Dengue haemorrhagic fever or dengue shock syndrome in children

Search date June 2008

Marissa Alejandria

ABSTRACT

INTRODUCTION: Dengue haemorrhagic fever and dengue shock syndrome are major causes of hospital admission and mortality in children. Up to 5% of people with dengue haemorrhagic fever die of the infection, depending on availability of appropriate supportive care. 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 June 2008 (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 13 systematic reviews or RCTs 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 carbazochrome sodium sulfonate, corticosteroids, or intravenous immunoglobulin to standard intravenous fluids; adding recombinant-activated factor VII to blood component transfusion; colloids; crystalloids; and intravenous fluids.

QUESTIONS

INTERVENTIONS

Key points

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

  Dengue haemorrhagic fever is characterised by: a sudden onset of high fever; haemorrhages in the skin, gastrointestinal tract, and mucosa; and low platelet counts. Plasma leakage results in fluid in the abdomen and lungs. It typically occurs in children under 15 years.

  Severe dengue haemorrhagic fever is called dengue shock syndrome.

  Dengue haemorrhagic fever and dengue shock syndrome are major causes of hospital admission and mortality in children. Up to 5% of people with dengue haemorrhagic fever die of the infection, depending on availability of appropriate supportive care.

- Intravenous fluids are the standard treatment to expand plasma volume and are likely to be beneficial, but studies to demonstrate their effectiveness would be unethical.

  Crystalloids seem as effective as colloids in children with moderately severe dengue shock syndrome, although we don't know whether they are beneficial in 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 carbazochrome sodium sulfonate (AC-17), corticosteroids, intravenous immunoglobulin, or recombinant activated factor VII to standard intravenous fluids reduces the risks of shock, pleural effusion, or mortality. We also don't know whether adding recombinant activated factor VII toblood component transfusion reduces the risk of bleeding episodes, shock, or mortality.

DEFINITION

Dengue infection is a mosquito-borne arboviral infection. The spectrum of dengue virus infection ranges from asymptomatic or undifferentiated febrile illness to dengue fever and dengue haemorrhagic fever or dengue shock syndrome. 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. **Dengue fever** is an acute febrile illness whose clinical presentation varies with age. Infants and young children may have an undifferentiated febrile disease with a maculopapular rash. Children aged 15 years or older and adults may have either a mild febrile illness, or the classic incapacitating disease (also called "breakbone fever"), presenting with high fever of sudden onset, and non-specific signs and symptoms of: severe headache; pain behind the eyes; muscle, bone, or joint pains; nausea; vomiting; and rash. **Dengue haemorrhagic fever** is characterised by four criteria: acute onset of high fever; haemorrhagic manifestations evidenced by a positive tourniquet test, skin haemorrhages, mucosal and gastrointestinal tract bleeding; thrombocytopenia; and evidence of plasma leakage manifested by a rise or drop in haematocrit, fluid in the lungs or abdomen, or hypoproteinaemia. Dengue haemorrhagic fever is classified into four grades of severity (see table 1, p 10). [1] Presence of thrombocytopenia and haemoconcentration differentiates dengue haemorrhagic fever grades I and II from dengue fever. Grades III and IV dengue haemorrhagic fever are considered **dengue shock syndrome**. [1] 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 free from dengue because *Aedes* mosquitoes do not survive at high altitudes. Worldwide, an estimated 50–100 million cases of dengue fever, and hundreds of thousands of dengue haemorrhagic fever, occur yearly. [2] 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. [3] [4] 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. [5]

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. *Ae 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. [3] [4] [6] [7] [8]

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 2–7 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. Case fatality ranges from 2.5–5.0%. Once shock sets in, fatality may be as high as 12–44%. [9] 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.

AIMS OF INTERVENTION

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

OUTCOMES

Mortality; recurrence of shock; symptom relief; renal failure; length of hospital stay; time to recovery; time off work; need for blood transfusion; fluid requirements; adverse effects (bleeding, fluid overload, hypersensitivity reactions, and secondary infections). Secondary outcomes include development of shock and development of pleural effusion.

METHODS

Clinical Evidence search and appraisal June 2008. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2008, Embase 1980 to June 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 2 (1966 to date of issue). An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language and containing more than 20 individuals of whom more than 80% were followed up. We may use sensitivity analysis that supports the strength of conclusions when losses to follow-up seem to be significant. Length of follow-up required to include studies was at least from admission until discharge from hospital or occurrence of a main outcome. We did not exclude RCTs described as "open", "open label", or not blinded. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. The author also retrieved additional material through hand searches and personal contact with experts in the field. 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 RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 11).

