ClinicalEvidence

Dengue haemorrhagic fever or dengue shock syndrome in children

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ABSTRACT

INTRODUCTION: Dengue haemorrhagic fever and dengue shock syndrome are major causes of hospital admission and mortality in children. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of supportive treatments for dengue haemorrhagic fever or dengue shock syndrome in children? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2014 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found nine studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: adding blood component transfusion to standard intravenous fluids; adding corticosteroids or intravenous immunoglobulin to standard intravenous fluids; and crystalloids versus colloids.

QUESTIONS

INTERVENTIONS

Key points

- Infection with the dengue virus, transmitted by the *Aedes* mosquito, ranges from asymptomatic or undifferentiated febrile illness to fatal haemorrhagic fever, and affects up to 100 million people per year worldwide.

  Non-severe dengue fever is characterised by a sudden onset of high fever associated with any of the following signs and symptoms: rash, severe aches and pains, and any of the following warning signs, abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement greater than 2 cm, and an increase in haematocrit concurrent with rapid decrease in platelet count. Presence of warning signs warrants strict observation.

  Severe dengue haemorrhagic fever (previously dengue haemorrhagic fever and dengue shock syndrome) is characterised by severe plasma leakage, severe bleeding, and severe organ involvement manifested as elevated liver enzymes, impaired sensorium, and myocarditis. Severe plasma leakage is manifested by a rise or drop in haematocrit, fluid in the lungs or abdomen leading to respiratory distress, and dengue shock syndrome.

  Dengue haemorrhagic fever and dengue shock syndrome are major causes of hospital admission and mortality in children. If untreated, mortality can be as high as 20%. With appropriate case management, mortality can be reduced to less than 1%, depending on the availability of appropriate supportive care.
- Crystalloids seem as effective as colloids in children with moderately severe dengue shock syndrome. We found no RCTs comparing crystalloids versus colloids in children with severe dengue shock syndrome.
- There is consensus that blood component transfusion (fresh frozen plasma, packed red blood cells, or platelets) should be added to intravenous fluids in children with coagulopathy or bleeding. The optimal time for beginning transfusion is unclear.
- We don't know whether adding corticosteroids or intravenous immunoglobulin to standard intravenous fluids reduces the risks of shock, pleural effusion, or mortality.

Clinical context

DEFINITION

Dengue infection is a mosquito-borne arboviral infection. An important criterion to consider in the diagnosis of dengue infection is history of travel or residence in a dengue-endemic area within 2 weeks of the onset of fever. The spectrum of dengue virus infection ranges from an asymptomatic or undifferentiated febrile illness to severe infection. In 2009, the classification of dengue into **dengue fever**, **dengue haemorrhagic fever,** and **dengue shock syndrome** was simplified into **non-severe** and **severe dengue**. Non-severe dengue is further divided into two subgroups — patients with warning signs and those without warning signs. This revised classification is aimed at guiding clinicians in deciding where and how patients should be observed and managed. Criteria for diagnosis of probable dengue include history of travel or residence in a dengue-endemic area, plus high grade fever of acute onset and two of the following signs and symptoms: nausea/vomiting, rash, severe aches and pains (also called 'breakbone fever'), positive tourniquet test, leukopenia, and any warning sign. Presence of any of the following warning signs — abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement greater than 2 cm, and an increase in haematocrit concurrent with rapid decrease in platelet count — will require strict observation and medical intervention. Criteria for severe dengue fever include severe plasma leakage, severe bleeding as evaluated by the clinician, and severe organ involvement. Severe plasma leakage is manifested by a rise or drop in haematocrit, fluid in the lungs or abdomen leading to respiratory distress, and dengue shock syndrome. Haemorrhagic manifestations include skin haemorrhages, mucosal and gastrointestinal tract bleeding, and pulmonary haemorrhage. Severe organ involvement is manifested by any of the following: elevated liver enzymes (AST, ALT >1000), impaired consciousness (dengue encephalopathy), and dengue myocarditis (see table 1, p 14). [1] The illness usually begins abruptly, occurring in three phases: febrile, critical, and recovery. The critical phase sets in during defervescence, when capillary permeability is increased accompanied by haemoconcentration, leading to hypovolaemic shock that can result in organ impairment, metabolic acidosis, disseminated intravascular coagulation, and severe haemorrhage. This review deals with interventions for dengue haemorrhagic fever and dengue shock syndrome in children.

