygen to maintain an arterial oxygen saturation in the range of 94–98%.
International Liaison Committee on Resuscitation (Nolan et al., 2010b)	There is insufficient evidence to recommend a specific inspired oxygen concentration for ventilation during resuscitation from cardiac arrest in infants and children. Once circulation is restored, it is reasonable to titrate inspired oxygen to limit hyperoxaemia.
American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science (2010): Part 14: Pediatric Advanced Life Support (Kleinman et al., 2010)	It is reasonable to ventilate with 100% <sup>a</sup> oxygen during cardiopulmonary resuscitation because there is insufficient information on the optimal inspired oxygen concentration. Once the circulation is restored, monitor systemic oxygen saturation. It may be reasonable, when the appropriate equipment is available, to titrate oxygen administration to maintain the oxyhaemoglobin saturation $\geq 94\%$ .
Australian Resuscitation Council/ New Zealand Resuscitation Council (2010)	It is reasonable to use 100% <sup>a</sup> oxygen initially for resuscitation (class A, expert consensus opinion). After resuscitation, the concentration of inspired oxygen should be reduced to a level that yields a satisfactory level of oxygen in arterial blood as measured by arterial blood gas analysis ( $\text{PaO}_2$ , 80–100 mmHg) or by percutaneous oximetry ( $\text{SpO}_2 \geq 95\text{--}\leq 100\%$ ).



GUIDELINE	OXYGEN SATURATION TARGET
Advanced Paediatric Life Support Australia (2012)	While 100% oxygen remains the recommendation for use during resuscitation outside the delivery room, once spontaneous circulation returns, hyperoxia can be detrimental to recovering tissues. Pulse oximetry should be used to monitor and adjust for oxygen requirements after successful resuscitation. Saturation should be maintained between 94% and 98%.
National Institute for Health and Care Excellence (United Kingdom) (2013)	Oxygen should be given to children with fever who have signs of shock or oxygen saturation (SpO <sub>2</sub> ) of < 92% when breathing air. Treatment with oxygen should also be considered for children with an SpO <sub>2</sub> > 92%, as clinically indicated.

<sup>a</sup> While the respective guidelines state use of 100% oxygen, there is little evidence to differentiate the effectiveness of providing oxygen at concentrations of 85–100% and 100%. The oxygen concentrators commonly available in low- and middle-income countries generally produce oxygen at concentrations > 85%, which is considered adequate.

SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS		
BENEFITS AND HARM	Do the desirable effects outweigh the undesirable effects? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain	In studies on children with pneumonia, oxygen therapy determined by pulse oximetry (SpO <sub>2</sub> < 90%) rather than clinical signs reduced mortality in children with hypoxaemia and pneumonia.  No evidence of harm of this intervention was found in children with ETAT emergency signs (who are not preterm neonates). Not treating hypoxaemia adequately may increase morbidity and mortality in children with ETAT emergency signs.
VALUES AND PREFERENCES; ACCEPTABILITY	Is there important uncertainty about or variation in how people value the options? <input type="checkbox"/> Major <input checked="" type="checkbox"/> Minor <input type="checkbox"/> Uncertain  Is the option acceptable to key stakeholders? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain	Oxygen therapy is widely available in developed countries and is a generally acceptable intervention for critically unwell children.  Studies of children with pneumonia show that those with respiratory diseases are usually managed with oxygen when the SpO <sub>2</sub> is < 90%. Use of SpO <sub>2</sub> ≥ 94% is not supported in studies in which oxygen was administered to children with signs of pneumonia.
FEASIBILITY AND RESOURCE USE	How large are the resource requirements? <input checked="" type="checkbox"/> Major <input type="checkbox"/> Minor <input type="checkbox"/> Uncertain  Is the option feasible to implement? <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Uncertain	Studies have demonstrated the feasibility of providing oxygen therapy to children identified as hypoxaemic by pulse oximetry. In hospital, oxygen is usually supplied from cylinders, which are expensive. Oxygen concentrators are less expensive, but there are other costs and system implications, such as maintenance of the equipment and training of staff. Demand for a potentially scarce resource will be higher if the decision is made to administer oxygen at a higher threshold. Use of pulse oximetry will rationalize the use of oxygen by better identification of children who need it.  The feasibility of applying this guideline in district hospitals in low-resource settings will depend on making pulse oximeters and sources of oxygen available. Resources will also be needed to maintain the equipment and train staff.

## RECOMMENDATION 1.1

Pulse oximetry is recommended to determine the presence of hypoxaemia in all children with ETAT emergency signs.<sup>a</sup> When the child has only respiratory distress, oxygen supplementation is recommended at SpO<sub>2</sub> < 90%. Children presenting with other ETAT emergency signs<sup>a</sup> with or without respiratory distress should receive oxygen therapy if their SpO<sub>2</sub> is < 94%.

<b>Strength of recommendation</b>	Strong
<b>Quality of evidence</b>	Very low
<b>Justification</b>	Although the quality of the evidence is very low, a strong recommendation was made because the group considered that the recommendation provides pragmatic guidance that will help health workers to make decisions on giving adequate, appropriate oxygen to children who are at high risk for mortality, and this would be likely to improve survival without great risk of harm.
<b>Subgroup considerations</b>	For children with signs of shock (cold extremities with capillary refill time > 3 s and weak and fast pulse), low or unmeasurable blood pressure, coma, very severe anaemia or severe heart failure, oxygen therapy should be started at SpO <sub>2</sub> < 94% to maintain oxygen saturation at ≥ 94%.
<b>Implementation considerations</b>	<ul style="list-style-type: none"><li>• The recommendation to give oxygen to all children with ETAT emergency signs if SpO<sub>2</sub> &lt; 94% should be weighed against the increased demand that would be placed on resources in developing countries where oxygen supplies may be scarce. A target saturation of ≥ 94% does not apply to continuous management after resuscitation, when diagnoses are clearer, the patient is stabilized and other deficits in oxygen delivery are addressed.</li><li>• A target saturation of ≥ 94% may help to compensate for potentially reduced oxygen delivery, which is more likely in children with ETAT emergency signs arising from conditions such as severe pneumonia, septic shock, severe anaemia, CNS infection or heart failure.</li><li>• Patients with severe anaemia and evidence of oxygen tissue deficit (such as lactic acidosis) who are given oxygen alone may reach the measured SpO<sub>2</sub> target of ≥ 94%, but this will not substantially increase their oxygen-carrying capacity and correct tissue hypoxia. They will require an urgent blood transfusion.</li></ul>
<b>Research priorities</b>	For infants and children presenting with emergency signs (as described in ETAT guidelines <sup>a</sup> ), at what oxygen saturation is oxygen therapy effective as compared with not giving oxygen in preventing morbidity and mortality?

<sup>a</sup> Emergency signs described in WHO ETAT guideline include:

- Obstructed or absent breathing
- Severe respiratory distress
- Central cyanosis
- Signs of shock, defined as cold extremities with capillary refill time > 3 s and weak and fast pulse
- Coma (or seriously reduced level of consciousness)
- Seizures
- Signs of severe dehydration in a child with diarrhoea with any two of the following signs: lethargy or unconscious, sunken eyes, very slow return after pinching the skin.

**Question 2. For infants and children presenting with emergency signs (as described in ETAT guidelines), at what oxygen saturation will stopping oxygen therapy as compared with continuing oxygen have no effect on morbidity or mortality?**

**Summary of evidence**

No systematic reviews or studies were identified that directly answered the specific question in children presenting with ETAT signs.

SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS		
<b>BENEFITS AND HARM</b>	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>Oxygen is scarce in low-resource settings and expensive. A cut-off for oxygen saturation is required for deciding when to stop oxygen for its efficient, effective use and to prevent wastage.</p> <p>Monitoring SpO<sub>2</sub> by pulse oximetry to make a decision to stop oxygen therapy, will rationalize use of oxygen. Studies of children with pneumonia show that deciding to give oxygen therapy on the basis of pulse oximetry rather than clinical signs reduces the mortality rate among children with hypoxaemia.</p> <p>No evidence was found of harm caused by this intervention in children with ETAT emergency signs (who are not preterm neonates). Not treating hypoxaemia adequately may increase morbidity and mortality in children with ETAT emergency signs.</p>
<b>VALUES AND PREFERENCES; ACCEPTABILITY</b>	<p>Is there important uncertainty about or variation in how people value the options?</p> <p><input type="checkbox"/> Major</p> <p><input checked="" type="checkbox"/> Minor</p> <p><input type="checkbox"/> Uncertain</p> <p>Is the option acceptable to key stakeholders?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>Physicians and nurses require an objective measure for making a rational decision on when to stop oxygen.</p> <p>An objective measure will increase judicious use of oxygen in low-resource settings, and oxygen is more likely to be available for all patients.</p> <p>Use of pulse oximetry instead of clinical signs provides an objective measure of when to stop oxygen.</p>
<b>FEASIBILITY AND RESOURCE USE</b>	<p>How large are the resource requirements?</p> <p><input checked="" type="checkbox"/> Major</p> <p><input type="checkbox"/> Minor</p> <p><input type="checkbox"/> Uncertain</p> <p>Is the option feasible to implement?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Uncertain</p>	<p>Oxygen is usually supplied in hospitals from cylinders, which are expensive. Oxygen concentrators are less expensive than cylinder oxygen, but there are other costs and system implications, such as maintenance of the equipment and training staff. Monitoring SpO<sub>2</sub> by pulse oximetry to make a decision to stop oxygen, which is a scarce resource in low-income settings, will rationalize use of oxygen.</p> <p>The feasibility of implementing this guideline in district hospitals in low-resource settings will depend on making pulse oximeters and sources of oxygen available. Resources will also be needed to maintain the equipment and train staff.</p>

## RECOMMENDATION 1.2

Oxygen therapy can be stopped when a child no longer has ETAT emergency signs<sup>a</sup> and maintains a peripheral capillary oxygen saturation  $\geq 90\%$  in room air.

<b>Strength of recommendation</b>	Conditional
<b>Quality of evidence</b>	Very low
<b>Justification</b>	Because the quality of the evidence is very low and oxygen availability varies by setting, the recommendation is conditional. This recommendation will promote the judicious use of oxygen in settings where it is expensive and scarce. In settings where oxygen is more routinely available, a higher threshold to stop oxygen may be used.
<b>Implementation considerations</b>	Monitoring the progress of children on oxygen is important, and WHO recommendations for the management of common childhood conditions (WHO, 2012b) regarding oxygen therapy should be followed. When the child is stable and improving, take the child off oxygen for 15 min. If the SpO <sub>2</sub> readings in room air remain $\geq 90\%$ , discontinue oxygen, but check again 30 min later and every 3 h thereafter on the first day off oxygen to ensure that the child remains stable.
<b>Research priorities</b>	For infants and children presenting with emergency signs (as described in ETAT guidelines <sup>a</sup> ), at what oxygen saturation will stopping oxygen therapy as compared with continuing oxygen have no effect on morbidity and mortality in the short and long term?

<sup>a</sup> Emergency signs described in WHO ETAT guideline include:

- Obstructed or absent breathing
- Severe respiratory distress
- Central cyanosis
- Signs of shock, defined as cold extremities with capillary refill time  $> 3$  s and weak and fast pulse
- Coma (or seriously reduced level of consciousness)
- Seizures
- Signs of severe dehydration in a child with diarrhoea with any two of the following signs: lethargy or unconscious, sunken eyes, very slow return after pinching the skin.

### 3.1.2 Oxygen flow rate and humidification in severely ill children with ETAT emergency signs

**Question 3. What flow rate for nasal delivery of oxygen restores normal oxygen saturation and/or the best clinical outcome in infants and children presenting with respiratory distress or other emergency signs (as described in WHO ETAT guidelines)?**

*(A systematic review of emergency oxygen therapy management in critically ill children: flow rate and humidification)*

#### Summary of evidence

- No systematic reviews were identified that directly answered the specific question. Four observational or interventional studies were conducted to determine whether higher flow rates result in better outcomes than lower flow rates (rather than identifying the best flow rate from a range of rates).
- Milési et al. (2013) reported outcomes in a prospective quasi-interventional design with a small sample size, in which 21 infants in a paediatric intensive care unit with acute respiratory syncytial virus bronchiolitis were studied at four increasing oxygen flow rates (1 L/min, 4 L/min, 6 L/min and 7 L/min). The mean positive pressure increased from 0.2 cm H<sub>2</sub>O (95% CI, -0.2–0.7) at 1 L/min to 4 cm H<sub>2</sub>O (95% CI, 3–5) at maximum flow ( $p = 0.0001$ ). Only flows  $> 6$  L/min increased the positive pressure during both inspiration and expiration. Increasing the flow from 1 to 7 L/min resulted in

significant reductions in respiratory rate ( $p = 0.007$ ) and modified Wood clinical asthma score ( $p = 0.0096$ ). No change in oxygen requirements was observed ( $p = 0.28$ ) or  $SpO_2$  ( $p = 0.28$ ). The authors concluded that flow rates  $\geq 2$  L/kg/min generate a clinically relevant positive pressure and improve the breathing pattern.

- Bressan et al. (2013) reported a benefit for 27 paediatric patients in an observational study when high flow oxygen was initiated at a flow rate calculated from the formula “weight (kg) + 1”. The  $SpO_2$  increased significantly from 88% to 97% in the first hour and stabilized thereafter. End-tidal carbon dioxide decreased in the first hour, from 37% to 30%, and stabilized thereafter. The respiratory rate fell from 70 to 50 in the first hour and then stabilized. End-tidal carbon dioxide and respiratory rate were highly significantly improved ( $p < 0.001$ ) for each comparison, but no effect was seen on heart rate or body temperature. The study showed that high-flow nasal cannulae (HFNC) reduced end-tidal carbon dioxide (by 7%) and respiratory rate (by 20 points); however, it did not fully answer the guideline question because exact flow rates for standard oxygen therapy were not given.
- Hough et al. (2014) conducted a prospective intervention study, in which 13 infants were randomly allocated to 2 L/min (low flow, 0.4 L/kg bw per min) or 8 L/min (high flow, 1.7 L/kg per min). The measures used were end-expiratory level, lung volume, oesophageal pressure at end expiration and other physiological measurements, including respiratory rate, heart rate,  $SpO_2$ , fraction of inspired oxygen ( $FiO_2$ ) and  $SpO_2:FiO_2$  ratio. Oesophageal pressure at end expiration increased significantly with the high flow rate, from  $-0.2 \pm 7.6$  cm  $H_2O$  to  $6.9 \pm 2.1$  cm  $H_2O$  ( $p = 0.045$ ) but only moderately at the low flow rate, from  $-1.9 \pm 4.8$  cm  $H_2O$  to  $-0.2 \pm 4.8$  cm  $H_2O$  ( $p$  not significant). The respiratory rate dropped significantly at the high flow rate, from  $68.5 \pm 6.0$  to  $56.9 \pm 3.2$  ( $p = 0.045$ ), but no other significant differences in physiological variables were seen, such as heart rate,  $FiO_2$ ,  $SPO_2$  or  $SpO_2:FiO_2$ .
- In a quasi-intervention study, Mayfield et al. (2013) investigated the use of oxygen through HFNC in 61 infants in comparison with 33 infants in a control group. HFNC was given at a rate of 2 L/kg bw per min to a maximum of 10 L/min, and  $FiO_2$  was titrated to maintain 94% saturation. The control treatment was low-flow sub-nasal oxygen. The physiological measures were heart rate, respiratory rate,  $SpO_2$ , temperature, a respiratory score for work of breathing and length of hospital stay. Of the 61 in the HFNC group, 53 responded; the 8 who did not were transferred to the paediatric intensive care unit. In the control group, 23/33 responded, and 10 had to be managed in the paediatric intensive care unit. The respiratory rate decreased significantly in both groups of responders after admission ( $p = 0.05$ ), as did the heart rate; however, the control group had a greater reduction. The length of hospital stay was similar in the two groups.

#### SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS

<b>BENEFITS AND HARM</b>	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>For some children with ETAT emergency signs, standard-flow oxygen may not resolve hypoxaemia, and higher flow rates may be required to reach a target <math>SpO_2</math> of <math>\geq 94\%</math>. With higher flow rates, some positive airway pressure should be achieved. It is important to check that all connections are secure, the oxygen flow rate is correct, the airways are not obstructed and there is no gastric distension, as described in the WHO <i>Pocket book</i> (2013b) on use of oxygen therapy in children. With flow rates <math>&gt; 4</math> L/min, humidification is needed.</p> <p>Higher than standard flow rates through nasal cannula are potentially harmful, including drying of nasal secretions if humidification is inadequate and resultant mucosal bleeding or ulceration, lung barotrauma, including pneumothorax, gastric distension leading to impaired lung expansion and retinal toxicity (in premature neonates only).</p>
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<b>VALUES AND PREFERENCES; ACCEPTABILITY</b>	<p>Is there important uncertainty about or variation in how people value the options?</p> <input type="checkbox"/> Major <input checked="" type="checkbox"/> Minor <input type="checkbox"/> Uncertain	<p>Prevention and management of hypoxaemia are highly valued in the community, because it has been shown that oxygen therapy reduces mortality in children with hypoxaemia and pneumonia. It is an accepted intervention (see other International guidelines) for seriously ill children, including those with ETAT emergency signs.</p> <p>Standard-flow oxygen therapy via nasal cannula is the most efficient, safest method of delivering oxygen</p> <ul style="list-style-type: none"> <li>• Oxygen in cylinders is expensive.</li> <li>• Oxygen concentrators are more efficient for delivering oxygen but require a continuous power supply and regular maintenance.</li> <li>• Other methods are available to deliver continuous positive airway pressure but are also moderately expensive</li> </ul>
<b>FEASIBILITY AND RESOURCE USE</b>	<p>Is the option acceptable to key stakeholders?</p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain	
	<p>How large are the resource requirements?</p> <input type="checkbox"/> Major <input checked="" type="checkbox"/> Minor <input type="checkbox"/> Uncertain	<p>Standard- and higher-than-standard-flow oxygen therapy is feasible even with oxygen cylinders and oxygen concentrators. The high flow rate is more resource intensive and requires humidification. Oxygen concentrators are less expensive than oxygen cylinders, and there are other costs and system implications, such as maintenance of the equipment and training of staff.</p>
	<p>Is the option feasible to implement?</p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain	<p>The feasibility of implementing this guideline in district hospitals in low-resource settings will depend on making pulse oximeters and sources of oxygen available. Resources will also be needed to maintain the equipment and train staff.</p>

### RECOMMENDATION 1.3

**Severely ill children with signs of obstructed breathing, central cyanosis, severe respiratory distress or signs of shock or who are unconsciousness should receive oxygen initially by nasal prongs at a standard flow rate (0.5–1 L/min for neonates, 1–2 L/min for infants and 2–4 L/min for older children) or through an appropriately sized face mask (> 4 L/min) to reach a peripheral capillary oxygen saturation  $\geq$  94%.**

<b>Strength of recommendation</b>	Strong
<b>Quality of evidence</b>	Very low
<b>Justification</b>	Although the quality of the evidence is very low, a strong recommendation was made because the group placed high value on the benefits of receiving oxygen at various specific flow rates, which outweighed the potential harm.
<b>Implementation considerations</b>	Humidification equipment will not be required if standard low-flow oxygen is used; however, humidification is necessary if higher flow rates (such as 2 L/kg bw per min) are used, and equipment will be needed.
<b>Research priorities</b>	What flow rate for nasal delivery of oxygen restores normal oxygen saturation and/or the best clinical outcomes in infants and children presenting with respiratory distress or other emergency signs (as described in WHO ETAT guidelines)?

**Question 4. Does humidified high-flow oxygen therapy result in better oxygen saturation or better clinical outcomes than non-humidified standard-flow oxygen therapy in infants and children presenting with respiratory distress or other emergency signs (as described in WHO ETAT guidelines)?**

**Summary of evidence**

- No studies were identified that answered the specific guideline question.
- The GDG therefore shared expert opinion in order to make a recommendation. The group noted, however, that, even if studies of the effects of humidification and high flow had been conducted, it would be difficult to disaggregate the effects of the two interventions on clinical outcomes.

SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS		
<b>BENEFITS AND HARM</b>	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>Heated, humidified HFNC oxygen therapy provides positive end-expiratory pressure, although the exact level is unknown and depends on several patient and equipment factors: the size of the child, whether the mouth is open or closed, the cannula size and the fit in the nostrils. Heated, humidified nasal cannula oxygen therapy can both increase oxygenation and reduce the work of breathing. It is an alternative to other continuous positive airway pressure methods. No adequately powered randomized trial has been conducted to compare heated, humidified nasal cannula oxygen therapy with other methods of ensuring continuous positive airway pressure.</p> <p>If higher-than-standard oxygen flow rates are used, humidification prevents drying of secretions and improves patient comfort. It is important to check that all connections are secure, the oxygen flow rate is correct, the airways are not obstructed and there is no gastric distension, as described in the WHO <i>Pocket book</i> (WHO, 2013b) on use of oxygen therapy in children.</p> <p>Lack of adequate humidification in high-flow oxygen therapy can lead to drying of secretions and patient discomfort.</p>
<b>VALUES AND PREFERENCES; ACCEPTABILITY</b>	<p>Is there important uncertainty about or variation in how people value the options?</p> <p><input type="checkbox"/> Major</p> <p><input checked="" type="checkbox"/> Minor</p> <p><input type="checkbox"/> Uncertain</p> <p>Is the option acceptable to key stakeholders?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>Humidification is not required for standard oxygen flow, whereas it is needed for HFNC therapy. Heated, humidified HFNC oxygen therapy is feasible only if there is appropriate equipment to deliver it. It requires (i) a source of gas that provides flow rates of <math>\leq 2</math> L/kg bw per min, (ii) capacity to blend oxygen and air, (iii) an effective method of humidification and (iv) an appropriate nasal interface (such as special nasal cannula that will resist the higher flows). Devices to deliver heated, humidified HFNC oxygen therapy are available on the market.</p> <p>Use of humidification in HFNC oxygen therapy is valuable for preventing drying of secretions and improves the comfort of children with hypoxaemia. It is an accepted intervention for seriously ill children, including those with ETAT emergency signs.</p>
<b>FEASIBILITY AND RESOURCE USE</b>	<p>How large are the resource requirements?</p> <p><input checked="" type="checkbox"/> Major</p> <p><input type="checkbox"/> Minor</p> <p><input type="checkbox"/> Uncertain</p> <p>Is the option feasible to implement?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Uncertain</p>	<p>Humidification is feasible in HFNC oxygen therapy but is resource intensive because of the costs and system implications, such as maintenance of the equipment and training of staff.</p> <p>The cost depends on the device. Equipment for continuous positive airway pressure, either heated, humidified nasal cannula oxygen therapy or other, simpler methods, can cost US\$ 1000–10 000.</p> <p>The feasibility of implementing this guideline in district hospitals in low-resource settings will depend on making heated humidification and sources of oxygen available. Resources will also be required to maintain the equipment and train staff. Studies have indicated that use of heated, humidified nasal cannula and simple methods of providing continuous positive airway pressure are feasible in developing countries.</p>

## RECOMMENDATIONS

1. 4 For standard flow oxygen therapy, humidification is not needed.

1. 5 In an emergency setting when a flow > 4 L/min through nasal cannulae is required for more than 1–2 h, effective heated humidification should be added.

<b>Strength of recommendations</b>	Strong (for both recommendations)
<b>Quality of evidence</b>	Very low (for both recommendations)
<b>Justification</b>	Although the quality of the evidence is very low, a strong recommendation was made because the group placed high value on providing humidification for HFNC oxygen therapy and because the benefits outweigh the potential harm.
<b>Implementation considerations</b>	The feasibility of implementing this guideline in district hospitals in low-resource settings will depend on making heated humidification and sources of oxygen available. Resources will also be required to maintain the equipment and train staff.
<b>Research priorities</b>	Does humidified high-flow oxygen therapy result in better oxygen saturation levels or better clinical outcomes (short- or long-term) than non-humidified standard-flow oxygen therapy in infants and children presenting with respiratory distress or other emergency signs (as described in WHO ETAT guidelines)?

### 3.2 Fluid management for critically ill children

#### Background

A critical component of the emergency care of very sick infants and children is fluid management in the first 1–2 h after initial assessment. In children in whom adequate tissue perfusion appears to be compromised, additional fluids are commonly given as a means of improving circulating volume. Children with a history of diarrhoea with severe dehydration urgently need additional fluids to restore circulating volume. In other sick children, for example those with malaria, pneumonia or meningitis and those without overt fluid loss, giving additional fluids may be detrimental.

Generating the evidence base for such practice is challenging because it is complex both practically and ethically to conduct randomized comparative studies of fluid types, volumes and rates in critically ill children. Undertaking such studies in low-resource settings, where the disease profile of children is likely to be very different from that in high-resource settings and where staffing levels and competencies are less consistent, is even more difficult.

The second edition of the WHO *Pocket book of hospital care for children* (WHO, 2013b) did not include a revision of fluid management in triage and emergency conditions, as the document was revised before publication of a large RCT on use of fluid boluses in sick infants and children with febrile illness and signs of circulatory impairment: the trial of fluid expansion as supportive therapy trial (FEAST) (Maitland et al., 2011). No other new data were available at the time of the revision of the *Pocket book*. The FEAST study investigators anticipated that the study would confirm the value of fluid boluses in such children and would help to identify the best fluid strategy in terms of fluid type and rate; however, the study was stopped prematurely by the Data Safety Monitoring Board because fluid boluses were found to increase rather than decrease mortality.

The findings of the FEAST study should be understood in the context of the children who were recruited into the study and the populations addressed by the WHO ETAT guidelines. The study recruited infants and children with febrile illness and some signs of circulatory impairment, while



WHO ETAT recommendations provide guidance on the management of children with a range of clinical presentations or combinations of clinical signs, including shock. The clinical definition of shock used by WHO, which can be assessed in resource-limited settings by non-specialist health workers, is the presence of three clinical signs at one time, i.e. cold extremities *with* capillary refill time > 3 s *and* a weak and fast pulse. The presence of one or two of these signs indicates nonspecific circulatory impairment that could be due to conditions other than circulatory shock. For example, cold extremities may be due to exposure; prolonged capillary refill may be due to exposure to cold; and a fast pulse may be due to pain or distress. Children in shock as defined by WHO, that is, who have all three signs, are at high risk for death.

There is no universally agreed definition of shock. International guidelines and training courses such as the Advanced Paediatric Life Support (Mackway-Jones et al., 2005) and Advanced Pediatric Life Support (Fuchs et al., 2007) provide lists of clinical signs that, if present, indicate that a child is in “shock” (Table 5); however, these guidelines and courses do not indicate how many signs must be present in order for shock to be diagnosed, nor is there a clear distinction between severe circulatory impairment, shock and severe shock. WHO refers only to “shock” with no other sub-classifications. If a child has only one or two of the three signs, the diagnosis is only circulatory impairment, whereas if all three signs are present the child is in “shock”.

TABLE 5

**Definitions and signs of shock in selected guidelines and training materials**

SOURCE AND DEFINITION OR STATEMENT	SIGNS
<p><b>Advanced Paediatric Life Support (United Kingdom) (European Resuscitation Council, 2005; Mackway-Jones et al., 2005)</b>  <i>Shock</i> results from an acute failure of circulatory function. Involves inadequate amounts of nutrients, especially oxygen, delivered to body tissues and inadequate removal of tissue waste products. Inadequate tissue perfusion resulting in impaired cellular respiration (i.e. shock) may result from defects of the pump (cardiogenic), loss of fluid (hypovolaemic), abnormalities of vessels (distributive), flow restriction (obstructive) or inadequate oxygen-releasing capacity of blood (dissociative). As these functions involve several body systems, there are several causes of shock; therefore, the clinician must consider which of several alternative emergency treatments will be effective for an individual patient.</p>	<p><b>Phase 1 (compensated) shock</b>  Mild agitation or confusion, skin pallor, increased heart rate and cold peripheral skin with decreased capillary return</p>
	<p><b>Phase 2 (uncompensated) shock</b>  The child has a falling blood pressure, very slow capillary return, tachycardia, cold extremities, acidotic breathing, depressed cerebral state and absent urine output.</p>
	<p><b>Phase 3 (irreversible) shock</b>  The diagnosis of irreversible shock is retrospective. During progression of shock, a point is reached at which the death of the patient is inevitable, despite therapeutic intervention.</p>
	<p><b>Early (compensated) septic shock</b>  Characterized by a raised cardiac output, decreased systemic resistance, warm extremities and a wide pulse pressure. The hyperdynamic state is recognized by hyperpyrexia, hyperventilation, tachycardia and mental confusion. All these signs may be minimal: mental confusion in particular should be looked for carefully if septic shock is not to be overlooked at this stage. Decreased capillary return is a useful sign in these circumstances.</p>
	<p><b>Dehydration and shock</b></p> <ul style="list-style-type: none"> <li>• tachycardia, usually associated with poor volume peripheral pulses</li> <li>• poor peripheral perfusion with prolonged capillary refill time and cool extremities</li> <li>• low blood pressure as a pre-terminal sign</li> <li>• alteration of mental state</li> <li>• metabolic acidosis with compensatory tachypnoea</li> <li>• poor urine output</li> </ul>

TABLE 5 continued

SOURCE AND DEFINITION OR STATEMENT	SIGNS
<p><b>Advanced Pediatric Life Support (USA) (Fuchs et al., 2007)</b>  <i>Shock</i> is a critical condition that results from inadequate tissue delivery of oxygen and nutrients to meet tissue metabolic demand. Shock is often, but not always, characterized by inadequate peripheral and end-organ perfusion. The definition of shock does not depend on blood pressure measurement; shock can occur with a normal, increased or decreased systolic blood pressure. In children, most shock is characterized by low cardiac output; however, in some types of shock (e.g. caused by sepsis or anaphylaxis), cardiac output may be high. All types of shock can result in impaired function of vital organs, such as the brain (decreased level of consciousness) and kidneys (low urine output, ineffective filtering).  Shock can result from:</p> <ul style="list-style-type: none"> <li>• inadequate blood volume or oxygen-carrying capacity (hypovolaemic shock, including haemorrhagic shock)</li> <li>• inappropriate distribution of blood volume and flow (distributive shock)</li> <li>• impaired cardiac contractility (cardiogenic shock)</li> <li>• obstructed blood flow (obstructive shock)</li> </ul>	<p><b>Hypovolaemic shock</b></p> <ul style="list-style-type: none"> <li>• airway typically patent unless level of consciousness is significantly impaired</li> <li>• tachypnoea without increased effort (quiet tachypnoea)</li> <li>• tachycardia</li> <li>• adequate systolic blood pressure, narrow pulse pressure or systolic hypotension with a narrow pulse pressure</li> <li>• weak or absent peripheral pulses</li> <li>• normal or weak central pulses</li> <li>• delayed capillary refill</li> <li>• cool-to-cold, pale, mottled, diaphoretic skin</li> <li>• dusky or pale distal extremities</li> <li>• oliguria</li> <li>• changes in level of consciousness</li> <li>• extremities often cooler than trunk</li> </ul> <hr/> <p><b>Distributive shock</b></p> <ul style="list-style-type: none"> <li>• airway usually patent unless level of consciousness is significantly impaired</li> <li>• tachypnoea, usually without increased work of breathing (quiet tachypnoea), unless the child has pneumonia or is developing acute respiratory distress syndrome or cardiogenic pulmonary oedema</li> <li>• tachycardia</li> <li>• bounding peripheral pulses</li> <li>• brisk or delayed capillary refill</li> <li>• warm, flushed skin peripherally (warm shock) or pale mottled skin with vasoconstriction (cold shock)</li> <li>• hypotension with a wide pulse pressure (warm shock) or with a narrow pulse pressure (cold shock) or normotension</li> <li>• oliguria</li> <li>• changes in level of consciousness</li> <li>• fever or hypothermia</li> <li>• extremities warm or cool</li> <li>• petechial or purpuric rash (septic shock)</li> </ul> <hr/> <p><b>Cardiogenic shock</b></p> <ul style="list-style-type: none"> <li>• airway usually patent unless level of consciousness is significantly impaired</li> <li>• tachypnoea; increased respiratory effort (retractions, nasal flaring, grunting) resulting from pulmonary oedema</li> <li>• tachycardia</li> <li>• normal or low blood pressure with a narrow pulse pressure</li> <li>• weak or absent peripheral pulses</li> <li>• normal and then weak central pulses</li> <li>• delayed capillary refill with cool extremities</li> <li>• signs of congestive heart failure (e.g. pulmonary oedema, hepatomegaly, jugular venous distension)</li> <li>• cyanosis (caused by cyanotic congenital heart disease or pulmonary oedema)</li> <li>• cold, pale, mottled, diaphoretic skin</li> <li>• oliguria</li> <li>• changes in level of consciousness</li> <li>• extremities often cooler than trunk</li> </ul> <hr/> <p><b>Obstructive shock</b></p> <p>The early clinical presentation of obstructive shock can be indistinguishable from hypovolaemic shock. Careful clinical examination, however, may reveal signs of systemic or pulmonary venous congestion that are not consistent with hypovolaemia.</p>

TABLE 5 *continued*

SOURCE AND DEFINITION OR STATEMENT	SIGNS
	<p><b>Anaphylactic shock</b></p> <ul style="list-style-type: none"> <li>• anxiety or agitation</li> <li>• nausea and vomiting</li> <li>• urticaria (hives)</li> <li>• angioedema (swelling of the face, lips and tongue)</li> <li>• respiratory distress with stridor or wheezing</li> <li>• hypotension</li> <li>• tachycardia</li> </ul>

Shock in children may be considered according to the underlying pathophysiology.

- Hypovolaemic shock, due to a marked decrease in blood volume, may follow haemorrhage due to major trauma or large fluid losses from burns, severe dehydration from vomiting and diarrhoea, heat stroke or water deprivation. These are major causes of mortality among children in developing countries. In children, hypovolaemic shock may also be associated with sepsis (broad systemic response to infection).
- Cardiogenic shock refers to failure of the heart to sustain an adequate output. The many causes include: excessive volume or pressure load on the heart chambers (e.g. congenital heart disease), dysfunction of the heart valves (e.g. valvular heart disease such as rheumatic or congenital valve stenosis or regurgitation), impaired cardiac muscle function (e.g. myocarditis), cardiomyopathy, acute arrhythmia (such as supraventricular tachycardia), obstruction of blood flow to or from the heart (e.g. tension pneumothorax, cardiac tamponade or pulmonary embolism); myocardial ischaemia (such as in Kawasaki disease); or severe acidosis.
- Vasodilatory shock, sometimes called “distributive shock”, is associated with hypotension due to vasodilation of blood vessels and, sometimes, leaky capillaries; it may be caused by sepsis, anaphylaxis, dengue or spinal cord injury.
- Septic shock in children can be a mixture of vasodilatory, hypovolaemic and cardiogenic shock. It may be due to bacteria, viruses (such as dengue), fungi or parasites (malaria). Sometimes, the specific pathogen is not identified.