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

OPTION INTRAVENOUS FLUIDS VERSUS NO TREATMENT*

We found no direct information about whether intravenous fluids are better than no active treatment or no treatment. There is consensus that immediate fluid replacement with crystalloids should be undertaken in a child who has dengue haemorrhagic fever or dengue shock syndrome.

For GRADE evaluation of interventions for dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 11 .

Benefits: **Intravenous fluids versus placebo or no treatment:**
We found no RCTs (see comment below).

Harms: **Intravenous fluids versus placebo or no treatment:**
We found no RCTs.

Comment: It would be considered unethical to compare intravenous fluids against placebo in children with dengue haemorrhagic fever or dengue shock syndrome in a no-treatment trial. There is widespread consensus that intravenous fluid replacement with crystalloids should be universally used in children with dengue haemorrhagic fever or dengue shock syndrome because these conditions lead to an acute increase in vascular permeability that leads to plasma leakage, resulting in increased haematocrit and decreased blood pressure.

OPTION CRYSTALLOIDS VERSUS COLLOIDS

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 dengue shock syndrome (moderate-quality evidence).

Ringer's lactate compared with colloids Ringer's lactate is as effective as Dextran 70 (6%), and 6% hydroxyethyl starch, at reducing the proportion of children with moderately severe dengue shock syndrome who need rescue colloids for initial resuscitation (high-quality evidence).

Dextran compared with starch solutions Dextran 70 (6%) and 6% hydroxyethyl starch are equally effective at reducing the proportion of children with severe dengue shock syndrome who require rescue fluid (moderate-quality evidence).

For GRADE evaluation of interventions for dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 11 .

Benefits: We found no systematic review but found three RCTs (see comment below). [10] [11] [12] The first RCT (50 Vietnamese children aged 5–15 years with dengue shock syndrome) compared four intra-

venous fluid regimens for acute resuscitation: two crystalloid regimens (sodium chloride or Ringer's lactate solution, 25 children) and two colloid regimens (dextran 70 or gelafundin, 25 children). [10] 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. All children recovered with fluid resuscitation alone (no deaths in any group). The RCT found no significant difference among groups in recurrence of shock (median: 1 episode in each group; P = 0.46), or 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 mm Hg. The RCT also found no significant difference among groups in median duration in shock (mean: 1.5 hours with sodium chloride *v* 5.0 hours with Ringer's *v* 2.8 hours with dextran 70 *v* 7.0 hours with gelafundin; P = 0.36). [10] The second RCT (222 Vietnamese children, aged 1–15 years with dengue shock syndrome) also compared four intravenous fluid regimens for acute resuscitation: two crystalloid regimens (sodium chloride or Ringer's lactate solution, 111 children) and two colloid regimens (dextran 70 or gelafundin, 111 children). [11] 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. All children recovered with fluid resuscitation (no deaths in any group). The RCT found no significant difference in the proportion of children who had recurrence of shock between crystalloids and colloids (24/90 [27%] with colloids *v* 20/81 [25%] with crystalloids; RR 1.02, 95% CI 0.56 to 1.85). It also found no significant difference among groups in the total volume of fluid infused until full recovery from shock (P = 0.95), or in the proportion of children who required further infusions after the first hour (17/56 [30%] with sodium chloride *v* 20/55 [36%] with Ringer's *v* 17/55 [31%] with dextran 70 *v* 15/56 [27%] with gelafundin; P = 0.75). [11] 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 greater than 10 mm Hg and up to 20 mm Hg; severe shock: pulse pressure 10 mm Hg or less). [12] The RCT's primary outcome measure was the need for supplemental intervention with rescue colloid at any time after the infusion of the study fluid. It compared Ringer's lactate (a crystalloid) versus either 6% dextran 70 (a colloid) or 6% hydroxyethyl starch (a colloid) in 383 children with moderately severe dengue shock syndrome. Each child received 15 mL/kg body weight of the allocated fluid within 1 hour, followed by 10 mL/kg over the second hour. The RCT found no significant difference between the groups in the proportion of children who needed rescue fluids (40/128 [31%] with Ringer's lactate *v* 31/126 [25%] with dextran *v* 43/129 [33%] with starch; P = 0.28). One child in the starch group died (less than 0.2% mortality overall in the RCT). In another 129 Vietnamese children with severe dengue shock syndrome, it compared the two colloids (6% dextran 70 and 6% hydroxyethyl starch). It did not compare Ringer's lactate in this group. In children with moderately severe shock, the RCT 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 to 1.47; P = 0.65; absolute numbers not reported). [12] In children with severe shock, it found no significant difference between dextran and starch in the proportion of children who required rescue colloid (28/67 [42%] with dextran *v* 23/62 [37%] with starch; RR 1.13, 95% CI 0.74 to 1.74; P = 0.59). [12] In a combined analysis, there was no significant difference in the risk of requiring rescue colloids between children given dextran compared with starch (59/193 [31%] with dextran *v* 66/191 [35%] with starch; RR 0.88, 95% CI 0.66 to 1.17; P = 0.38). [12]