INCIDENCE/ PREVALENCE

Dengue fever and dengue haemorrhagic fever are public health problems worldwide, particularly in low-lying areas where *Aedes aegypti*, a domestic mosquito, is present. Cities near to the equator but high in the Andes are generally free from dengue because *Aedes* mosquitoes do not survive at high altitudes. However, variations in the climate system (particularly climate warming) has increased the geographic distribution of *Aedes* mosquitoes. The highest published elevation records for *Aedes aegypti* in the Americas are 1700–2130 m for Mexico and 2200 m for Colombia. [2] Worldwide, an estimated 50–100 million cases of dengue fever, and hundreds of thousands of dengue haemorrhagic fever, occur yearly. [3] Recent estimates using novel mapping techniques (based on an extensive database of 10,000 clinical records) provided a global estimate of 390 million new infections per year, with symptomatic and asymptomatic dengue case burden at 96 and 294 million, respectively. [4] Endemic regions are the Americas, South East Asia, the western Pacific, Africa, and the eastern Mediterranean. Major global demographic changes and their consequences (particularly, increases in the density and geographic distribution of the vector with declining vector control, unreliable water supply systems, increasing non-biodegradable container and poor solid waste disposal, increased geographic range of virus transmission due to increased air travel, and increased population density in urban areas) are responsible for the resurgence of dengue in the past century. [5] [6] The WHO estimates that global temperature rises of 1.0–3.5°C may increase transmission of dengue fever by shortening the extrinsic incubation period of viruses within the mosquito, adding 20,000–30,000 more fatal cases annually. [7]

AETIOLOGY/ RISK FACTORS

Dengue virus serotypes 1–4 (DEN 1, 2, 3, 4) belonging to the flavivirus genus are the aetiological agents. These serotypes are closely related, but antigenically distinct. *Aedes aegypti*, the principal vector, transmits the virus to and between humans. Dengue haemorrhagic fever and dengue shock syndrome typically occur in children under the age of 15 years, although dengue fever primarily occurs in adults and older children. Important risk factors influencing who will develop dengue haemorrhagic fever or severe disease during epidemics include the virus strain and serotype, immune status of the host, age, and genetic predisposition. There is evidence that sequential infection or pre-existing antidengue antibodies increases the risk of dengue haemorrhagic fever through antibody-dependent enhancement. [5] [6] [8] [9] [10] **Diagnosis** To confirm dengue infection, identification of virus/viral RNA/viral antigen and the detection of an antibody response are preferred than either approach alone. During the first 4 to 5 days of illness, while the patient is febrile, dengue infections may be diagnosed by virus isolation in cell culture, by detection of viral RNA by nucleic acid amplification tests, or by detection of viral antigens by ELISA or rapid antigen detection tests using serum or plasma and other tissues. After day 5, dengue viruses and antigens disappear from the blood co-incident with the appearance of specific antibodies. Hence, at the end of the acute phase of infection, serology is the method of choice for diagnosis. Antibody response to infection

differs according to the immune status of the host. In primary dengue infection, the antibodies rise slowly. IgM antibodies are the first to appear, detectable in 50% of patients by days 3 to 5 after onset of illness, increasing to 80% by day 5, and 99% by day 10. IgM levels peak about 2 weeks after the onset of symptoms and then decline to undetectable levels over 2 to 3 months. Anti-dengue serum IgG is detectable at low titres at the end of the first week of illness, increasing slowly thereafter. Serum IgG remains detectable after several months, and probably even for life. [1] During a secondary dengue infection antibody titres rise rapidly with IgG as the dominant immunoglobulin. IgG is detectable at high levels, even in the acute phase, and persists for periods lasting from 10 months to life. Early convalescent stage IgM levels are significantly lower in secondary infections than in primary ones and may be undetectable in some cases, depending on the test used. To distinguish primary and secondary dengue infections, IgM/IgG antibody ratios are commonly used. [1]

PROGNOSIS

Dengue fever is an incapacitating disease, but prognosis is favourable in previously healthy adults, although dengue haemorrhagic fever and dengue shock syndrome are major causes of hospital admission and mortality in children. Dengue fever is generally self-limiting, with less than 1% case fatality. The acute phase of the illness lasts for 2 to 7 days, but the convalescent phase may be prolonged for weeks associated with fatigue and depression, especially in adults. Prognosis in dengue haemorrhagic fever and dengue shock syndrome depends on prevention, or early recognition and treatment of shock. Once shock sets in, fatality may be as high as 12% to 44%. [11] However, in centres with appropriate intensive supportive treatment, fatality can be less than 1%. There is no specific antiviral treatment. The standard treatment is to give intravenous fluids to expand plasma volume. People usually recover after prompt and adequate fluid and electrolyte supportive treatment. The optimal fluid regimen, however, remains the subject of debate. This is particularly important in dengue, where one of the management difficulties is to correct hypovolaemia rapidly without precipitating fluid overload. WHO guidelines published in 2009 provide guidance on fluid management and blood transfusions. [1]

AIMS OF INTERVENTION

To prevent mortality and improve symptoms, with minimal adverse effects.