The treatment required depends on the type of shock. The progression of shock is commonly divided into three phases: compensated, uncompensated and irreversible, describing the opportunities for intervention to improve outcome.

The fluid management strategy is decided on the basis of whether some or all signs of impaired circulation are present and characterization of the type and underlying shock, if present. Fluid bolus management may be entirely appropriate in some settings, such as hypovolaemic shock due to severe dehydration, but may be harmful if cardiogenic shock due to myocarditis is the underlying problem.

The management of critically ill infants and children depends on the skill and competence of health workers in identifying these children, the availability of basic equipment for detecting hypotension and hypoxaemia and the time available to adequately monitor and reassess the response of children to treatment.

At the scoping meeting in March 2013, members of the GDG prioritized PICO questions 5 and 6.

**Question 5. In infants and children presenting with emergency signs (as described in WHO ETAT guidelines), which clinical signs or disease markers or combination of signs or other markers indicate severely impaired circulation and the need for intravenous fluids?**

**Question 6. In infants and children with severely impaired circulation, which intravenous fluids, at what rate and for how long are associated with the lowest risk for mortality?**

During the guideline development meeting, the GDG reframed question 6 and the discussion as follows:

**Question 6a. In infants and children who are not in shock but have signs of severely impaired circulation, which intravenous fluids, at what rate and for how long are associated with the lowest risk for mortality?**

and

**Question 6b. In infants and children in shock, which intravenous fluids, at what rate and for how long are associated with the lowest risk for mortality?**

During the scoping meeting in March 2013, the GDG considered that there was no new evidence and no concern that would warrant a review of current WHO recommendations on fluid management of children with severe dehydration. The GDG noted that WHO recommendations on the management of children with dengue shock syndrome, including fluid management, had been updated in 2012 (WHO & Special Programme for Research and Training in Tropical Diseases, 2012) and there was no further evidence or concern that would warrant an additional review of these recommendations. The recommendations provide important evidence-based guidance to health care workers on the management of such children, and the group decided that the recommendations should be included in this guideline as they provide a context for other recommendations. Extracts of the recommendations are shown below.

#### *Diarrhoea with severe dehydration (from WHO, 2013b)*

Children with diarrhoea and signs of severe dehydration should receive infusion of fluids to correct fluid losses, followed by maintenance fluids, as outlined in WHO guidelines on treatment of diarrhoea (plan C).

#### *Dengue shock syndrome (from WHO & Special Programme for Research and Training in Tropical Diseases, 2012)*

Fluid resuscitation must be clearly separated from simple fluid administration. Fluid resuscitation is a strategy in which larger volumes of fluids (e.g. boluses of 10–20 mL/kg bw) are administered for a limited time under close supervision to evaluate the patient's response and to avoid the development of pulmonary oedema. These fluids should not contain glucose.

The plan for treating patients with **compensated shock** is as follows:

Obtain a reference haematocrit before starting IV fluid therapy. Start IV fluid resuscitation with isotonic crystalloid solutions at 5–10 mL/kg bw per h over 1 h in adults and 10–20 mL/kg bw per h over 1 h in infants and children. Then reassess the patient's condition (vital signs, capillary refill time, haematocrit, urine output).

- If the condition of the **infant or child** improves, IV fluids should be reduced to 10 mL/kg bw per h for 1–2 h, then to 7 mL/kg bw per h for 2 h, 5 mL/kg bw per h for 4 h and then to 3 mL/kg bw per h for up to 24–48 h. Consider reducing IV fluid earlier if oral fluid intake improves. The total duration of IV fluid therapy should not exceed 48 h.

If vital signs are still unstable (i.e. shock persists), check the haematocrit after the first bolus.

In infants and children:

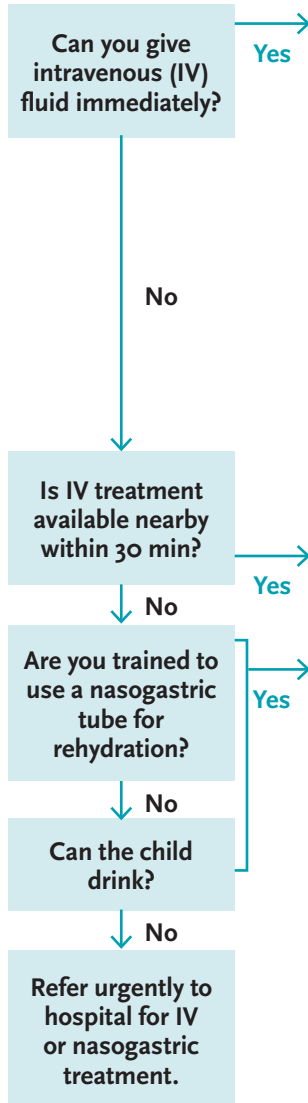
- If the haematocrit increases or is still high, change to colloid solution at 10–20 mL/kg bw per h. After the initial dose, reduce the rate to 10 mL/kg bw per h for 1 h, then reduce to 7 mL/kg bw per h. As mentioned above, change to crystalloid solutions when the patient's condition improves.

If the haematocrit decreases from the initial reference value (especially if the repeat haematocrit is below the baseline, for example, < 35–40%) **and** the patient still has **unstable vital signs**, look for severe bleeding. Cross-match fresh whole blood or fresh packed red cells and transfuse if there is

## PLAN C

→ Follow the arrows. If the answer is **YES**, go across. If **NO**, go down.

### START HERE



- ▶ Start IV fluid immediately. If the child can drink, give ORS by mouth while the drip is being set up. Give 100 ml/kg Ringer's lactate solution (or, if not available, normal saline), divided as follows:

Age	First give 30 ml/kg in:	Then give 70 ml/kg in:
Infants (< 12 months)	1 h <sup>a</sup>	
Children (12 months to 5 years)	30 min <sup>a</sup>	2.5 h

<sup>a</sup> Repeat once if radial pulse is still weak or not detectable

- Reassess the child every 15–30 min. If hydration status is not improving, give the IV drip more rapidly. Also watch for over-hydration.
- ▶ Also give ORS (about 5 ml/kg per h) as soon as the child can drink: usually after 3–4 h (infants) and 1–2 h (children).
- Reassess an infant after 6 h and a child after 3 h. Classify dehydration. Then choose the appropriate plan (A, B or C) to continue treatment.

- ▶ Refer **urgently** to hospital for IV treatment.
- ▶ If the child can drink, give the mother ORS solution, and show her how to give frequent sips during the trip.

- ▶ Start rehydration by tube (or mouth) with ORS solution: give 20 ml/kg per h for 6 h (total, 120 ml/kg).
- Reassess the child every 1–2 h:
  - If there is repeated vomiting or increasing abdominal distension, give the fluid more slowly.
  - If hydration status is not improving after 3 h, send the child for IV therapy.
- After 6 h, reassess the child and classify dehydration. Then, choose the appropriate plan (A, B or C) to continue treatment.

**Note:** If possible, observe the child for at least 6 h after rehydration to be sure the mother can maintain hydration by giving the child ORS solution by mouth.

severe overt bleeding. If there is no bleeding, give a bolus of 10–20 mL/kg bw of colloid over 1 h, repeat clinical assessment and determine the haematocrit. A senior staff member should carry out a review to consider blood transfusion.

- Further boluses of crystalloid or colloidal solutions may have to be given during the next 24–48 h.

### Treatment of profound shock (hypotensive; undetectable pulse and blood pressure)

All patients (infants, children and adults) with **hypotensive shock** should be managed more vigorously. The plan for treating patients with hypotensive shock is outlined below. For all patients (infants, children and adults), initiate IV fluid resuscitation with crystalloid or colloid solution at 20 mL/kg bw as a bolus given over 15–30 min to bring the patient out of shock as quickly as possible. Colloids may be preferred if the blood pressure has to be restored urgently, i.e. in patients with a pulse pressure < 10 mm Hg. If the patient's condition improves:

In **infants and children**, give colloid infusion of 10 mL/kg bw per h for 1 h. Then, continue with crystalloid solution at 10 mL/kg bw per h for 1 h, then to 7.5 mL/kg bw per h for 2 h, to 5 mL/kg bw per h for 4 h and to 3 mL/kg bw per h for up to 24–48 h. Consider reducing IV fluid earlier if oral fluid intake and urine output improve. The total duration of IV fluid therapy should not exceed 48 h.

#### 3.2.1 Children who are not in shock but have signs of circulatory impairment

**Question 6a. In Infants and children who are not in shock but have signs of severely impaired circulation, which intravenous fluids, at what rate and for how long are associated with the lowest risk for mortality?**

*(Fluid resuscitation of critically ill children aged 2 to 59 months with impaired circulation)*

#### Summary of evidence

The search initially identified 1600 references, including three RCTs, only one of which met the inclusion criteria. The “fluid expansion as supportive therapy” (FEAST) trial (Maitland et al., 2011) provided evidence for the population directly addressed by this recommendation.

In the FEAST trial, children were enrolled in two strata (A without and B with severe hypotension) in general paediatric hospital wards in six centres, one in Kenya, four in Uganda and one in the United Republic of Tanzania. The three arms of the study were: saline bolus, albumin bolus and no bolus. The intervention arms received either IV 0.9% saline solution (20 mL/kg bw over 1 h) or IV albumin solution (20 mL/kg bw over 1 h), and children in the comparator arm received no bolus. The saline versus no bolus comparison was the most relevant for the guideline. All three treatment arms received IV maintenance fluids (2.5–4.0 mL/kg per h); 90% received hypotonic maintenance fluids (5% dextrose). Participants also received antimalarial, antipyretic and anticonvulsant drugs. Treatment for hypoglycaemia and blood transfusions were provided if necessary. Additional boluses of 20 mL/kg bw over 1 h were given if impaired perfusion persisted. If severe hypotension (defined as systolic blood pressure < 50 mm Hg in children < 12 months, < 60 mm Hg in children aged 1–5 years and < 70 mm Hg in children > 5 years of age) developed in children in stratum A, 40 mL/kg boluses of study fluid or saline (no bolus group) were given. The initial boluses were increased to 40 mL/kg after a protocol amendment. Three reasons for increasing the initial bolus are provided in a commentary on the FEAST trial: (i) the original initial bolus fluid volume (20 mL/kg bw) might have been insufficient to answer the study question; (ii) if international guidelines on fluid bolus volume were not followed, policy-makers would not be convinced by the results; and (iii) only 1% of trial participants had severe hypotensive shock (whereas 5% had been predicted in the trial design), which might have affected the saline versus albumin comparison (secondary end-point).

Stratum B (children with severe hypotension) comprised two treatment arms: IV 0.9% saline solution (40 mL/kg bw over 1 h) and IV albumin (40 mL/kg bw over 1 h). Additional boluses of 20 mL/kg bw were given after 1 h if impaired perfusion persisted. Initial boluses were increased to 60 mL per kg bw after a protocol amendment in June 2010 (reasons as described for stratum A). Other treatments were the same as reported for stratum A.

The primary outcome of the trial was mortality 48 h after randomization, and the secondary outcomes were mortality at 4 weeks, neurological sequelae, episodes of hypotensive shock 48 h after randomization and adverse events. The children were followed up for 4 weeks, and any child with neurological impairment was followed up at 24 weeks.

Stratum A comprised 3141 children aged 60 days to 12 years, with a median age of 23–25 months (interquartile range, 13–40 months), and 46–48% were female. The median systolic blood pressure was 92–93 mm Hg; 58–60% had a positive temperature gradient, and 69–71% had severe tachycardia. The proportion of children with a capillary refill time  $\geq 2$  s was 64–69%, and 25–29% had a capillary refill time  $\geq 3$  s. One third of the children had severe anaemia (33% in both groups), and about 15% were in a coma; 58% had malaria parasitaemia. The trial excluded children with severe malnutrition, gastroenteritis, non-infectious causes of shock and conditions for which volume expansion was contraindicated

Stratum B comprised 29 children with severe hypotension. The median age was 21 months (interquartile range, 10–47 months) in the saline bolus group and 28 months (22–84 months) in the albumin bolus group; 50% of children given a saline bolus and 38% of those given the albumin bolus were girls. The median systolic pressure was 56–59 mmHg; 77–88% had a positive temperature gradient, and 42–43% had severe tachycardia. The capillary refill time was  $\geq 2$  s in 8–19% of children and  $\geq 3$  s in 69–77%. The proportion of children with severe anaemia was 38% in the group given saline bolus and 58% that given albumin bolus; 56% and 77% of children in the two groups, respectively, were in a coma. Malaria parasitaemia was found in 31% and 62% of the children, respectively.

Similar mortality rates in the first hour after randomization were observed among children in the two groups who had severe febrile illness complicated by impaired consciousness, respiratory distress or both and with impaired perfusion recognized by a capillary refill time of  $\geq 3$  s, lower limb temperature gradient, weak radial pulse volume or severe tachycardia (1.1% in the saline-bolus group and 1.3% in the no-bolus group). At 48 h, however, the children who received a saline bolus had a statistically significantly greater risk of dying than children randomized to receive no fluid bolus (RR, 1.44; 95% CI, 1.09–1.90;  $p = 0.01$ ). The difference in mortality rates between the groups was maintained at 4 weeks (RR, 1.38; 95% CI, 1.07–1.78;  $p = 0.01$ ). Few results were reported for children in stratum B. The mortality rates in the two groups were not statistically significantly different (RR, 1.23; 95% CI, 0.70–2.16;  $p = 0.45$ )

The GDG agreed that the FEAST trial demonstrated clear harm “if rapid infusions of IV fluids are given” to children who have febrile illnesses such as pneumonia, malaria and meningitis, or have severe anaemia and do not fulfil all the criteria for the WHO definition of “shock”. The adverse outcomes may have been due to fluid overload, including pulmonary oedema, heart failure and cerebral oedema, but other mechanisms might also have been involved, as the FEAST investigators rarely identified cerebral or pulmonary oedema.

The GDG noted that the trial excluded children with a history of diarrhoea and severe dehydration and children with clinical signs of severe acute malnutrition.

**SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS**

<p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>BENEFITS AND HARM</b></p>	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>The evidence is consistent with current understanding of the pathophysiology of impaired circulation and responses to IV fluids. In the absence of shock, excessive fluids can result in fluid overload. Children with febrile illness, severe pneumonia, severe malaria, meningitis, severe acute malnutrition or severe anaemia do not require fluids additional to those for maintaining normal hydration. Inappropriate administration of IV fluids to these children, especially if given rapidly, can precipitate heart failure and lung congestion, cause cerebral oedema and exacerbate anaemia by further haemodilution. Fluid boluses may also result in adverse outcomes by mechanisms other than direct fluid overload, including blunting protective cardiovascular responses, such as vasoconstriction and tachycardia due to high levels of circulating catecholamines. Instead, the initial care for these children must involve identification of the underlying cause of their condition and provision of appropriate treatment.</p> <p>The GDG noted, however, that children presenting with some signs of impaired circulation are at risk for clinical deterioration. Early, careful assessment, especially to determine a history of diarrhoeal illness and dehydration, appropriate treatment and further monitoring of these children are essential for effective management and to prevent other complications.</p>
<p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>VALUES AND PREFERENCES; ACCEPTABILITY</b></p>	<p>Is there important uncertainty about or variation in how people value the options?</p> <p><input type="checkbox"/> Major</p> <p><input checked="" type="checkbox"/> Minor</p> <p><input type="checkbox"/> Uncertain</p> <p>Is the option acceptable to key stakeholders?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>The GDG considered that all health workers would wish to understand the basis for and provide the appropriate fluids to sick infants and children. Health workers would recognize the potential harm of inappropriate excess IV fluids while acknowledging that infants and children with a history of diarrhoea require adequate, timely replacement of fluid deficits, either with oral rehydration solution or with IV fluids in cases of severe dehydration.</p>
<p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>FEASIBILITY AND RESOURCE USE</b></p>	<p>How large are the resource requirements?</p> <p><input type="checkbox"/> Major</p> <p><input checked="" type="checkbox"/> Minor</p> <p><input type="checkbox"/> Uncertain</p> <p>Is the option feasible to implement?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>The GDG considered that targeted use of IV fluids in sick infants and children can be done easily and does not require special equipment or skills. More explicit, focused use of IV fluids will not only improve outcomes but also conserve valuable resources such as IV fluids and IV cannulae. Training will be required to define when fluids are indicated for children who are well and, especially, to ensure that children with severe dehydration are not inadvertently deprived of the required fluids.</p>



## RECOMMENDATIONS

- 2.1 Children with only one or two signs of impaired circulation – either cold extremities *or* capillary refill time > 3 s *or* a weak and fast pulse – but who do not have the full clinical features of shock, i.e. all three signs present together, should not receive rapid infusions of fluids but should still receive maintenance fluids appropriate for their age and weight (WHO, 2013b).
- 2.2 In the absence of shock, rapid intravenous infusions of fluids may be particularly harmful to children with severe febrile illness, severe pneumonia, severe malaria, meningitis, severe acute malnutrition, severe anaemia, congestive heart failure with pulmonary oedema, congenital heart disease, renal failure or diabetic ketoacidosis.
- 2.3 Children with any sign of impaired circulation, i.e. cold extremities, or prolonged capillary refill or a weak and fast pulse, should be prioritized for full assessment and treatment and reassessed within 1 h.