Harms:

The first RCT found no adverse effects attributable to colloids or crystalloids, but it may have been underpowered to detect clinically important adverse effects. [10] In the second RCT, six children developed fever and chills after completing colloid treatment. [11] Two children receiving colloids had recurrence of shock, which responded to treatment with crystalloids. One child in the gelafundin group had severe epistaxis requiring transfusion, and another child in the dextran group developed a large haematoma at a site of minor trauma. A total of 35 children equally distributed among the four groups required diuretic treatment for 1 or 2 days after recovery from shock. [11] The third RCT found no significant difference in any adverse effects of the different fluids used, except in the incidence of allergic type reactions. [12] Overall, 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 one child in the starch group developed an urticarial rash without fever at the end of the infusion (in moderately severe shock: 9/126 [7%] with dextran *v* 1/129 [1%] with starch *v* 0/128 [0%] with Ringer's; P less than 0.001; in severe shock: 6/67 [9%] with dextran *v* 0/62 [0%] with starch; P = 0.03). [12] All children responded to symptomatic treatment alone, but one child died. 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. [12]

Drug safety alert:
June 2013, hydroxyethyl starch 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/)

Comment: The first two RCTs comparing crystalloids versus colloids are likely to have been underpowered to detect a clinically important difference in outcomes. [10] [11] 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. [13] 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. [12] In children with severe shock, the effectiveness of Ringer's lactate remains untested in a large RCT.

OPTION ADDING CARBAZOCHROME SODIUM SULFONATE (AC-17) TO STANDARD INTRAVENOUS FLUIDS

Symptom severity
Compared with placebo We don't know whether adding carbazochrome sodium sulfonate to standard intravenous fluids is more effective at reducing pleural effusions or the development of shock in children with dengue haemorrhagic fever or dengue shock syndrome. Adding carbazochrome sodium sulfonate to standard intravenous fluids may be no more effective at reducing the duration of hospital stay in children with dengue haemorrhagic fever or dengue shock syndrome. (very low-quality evidence).

For GRADE evaluation of interventions for dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 11 .

Benefits: We found no systematic review but found two RCTs. [14] [15] The first RCT (95 Thai children aged 1.8–14.8 years with dengue haemorrhagic fever/dengue shock syndrome confirmed by serological examinations and/or viral cultures, admitted before the onset of shock, receiving standard iv fluids) compared adding carbazochrome sodium sulfonate (AC-17) versus adding B vitamins as placebo. [14] Carbazochrome sodium sulfonate was given as an initial bolus injection followed by a continuous drip infusion for 3 days. The RCT found no significant difference in the development of shock during the course of treatment between adding carbazochrome sodium sulfonate to intravenous fluids and adding placebo to intravenous fluids (4/45 [9%] with carbazochrome sodium sulfonate *v* 3/50 [6%] with placebo; P = 0.44). It also found no significant difference between groups in the mean duration of hospital stay (mean: 4 days with carbazochrome sodium sulfonate *v* 4 days with placebo; reported as not significant, P value not reported) and in the overall development of pleural effusion (15/45 [33%] with carbazochrome sodium sulfonate *v* 15/50 [30%] with placebo; P = 0.89). [14] The RCT found no significant difference between groups in pleural effusion occurring on day 1, 2, or 3 after admission (day 1: 20% with carbazochrome sodium sulfonate *v* 14% with placebo; day 2: 31% with carbazochrome sodium sulfonate *v* 28% with placebo; day 3: 20% with carbazochrome sodium sulfonate*v* 14% with placebo; reported as not significant, P values not reported). [14] The second RCT (77 Indonesian children aged 6 months to 12 years with serologically confirmed grade II dengue haemorrhagic fever, receiving standard iv fluids; see comment below) compared adding carbazochrome sodium sulfonate versus adding 0.9% sodium chloride as placebo. [15] The RCT found no significant difference between groups in the development of pleural effusion on the first day after admission (13/37 [35%] with carbazochrome sodium sulfonate *v* 21/39 [54%] with placebo; P less than 0.20), but found that adding carbazochrome sodium sulfonate significantly decreased the development of pleural effusion compared with intravenous fluids alone on the second day after admission (8/38 [21%] with carbazochrome sodium sulfonate *v* 19/36 [53%] with placebo; P less than 0.005) and on the third day after admission (5/37 [14%] with carbazochrome sodium sulfonate *v* 16/38 [42%] with placebo; P less than 0.01). [15] The analysis was not by intention to treat.