OUTCOMES

Mortality; **symptom severity** (including recurrence of shock, duration of shock, fluid requirements, length of hospital stay, need for blood transfusion, complications, and symptom relief); **adverse effects**.

METHODS

BMJ Clinical Evidence search and appraisal March 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2014, Embase 1980 to March 2014, and The Cochrane Database of Systematic Reviews 2014, issue 3 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, any level of blinding (including open studies) containing at least 20 individuals (at least 10 per arm) of whom at least 80% were followed up. There was no minimum length of follow-up. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA that are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of supportive treatments for dengue haemorrhagic fever or dengue shock syndrome in children?**

OPTION **CRYSTALLOIDS VERSUS COLLOIDS**

- For GRADE evaluation of interventions for Dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 15 .
- Crystalloids seem as effective as colloids in children in moderately severe and severe dengue shock syndrome.

Benefits and harms

Crystalloids versus colloids:

We found one systematic review (search date 2008), [12] which included three RCTs. The review did not pool data so we have reported the three RCTs from their original reports. [13] [14] [15] The third RCT (512 Vietnamese children aged 2–15 years with dengue shock syndrome) stratified children into those with moderately severe shock or severe shock according to their pulse pressure at admission (moderate severity: pulse pressure >10–20 mmHg; severe shock: pulse pressure 10 mmHg or less). [15] It compared Ringer's lactate (a crystalloid) with either 6% dextran 70 (a colloid) or 6% hydroxyethyl starch (a colloid) in 383 children with moderately severe dengue shock syndrome. However, the RCT did not report a direct analysis of Ringer's lactate versus dextran alone, and only reported an among-group analysis, so we have reported this. In the remaining 129 Vietnamese children with severe dengue shock syndrome, it compared the two colloids (6% dextran 70 and 6% hydroxyethyl starch). We did not compare colloids versus colloids in this review and excluded hydroxyethyl starch as a direct comparator so we have not reported this analysis here, but have reported adverse events from this analysis in the adverse effects section below. [15] We have excluded trials using hydroxyethyl starch in this review due to warnings on its use (see Comment section).

Symptom severity

Crystalloids compared with colloids Crystalloids and colloids seem equally effective at reducing shock recurrence and the need for rescue colloids in children with moderately severe dengue shock syndrome. Ringer's lactate seems to be as effective as 6% dextran 70, and 6% hydroxyethyl starch, at reducing the proportion of children with moderately severe dengue shock syndrome who need rescue colloids for initial resuscitation. We found insufficient evidence in severe dengue fever (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence of shock					
[13] RCT **4-armed trial**	50 Vietnamese children aged 5–15 years with dengue shock syndrome	**Median recurrence of shock** 1 episode with sodium chloride (crystalloid regimen) 1 episode with Ringer's lactate (crystalloid regimen) 1 episode with dextran 70 (colloid regimen) 1 episode with gelafundin (colloid regimen) See Further information on studies	Difference among groups P = 0.46	⟷	Not significant
[14] RCT	222 Vietnamese children, aged 1–15 years with dengue shock syndrome	**Recurrence of shock** 20/81 (25%) with crystalloid regimens (sodium chloride or Ringer's lactate) 24/90 (27%) with colloid regimens (dextran 70 or gelafundin) See Further information on studies	RR 1.02 95% CI 0.56 to1.85	⟷	Not significant
Duration of shock					
[13] RCT **4-armed trial**	50 Vietnamese children aged 5–15 years with dengue shock syndrome	**Mean duration in shock** 1.5 hours with sodium chloride (crystalloid regimen)	Difference among groups P = 0.36	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		5.0 hours with Ringer's lactate (crystalloid regimen) 2.8 hours with dextran 70 (colloid regimen) 7.0 hours with gelafundin (colloid regimen) See Further information on studies			
Fluid requirements					
[13] RCT **4-armed trial**	50 Vietnamese children aged 5–15 years with dengue shock syndrome	**Requirement for further fluid infusions , between the 2-hour infusion and full recovery from shock** with sodium chloride (crystalloid regimen) with Ringer's lactate (crystalloid regimen) with dextran 70 (colloid regimen) with gelafundin (colloid regimen) See Further information on studies	The RCT found no significant difference among groups in requirement for further infusions of crystalloids (P = 0.16) or colloids (P = 0.70) between the 2-hour infusion and full recovery from shock (recovery from shock was defined as a pulse pressure of at least 20 mmHg)	⟷	Not significant
[14] RCT **4-armed trial**	222 Vietnamese children, aged 1–15 years with dengue shock syndrome	**Proportion requiring further infusions , after the first hour** 17/56 (30%) with sodium chloride (crystalloid regimen) 20/55 (36%) with Ringer's lactate (crystalloid regimen) 17/55 (31%) with dextran 70 (colloid regimen) 15/56 (27%) with gelafundin (colloid regimen)	Difference among groups P = 0.75	⟷	Not significant
[14] RCT **4-armed trial**	222 Vietnamese children, aged 1–15 years with dengue shock syndrome	**Total volume of fluid infused , until full recovery from shock** with sodium chloride (crystalloid regimen) with Ringer's lactate (crystalloid regimen) with dextran 70 (colloid regimen) with gelafundin (colloid regimen) See Further information on studies	Difference among groups P = 0.95	⟷	Not significant
[15] RCT **3-armed trial**	383 Vietnamese children aged 2–15 with moderately severe dengue shock syndrome (moderate severity: pulse pressure >10 mmHg and up to 20 mmHg) Subgroup analysis	**Proportion of children who needed rescue fluids** 40/128 (31%) with Ringer's lactate (crystalloid regimen) 31/126 (25%) with 6% dextran 70 (colloid regimen) 43/129 (33%) with 6% hydroxyethyl starch (colloid regimen) See Further information on studies and see the Drug safety alert on hydroxyethyl starch in Comments	Difference among groups P = 0.28 The RCT also found no significant difference between Ringer's lactate and either of the colloid solutions in the proportion of children who required rescue colloid (RR 1.08, 95% CI 0.78–1.47; P = 0.65; absolute numbers not reported); see Further information on studies	⟷	Not significant