<b>Strength of recommendations</b>	Strong (for all recommendations)
<b>Quality of evidence</b>	High (for all recommendations)
<b>Justification</b>	<p>The GDG agreed that the quality of the evidence for these recommendations was high because, although only one study was identified, there was a large effect in the population of direct interest in a high-quality RCT with a large sample.</p> <p>The GDG agreed that the recommendations should be <b>strong</b> in view of the high quality of the evidence on a clinical outcome of critical importance in a specific population and that the recommendations could be generalized to all settings.</p> <p>Populations not included in the study, i.e. children with diarrhoea and with severe acute malnutrition, are clearly described in other WHO recommendations; for this reason, they are not included in these recommendations. Health workers are directed to the other recommendations.</p> <p>The GDG noted that the recommendation is “negative”; however, there was consensus that, given the serious consequences of giving unnecessary fluids to already sick children, it was important to stress the occasions on which additional IV fluids should not be given as well as providing guidance on when additional IV fluids are indicated.</p>
<b>Implementation considerations</b>	<p>The GDG noted that:</p> <ul style="list-style-type: none"> <li>• Full assessment should include re-evaluation of children’s circulatory status to exclude progression to shock or signs of fluid overload related to fluid management as well as to identify signs of the underlying condition.</li> <li>• The WHO <i>Pocket book</i> (WHO, 2013b) specifies administration of maintenance fluids by age and weight and consideration of the underlying disease.</li> <li>• Maintenance fluids might have to be given intravenously until the child is able to take and retain oral fluids.</li> </ul>
<b>Research priorities</b>	None

### 3.2.2 Children in shock

**Question 6b. In infants and children who are in shock, which intravenous fluids, at what rate and for how long are associated with the lowest risk for mortality?**

#### Summary of evidence

The systematic review (*Fluid resuscitation of critically ill children aged 2 to 59 months with impaired circulation*) identified only one RCT (Maitland et al., 2011), the FEAST trial, that provided some evidence for the population of infants and children presenting with the WHO criteria for shock, who are directly addressed by this recommendation.

In the FEAST trial (see the summary of evidence for the above recommendation), 65 of 3141 (2%) infants and children with severe febrile illness enrolled into stratum A exhibited all three signs of severely impaired circulation, i.e. cold extremities with capillary refill time > 3 s and a weak and fast pulse, thereby fulfilling the WHO definition of shock. The outcomes of this small group of children and subgroup analyses, such as for children with moderate hypotension, were consistent with the findings in the main study population: boluses of additional fluids were associated with increased mortality rates. The study did not, however, have enough power to detect differences in the subgroup s, and any differences may have occurred by chance. Interpretation of this subgroup analysis was also difficult because, although the children in the study were randomized, the small number in shock were not equally distributed between the intervention and control arms, with 50 in the groups receiving boluses and 15 in the maintenance group. (Note that randomization was not stratified according to this criterion.) No generalizable conclusions could be drawn from these data about the management of children in shock. No other randomized trials of bolus fluids versus no bolus were identified.

Another systematic review (*Signs of severe circulatory impairment in children*) was conducted to determine whether clinical signs can predict whether a child with severely impaired circulation will respond to fluids. This review identified only observational and non-randomized studies.

A background paper on the physiology of shock was prepared for the guideline meeting (*Physiological basis for the administration of intravenous fluids to children with shock*). This and the second systematic review provided some additional evidence.

- In high-resource settings, no clinical signs have been found to predict a response to fluid management. Some invasive measurements, such as stroke volume and cardiac output, may be helpful, and a haemodynamic response to passive leg raising is likely to be associated with increased blood pressure if fluids are given subsequently. Improvements in these signs or an initial response to IV fluids do not, however, necessarily predict recovery or survival.
- Initial blood pressure is not predictive of outcome, but blood pressure measurements are helpful for monitoring responses to interventions.
- Immediate responses to fluid bolus are not necessarily predictive of outcomes.
- Children with severely impaired circulation are likely to have raised titres of antidiuretic hormone. Giving excess fluids to this group of children may precipitate fluid overload and congestive heart failure.
- Observational data in both low- and high-resource settings, including the results of invasive monitoring, indicate that 20–40 mL/kg bw of IV fluid over 30–60 min are required to restore circulating volume in children with septic shock.

**SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS**

<p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>BENEFITS AND HARM</b></p>	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Uncertain</p>	<p>The group agreed that the findings of the FEAST trial must be carefully considered in order to determine whether they are generalizable. They also agreed that fluid management of children in shock must be judicious, and the clinical condition of the children should be carefully monitored to identify positive or detrimental responses. Decisions on fluid management in children in shock should be guided by frequent reassessments after fluid provision. The group acknowledged that this may be difficult in settings where there are few staff and many children to manage.</p> <p>The group noted that it might be difficult for health workers to determine rapidly whether a child in shock has a history of diarrhoea and also has severe dehydration, for which rapid fluid provision is an essential part of management. Similarly, health workers may not accurately assess children for severe acute malnutrition, which requires a conservative approach to fluid management, even when the children have had diarrhoea.</p> <p>The GDG noted that international practice favours use of fluid boluses in the management of children in shock; however, this reported practice is common in settings in which invasive physiological monitoring is available to guide management and inotropic and ventilator support is available to manage fluid overload.</p>
<p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>VALUES AND PREFERENCES; ACCEPTABILITY</b></p>	<p>Is there important uncertainty about or variation in how people value the options?</p> <p><input checked="" type="checkbox"/> Major</p> <p><input type="checkbox"/> Minor</p> <p><input type="checkbox"/> Uncertain</p> <p>Is the option acceptable to key stakeholders?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Uncertain</p>	<p>The GDG considered that the general population would be unable to judge the merits of one fluid strategy versus another. Communities would have difficulty in interpreting the specificity of the population studied in the FEAST trial, i.e. with a high prevalence of malaria and anaemia requiring transfusion, and the limits of the subgroup analyses and how they should be interpreted in relation to international guidelines.</p> <p>Similarly, health workers are likely to have difficulty in interpreting the findings of the FEAST trial and their relation to international guidelines.</p> <p>GDG members noted the risk associated with inappropriate use of very conservative fluid management for children with severe dehydration. Every effort should be made to send the consistent message that children with diarrhoea and dehydration require additional fluid in the form of oral rehydration solution or IV fluid for children with severe dehydration.</p>
<p style="writing-mode: vertical-rl; transform: rotate(180deg);"><b>FEASIBILITY AND RESOURCE USE</b></p>	<p>How large are the resource requirements?</p> <p><input type="checkbox"/> Major</p> <p><input checked="" type="checkbox"/> Minor</p> <p><input type="checkbox"/> Uncertain</p> <p>Is the option feasible to implement?</p> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input checked="" type="checkbox"/> Uncertain</p>	<p>Changes in fluid management recommendations are unlikely to require major additional resources. Health workers in low-resource settings require simple algorithms to guide emergency management of sick children. Health workers should be trained and supported in using new algorithms, which and will require funds.</p> <p>While simplifying the clinical algorithms for use in low-resource settings is important for improving the outcomes of sick infants and children presenting to primary or second-level health facilities, it is equally or more important to improve the skills and competence of health workers for correct assessment, triage and initial management of such children. In low-resource settings, the outcomes of critically ill children are also influenced by access to oxygen and good monitoring, including with pulse oximetry, and the availability of other forms of respiratory support, such as simple methods of continuous positive airway pressure.</p> <p>The GDG was uncertain about the feasibility of implementing the recommendation because of wide variation in staffing levels and infrequent training and supervision of front-line health workers</p>

## RECOMMENDATIONS

- 2.4 Children in shock, i.e. who have all the following signs: cold extremities *with* capillary refill time > 3 s *and* a weak and fast pulse, should receive 10–20 mL/kg bw of isotonic crystalloid fluids over 30–60 min. They should be fully assessed, an underlying diagnosis made, receive other relevant treatment and their condition monitored. They should be reassessed at the completion of infusion and during subsequent hours to check for any deterioration.
- If the child is still in shock, consider giving a further infusion of 10 mL/kg bw over 30 min.
  - If shock has resolved, provide fluids to maintain normal hydration status only (maintenance fluids).
  - If, at any time, there are signs of fluid overload, cardiac failure or neurological deterioration, the infusion of fluids should be stopped and no further intravenous infusions of fluids should be given until these signs resolve.
- 2.5 Children in shock and with severe anaemia (erythrocyte volume fraction < 15 or haemoglobin < 5 g/dL, as defined by WHO, 2013b) should receive a blood transfusion as early as possible and receive other intravenous fluids only to maintain normal hydration.
- 2.6 Children with severe acute malnutrition who are in shock should receive 10–15 mL/kg bw of intravenous fluids over the first hour. Children who improve after the initial infusion should receive only oral or nasogastric maintenance fluids. Any child who does not improve after 1 h should be given a blood transfusion (10 mL/kg bw slowly over at least 3 h) (WHO, 2013a).

<b>Strength of recommendations</b>	2.4 Conditional 2.5 Strong 2.6 Strong
<b>Quality of evidence</b>	Low (for all recommendations)
<b>Justification</b>	<p>The GDG agreed that the quality of the evidence for these recommendations was low because there were minimal data for the population of direct interest – children who fulfil the WHO definition of shock. The evidence was downgraded to “low” because of indirectness; i.e. children with diarrhoea and severe acute malnutrition were excluded. The generalizability of the evidence from the one clinical trial was limited because children with severe dehydration or severe acute malnutrition were excluded, and there was a high prevalence of malaria and of severe anaemia.</p> <p>The additional systematic review on clinical signs and the background paper provided largely observational data and did not significantly improve the quality of the overall evidence. The group noted that the observational data from both high- and low-resource settings and the outcomes reported in the multi-country RCT were inconsistent. The group could not reconcile these inconsistencies.</p> <p>The GDG agreed that there was no evidence to support a change in the WHO clinical criteria for shock.</p> <p>The GDG agreed by consensus that the first recommendation, on the range of volumes and time of fluid management, should be <b>conditional</b> in view of the low quality of evidence and the uncertainty about the generalizability of the evidence. The group agreed that the volume of fluid to be given to children who fulfil the WHO criteria for shock depends on the context; therefore, a more precise range of volumes could not be recommended in the absence of more evidence.</p>

<p><b>Justification continued</b></p>	<p>The GDG <i>considered it inappropriate</i> to generalize the finding in the one randomized trial (FEAST) of increased mortality rates among children <b>who did not fulfil the WHO criteria for shock</b> and who received IV boluses of fluids (noting that children with severe dehydration were excluded from the trial). The GDG considered that this finding was not necessarily applicable to children <b>who do fulfil the WHO criteria for shock</b>, even though subgroup analyses in the FEAST trial indicated increased mortality in response to fluid boluses in the study population with these characteristics.</p> <p>The GDG noted that international practice, while based largely on observational data, is to give IV boluses of crystalloid fluid to children in shock, especially when inotropic and ventilation support are available. The data from the FEAST trial are inconsistent with this approach, but the populations and the context are very different. In many Australian, European and North American centres, the trend is to give a 10-mL/kg bw fluid challenge and reassess the child before any further boluses are given. The GDG concluded that a range of initial fluid volumes and rates should be recommended to permit national authorities and other expert and professional groups to determine those that are appropriate in their settings.</p> <p>The two other recommendations were considered to be <b>strong</b>, even though the quality of the evidence was also low. These recommendations support either recognized best practice or current WHO recommendations and were considered to give health workers clear guidance for improving the safety and health outcomes of children presenting with emergency signs.</p>
<p><b>Implementation considerations</b></p>	<p>When adapting recommendations to the national context, country teams should consider the following points as they consider adopting either a more conservative approach, i.e. a smaller fluid volume over a longer time, or a more permissive approach, i.e. a larger fluid volume over a shorter time:</p> <ul style="list-style-type: none"> <li>• the disease profile of children presenting with emergency signs, e.g. the prevalence of malaria or severe anaemia;</li> <li>• the competence of the health workers who will be trained in applying these recommendations, including their ability to differentiate the causes of shock and to detect congestive heart failure or other signs of fluid overload;</li> <li>• the number of health workers at health facilities who will be available to treat and monitor children presenting with emergency signs; and</li> <li>• the availability of monitoring and support equipment, such as blood pressure measuring devices and ventilation support.</li> </ul> <p>Children in shock who respond partially or not at all to fluid boluses require a differentiated response, depending on the cause. A careful history should be taken, with a clinical examination, investigations (such as echocardiography if available) and treatment. Specific supportive treatment may include oxygen, adrenaline for anaphylaxis, inotropic drugs (such as adrenaline or dopamine) for poor cardiac function, vasoconstrictor drugs (such as noradrenaline) and antibiotics for septic vasodilatation (“warm shock” with low blood pressure), diuretics and positive airway pressure (including continuous) if congestive heart failure is present.</p> <p>In all settings:</p> <ul style="list-style-type: none"> <li>• In considering the underlying diagnosis, health workers should check for a history of heart disease, ingestion of poisons or toxins, allergy, snake or spider bites and signs of heart failure. If any of these is present, fluid management should be reviewed and treated accordingly.</li> </ul>

<b>Implementation considerations</b> <i>continued</i>	<ul style="list-style-type: none"> <li>• Fluid therapy alone may not be sufficient for the management of many children presenting with shock. Early inotropic or ventilator support may be required.</li> <li>• After resolution of shock, the child's condition should be continuously monitored and assessed to direct further management.</li> </ul>
<b>Other remarks</b>	<p><b>The following points were discussed in plenary:</b></p> <ul style="list-style-type: none"> <li>• Decisions on fluid management in children presenting with severely impaired circulation must take into account the cause of shock and the ability of health workers to evaluate the children accurately.</li> <li>• Health workers tend to interpret clinical signs in the clinical context in which they practise, e.g. the conditions that are especially prevalent and the clinical history of the child for whom they are caring. For this reason, health care workers must rapidly take a history from the caregiver when the child first presents, in addition to a full history and assessment after initial treatment.</li> <li>• Even in high-resource settings, IV fluid management of children with severe circulatory impairment can result in fluid overload, which may be harmful. Fluid overload generally indicates the need for inotrope and ventilation support.</li> <li>• Observational studies in high-resource settings demonstrate that children with septic shock or who are severely hypotensive require rapid expansion of the cardiac volume up to 30 mL/kg bw within 15 min in order to restore initial circulation; however, the correlation of this short-term outcome with long-term outcomes is not known.</li> <li>• In high- and middle-income countries or settings, the availability of inotropes, ventilation support, technical monitoring equipment and adequate human resources greatly influence decisions about fluid management of children who present with shock.</li> <li>• The absence of such facilities in many low-resource settings complicates decisions about what is generally advisable for children presenting with shock.</li> <li>• Other aspects of care, such as early assessment and reassessment, substantially influence the outcomes of children, including their response to fluids within the first 30–60 min.</li> <li>• Children presenting with severely impaired circulation require not only initial triage and treatment but also reassessment and continuous monitoring to guide further fluid management and other interventions.</li> <li>• Children with severe anaemia should receive blood as soon as possible. The group noted, however, the practical difficulty of providing blood rapidly as part of emergency treatment in most low-resource settings.</li> <li>• In some children with severe anaemia, the circulating volume is normal or even expanded, so, although a blood transfusion is urgently required, it should be given slowly. If it is given too rapidly, it can lead to circulatory overload. For children in haemorrhagic shock, blood should be infused rapidly, but for those in shock associated with severe anaemia, with no loss of blood volume, blood should be given over 2–4 h. In patients with normal or expanded circulating volume and shock associated with severe anaemia, furosemide should be given with the blood transfusion so that it can be infused more rapidly without causing circulatory overload.</li> <li>• Additional research is required to provide further high-quality evidence for this specific population and greater insight into this complex question.</li> </ul>

<b>Research priorities</b>	<ul style="list-style-type: none"> <li>• What is the optimal fluid management of children in shock (as defined by WHO) who also have severe acute malnutrition or severe anaemia?</li> <li>• What is the role of blood transfusion in the management of children with shock and severe anaemia?</li> </ul>
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<sup>a</sup> Emergency signs described in WHO ETAT guideline include:

- Obstructed or absent breathing
- Severe respiratory distress
- Central cyanosis
- Signs of shock, defined as cold extremities with capillary refill time > 3 s and weak and fast pulse
- Coma (or seriously reduced level of consciousness)
- Seizures
- Signs of severe dehydration in a child with diarrhoea with any two of the following signs: lethargy or unconscious, sunken eyes, very slow return after pinching the skin.

<sup>b</sup> In infants and children 6–59 months of age, severe acute malnutrition is defined as weight-for-height < -3 Z-score 1 of the median of the WHO growth standards or clinical signs of bilateral oedema of nutritional origin, even if other measures are above specified cut-off values (WHO, 2009a).

### 3.3 Management of seizures

#### Background

Seizures with altered consciousness are common in children; they are associated with mortality and long-term neurocognitive sequelae. Children with seizures often present with their caregivers to the nearest medical facility, which in low- and middle-income countries are staffed mainly by nurses and clinical officers. In these settings, the ability of health workers to diagnose and manage these children may be limited by the resources available.