Harms: In the first RCT the occurrence of bleeding during treatment was similar between the carbazochrome sodium sulfonate and placebo groups (2/45 [2%] children with carbazochrome sodium sulfonate *v* 3/50 [6%] children with placebo). [14] All bleeding manifestations were mild; four children had epistaxis that needed local packing and one child had blood-stained vomitus. None of the children needed a blood transfusion. The second RCT did not report on adverse effects. [15]

Comment: Neither RCT reported mortality as a primary outcome. [14] [15] Only intermediate outcomes, such as the development of shock and pleural effusion as a marker of plasma leakage, were reported.

The second RCT may have had methodological flaws, which could have overestimated the treatment effect. [15] It did not report the randomisation scheme and allocation concealment, how the identity of the experimental drug and the placebo were masked from the healthcare providers, or the baseline comparability of the two groups in terms of age and duration of illness prior to treatment. [15]

OPTION ADDING CORTICOSTEROIDS TO STANDARD INTRAVENOUS FLUIDS

Symptom severity

Compared with placebo Adding corticosteroids to standard intravenous fluids may be no more effective at reducing serious complications, such as pulmonary haemorrhage, convulsions, or the need for blood transfusions or mean hospital stay, in childen with serologically confirmed dengue shock syndrome (very-low quality evidence).

Mortality

Compared with placebo Adding corticosteroids to standard intravenous fluids may be no more effective at reducing mortality in childen with serologically confirmed dengue shock syndrome (very low-quality evidence).

For GRADE evaluation of interventions for dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 11 .

Benefits: We found one systematic review (search date 2006, 4 RCTs, 284 children) comparing corticosteroids versus no treatment in children with serologically confirmed dengue shock syndrome receiving intravenous fluids. [16] Two of the trials identified by the review were conducted in Thailand, one in Indonesia, and one in Burma. The review found that corticosteroids did not significantly reduce mortality or the need for blood transfusions (4 RCTs, 284 children, mortality: 21/134 [16%] with corticosteroids *v* 32/150 [21%] with no corticosteroids; RR 0.68, 95% CI 0.42 to 1.11; blood transfusions: 2 RCTs, 89 children, 11/39 [28%] with corticosteroids *v* 12/50 [24%] with no corticosteroids; RR 1.08, 95% CI 0.52 to 2.24). In one RCT identified by the review (63 children) corticosteroids did not significantly decrease the number of serious complications (pulmonary haemorrhage: 1/32 [3%] with corticosteroids *v* 1/31[3%] with no corticosteroids; RR 0.97 95% CI 0.06 to 14.82; convulsions: 3/32 with corticosteroids *v* 0/31 with placebo, RR 6.79, 95% CI 0.36 to 126.24; proportion of children who needed blood transfusion: 11/32 [34%] with methylprednisolone *v* 8/31 [26%] with placebo; RR 1.33, 95% CI 0.62 to 2.86; mean hospital stay: 7.3 days with methylprednisolone *v* 6.2 days with placebo; RR +1.10, 95% CI –1.83 to +4.03; P greater than 0.2). [17]

Harms: The systematic review did not assess adverse effects. [16] In the first RCT identified by the review, the frequency of episodes of infection (pneumonia, bacteraemia) and pulmonary haemorrhage were similar with methylprednisolone compared with placebo. [17] Three children taking methylprednisolone had convulsions. 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 two groups. [17] The other two RCTs gave no information on adverse effects. [18] [19] The fourth clinical trial found that, in people receiving hydrocortisone, there were higher rates of infection of the cutdown site (2/7 [28%] with hydrocortisone *v* 0/19 [0%] with intravenous fluids alone), gastrointestinal bleeding (6/7 [86%] with hydrocortisone *v* 7/19 [37%] with intravenous fluids alone), and bleeding from the cutdown site (4/7 [57%] with hydrocortisone *v* 8/19 [42%] with intravenous fluids alone (significance not assessed for any outcome). [20]

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. [19] 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. [19] 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 [17] [18] did not find the mortality reduction found in the first RCT. [19] The controlled trial had gross imbalance in the number of children in the 2 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.