Mortality

Crystalloids compared with colloids We don't know how effective crystalloids and colloids are, compared with each other, at reducing mortality in children with dengue shock syndrome as we found insufficient evidence (low-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[13] RCT **4-armed trial**	50 Vietnamese children aged 5–15 years with dengue shock syndrome	**Deaths** 0 deaths with sodium chloride (crystalloid regimen) 0 deaths with Ringer's lactate (crystalloid regimen) 0 deaths with dextran 70 (colloid regimen) 0 deaths with gelafundin (colloid regimen) See Further information on studies	Significance not reported		
[14] RCT **4-armed trial**	222 Vietnamese children, aged 1–15 years with dengue shock syndrome	**Deaths** 0 deaths with sodium chloride (crystalloid regimen) 0 deaths with Ringer's lactate (crystalloid regimen) 0 deaths with dextran 70 (colloid regimen) 0 deaths with gelafundin (colloid regimen) See Further information on studies	Significance not reported		
[15] RCT **3-armed trial**	383 Vietnamese children aged 2–15 with moderately severe dengue shock syndrome (moderate severity: pulse pressure >10 mmHg and up to 20 mmHg) Subgroup analysis	**Deaths** 0/128 (0%) with Ringer's lactate (crystalloid regimen) 0/126 (0%) with 6% dextran 70 (colloid regimen) 1/129 (0.8%) with 6% hydroxyethyl starch (colloid regimen) See Further information on studies and see the Drug safety alert on hydroxyethyl starch in Comments	Significance not reported		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] RCT	222 Vietnamese children, aged 1–15 years with dengue shock syndrome	**Fever and chills** 0 children with crystalloid regimens (sodium chloride or Ringer's lactate) 6 children with colloid regimens (dextran 70 or gelafundin)	Significance not reported		
[14] RCT	222 Vietnamese children, aged	**Recurrence of shock**	Significance not reported A total of 35 children equally distributed among the four groups		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	1–15 years with dengue shock syndrome	0 children with crystalloid regimens (sodium chloride or Ringer's lactate) 2 children with colloid regimens (dextran 70 or gelafundin) The 2 children responded to crystalloid treatments	required diuretic treatment for 1 or 2 days after recovery from shock		
[14] RCT	222 Vietnamese children, aged 1–15 years with dengue shock syndrome	**Bleeding** 0 children with crystalloid regimens (sodium chloride or Ringer's lactate) 2 children with colloid regimens (dextran 70 or gelafundin)	Significance not reported 1 child receiving gelafundin had severe epistaxis requiring transfusion, while 1 child receiving dextran developed a large haematoma at a site of minor trauma		
[15] RCT **3-armed trial**	383 Vietnamese children aged 2–15 with moderately severe dengue shock syndrome (moderate severity: pulse pressure >10 mmHg and up to 20 mmHg)	**Allergic type reactions** 0/128 (0%) with Ringer's lactate (crystalloid regimen) 9/126 (7%) with 6% dextran 70 (colloid regimen) 1/129 (1%) with 6% hydroxyethyl starch (colloid regimen) See the Drug safety alert on hydroxyethyl starch in Comments	Difference among groups P < 0.001 Of the additional 129 children in the RCT with severe shock, allergic reactions were reported in 6/67 [9%] with dextran *v* 0/62 [0%] with starch; P = 0.03 Overall in the RCT, 15 children receiving dextran had severe reactions (transient high fever and rigors without cardiorespiratory compromise) that occurred within 6 hours of infusing the study fluid, and 1 child in the starch group developed an urticarial rash without fever at the end of the infusion All children responded to symptomatic treatment alone, but 1 child died		