The aim of treatment of acute seizures is early cessation in order to prevent progression to status epilepticus, cardiorespiratory compromise and cerebral damage. Delayed intervention may result in a protracted seizure episode that is more difficult to control, with significant subsequent neurological morbidity and possibly death. Seizures lasting more than 5 min, recurrent seizures, delayed recovery of consciousness and a compromised cardiorespiratory system warrant emergency drug treatment. The ideal anticonvulsant medication is one that can be given safely and easily, acts rapidly, has minimum cardiorespiratory adverse effects, has a long-lasting effect and is inexpensive. Often, in emergency situations, rapid, reliable provision of anticonvulsant medications is difficult. IV administration of drugs is fast, but it may be difficult to achieve peripheral venous access in a convulsing child. Therefore, especially in resource-limited settings, non-IV routes, such as IM injections and oral, sublingual and intranasal administration, may be useful options as the first line for administration of anticonvulsant medications; in many settings, rectal administration of drugs is the preferred approach. Each route has its disadvantages, however, including pain, erratic absorption, variable first-pass metabolism and retention of the drug at the site of administration until absorbed. The pharmacokinetics of the intervention must also be considered in selecting the most appropriate anticonvulsant medication for seizure control, including, for example, the duration of action and the mode of administration. Until recently, diazepam has been the drug of choice for IV administration of benzodiazepines. Lorazepam is now suggested as the preferred option in view of perceived better efficacy, reduced risk for respiratory depression and long duration of action (Appleton et al., 2008; Aneja, 2012). Lorazepam, however, must be refrigerated when stored, which may limit its use in low- and middle-income countries (Gottwald et al., 1999; Aneja, 2012).

When first-line medications are not sufficient to stop seizures, status epilepticus is established. This is a medical emergency that can result in profound systemic and neurological damage and is associated with significant mortality in the short and long term. Approximately 30–40% of all patients fail to respond to initial treatment with benzodiazepines and require further treatment with other IV anticonvulsant drugs (Trinka, 2009; Trinka et al., 2014). IV phenytoin or phenobarbital has long been used to treat benzodiazepine-resistant status epilepticus. Both may cause cardiac arrhythmia,

hypotension and respiratory depression, although the last can be due to prior administration of benzodiazepines (Trinka, 2009). More recently, use of IV formulations of other anticonvulsant medications, such as valproate, has increased in benzodiazepine-resistant status epilepticus. While newer drugs may offer advantages in terms of safety and better tolerability, their availability and cost are issues.

Febrile seizures are the most common type of seizure in childhood, with an average lifetime prevalence of 2–6% (Pavlidou et al., 2013). Although there are various definitions of febrile seizures, the international definition is “a seizure occurring in childhood after 1 month of age associated with a febrile illness not caused by an infection of the CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures” (International League against Epilepsy, 1993). Febrile seizures are classified as simple or complex; a complex febrile seizure lasts > 15 min, is focal rather than generalized and/or recurs within 24 h (American Academy of Pediatrics, 2008). While the type of febrile seizure does not predict a risk for recurrence, complex febrile seizures are often predictive of CNS infection; therefore, management should focus on excluding and treating the underlying CNS infection. Although the prognosis of febrile seizures is generally excellent, recurrent and prolonged febrile seizures, including febrile status epilepticus, have been associated with significant neurodevelopmental sequelae and a risk for epilepsy (Annegers et al., 1987; Visser et al., 2012). It is unclear whether administration of antipyretics or anticonvulsants (intermittently or continuously) can indeed prevent recurrences. WHO recommendations (WHO, 2009b) state that “intermittent antipyretics may be no more effective than placebo in treating episodes of fever to prevent seizure recurrence in children with one or more previous simple febrile seizures.” They also state that “intermittent anticonvulsants (diazepam or clobazam) are / may be more effective at reducing the risk of febrile seizure recurrence in children with a history of simple or complex febrile seizures,” while highlighting their potential adverse effects.

Acute symptomatic seizures occur in close temporal relation to a brain insult such as trauma, infection or metabolic or structural abnormalities. Acute seizures are particularly common in low- and middle-income countries due to the high incidence of infections, yet investigations may not have been conducted to identify the causes, because of limited resources. Distinguishing between acute symptomatic seizures and febrile seizures is important in terms of management and prognosis. The diagnostic investigations that can be used to determine the causes include blood testing, lumbar puncture, electroencephalography (EEG) and neuroimaging. These investigations may be difficult to perform in low-resource settings and may be associated with other complications. They should therefore be conducted only if the results will directly influence management and outcome.

### 3.3.1 *Choice of anticonvulsant medicines for children with acute seizures when IV access is not available*

**Question 7. For children with acute convulsive seizures in first-level care or in the community (with no IV access), which antiepileptic medicines are the most beneficial or harmful for the specified outcomes?**

*(Treatment of acute convulsive seizures in children in first level care or in the community (when no IV access is available))*

#### **Summary of evidence**

Three systematic reviews (Appleton et al., 2008; McMullan et al., 2010; Prasad et al., 2014) were identified that addressed the question summarized in the PICO table.

An updated Cochrane review by Prasad et al. (2014) on anticonvulsant therapy for status epilepticus covered 18 studies with 2755 participants, in which the effectiveness and safety of anticonvulsants were compared with each other and with a placebo. Participants with premonitory, early, established or refractory status epilepticus were truly randomly or quasi-randomly allocated to treatments;



however, few studies used the same intervention. IV diazepam was superior to placebo in reducing the risks for non-cessation of seizures (RR, 0.73; 95% CI, 0.57–0.92), a requirement for ventilatory support (RR, 0.39; 95% CI, 0.16–0.94) or continuation of status epilepticus requiring use of a different drug or general anaesthesia (RR, 0.73; 95% CI, 0.57–0.92). IV lorazepam was better than placebo for reducing the risk for non-cessation of seizures (RR, 0.52; 95% CI, 0.38–0.71) and for continuation of status epilepticus requiring a different drug or general anaesthesia (RR, 0.52; 95% CI, 0.38–0.71). IV lorazepam was better than IV diazepam for reducing the risk for non-cessation of seizures (RR, 0.64; 95% CI, 0.45–0.90) and for continuation of status epilepticus requiring a different drug or general anaesthesia (RR, 0.63; 95% CI, 0.45–0.88). IV lorazepam was better than IV phenytoin for reducing the risk for non-cessation of seizures (RR, 0.62; 95% CI, 0.45–0.86). Diazepam gel was better than placebo gel in reducing the risk for non-cessation of seizures (RR, 0.43; 95% CI, 0.30–0.62). For pre-hospital treatment, IM midazolam was at least as effective as (probably more effective than) IV lorazepam for control of seizures (RR, 1.16; 95% CI, 1.06–1.27) and reducing the frequency of hospitalization (RR, 0.88; 95% CI, 0.79–0.97) or admission to intensive care (RR, 0.79; 95% CI, 0.65–0.96). It was uncertain whether IV valproate was better than IV phenytoin in reducing the risk for non-cessation of seizures (RR, 0.75; 95% CI, 0.28–2.00). Levetiracetam and lorazepam were equally effective in aborting seizures (RR, 0.97; 95% CI, 0.44–2.13).

Appleton et al. (2008) conducted a systematic review to compare the efficacy and safety of midazolam, diazepam, lorazepam, phenobarbital, phenytoin and paraldehyde in treating acute tonic-clonic seizures and convulsive status epilepticus in children treated in hospital. The review covered four randomized and quasi-randomized controlled trials (Appleton et al., 1995; Lahat et al., 2000; McIntyre et al., 2005; Ahmad et al., 2006) with a total of 383 participants. IV lorazepam was at least as effective as IV diazepam and was associated with fewer adverse events in the treatment of acute tonic-clonic seizures (19/27, 70% versus 22/34, 65%; RR, 1.09; 95% CI, 0.77–1.54); rectal lorazepam was more effective than rectal diazepam (6/6 versus 6/19, 31%; RR, 3.17; 95% CI, 1.63–6.14). Oral midazolam controlled seizures in 61/109 (56%) episodes and rectal diazepam in 30/110 (27%) episodes (RR, 2.05; 95% CI, 1.45–2.91). Intranasal midazolam was as effective as IV diazepam in the treatment of prolonged febrile convulsions (23/26, 88%, and 24/26, 92%; RR, 0.96; 95% CI, 0.8–1.14). There was moderate evidence that intranasal lorazepam was more effective than IM paraldehyde in controlling acute tonic-clonic seizures; patients treated with intranasal lorazepam were significantly less likely to require further anticonvulsants to control continuing seizures (8/80; 10% versus 21/80; 26%; RR, 0.58; 95% CI, 0.42–0.79).

In a meta-analysis of six studies with a total of 774 participants, midazolam was compared with diazepam for the treatment of status epilepticus in children and young adults (McMullan et al., 2010). Midazolam by any route was superior to diazepam in treating status epilepticus (RR, 1.52; 95% CI, 1.27–1.82). Midazolam given by other routes was as effective as IV diazepam (RR, 0.79; 95% CI, 0.19–3.36), and oral midazolam was superior to rectal diazepam in controlling seizures (RR, 1.54; 95% CI, 1.29–1.85). Midazolam was administered faster than diazepam (mean difference, 2.46 min; 95% CI, 1.52–3.39 min), with similar delays between drug administration and seizure cessation. The prevalence of respiratory complications requiring intervention was similar, regardless of the administration route (RR, 1.49; 95% CI, 0.25–8.72).

**SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS**

<p><b>BENEFITS AND HARM</b></p>	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No  <input type="checkbox"/> Uncertain</p>	<p>No clinically important difference was found between administration of benzodiazepines by IV or by another route.</p> <p>As the evidence from direct comparisons of interventions other than IV is of low to very low quality, it is not possible to conclude whether the various forms of non-IV anticonvulsant medications differ in a clinically important way in controlling acute seizures.</p> <p>Few studies reported on respiratory depression. In those that did, all treatments appeared to be similar in relation to respiratory depression requiring intubation.</p> <p>Given that the evidence is limited, it is not possible to determine whether there are clinically important differences between IM midazolam and IV lorazepam or between intranasal lorazepam and IV lorazepam.</p>
<p><b>VALUES AND PREFERENCES; ACCEPTABILITY</b></p>	<p>Is there important uncertainty about or variation in how people value the options?</p> <p><input type="checkbox"/> Major  <input checked="" type="checkbox"/> Minor  <input type="checkbox"/> Uncertain</p> <p>Is the option acceptable to key stakeholders?</p> <p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No  <input type="checkbox"/> Uncertain</p>	<p>It may be difficult to establish IV access in a convulsing child. Lack of trained health care workers and of IV equipment exacerbate the problem of IV drug administration in resource-limited settings.</p> <p>Patients and their families may find treatment options other than IV administration more satisfactory.</p> <p>In some settings, rectal administration may not be acceptable.</p> <p>Intranasal administration of anticonvulsant medicines can cause discomfort in children with focal seizures and in partially conscious children.</p> <p>IM administration of diazepam is less reliable because of erratic absorption.</p> <p>The sedative effects of benzodiazepines may interfere with neurological examinations.</p>
<p><b>FEASIBILITY AND RESOURCE USE</b></p>	<p>How large are the resource requirements?</p> <p><input type="checkbox"/> Major  <input checked="" type="checkbox"/> Minor  <input type="checkbox"/> Uncertain</p> <p>Is the option feasible to implement?</p> <p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No  <input type="checkbox"/> Uncertain</p>	<p>Oral and intranasal preparations of midazolam and lorazepam are not readily available. In most studies, the available IV preparation was administered orally or intranasally. These alternative routes may be acceptable.</p> <p>Both IV lorazepam and IV diazepam are on the WHO essential medicines list (WHO, 2015). IV midazolam is also included but in the section for preoperative medication and sedation for short-term procedures, and not as an anticonvulsant.</p> <p>Use of IV paraldehyde is associated with particular issues of feasibility in resource-limited settings, including the requirement for a glass syringe, light sensitivity (therefore requiring particular storage conditions) and its absence from the WHO essential medicines list, further complicating its availability.</p>

### RECOMMENDATION 3.1

When intravenous access is not available for the control of acute seizures in children, nonparenteral routes of benzodiazepine administration should be used. Options include rectal diazepam, oral or intranasal midazolam and rectal or intranasal lorazepam. Some benzodiazepines (lorazepam and midazolam) may be given intramuscularly, which involves additional expertise and expense.

The preference may be guided by availability, expertise and social preference.

<b>Strength of recommendation</b>	Strong
<b>Quality of evidence</b>	Low
<b>Justification</b>	Although the quality of the evidence is moderate to low, there is no clinically important difference in outcome between non-IV and IV routes of administering benzodiazepines for managing acute seizures. In a convulsing child, establishing IV access may be difficult and/or trained health care workers and equipment may be lacking in resource-limited settings. Non-IV routes may therefore be more feasible. Patients and their families may find non-IV treatment options more satisfactory. The limited availability of non-parenteral formulations of benzodiazepines may, however, reduce feasibility. A strong recommendation was made even on the basis of low-quality evidence, because the risk associated with not attempting to control seizures (e.g. sequelae of prolonged seizure or death) far outweighs any harm associated with using the recommended interventions.
<b>Implementation considerations</b>	Relevant scenarios for the use of non-IV formulations include the community (before hospitalization) and first-line treatment in a health care facility or in a health care facility that is not equipped to administer IV drugs or which does not have trained health care workers.  IV formulations can be administered by some non-IV routes. If this is done, particular caution should be paid to dosage to avoid errors.  IV administration of diazepam is not recommended because of erratic absorption.
<b>Research priorities</b>	Further direct comparisons of IV and various non-IV interventions are required to determine whether the clinical outcome is significantly different. The results could inform future recommendations.

### 3.3.2 Choice of anticonvulsant medicines for children with acute seizures when intravenous access is available

**Question 8. For children with acute convulsive seizures where IV access is available, which first-line anticonvulsant medications should be used to abort seizures?**

*(First line treatment of acute convulsive seizures in children where intravenous administration is available)*

#### Summary of evidence

A recent Cochrane review (Prasad et al., 2014) was used to inform the guideline. Two additional studies (Gathwala et al., 2012; Chamberlain et al., 2014) that addressed the PICO question but were not included in the Cochrane review were also available.

The analysis of studies of IV lorazepam versus IV diazepam in the treatment of acute seizures provided moderate-quality evidence that they do not differ in preventing non-cessation of seizures (37/200 versus 47/214 participants; RR, 0.84; 95% CI, 0.58–1.22). The meta-analysis of the outcomes non-cessation of seizures and requirement for ventilator support was based on the three studies in

children (Appleton et al., 1995; Gathwala et al., 2012; Chamberlain et al., 2014). There was moderate-quality evidence of no difference between lorazepam and diazepam in stopping continuation of status epilepticus requiring a different drug or general anaesthesia (25/200 participants versus 32/214; RR, 0.0.84; 95% CI, 0.52–1.36). For the outcome of death, the Cochrane review (Prasad et al., 2014) was used, because deaths were not reported in any of the studies on children. The pooled analysis provided very low-quality evidence of no statistically significant difference between the two groups (5/103 versus 3/100 participants; risk difference, 0.02; 95% CI, –0.04 to 0.08).

A single randomized, blinded study (Treiman et al., 1998) provided the results of comparisons of four treatments for convulsive status epilepticus (IV lorazepam, IV phenobarbital, IV diazepam plus phenytoin, phenytoin alone). A single randomized open-label study (McCormick et al., 1999) provided evidence from a comparison of IV midazolam with IV lorazepam in status epilepticus. Evidence from a comparison of IV midazolam and IV diazepam was derived from Gathwala et al. (2012).

For the outcome “non-cessation of seizures”, there was low-quality evidence in favour of IV lorazepam rather than IV phenytoin (34/97 versus 57/101; RR, 0.62; 95% CI, 0.45–0.86) but no differences in comparisons of all other drugs. For the outcome “requirement for ventilatory support”, very low-quality evidence indicated no difference between midazolam, lorazepam and diazepam. Mortality outcomes were not reported.

SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS		
<b>BENEFITS AND HARM</b>	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>As the evidence is inconclusive, it is not possible to determine whether there is a clinically important difference between IV lorazepam and IV diazepam in the treatment of status epilepticus in children.</p> <p>As the evidence is inconclusive, it is not possible to determine whether there is a clinically important difference between IV lorazepam and IV phenobarbital, IV lorazepam and IV midazolam or IV diazepam and IV midazolam.</p> <p>Similarly, the evidence for adverse effects of these drugs is inconclusive; therefore, it is not possible to determine whether there is a clinically important difference between these pharmacological interventions in the requirement for ventilator support or for death.</p>
<b>VALUES AND PREFERENCES; ACCEPTABILITY</b>	<p>Is there important uncertainty about or variation in how people value the options?</p> <p><input type="checkbox"/> Major</p> <p><input checked="" type="checkbox"/> Minor</p> <p><input type="checkbox"/> Uncertain</p> <p>Is the option acceptable to key stakeholders?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>Control of status epilepticus is of critical importance, as it is a medical emergency and is associated with substantial mortality in children. An additional percentage of people with this condition have permanent sequelae, such as cognitive difficulties.</p> <p>Potential complications of treatment of status epilepticus with the benzodiazepines or phenobarbital include hypotension and respiratory arrest. People treated for status epilepticus may require monitoring and ventilatory support; thus, secondary care is necessary.</p> <p>The sedative effects of benzodiazepines may interfere with neurological examinations.</p>
<b>FEASIBILITY AND RESOURCE USE</b>	<p>How large are the resource requirements?</p> <p><input type="checkbox"/> Major</p> <p><input type="checkbox"/> Minor</p> <p><input checked="" type="checkbox"/> Uncertain</p> <p>Is the option feasible to implement?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>Both IV lorazepam and IV diazepam are on the WHO essential medicines list (WHO, 2015). IV midazolam is also included but in the section on preoperative medication and sedation for short-term procedures, but not under anticonvulsants. IV lorazepam and IV midazolam may not be readily available in low- and middle-income countries.</p> <p>Of concern is the temperature stability of lorazepam, which undergoes degradation at high temperatures and hence requires refrigeration. This may limit its use in field settings in low- and middle-income countries.</p>

### RECOMMENDATION 3.2

In children presenting with acute seizures or status epilepticus where intravenous administration is available, either intravenous diazepam or intravenous lorazepam should be used to terminate the seizure.

<b>Strength of recommendation</b>	Conditional
<b>Quality of evidence</b>	Very low
<b>Justification</b>	<p>Although the quality of the evidence is very low, the benefits of anticonvulsant medications outweigh their harm, as control of acute convulsive seizures, which are associated with substantial morbidity and mortality, is of critical importance. Both IV lorazepam and IV diazepam are included in the <i>WHO model list of essential medicines for children</i> (WHO, 2015).</p> <p>No recommendation can be made about IV use of midazolam, phenobarbital or phenytoin because of insufficient evidence.</p> <p>The “conditional” nature of the recommendation is due to the choice between IV diazepam and lorazepam; it should not be misunderstood to infer that non-intervention is appropriate.</p>
<b>Implementation considerations</b>	In field settings where environmental temperatures are high and refrigeration is not available, IV diazepam may be preferable because of its thermal stability.
<b>Research priorities</b>	Further comparisons of midazolam with lorazepam or diazepam are required to make recommendations on use of this medication.

### 3.3.3 Choice of second-line anticonvulsant medicines in children with established status epilepticus resistant to first-line benzodiazepines

**Question 9. In children with established status epilepticus, i.e. seizures persisting after treatment with the first-line agent (benzodiazepine-resistant status epilepticus), which antiepileptic drugs are associated with better clinical outcomes (seizure cessation and fewer adverse effects)?**

*(Treatment in established status epilepticus, i.e. seizures persisting after the first line agent (benzodiazepine-resistant status epilepticus))*

#### Summary of evidence

A systematic review identified two RCTs that addressed the PICO question on management of children with benzodiazepine-resistant status epilepticus with anticonvulsant drugs (Agarwal et al., 2007; Malamiri et al., 2012) and a systematic evaluation of the efficacy of different IV anticonvulsant drugs (Yasiry & Shorvon, 2014).

Agarwal et al. (2007) reported the findings of a randomized open-label trial in which adults and children with status epilepticus that did not respond to IV diazepam received either IV valproate or IV phenytoin. IV valproate was as effective as IV phenytoin in stopping status epilepticus (44/50 versus 42/50; RR, 1.05; 95% CI, 0.89–1.23). No difference between the treatments was seen for recurrence after 12 h or 7 days. While the number of adverse events did not differ significantly between the two groups (4/50 versus 8/50; RR, 0.50; 95% CI, 0.16–1.56), the four participants who received IV valproate and reported adverse events had a mild increase in liver enzyme activity, while the adverse events in patients who received IV phenytoin were more severe, including hypotension (six cases) and respiratory depression (two cases). IV valproate was easier to administer.

Malamiri et al. (2012) conducted a randomized double-blind study of the efficacy and safety of IV valproate and IV phenobarbital in children with status epilepticus that did not respond to IV diazepam.

Rapid loading of IV valproate was as effective as phenobarbital in terminating seizures (27/30 versus 23/30; RR, 1.17; 95% CI, 0.93–1.48). There was low-quality evidence that fewer adverse effects occurred with IV valproate than with IV phenytoin (7/30 versus 22/30; RR, 0.32; 95% CI, 0.16–0.63).

Yasiry & Shorvon (2014) conducted a meta-analysis of studies of the efficacy of five IV anticonvulsant drugs (lacosamide, levetiracetam, valproate, phenytoin and phenobarbital) in benzodiazepine-resistant convulsive status epilepticus. They identified 27 studies (798 cases of convulsive status epilepticus), of which 22 were included in the meta-analysis, comprising one randomized double-blind trial, five open-label trials, 18 case series and three case reports. The outcome of interest was seizure cessation, measured by event rate (proportion of episodes with seizure cessation, calculated for the all the drugs individually with no comparators). The efficacy was 68.5% (95% CI, 56.2–78.7) for levetiracetam, 73.6% (95% CI, 58.3–84.8) for phenobarbital, 50.2% (95% CI, 34.2–66.1%) for phenytoin and 75.7% (95% CI, 63.7–84.8%) for valproate.

The limitations of this systematic review included multiple sources of heterogeneity: in study design (retrospective, prospective, randomized and non-randomized, blinded and non-blinded); demographics (age, gender, comorbid conditions and previous medications); intervention characteristics (dosage, rate of infusion, manufacturer, dose); condition characteristics (cause, semiology, duration of seizures to be considered status epilepticus, duration of status before intervention); and response characteristics (time to seizure termination, follow up period for recurring seizures).

#### *Additional evidence used by the GDG but not included in the GRADE tables*

The meta-analysis by Yasiry et al. (2014) included eight studies on the use of phenytoin in 294 episodes of status epilepticus. The studies had various designs: randomized (Agarwal et al., 2007), quasi-randomized (Ogutu et al., 2003) and observational retrospective (Brevoord et al., 2005; Franzoni et al., 2006; Miyahara et al., 2009; Tiamkao & Sawanyawisuth, 2009; Alvarez et al., 2011; Ismail, 2012). The study by Agarwal et al. (2007), an RCT, has already been discussed; the remainder were observational studies. The overall risk for bias was serious: in the study by Agarwal et al. (2007), the randomization method was not clear, concealment of allocation was not mentioned, and the study was not blinded; the study by Ogutu et al. (2003) was quasi-randomized, with no concealment of allocation; Alvarez et al. (2011) conducted a retrospective study, and the baseline prognostic variables were different in the three groups (baseline confounding); and the studies by Brevoord et al. (2005), Franzoni et al. (2006), Miyahara et al. (2009) and Ismail (2012) had a high risk for bias as no comparators were used and all were retrospective. Tiamkao & Sawanyawisuth (2009) studied adults (> 15 years) with benzodiazepine-resistant status epilepticus in whom valproate was used as either as first- or second-line therapy. Although the study was not designed to be comparative, seizure cessation was also described in the group given phenytoin. The samples were small and uneven (12 patients given valproate and 37 given phenytoin). The studies also showed serious indirectness: Ogutu et al. (2003) included children with severe falciparum malaria and status epilepticus, Alvarez et al. (2011) included adults, Tiamkao & Sawanyawisuth (2009) included people > 15 years of age, Ismail (2012) included children with febrile status epilepticus, and Miyahara et al. (2009) included cases of progressive myoclonic epilepsy. Meta-analysis of the pooled effect sizes showed a mean efficacy of 50.2% (95% CI, 34.2–66.1). Heterogeneity calculated with the  $I^2$  statistic was 16.45%.

The meta-analysis of Yasiry & Shorvon (2014) also included eight studies of treatment with IV sodium valproate in 250 benzodiazepine-resistant episodes. The studies included had various designs: randomized (Agarwal et al., 2007; Malamiri et al., 2012), different comparators (phenytoin in Agarwal et al., 2007; phenobarbital in Malamiri et al., 2012) and observational studies (Yu et al., 2003; Olsen et al., 2007; Chen et al., 2009; Tiamkao & Sawanyawisuth, 2009; Chang et al., 2010; Alvarez et al., 2011). Three of the eight studies were in adults (Olsen et al., 2007; Tiamkao & Sawanyawisuth, 2009; Alvarez et al., 2011), and Chen et al. (2009) studied children and adults with status epilepticus resistant to IV diazepam and IM phenobarbital. Heterogeneity calculated with  $I^2$  was 12.73%. The meta-analysis showed a mean effect size for valproate of 75.7% (95% CI, 63.7–84.8).

Finally, the meta-analysis by Yasiry & Shorvon (2014) included two studies of treatment with IV phenobarbital of 42 episodes of benzodiazepine-resistant status epilepticus. The study by Malamiri et al. (2012) was a randomized open-label comparison of valproate with phenobarbital in children with benzodiazepine-resistant status epilepticus. The study of Kokwaro (2003) was an observational study in 12 children with severe falciparum malaria and convulsions. The heterogeneity (I<sup>2</sup>) was 0% because of the number of studies. The meta-analysis revealed a mean efficacy of 73.6% (95% CI, 58.3–84.8).

In order to address this PICO question, studies of IM phenobarbital were also considered. The two RCTs identified by the search (White et al., 1988; Crawley et al., 2000) reported on the tolerability and the effects on seizure frequency in a total of 340 children who were admitted for cerebral malaria and given one IM dose of phenobarbital or placebo. IM phenobarbital alone was tolerated in both studies. Use of IM phenobarbital with three or more doses of diazepam greatly increased the risk for respiratory depression and death in the study by Crawley et al., in which a dose of 20 mg/kg bw was given, in contrast to 3.5 mg/kg bw given in the study by White et al. Seizure frequency decreased significantly in both studies with use of IM phenobarbital. The quality of these two studies is low, due mainly to their small size (few participants and events) and the indirectness of the study population (benzodiazepine-resistant convulsive status epilepticus versus cerebral malaria). A recommendation for the optimum dose cannot be made on the basis of only two RCTs.

The three uncontrolled studies (Sternowsky & Lagenstein, 1981; Kuile et al., 1992; Murri et al., 1992), with varied study populations (41 children with simple febrile seizures, 20 children with malaria and 390 adults and children aged 10–65 years with head injuries, respectively) investigated tolerance of IM phenobarbital and its prophylactic effects on seizure frequency. There were no notable adverse effects, apart from a “tendency” of phenobarbital to deepen coma or render patients sleepy in the study by Kuile et al. (1992), in which only 11 children received the intervention. A recommendation for the optimum dose cannot be made on the basis of these studies.

SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS	
BENEFITS AND HARM	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p> <p>The evidence from the comparative studies is inconclusive regarding a clinically important difference in efficacy between IV phenytoin, phenobarbital and valproate for the treatment of benzodiazepine-resistant status epilepticus in children. This statement is based on low-quality evidence from two RCTs (total N = 160).</p> <p>In the meta-analysis of non-randomized studies, a high proportion (50–75%) of patients treated with valproate, phenytoin and phenobarbital showed clinically relevant improvement. The estimated efficacy of the drugs assessed in the systematic review was 73.6% (95% CI, 58.3–84.8) for phenobarbital, 50.2% (95% CI, 34.2–66.1) for phenytoin and 75.7% (95% CI, 63.7–84.8) for valproate.</p> <p>IM phenobarbital may be considered a feasible alternative when IV delivery of drugs is difficult. Evidence on the use of IM phenobarbital is limited, except in children with cerebral malaria.</p> <p>Only one comparative study reported on adverse effects or deaths after IV administration of these drugs, but it was of very low quality. Three non-randomized studies in indirect populations showed very few adverse effects after IM use of phenobarbital, although the quality of these studies was very low. The evidence is therefore inconclusive, and it is not possible to determine whether there is a clinically important difference in the occurrence of adverse effects or death after the use of these pharmacological interventions.</p> <p>The evidence for the efficacy and use of IV levetiracetam was not comprehensively reviewed for this guideline and was not therefore considered in the recommendations.</p>

<b>VALUES AND PREFERENCES; ACCEPTABILITY</b>	<p>Is there important uncertainty about or variation in how people value the options?</p> <p><input type="checkbox"/> Major  <input checked="" type="checkbox"/> Minor  <input type="checkbox"/> Uncertain</p> <p>Is the option acceptable to key stakeholders?</p> <p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No  <input type="checkbox"/> Uncertain</p>	<p>Most consensus guidelines recommend the use of phenytoin or phenobarbital to prevent recurrence of seizures and for seizures that continue after administration of benzodiazepines. IV valproate has been used for the past 10–15 years but often only after failure of phenytoin or phenobarbital. Recent evidence suggests it can be as effective as phenytoin and phenobarbital as the next-line treatment in established status epilepticus after a benzodiazepine.</p> <p>Control of status epilepticus is of critical importance, as it is a medical emergency and is associated with substantial mortality in children. An additional percentage of children with this condition have permanent sequelae, such as permanent cognitive difficulties. People treated for established status epilepticus must be monitored and may require ventilatory support; thus, secondary care is necessary.</p> <p>The advantages of valproate include a lower risk for cardiorespiratory side-effects.</p> <p>Valproate may be hepatotoxic and is contra-indicated in children with liver disease. It should also be used with caution in young children with suspected inborn error of metabolism. These conditions may not be evident when the child is admitted while convulsing and requires emergency treatment.</p> <p>Phenobarbital causes sedation and may result in respiratory depression. The risk may be increased if it is used after benzodiazepines, whether intravenously or intramuscularly.</p> <p>Phenytoin is associated with risks for arrhythmia and hypotension and is difficult to administer.</p>
<b>FEASIBILITY AND RESOURCE USE</b>	<p>How large are the resource requirements?</p> <p><input type="checkbox"/> Major  <input type="checkbox"/> Minor  <input checked="" type="checkbox"/> Uncertain</p> <p>Is the option feasible to implement?</p> <p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No  <input type="checkbox"/> Uncertain</p>	<p>The <i>WHO model list of essential medicines for children</i> (WHO, 2015) is a list of the minimum requirements for medicines in a basic health care system, listing the most effective, safe, cost-effective medicines for priority conditions. The anticonvulsants phenytoin and phenobarbital have been on the list for children in IV form for several years. IV valproate was added to the fifth edition of the list, in April 2015. Despite inclusion of these three treatments, many low- and middle-income countries have serious difficulty in obtaining medicines, particularly phenobarbital, which is a controlled medication, and undergo complete stock-outs for long periods.</p> <p>The cost of IV valproate remains high, and it may not be an affordable option in low- and middle-income countries.</p> <p>The group also noted the very high cost of IV levetiracetam, which is not generally available in low- and middle-income countries.</p>



### RECOMMENDATION 3.3

In children with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, intravenous valproate, intravenous phenobarbital or intravenous phenytoin can be used, with appropriate monitoring.

The choice of these drugs depends on local resources, including availability and facilities for monitoring. If available, intravenous valproate is preferred to intravenous phenobarbital or intravenous phenytoin because of its superior benefit–risk profile.

Intramuscular phenobarbital remains an option in settings where intravenous infusion or monitoring is not feasible. Phenytoin and valproate should not be given intramuscularly.

<b>Strength of recommendation</b>	Conditional
<b>Quality of evidence</b>	Low
<b>Justification</b>	<p>Status epilepticus is a medical emergency, as it is associated with substantial mortality; its control is therefore of critical importance. Although the quality of the evidence is low, the benefits of IV phenytoin, phenobarbital and valproate outweigh their harm, with no clinically relevant difference among these interventions when compared directly in the management of established status epilepticus.</p> <p>The evidence for the efficacy and use of IV levetiracetam was not comprehensively reviewed for this guideline, and it was not therefore considered as part of the recommendations.</p>
<b>Implementation considerations</b>	<p>The above medications should be initiated when seizures persist after two doses of benzodiazepines.</p> <p>The choice of medication is affected by a number of factors, including availability, cost and side-effects.</p> <p>The advantages of valproate include a smaller risk for cardiorespiratory side-effects. Valproate is a broad-spectrum medication that is active against all types of seizures; hence, it may be useful for maintenance therapy after the acute control of seizures in idiopathic generalized epilepsy or when the type of seizure or epilepsy syndrome is not clear. Valproate has, however, been associated with risks for hepatotoxicity and pancreatitis. Phenobarbital may cause sedation and respiratory depression, and the risk may be increased if it is used after benzodiazepines. Phenytoin is associated with risks for arrhythmia and hypotension, and it is difficult to administer.</p>
<b>Research priorities</b>	The effectiveness of IV levetiracetam to control benzodiazepine-resistant seizures in low-resource settings

#### 3.3.4 Pharmacological interventions for prophylaxis of recurrence of febrile seizures

**Question 10. Which prophylactic pharmacological interventions will prevent recurrence of febrile seizures, and what are the benefits and harm in specific outcomes?**

*(Prophylaxis to prevent recurrence of febrile seizures)*

##### Summary of evidence

Previous systematic reviews were reviewed to address this PICO question. Two systematic reviews were identified (Offringa & Newton, 2013; Rosenbloom et al., 2013) of randomized and quasi-randomized trials of antipyretics and placebo, intermittent anticonvulsants and placebo and continuous anticonvulsants and placebo in the populations of interest. Offringa & Newton (2013)

included all randomized and quasi-randomized trials of comparisons of antipyretic or antiepileptic agents with each other, with placebo or with no treatment in children with febrile seizures. Trials conducted between 1966 and December 2011 were included; in the 26 trials, 13 comparisons were identified, of which five were analysed in the meta-analysis: there were insufficient trials for eight of the comparisons. Rosenbloom et al. (2013) conducted a systematic review of trials of antipyretics versus placebo for prevention of febrile seizures.