No data from the following reference on this outcome. [13]

Further information on studies

[13] Crystalloids or colloids were infused at a rate of 20 mL/kg for the first hour followed by 10 mL/kg for the second hour. All children then received further intravenous infusions on an open basis at the discretion of the attending physician according to WHO guidelines. Adverse effects: the first RCT found no adverse effects attributable to colloids or crystalloids, but it may have been underpowered to detect clinically important adverse effects.

[14] The fluids were infused at a rate of 20 mL/kg for the first hour. All children then received further infusions of Ringer's lactate solution according to WHO guidelines. However, children who failed to improve or who deteriorated were given additional colloid (dextran 70) infusions at the discretion of the attending physician.

[15] Each child received 15 mL/kg body weight of the allocated fluid within 1 hour, followed by 10 mL/kg over the second hour. Adverse effects: this RCT found no significant difference in any adverse effects of the different fluids used, except in the incidence of allergic type reactions. There were no significant differences among the fluid treatment groups in the development of new bleeding manifestations, clinical fluid overload, depth of right pleural effusion, volume of ascites, and the use of diuretic treatment.

[13] [14] [15] None of the trials were adequately powered to estimate mortality. One trial reported that only one child died. [15] Mortality was not a primary endpoint in these trials because of the expected low mortality in dengue.

Comment: The first two RCTs comparing crystalloids with colloids are likely to have been underpowered to detect a clinically important difference in outcomes. [13] [14] The RCTs measured outcomes at 1 or 2 hours after fluid infusion, so a clinically important effect within the first hour of fluid resuscitation may have been overlooked. Regardless of whether colloid or crystalloid is more effective, if equal volumes are infused, there is no difference between them with regard to fluid overload. [16] The high-quality, adequately powered third RCT provides strong evidence that Ringer's lactate or isotonic crystalloid solutions are safe, and are as effective as colloid solutions for the initial resuscitation of children with moderately severe dengue shock syndrome, in terms of the requirement for rescue colloid. [15] In children with severe shock, the effectiveness of Ringer's lactate remains untested in a large RCT.

Drug safety alert

Hydroxyethyl starch In an alert issued in June 2013,the Medicines and Healthcare products Regulatory Agency (MHRA) has suspended the use of hydroxyethyl starch (HES) products in the UK. This was done after results from large randomised clinical trials reported an increased risk of renal dysfunction and mortality in critically ill or septic patients who received HES rather than crystalloids.(www.mhra.gov.uk/)

In a further alert issued in December 2014, which superseded this, the European Medicines Agency concluded that HES should be contraindicated in critically ill patients or patients with sepsis or burns. However, HES can be used in patients with acute blood loss, where treatment with crystalloids alone is not sufficient. As well as new contraindications, HES use will be subject to updated warnings in the information leaflets supplied with HES products. (For full details on contraindications and limitations on usage see www.gov.uk.)

Clinical guide

The optimal fluid regimen for dengue fever remains the subject of debate. WHO guidelines published in 2009 provide guidance on fluid management and blood transfusions. [1]

OPTION ADDING CORTICOSTEROIDS TO STANDARD INTRAVENOUS FLUIDS

- For GRADE evaluation of interventions for Dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 15 .
- We don't know whether adding corticosteroids to standard intravenous fluids is more effective than adding placebo or no corticosteroids at reducing mortality, pulmonary haemorrhage, convulsions, the need for blood transfusions, or in reducing mean hospital stay.

Benefits and harms

Adding corticosteroids to standard intravenous fluids versus adding placebo or no corticosteroids:

We found one systematic review (search date 2009, 4 RCTs, 284 children) comparing corticosteroids with no corticosteroids in children with serologically confirmed dengue shock syndrome receiving intravenous fluids. [17] Two of the trials identified by the review were conducted in Thailand [18] [19] , one in Indonesia [20] , and one in Burma. [21]

Symptom severity

Adding corticosteroids to standard intravenous fluids versus adding placebo or no corticosteroid We don't know whether adding corticosteroids to standard intravenous fluids is more effective than adding placebo or no corticosteroids at reducing pulmonary haemorrhage, convulsions, or the need for blood transfusions, or in reducing mean hospital stay, in children with serologically confirmed dengue shock syndrome (very-low quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Length of hospital stay					
[17] Systematic review	63 children with serologically confirmed dengue shock syndrome receiving intravenous fluids Data from 1 RCT	**Mean days in hospital** 7.3 days with methylprednisolone 6.2 days with placebo	MD 1.10 days 95% CI –1.83 days to +4.03 days	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for blood transfusions					
[17] Systematic review	Children with serologically confirmed dengue shock syndrome receiving intravenous fluids 2 RCTs in this analysis	**Blood transfusions** 11/39 (28%) with corticosteroid 12/50 (24%) with no corticosteroid/placebo	RR 1.08 95% CI 0.52 to 2.24 P = 0.84	⟷	Not significant
Complications					
[17] Systematic review	63 children with serologically confirmed dengue shock syndrome receiving intravenous fluids Data from 1 RCT	**Pulmonary haemorrhage** 1/32 (3%) with methylprednisolone 1/31 (3%) with placebo	RR 0.97 95% CI 0.06 to 14.82	⟷	Not significant
[17] Systematic review	63 children with serologically confirmed dengue shock syndrome receiving intravenous fluids Data from 1 RCT	**Convulsions** 3/32 (9%) with methylprednisolone 0/31 (0%) with placebo	RR 6.79 95% CI 0.36 to 26.24	⟷	Not significant

Mortality

Adding corticosteroids to standard intravenous fluids versus adding placebo or no corticosteroids We don't know whether adding corticosteroids to standard intravenous fluids is more effective than adding or no corticosteroids placebo at reducing mortality in children with serologically confirmed dengue shock syndrome (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[17] Systematic review	Children with serologically confirmed dengue shock syndrome receiving intravenous fluids 4 RCTs in this analysis	**Deaths** 21/134 (16%) with corticosteroid 32/150 (21%) with no corticosteroid/placebo	RR 0.68 95% CI 0.42 to 1.11 P = 0.12	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT	63 children with serologically confirmed dengue shock syndrome receiving intravenous fluids	**Secondary infections** with methylprednisolone with placebo The frequency of episodes of infection (pneumonia, bacteraemia) was similar with methylprednisolone compared with placebo			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[18] RCT	63 children with serologically confirmed dengue shock syndrome receiving intravenous fluids	**Adverse effects , 2 weeks** with methylprednisolone with placebo All surviving children were followed up 2 weeks after treatment, and sequelae rates (including haematomas, stiff joints, otitis media, abscesses, and gingivitis) were similar between the 2 groups			
[19] RCT	26 children with serologically confirmed dengue shock syndrome receiving intravenous fluids	**Infection of the cut-down site** 2/7 (28%) with hydrocortisone 0/19 (0%) with no hydrocortisone			
[19] RCT	26 children with serologically confirmed dengue shock syndrome receiving intravenous fluids	**Bleeding from the cut-down site** 4/7 (57%) with hydrocortisone 8/19 (42%) with no hydrocortisone			
[19] RCT	26 children with serologically confirmed dengue shock syndrome receiving intravenous fluids	**Gastrointestinal bleeding** 6/7 (86%) with hydrocortisone 7/19 (37%) with no hydrocortisone			

No data from the following reference on this outcome. [17]

Comment:

One of the RCTs included in the systematic review was an open trial with unclear randomisation scheme and allocation concealment, which could have overestimated the effect of adding hydrocortisone. [21] Baseline characteristics of the two groups in the RCT were not comparable, with a greater proportion of children aged under 2 years and longer duration of shock in the children who did not receive corticosteroids, which could have contributed to the higher mortality in these children. [21] There was also a slight discrepancy between what was reported in the text of the article and what was reported in the table about the number of children receiving intravenous fluids alone who died; the figure reported in the table was 19/50, which gives a slightly different result (9/48 [19%] with hydrocortisone plus intravenous fluids *v* 19/50 [38%] with iv fluids alone; RR 0.49, 95% CI 0.25 to 0.98). The other RCTs [18] [20] did not find the mortality reduction found in the first RCT. [21] The controlled trial had gross imbalance in the number of children in the two groups (7 in the hydrocortisone plus intravenous fluid group *v* 19 in the intravenous fluids alone group). Differences in quality of methods of the trials and improvements in supportive care in the 1990s may account for the inconsistent results.