### *Antipyretics*

The review by Offringa & Newton (2013) covered two studies of the use of antipyretics in reducing the risk for seizure recurrence. In an RCT of intermittent ibuprofen and placebo, 230 children aged 1–4 years with a first episode of febrile seizures and with at least one risk factor for seizure recurrence were included. There was no statistically significant reduction in risk with ibuprofen administration (van Stuijvenberg et al., 1998). The second study was a placebo-controlled, double-blinded trial in which paracetamol (acetaminophen) and low doses of diazepam were evaluated against placebo. After their first febrile seizure, children were assigned to receive either one rectal dose of diazepam and, after 6 h, oral doses of 0.2 mg/kg bw three times a day for the first 2 days or a placebo in a similar dosing format during further febrile episodes. In addition, each febrile episode was randomly assigned to treatment with paracetamol or the placebo. Neither paracetamol nor diazepam nor the combination of antipyretic agents with anticonvulsant medication reduced the recurrence of febrile seizures (Uhari et al., 1995).

The systematic review by Rosenbloom et al. (2013) comprised three RCTs (Uhari et al., 1995; van Stuijvenberg et al., 1998; Strengell et al., 2009) of antipyretics versus placebo for prevention of febrile seizure recurrence. The three studies involved a total of 540 children aged 6–72 months with a previous episode of febrile seizure. Of these, 348 received antipyretics (paracetamol, ibuprofen or diclofenac), and 192 received placebo for prevention of subsequent febrile seizures for a 1–2-year follow-up period. Febrile seizures recurred during follow-up in 79 patients (22.7%) given antipyretics and 47 (24.4%) given placebo. The difference was not statistically significant (odds ratio, 0.9; 95% CI, 0.57–1.43).

### *Intermittent anticonvulsant therapy*

Offringa & Newton (2013) reviewed 17 studies of the use of various anticonvulsants as prophylactic intermittent therapy for febrile seizures. Overall, a significant reduction in recurrent febrile seizures was found with intermittent oral diazepam as compared with placebo: RR, 0.67 (95% CI, 0.48–0.94) at 24 months (Rosman et al., 1993; Verrottia et al., 2004) and RR, 0.61 (95% CI, 0.15–0.89) at 48 months (Verrottia et al., 2004). No significant benefit was seen at 6-, 12- or 72-month intervals (Ramakrishnan & Thomas, 1986; Autret et al., 1990; Rosman et al., 1993; Verrottia et al., 2004). Intermittent rectal diazepam was associated with reduced seizure recurrence at 6, 12, 18 and 36 months but not at 24 months: RR, 0.60 (95% CI, 0.41–0.86) at 6 months (Knudsen, 1985a; Knudsen, 1985b; Mosquera et al., 1987; Uhari et al., 1995; Pavlidou et al., 2006); RR, 0.65 (95% CI, 0.49–0.87) at 12 months (Knudsen, 1985a; Knudsen, 1985b; Mosquera et al., 1987; Uhari et al., 1995; Pavlidou et al., 2006); RR, 0.2 (95% CI, 0.10–0.39) at 18 months (Knudsen, 1985a; Knudsen, 1985b); and RR, 0.36 (95% CI, 0.18–0.71) at 36 months (Pavlidou et al., 2006). Intermittent clobazam significantly reduced the risk for recurrence of febrile seizure as compared with placebo in one study (Bajaj et al., 2005); however, the sample size was small, the outcome was measured at 6 months only, and there was an exceptionally high rate of recurrence of febrile seizure in controls (83.3%), which is far higher than that reported in other studies (9/30 recurrent seizures with clobazam, 25/30 with placebo): RR, 0.36 (95% CI, 0.20–0.64). When compared with intermittent rectal diazepam, intermittent clobazam resulted in similar seizure recurrence, with four episodes among 127 febrile episodes (3.7%) with clobazam group and two episodes among 116 febrile episodes (1.7%) with diazepam ( $p = 0.47$ ); however, more adverse

events (sedation) occurred with diazepam than with clobazam ( $p < 0.0001$ ) (Khosroshahi et al., 2011). Intermittent phenobarbital had no significant benefit over no treatment (Mackintosh, 1970; Wolf, 1977; Ramakrishnan & Thomas, 1986), and intermittent rectal diazepam had no significant benefit over intermittent valproate (Daugbjerg et al., 1990).

### Continuous anticonvulsant treatment

Prophylactic therapy for febrile seizure recurrence has been studied with phenytoin versus placebo, phenobarbital versus placebo or no treatment and valproate versus placebo or no treatment. Continuous phenytoin versus placebo did not significantly reduce the risk for febrile seizure recurrence at 12 months: RR, 0.98 (95% CI, 0.55–1.73) (Bacon et al., 1981a; Bacon et al., 1981b). Continuous valproate as compared with placebo resulted in no significant reduction in risk at 6 months (Mosquera et al., 1987; McKinlay & Newton, 1989): RR, 1.2 (95% CI, 0.55–2.62), 12 months (Williams et al., 1979; Ngwane & Bower, 1980; Mosquera et al., 1987; McKinlay & Newton, 1989): RR, 0.83 (95% CI, 0.52–1.29), 18 months (Mamelle et al., 1984): RR, 0.27 (95% CI, 0.06–1.15) or 24 months (Mosquera et al., 1987; McKinlay & Newton, 1989): RR, 1.26 (95% CI, 0.73–2.18). Phenobarbital did reduce the risk for seizure recurrence at 6, 12 and 24 months as compared with placebo or no treatment, but not at 18 or 72 months. The RR was 0.6 (95% CI, 0.42–0.84) at 6 months (Mackintosh, 1970; Heckmatt, 1976; Wolf, 1977; Camfield et al., 1980; McKinlay & Newton, 1989; Farwell et al., 1990); RR, 0.59 (95% CI, 0.46–0.75) at 12 months (Wolf, 1977; Camfield et al., 1980; Ngwane & Bower, 1980; Bacon et al., 1981a; Bacon et al., 1981b; McKinlay & Newton, 1989; Farwell et al., 1990; Thilothammal et al., 1993); and RR, 0.6 (95% CI, 0.49–0.88) at 24 months (Wolf et al., 1977; McKinlay & Newton, 1989; Farwell et al., 1990). Behavioural change or sleep disturbance was seen in 15 of 35 (42.8%) children allocated to the phenobarbital group and 8 of 30 (26.3%) children given placebo: RR, 1.61 (95% CI, 0.79–3.26) at 12 months of follow-up (Camfield et al., 1979).

## SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS

<b>BENEFITS AND HARM</b>	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Uncertain</p>	<p>There is no evidence that use of antipyretics (ibuprofen, paracetamol or diclofenac) reduces the recurrence of febrile seizures. Hence, there is no benefit in giving antipyretics with this objective.</p> <p>There is some evidence that use of intermittent rectal diazepam is beneficial, reducing recurrent febrile seizures as compared with placebo; however, the quality of the studies for this conclusion is low.</p> <p>Intermittent clobazam had a significant effect in decreasing the recurrence of febrile seizures in one study; however, the quality of the study was low.</p> <p>There is some evidence that use of continuous phenobarbital reduces the recurrence of febrile seizures as compared with placebo. Neither intermittent diazepam nor continuous phenobarbital reduced the risk of children with febrile seizures for subsequent epilepsy.</p> <p>The adverse effects of anticonvulsants were studied in various ways in the RCTs. In general, adverse effects occurred in about one third of children. There is, however, enough published evidence that phenobarbital has considerable side-effects, including cognitive impairment and behavioural problems, such as hyperactivity, irritability and aggression. Diazepam has been associated with sedation, lethargy, irritability and problems in speech and sleep. Clobazam is associated with ataxia and sedation.</p> <p>Antipyretics (particularly diclofenac and ibuprofen) can have adverse effects in children such as those with dengue fever.</p>
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<b>VALUES AND PREFERENCES; ACCEPTABILITY</b>	<p>Is there important uncertainty about or variation in how people value the options?</p> <p><input type="checkbox"/> Major <input checked="" type="checkbox"/> Minor <input type="checkbox"/> Uncertain</p> <p>Is the option acceptable to key stakeholders?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Uncertain</p>	<p>Most febrile seizures are “benign”, and children have an excellent outcome.</p> <p>Recurrent febrile seizures, particularly when they are prolonged, are of great concern to parents.</p> <p>Febrile status epilepticus can have serious consequences if it is not managed properly. Hence, reduction of recurrent prolonged febrile seizures is important.</p> <p>Parents and non-specialist health care providers can be trained to recognize and manage febrile seizures when they occur.</p>
<b>FEASIBILITY AND RESOURCE USE</b>	<p>How large are the resource requirements?</p> <p><input type="checkbox"/> Major <input checked="" type="checkbox"/> Minor <input type="checkbox"/> Uncertain</p> <p>Is the option feasible to implement?</p> <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain</p>	<p>The cost of benzodiazepines is low, and their availability may not be a problem. The cost can increase, however, if intermittent prophylactic treatment is administered over a long period.</p> <p>Administration of oral intermittent anticonvulsant medication is not difficult for parents if they have received sufficient explanation</p>

### RECOMMENDATION 3.4

**Prophylactic treatment with intermittent antipyretics, intermittent anticonvulsant medications (diazepam or clobazam) or continuous anticonvulsant medications (phenobarbital or valproic acid) should not be used in febrile seizures.**

<b>Strength of recommendation</b>	Strong
<b>Quality of evidence</b>	Low
<b>Justification</b>	<p>Most febrile seizures are “benign”. While recurrent febrile seizures are of concern, education in recognizing seizures and management of recurrence can improve the outcome.</p> <p>Use of prophylactic therapy for recurrent febrile seizures has more side-effects than benefits and is thus not warranted in the majority of cases.</p>
<b>Implementation considerations</b>	<p>The risk factors for febrile status epilepticus may include young age at onset (&lt; 1 year) and low temperature at the time of the febrile seizure. This population group is also likely to have more recurrences of febrile seizures. This should be explained to the parents and non-IV administration of benzodiazepine advised in case the child has febrile seizures at home.</p>
<b>Research priorities</b>	<p>Determine the risk factors and the characteristics of the subgroup of children who are at higher risk for recurrent febrile seizures, who might benefit from prophylactic anticonvulsant therapy.</p>

### 3.3.5 *Role of diagnostic tests in the management of seizures and altered consciousness, particularly when used by non-specialists in low- and middle-income countries*

**Question 11. What is the role of diagnostic tests in the management of seizures and altered consciousness, particularly when used by non-specialists in low- and middle-income countries?**

*(The role of diagnostic tests in children with seizures and altered consciousness)*

#### **Summary of evidence**

No systematic reviews or RCTs were identified that specifically addressed the full scope of the question, but a number of reviews were relevant for components of the question. In addition, and in order to include current recommendations for diagnostic testing in infants and children presenting with seizures and altered consciousness, a number of international paediatric emergencies guidelines were reviewed.

The guidelines reviewed were based either on the GRADE method for assessing evidence from a specific investigation and formulating a recommendation or on input from a multidisciplinary panel of experts in paediatric emergency medicine, pre-hospital medicine and/or evidence-based guideline development. The guidelines reviewed were that for paediatric pre-hospital seizure management by Shah et al. (2014) in the USA; the American Academy of Paediatrics (2008) guideline on simple febrile seizures; the British Columbia guidelines on complex febrile seizures (Canada) (British Columbia Guidelines and Protocols Advisory Committee. 2010); the Canadian Medical Association recommendation for epilepsy (Blume, 2003); the National Institutes of Health (USA) guidelines on febrile seizures (Anon., 1980); the National Institute for Health and Care Excellence guidelines on epilepsies (United Kingdom) (National Institute for Health and Care Excellence, 2012); the Royal Children's Hospital guidelines on afebrile seizures (Australia) (Royal Children's Hospital Melbourne, 2011); the Advanced Paediatric Life Support guidelines (Mackway-Jones et al., 2005); and the Advanced Pediatric Life Support guidelines (Fuchs et al., 2007). These guidelines are widely used in current paediatric practice and are summarized in the complete set of systematic reviews, including GRADE tables, related to the management of seizures with altered consciousness, which are to be published separately. There is low-quality evidence suggesting that blood tests and lumbar puncture are associated with improved diagnosis, the benefits clearly outweighing the harm of these procedures.

No systematic reviews, randomized trials or comparisons were identified in which the outcome of managing children with febrile seizures with diagnostic tests was studied in low- and middle-income countries. Primary studies in low- and middle-income countries include descriptions of children with acute seizures or altered consciousness seen at health care facilities or admitted to hospital. The reporting of diagnostic tests is highly variable. Most of the studies that reported tests were conducted in secondary hospitals located in urban centres or in hospitals with good diagnostic facilities, so that they are indirectly associated with this research question (Canagarayar & Soysa, 1987; Akpede et al., 1992; Akpede & Sykes, 1993; Akpede et al., 1993a; Akpede et al., 1993b; Okoji et al., 1993; Obi et al., 1994; Idro et al., 2008; Mahyar et al., 2010; Kariuki et al., 2011; Sasidaran et al., 2012; Adhikari et al., 2013; Kariuki et al., 2013; Winkler et al., 2013).

#### *Blood tests for glucose and sodium*

Most authorities state that routine measurement of blood glucose is not required for all children with febrile seizures (Rutter & Smales, 1977; Gerber & Berliner, 1981; Chamberlain & Gorman, 1988; American Academy of Pediatrics, 1996). One study of British children presenting with a first febrile seizure found that only 1/269 had hypoglycaemia, although 22 (8%) had hyperglycaemia (Rutter & Smales, 1977). The yield of information for diagnosis from blood cultures of children with febrile seizures is not significantly different from that obtained in paediatric emergency departments (Chamberlain & Gorman, 1988; American Academy of Pediatrics, 1996).

For children presenting with acute convulsive seizures, however, the guidelines suggest that blood glucose levels should be checked, as the yield of diagnostic information could significantly improve outcome. Shah et al. (2014) examined the value of blood glucose measurement in children with seizures before hospital admission and made a weak recommendation that this measure be checked in children presenting with convulsive seizures and/or status epilepticus. They considered that the evidence was of low to very low quality and made a strong recommendation for treatment of hypoglycaemia diagnosed before arrival at the hospital with dextrose or glucagon. The expert guidelines reviewed recommend testing for blood sodium only if signs of dehydration or severe diarrhoea are present.

### *Lumbar puncture*

One observational study addressed a primary research question in low- and middle-income countries: the use of lumbar puncture in children attending an emergency department (Akpede et al., 1992). This prospective study conducted in an urban hospital in Nigeria included 522 children aged 1 month to 6 years who initially presented with convulsions and fever. Lumbar puncture was performed for cerebral spinal fluid samples, resulting in a diagnosis of bacterial meningitis in 13. The authors concluded that the infection occurs in a reasonable proportion of children, even beyond infancy, that convulsions are associated with fever of acute onset and that a decision to perform lumbar puncture should be guided by clinical features. Other studies have also suggested that, in resource-poor countries, where the incidence of serious CNS infections is high, lumbar puncture may be indicated in children presenting with fever and seizures. In a study of 111 children presenting with febrile seizures to a tertiary hospital in the Islamic Republic of Iran, four cases of bacterial meningitis were identified (Shiva & Hashemian, 1998). In a study of 608 Ghanaian children presenting to a tertiary hospital with fever and seizures, a lumbar puncture was performed in 186, of whom 19 (10.2%) were found to have bacterial meningitis (Owusu-Ofori et al., 2004). The potential problems associated with lumbar puncture in low- and middle-income countries are lack of training of health care staff in first-level care facilities in this procedure and/or inadequate laboratory facilities to process the specimens (Simoes et al., 2003).

Studies of varying validity have been conducted in hospitals to determine the probability of meningitis. The signs that indicated an increased risk for meningitis of a child with seizure and fever were: drowsiness before the seizure, neck stiffness, petechial rash, bulging fontanelle and a Glasgow coma scale score of  $< 15 > 1$  h after the seizure (Offringa et al., 1992; Offringa & Moyer, 2001). This evidence was rated as level III, with Delphi consensus and a grade C recommendation. The risk of children presenting with fever and seizure for bacterial meningitis is about 3% (McIntyre et al., 1990) and that for a complex seizure is about 9%. The diagnostic yield of lumbar puncture in these cases could contribute greatly to improving outcomes.

A Delphi survey of medical and nursing staff involved in caring for children with seizures suggested that those with complex febrile seizures and no clinical signs of meningitis should be observed closely and reviewed within 2 h by a paediatrician of at least registrar or resident level to decide whether lumbar puncture should be conducted (Armon et al., 2003).

### *Electroencephalography*

Electroencephalography (EEG) is not recommended for children with simple or complex febrile seizures. The prevalence of paroxysmal EEG abnormalities in children with febrile seizures varies widely, from 2% to 86% (Maytal et al., 2000), due to differences in age, the selection of patients for EEG, the cause of the seizure, the definition of paroxysmal discharge and the delay between the occurrence of the febrile seizures and the EEG. EEG adds little to the diagnosis in simple febrile seizures (Gerber & Berliner, 1981; Maytal et al., 2000) and is not useful for predicting recurrence of febrile seizures or epilepsy (Stores, 1991; Kuturec et al., 1997).

Guideline recommendations on EEG for first presentation with seizure vary and depend on the presentation. In low- and middle-income countries, obtaining an EEG can be difficult.