We found a randomized, placebo-controlled, blinded trial of early corticosteroid therapy in 225 Vietnamese children and young adults aged 5 to 20 years with suspected dengue virus infection and fever for up to 72 hours. [22] Patients with evidence of any dengue-related complications were excluded. The study participants were randomly allocated to receive low-dose or high-dose regimens of oral prednisolone or placebo once-daily for 3 days. The primary objective of this trial was to assess the safety of short-course oral corticosteroid therapy given early during the acute phase of dengue infection. Except for transient hyperglycaemia in 9/75 (12%) cases in the high-dose group and 5/75 (7%) in the low-dose group, use of short course oral prednisolone during the early phase of dengue infection was not associated with significant clinical or virological adverse effects. Specifically, there was no evidence of significantly increased or prolonged viraemia with prednisolone use, nor was

there evidence of a beneficial effect on thrombocytopenia or percentage haemo-concentration. NS1 antigenaemia was relatively prolonged, and many patients remained positive at discharge. Fever clearance times were similar across the treatment arms. Although the study was not powered to assess efficacy, the development of recognised complications of dengue virus infection (such as shock, significant bleeding, and coagulopathy) was not reduced with corticosteroid administration. This well-conducted study provides high-quality evidence that short course corticosteroids do not provide benefit early in the course of dengue virus infection.

OPTION ADDING INTRAVENOUS IMMUNOGLOBULIN TO STANDARD INTRAVENOUS FLUIDS

- For GRADE evaluation of interventions for Dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 15 .
- We found no direct information about the effects of intravenous immunoglubulin (IVIG) in people with dengue haemorrhagic fever or dengue shock syndrome.
- We found one unpublished thesis that found that IVIG may reduce mortality compared with placebo; however, these data have never been published, so the results should be interpreted with caution.

Benefits and harms

Adding intravenous immunoglubulin (IVIG) to standard intravenous fluids versus no IVIG:

We found no systematic reviews but found one RCT (31 Filipino children with secondary dengue infection) comparing high doses of IVIG with no immunoglobulin. [23] Children in both groups (15 in IVIG group and 16 in control) received standard intravenous fluids according to WHO guidelines. The RCT did not report on mortality and only reported on surrogate outcomes. We also found one RCT [24] that did not meet *BMJ Clinical Evidence* inclusion criteria (see Comments).

Symptom severity

Adding intravenous immunoglubulin (IVIG) to standard intravenous fluids versus no IVIG Adding IVIG to standard intravenous fluids may be no more effective at reducing the duration of severe thrombocytopenia, or at increasing platelet counts from the day IVIG treatment is initiated to day seven of hospitalisation, in children with secondary dengue infection who are at risk of developing dengue haemorrhagic fever (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom relief					
[23] RCT	31 Filipino children with secondary dengue infection receiving standard intravenous fluids according to WHO guidelines	**Mean duration of severe thrombocytopenia** 3.1 days with intravenous immunoglobulin (15 children) 2.5 days with no IVIG (16 children)	P = 0.11 The RCT is likely to have been underpowered to detect a clinically important difference.	⟷	Not significant
[23] RCT	31 Filipino children with secondary dengue infection receiving standard intravenous fluids according to WHO guidelines	**Mean increase in platelet counts (x10^3/microlitres) , from day of initiation of IVIG treatment until day 7 of hospitalisation** 54.9 with intravenous immunoglobulin (15 children) 48.0 with no IVIG (16 children)	P = 0.15 The RCT is likely to have been underpowered to detect a clinically important difference.	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [23]

Comment: One unpublished, double blind RCT, conducted in a tertiary university teaching hospital in the Philippines (216 Filipino children, age 6 months to 14 years, 205 with serologically confirmed dengue shock syndrome) compared intravenous immunoglobulin (0.4 g/kg once-daily for 3 days) with placebo (personal communication, Frias MV, 2003). [25] All children received standard intravenous crystalloids as prescribed by WHO guidelines. The RCT found that immunoglobulin significantly reduced mortality compared with placebo (18/108 [17%] with iv immunoglobulin *v* 31/108 [29%] with placebo; RR 0.58, 95% CI 0.35 to 0.97; NNT 8, 95% CI 4 to 102). [25] It found a similar duration of hospital stay between intravenous immunoglobulin and placebo. More children had a rash with intravenous immunoglobulin than with placebo, but the difference was not significant (RR 1.6, 95% CI 0.95 to 2.68). [25]

We found one placebo controlled RCT conducted in the Philippines (27 children; 11 male, 16 female; meeting WHO criteria for dengue haemorrhagic fever with severe thrombocytopenia [platelets 50,000/mm^3 or less]), [24] which compared intravenous anti-D immune globulin 50 microgram/kg (250 IU/kg) with placebo. One 5-year-old girl randomised to the anti-D arm died 48 hours after dosing, which was attributed by the investigator to complications of dengue shock syndrome (DSS), and was unlikely to be associated with the administration of anti-D. The primary focus of the paper was the change in platelet counts.