In children with altered consciousness, EEG is used to detect seizures in paralysed and ventilated patients, detect non-convulsive seizures, suggest a diagnosis (e.g. herpes encephalitis or sub-acute sclerosing pan-encephalitis) and follow prognosis. Studies of use of EEG in unconscious children have been reported in Kenya (Crawley et al., 1996; Gwer et al., 2012), and Malawi (Mallewa & Birbeck, 2013); however, few centres have facilities for prolonged monitoring.

### Neuroimaging

The skull and brain can be imaged by X-ray, CT or MRI, although CT and MRI facilities are often not available in secondary care facilities, particularly in resource-poor settings. There is no evidence that skull X-ray is useful in the diagnosis of febrile seizures. CT scan abnormalities were found in 3/17 children who presented with complicated febrile seizures to an emergency department at a tertiary hospital in the USA (Garvey et al., 1998), while in another study (Farwell et al., 1990), none of 13 patients with complex febrile seizures had abnormal CT scans. MRI is more sensitive than CT scanning. In a study of 159 children presenting with a first febrile seizure, abnormalities were detected in 20 (13%) children by MRI, with a higher prevalence in those with focal seizures, but these findings did not change the management of the child, unless there were other neurological features (Hesdorffer et al., 2008). In 17 Japanese children with prolonged febrile seizure, transient abnormalities were seen on diffusion weighted imaging and T2-weighted images between 9 and 13 days after the seizure (Takanashi et al., 2006; Natsume et al., 2007). Neither CT scans nor MRI detected any intracranial signs that required emergency treatment in 23 children presenting with complex febrile seizure to a tertiary hospital in the USA (Teng et al., 2006).

The expert guidelines that were reviewed recommend neuroimaging in the management of initial presentation with acute convulsive seizure only if there is altered consciousness with a focal neurological sign. In these instances, neuroimaging can profoundly influence the management of the child, by facilitating a diagnosis (such as cerebral haemorrhage), identifying complications and following prognosis.

**SUPPORTING EVIDENCE AND ADDITIONAL CONSIDERATIONS**

<p><b>BENEFITS AND HARM</b></p>	<p>Do the desirable effects outweigh the undesirable effects?</p> <p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No  <input type="checkbox"/> Uncertain</p>	<p>The investigations and tests reviewed provide valuable information for excluding infectious causes of seizures or otherwise guiding management of infants and children presenting with seizures or altered consciousness. Most of the tests are relatively simple to perform, even in resource-limited settings. Other international guidelines and expert opinion recommend use of these tests, despite the limited clinical evidence of their effect on long-term outcomes. Low-quality evidence suggests that blood tests and lumbar puncture are associated with improved outcome due to better diagnosis.</p> <p>Some of the tests are invasive and painful, e.g. blood tests and lumbar puncture.</p> <p>Lumbar punctures can cause morbidity and can precipitate death from herniation.</p> <p>Some neuroimaging techniques, such as CT scanning, expose children to radiation, others may require sedation (e.g. MRI), and children may react to the contrast medium.</p>
<p><b>VALUES AND PREFERENCES; ACCEPTABILITY</b></p>	<p>Is there important uncertainty about or variation in how people value the options?</p> <p><input type="checkbox"/> Major  <input checked="" type="checkbox"/> Minor  <input type="checkbox"/> Uncertain</p> <p>Is the option acceptable to key stakeholders?</p> <p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No  <input type="checkbox"/> Uncertain</p>	<p>Parents and health care providers may want further investigations to determine the cause of seizures or altered consciousness.</p> <p>Some parents may not want a lumbar puncture to be performed, as it can frighten children.</p> <p>The diagnostic value of tests may be reduced by delayed presentation to a health care facility or prior administration of antimicrobial agents.</p>
<p><b>FEASIBILITY AND RESOURCE USE</b></p>	<p>How large are the resource requirements?</p> <p><input type="checkbox"/> Major  <input type="checkbox"/> Minor  <input checked="" type="checkbox"/> Uncertain</p> <p>Is the option feasible to implement?</p> <p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No  <input type="checkbox"/> Uncertain</p>	<p>Resource requirements were not formally assessed in the systematic reviews.</p> <p>The resources required to perform blood and urine cultures, lumbar puncture and other analyses of cerebrospinal fluid may not be available in many health care facilities in low- and middle-income countries.</p> <p>Some of the tests are expensive and may be either unaffordable or unavailable, such as MRI.</p> <p>The feasibility depends on the training of clinical staff to perform and interpret diagnostic tests and the availability of these tests in health care facilities.</p>



## RECOMMENDATIONS

3.5 The following diagnostic tests should be performed in children with acute seizures and/or altered consciousness:

- Blood glucose
- Blood sodium in children with severe dehydration or diarrhoea
- Lumbar puncture in febrile children with signs of meningitis

3.6 Lumbar puncture should be considered for any infant or child who appears to be severely ill (e.g. high fever with altered consciousness or seizure), with any of the following:

- age < 18 months and especially those < 6 months;
- complex febrile seizures (prolonged, focal or recurrent during the same febrile illness);
- when antimicrobial agents have been given before assessment; and
- those not vaccinated against *Haemophilus influenzae* type b or *Streptococcus pneumoniae*, or if immunization status is unknown.

3.7 Lumbar puncture should be delayed and performed only when complications have been managed in infants and children with any of the following clinical signs:

- unresponsive or in a coma (based on ETAT AVPU scale);
- focal neurological signs;
- signs of brainstem herniation;
- signs of raised intracranial pressure;
- signs of respiratory compromise;
- ETAT signs of shock;
- infection in the skin overlying the site of a proposed lumbar puncture; and
- evidence of a bleeding disorder.

3.8 Neuroimaging (ultrasound in young infants, CT or MRI) should be considered in children with altered consciousness or a new focal neurological deficit.

<b>Strength of recommendation</b>	Strong
<b>Quality of evidence</b>	Very low
<b>Justification</b>	It is unlikely that stronger evidence (i.e. clinical trials) will become available to determine the usefulness of measuring blood glucose or sodium or performing lumbar puncture in children with acute seizures or altered consciousness. Nevertheless, the clinical benefits of these investigations (e.g. improved diagnosis and subsequent treatment and therefore potentially reduced mortality and morbidity) far outweigh any potential adverse effect of the investigations. Thus, even though the quality of the evidence is very low, a strong recommendation was made.
<b>Implementation considerations</b>	Feasibility depends on training clinical staff to carry out and interpret the diagnostic tests and the availability of these tests in health care facilities.  The resources required to perform blood and urine cultures, lumbar puncture and analysis of cerebrospinal fluid may not be available in many health care facilities in low- and middle-income countries.  Neuroimaging may be limited by cost and availability.
<b>Research priorities</b>	Determine the usefulness of neuroimaging in these circumstances, particularly with regard to cost.

# 4. Dissemination, adaptation and implementation

## Dissemination

The recommendations in this guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, other United Nations agencies and nongovernmental organizations. They will also be published on the WHO website. Strategic dissemination to key stakeholders will ensure that the guideline reaches the users most likely to benefit from it.

## Adaptation and implementation

The first step in implementation after approval of this guideline will be to revise all WHO publications that are relevant to infants and children presenting with critical illnesses. These include *Integrated management of childhood illness* (WHO, 2014a), *Pocket book of hospital care for children* (WHO, 2013b) and *Emergency triage assessment and treatment* (WHO, 2005a) and supporting training materials.

WHO will work with ministries of health and established partners involved in training on ETAT and in the supervision of health workers at first-level health facilities. Successful introduction of evidence-based policies for the management of critically ill infants and children into national programmes and health care services depends on well-planned, participatory consensus on adaptation and implementation, which may include the preparation or revision of existing national guidelines or protocols. It is expected that each country will adapt these recommendations to suit their local social, cultural and economic contexts. Countries will be encouraged to hold discussions with key stakeholder to make decisions on the use and introduction of the recommendations into national programmes. Frameworks for assisting policy-makers, such as DECIDE ([http://ec.europa.eu/research/health/public-health/clinical-outcome-into-practice/projects/decide\\_en.html](http://ec.europa.eu/research/health/public-health/clinical-outcome-into-practice/projects/decide_en.html)), will be shared.

An enabling environment should be created for use of these recommendations, including changing the behaviour of health care practitioners to use evidence-based practices. Local professional societies may play important roles, and an all-inclusive participatory process should be encouraged. WHO's department of MCA has substantial experience in introducing WHO guidelines and tools into national programmes.

The drugs recommended in this document are on the *WHO model list of essential medicines for children* (WHO, 2015). Essential medicines are intended to be available in functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality and at a price the individual and the community can afford. The model list is a guide for preparing national and institutional lists of essential medicines. Therefore, programme managers should ensure that adequate quantities of the necessary drugs in the recommended dosages are available to health workers. Drugs are usually provided through existing health system supply chains.

WHO's report on global surveillance of antimicrobial resistance (WHO, 2014b) demonstrates that antibiotic resistance is a serious, growing problem across the world. This is relevant to any review of national drug lists and policy, and countries should strengthen their plans to control antimicrobial resistance.

## Monitoring and evaluation of guideline implementation

Monitoring and evaluation should be built into implementation in order to provide lessons for use and further implementation. Priority should be given to monitoring and evaluating the impact of the strong recommendations on quality of care.

This guideline should be used by national child health programmes in collecting and reporting data on the management of sick infants and children. Putting this into practice may require a review of existing patient monitoring systems, including reporting tools, to ensure that the conditions are adequately addressed.

Areas that might require monitoring include:

- the prevalence of critically ill infants and children presenting at first-level health facilities;
- outcomes of management;
- risks for side-effects, especially of anticonvulsive treatment;
- new anticonvulsants coming onto the market that may have a more favourable safety profile than those currently used;
- service delivery (including use of metrics to track coverage, quality of care and adherence to treatment protocols); and
- support systems, including supplies, logistics and supervision.

The MCA will monitor implementation of the guideline by using indicators such as the number of requests from countries for assistance in using the guideline and to WHO headquarters and regional offices for monitoring and evaluation in countries that are applying the guideline. MCA will work with WHO regional offices to monitor the number of countries using this guideline. Additionally, MCA will monitor the number of downloads of the guideline document from the websites of WHO and its partners and the number of hard copies of the guidance requested and distributed through the WHO documents centre.

## Implications for future research

A number of clinical research questions were identified in the discussions on recommendations (see individual recommendations). In addition, implementation research will be conducted.

Policy adoption and ensuring an enabling environment for implementation will require dialogue with policy-makers and national stakeholders. Programme managers will require technical support for preparing and implementing operational plans and programmes from experts with experience in delivering these interventions. Small-scale demonstration projects may support the design and scaling-up of training and implementation at country level.

## Plans for updating the guideline

In 2019, the WHO steering committee will constitute another GDG to review the literature and update the recommendations, as needed. In the interim, the steering committee will continue to identify new studies, interim research results and reports of adverse events. If relevant information becomes available that indicates urgent changes to the recommendations before 2019, a GDG will be constituted at that time.

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## ANNEX 1

# Declarations of interest

(approved by the WHO steering group, October 2014)

LAST NAME	FIRST NAME	INSTITUTION	DECLARED INTEREST
<b>GDG</b>			
Argent	Andrew	University of Cape Town, South Africa	<p>Research funding from the Wellcome Trust, United Kingdom (ZAR 3 million over 2–3 years) for a project reviewing the pathways to care of critically ill children</p> <p>Financial support from Astra Zeneca (ZAR 20 000 per annum) for transport and accommodation to attend a number of congresses each year. No honorarium.</p> <p>Honorarium (HK\$ 12 000) from the Hong Kong Health Authority to cover transport, accommodation and time for teaching on intensive care in Hong Kong.</p> <p>Course director for the Advanced Paediatric Life Support course (United Kingdom) in South Africa and so could be seen to have supported a particular view on fluid resuscitation. I teach on the course but have not been asked to support a particular perspective in my private capacity.</p>
Brierley	Joe	Great Ormond Street Hospital, London, United Kingdom	<p>I am a member of the American Society of Critical Care Medicine Hemodynamic Parameter Guideline Group. In this capacity I am contributing to the literature review in the area, my specific group is looking a vasodilator therapy not fluids. Received travel support from VOK-Medical to attend and teach at an ICU meeting in the Russian Federation in 2013, but less than the US\$ 1000 as above</p>
Campbell	Harry	University of Edinburgh Medical School, Scotland	<p>Employed as a consultant paediatrician, University of Edinburgh</p> <p>Contracts between University of Edinburgh and Gates Foundation, WHO and the United Nations Children’s Fund to provide health advice on child health topics. Benefits to employer and to me</p> <p>Research grants from Gates Foundation and WHO for research; benefits to my employer and me</p> <p>Non-monetary support for travel and conference attendance from WHO and the World Society for Pediatric Infectious Diseases</p>
Dube	Queen	College of Medicine, Blantyre, Malawi	None declared

LAST NAME	FIRST NAME	INSTITUTION	DECLARED INTEREST
<b>GDG continued</b>			
Duke	Trevor	University of Melbourne, Australia	None declared
English	Mike	KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya	<p>Research support – I have received research support from the Wellcome Trust to examine uptake of guidelines and training in Kenya that include parts of ETAT</p> <p>I have also been the grant holder on sub-contracted funds from the Liverpool School Tropical Medicine originating from a DFID grant to support guideline development in Kenya including the topic of fluid resuscitation. Current work activities – I remain actively involved in the development of the ETAT+ training programme that is used in Kenya and other countries. All materials for this training programme are freely accessible, and I do not receive any personal income or emoluments for this work.</p>
Hartmann	Hans	Hanover Medical School, Germany	<p>Award from Nutricia Metabolics (US\$ 500) to serve as technical expert on ketogenic diet for epilepsy to speak at the meeting of the international PDE consortium in Barcelona in 2013. This meeting was supported by Nutricia. I did not receive any support for my travel arrangements.</p> <p>Award from Nutricia (US\$ 400) to serve as technical expert on lysine restricted diet for pyridoxine dependent epilepsy. (Chair a workshop on occasion of the 2014 European Metabolic Group meeting in Zurich. This meeting was supported by Nutricia, who also covered my travel expenses. I did not receive any further bursaries.)</p>
Hazir	Tabish	Pakistan Institute of Medical Sciences, Islamabad, Pakistan	None declared
Kakooza-Mwesige	Angelina	Makerere University College of Health Sciences, Kampala, Uganda	<p>Research support. Royal College of Paediatrics and Child Health United Kingdom (US\$ 10 000, from 2012 for a three-year project) to Research Unit, Department of Paediatrics and Child Health. To carry out training for undergraduate medical, nursing, clinical students and postgraduate paediatric trainees</p> <p>Royal College of Paediatrics and Child Health, United Kingdom, to Research Unit of Department of Paediatrics and Child Health for same as above. I have not participated in any of the ETAT training nor received any financial or non-monetary support from this collaboration.</p>
Kissoon	Niranjan “Tex”	University of British Columbia, Vancouver, Canada	None declared
Kokeb	Mehretie	University of Gondar, Ethiopia	None declared

LAST NAME	FIRST NAME	INSTITUTION	DECLARED INTEREST
<b>GDG continued</b>			
Korff	Christian	Geneva University Hospitals, Switzerland	Research support from UCB Pharma, Switzerland (CHF 2000) paid to research unit in 2014
Lang	Eddie	University of Calgary, Canada	Consultant 1b. GRADE consultant to the National Transportation Safety Agency and Emergency Medical Services for Children (US Federal agency) for the development of a guideline on prehospital management of seizures (US\$ 7000 for entire contract, 2011) Consultant 1b. GRADE consultant to the International Liaison Committee on Resuscitation supporting all task forces including post-arrest targeting of PaO <sub>2</sub> . Considered significant funding. Ongoing.
Linn	Kyaw	Yangon Children's Hospital, Myanmar	None declared
Lozano León	Juan Manuel	Florida International University, Miami, USA	None declared
Namzova-Baranova	Leyla	Russian Academy of Medical Science, Moscow, Russian Federation	None declared
Patel	Archana	Indira Gandhi Government Medical College, Nagpur, India	None declared
Safitri Laksono	Ida	Gadjah Mada University, Yogyakarta, Indonesia	None declared
Singhi	Sunit	Post-graduate Institute of Medical Education and Research, Chandigarh, India	None declared
Taha	Manal Hassan	Federal Ministry of Health, Khartoum, Sudan	None declared
<b>OBSERVERS</b>			
Maconochie	Ian	St Mary's Hospital, London, United Kingdom	None declared
Meaney	Peter	University of Pennsylvania, Philadelphia, USA	Grant programme. American Heart Association. Employer (CHOP). US\$ 328 000 Grant programme. Ronald McDonald House Charities. Employer (CHOP). US\$ 200 000. (The above financial support is to support paediatric emergency training programmes in Molepolole, Botswana, which I serve as medical director.
<b>TECHNICAL SUPPORT</b>			
Newton	Charles	KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya	None declared
Lodha	Rakesh	All-India Institute of Medical Sciences, New Delhi, India	None declared

**TECHNICAL SUPPORT** *continued*

Playfor	Stephen	Royal Manchester Children's Hospital, United Kingdom	I received honoraria in return for speaking at 6 Forte educational events from Baxter Healthcare PLC. (6 x £ 1300). As the only balanced intravenous electrolyte solution available with dextrose, my unit started stocking and clinically using Plasma-Lyte 148. This attracted the interest of the company who asked if I would speak at their Forte educational events on the subject of using IV fluids in children, using my own unadulterated material. On each of the 6 occasions I spoke at these events. I received honoraria of £ 1300.
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**For more information, please contact:**

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