OPTION ADDING BLOOD COMPONENT TRANSFUSION TO STANDARD INTRAVENOUS FLUIDS

- For GRADE evaluation of interventions for Dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 15 .
- We found no direct information about blood component transfusion in children with dengue haemorrhagic fever or dengue shock syndrome.
- Current consensus is that children with active bleeding should receive blood component transfusion — either packed red blood cells, fresh frozen plasma, or platelet concentrates. The optimal time for commencing transfusion is unclear, and there is much variation in clinical practice.

Benefits and harms

Adding blood component transfusion to standard intravenous fluids:

We found no systematic review or RCTs assessing platelet transfusions in children with dengue haemorrhagic fever or dengue shock syndrome.

Comment: **Clinical guide**
It is widely accepted that children with dengue haemorrhagic fever or dengue shock syndrome with active bleeding should receive blood component transfusion (packed red blood cells, fresh frozen plasma, or platelet concentrates), depending on the degree of bleeding and volume status of the child. Transfusion is associated with serious adverse effects, such as fluid overload, if used injudiciously. The optimal time for commencing transfusion is unclear, and there is much variation in clinical practice. It would be considered unethical to assess blood component transfusion in a placebo-controlled RCT.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Tourniquet test A test performed by inflating the blood pressure cuff to a point midway between systolic and diastolic pressures for 5 minutes. It involves then deflating the cuff, waiting for the skin to return to its normal colour, and then counting the number of petechiae visible in a 2.5 cm square in the ventral surface of the forearm. Twenty or more petechiae in square patch (6.25 cm^2) constitutes a positive tourniquet test.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Adding intravenous immunoglubulin to standard intravenous fluids One RCT found, [24] which did not meet the *BMJ Clinical Evidence* inclusion criteria. Categorisation unchanged (unknown effectiveness).

Adding corticosteroids to standard intravenous fluids One systematic review updated. [17] One study added to Comment section. [22] Categorisation unchanged (unknown effectiveness).

Crystalloids versus colloids One systematic review added. [12] Categorisation unchanged (likely to be beneficial).

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Disclaimer

TABLE 1 **WHO suggested dengue case classification and levels of severity.** [1]

Criteria for dengue with or without warning signs		Criteria for severe dengue
Probable dengue Live in/travel to dengue-endemic areas Fever and 2 of the following criteria: nausea, vomiting; rash; aches and pains; tourniquet test positive; leukopenia; any warning sign. **Laboratory-confirmed dengue** (important when no sign of plasma leakage)	**Warning signs*** Abdominal pain or tenderness; persistent vomiting; clinical fluid accumulation; mucosal bleed; lethargy, restlessness; liver enlargement >2 cm; laboratory: increase in HCT concurrent with rapid decrease in platelet count *(requiring strict observation and medical intervention)	**Severe plasma leakage** Shock (DSS); fluid accumulation with respiratory distress **Severe bleeding** As evaluated by clinician **Severe organ involvement** Liver: AST or ALT >=1000; CNS: impaired consciousness; heart and other

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GRADE **Evaluation of interventions for Dengue haemorrhagic fever or dengue shock syndrome in children.**

Important outcomes					Mortality, Symptom severity				
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of supportive treatments for dengue haemorrhagic fever or dengue shock syndrome in children?									
3 (655) [13] [14] [15]	Symptom severity	Crystalloids versus colloids	4	0	0	–1	0	Moderate	Directness point deducted for small RCTs (may have been underpowered to detect a clinically significant difference in outcomes)
3 (655) [13] [14] [15]	Mortality	Crystalloids versus colloids	4	0	0	–2	0	Low	Directness points deducted for RCT being underpowered to detect difference in outcome (1 event only) and no statistical analysis between groups
2 (89) [17]	Symptom severity	Adding corticosteroids to standard intravenous fluids versus adding placebo or no corticosteroids	4	–3	0	–2	0	Very low	Quality points deducted for sparse data and methodological weaknesses (open label trial with unclear randomisation and allocation concealment); directness points deducted for baseline differences between groups and disparity in numbers of participants in comparator groups
4 (284) [17]	Mortality	Adding corticosteroids to standard intravenous fluids versus adding placebo or no corticosteroids	4	–3	–1	–2	0	Very low	Quality points deducted for methodological weaknesses (open label trial with unclear randomisation and allocation concealment, and disparities in reporting of results in text article and table of results); consistency point deducted for conflicting results; directness points deducted for baseline differences between groups and disparity in numbers of participants in comparator groups
1 (31) [23]	Symptom severity	Adding intravenous immunoglubulin (IVIG) to standard intravenous fluids versus no IVIG	4	–1	0	–2	0	Very low	Quality point deducted for sparse data; directness points deducted for population not having fever or shock and limited outcomes (non-clinical)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.