OPTION ADDING INTRAVENOUS IMMUNOGLOBULIN TO STANDARD INTRAVENOUS FLUIDS

Symptom severity

Intravanous immunoglubulin (IVIG) compared with no IVIG Adding IVIG to standard intravenous fluids is no more effective at reducing the duration of thrombocytopenia, or at increasing platelet counts from the day IVIG treatment is initiated to day 7 of hospitalisation, in children with secondary dengue infection who are at risk of developing dengue haemorrhagic fever (moderate-quality evidence).

Mortality
Compared with adding placebo Adding IVIG to standard intravenous fluids is more effective at reducing mortality in children with serologically confirmed dengue shock syndrome (high-quality evidence).

Note
We found no direct information about the effects of IVIG in people with dengue haemorrhagic fever or dengue shock syndrome.

For GRADE evaluation of interventions for dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 11 .

Benefits: We found no systematic review but found one RCT (31 Filipino children with secondary dengue infection) comparing high doses (0.4 g/kg/day for 3 days) of intravenous immunoglobulin (IVIG) versus no immunoglobulin. [21] Children in both groups (15 in IVIG group and 16 in control) received standard intravenous fluids according to WHO guidelines. The RCT found no significant difference in the duration of severe thrombocytopenia (mean days of severe thrombocytopenia: 3.1 days with IVIG *v* 2.5 days with no IVIG; P = 0.11) or in an increase in platelet counts from the day of initiation of IVIG treatment until day 7 of hospitalisation (mean platelet counts x 10^3/microlitres: 54.9 with IVIG *v* 48.0 with no IVIG; P = 0.147). The RCT is likely to have been underpowered to detect a clinically important difference. The RCT did not report on mortality but only reported surrogate outcomes. [21]

Harms: The RCT reported no adverse effects during or after IVIG treatment. The time for platelet counts to return to normal was not shortened with IVIG. [21]

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) versus placebo (personal communication, Frias MV, 2003). [22] 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). [22] 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). [22]

OPTION ADDING BLOOD COMPONENT TRANSFUSION TO STANDARD INTRAVENOUS FLUIDS

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.

For GRADE evaluation of interventions for dengue haemorrhagic fever or dengue shock syndrome in children, see table, p 11 .

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

Harms: We found no RCTs.

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.

OPTION ADDING RECOMBINANT-ACTIVATED FACTOR VII TO BLOOD COMPONENT TRANSFUSION

Symptom severity

Compared with placebo Adding recombinant-activated factor VII to blood component transfusion is no more effective at reducing the incidence of partially controlled or uncontrolled bleeding or at reducing the need for platelets, packed red blood cells, and frozen fresh plasma infusions in children with serologically confirmed dengue haemorrhagic fever (moderate-quality evidence).

For GRADE evaluaton of interventions for dengue haemorrhagic fever or dengue shock syndrome in children, **see table, p 11 .**

Benefits: We found one RCT (25 Thai and Filipino children aged less than 18 years with serologically confirmed dengue haemorrhagic fever) comparing recombinant activated factor VII (rFVIIa) given by intravenous injection at 100 microgram/kg body weight versus placebo in children with active bleeding receiving blood component transfusion. [23] If the bleeding was not effectively controlled, a second dose (100 microgram/kg) of recombinant factor VII was given 30 minutes after the first dose. Blood components were transfused any time after the first dose of trial medication, depending on the clinical status of the child as assessed by the investigators. The children also received supportive treatment, airway management, fluid and electrolyte infusions, and appropriate antibiotics as deemed necessary. At two hours and at 24 hours after blood infusion, the addition of rFVIIa did not significantly reduce the incidence of partially controlled or uncontrolled bleeding compared with placebo (bleeding at 2 hours after infusion 4/16 [25%] with rFVIIa *v* 5/9 [56%] with placebo; RR 0.45, 95% CI 0.16 to 1.26; bleeding at 24 hours after infusion 5/16 [31%] with rFVIIa *v* 3/9 [33%] with placebo, RR 0.94, 95% CI 0.29 to 3.04). At 24 hours after blood transfusion, the addition of rFVIIa did not significantly reduce the need for platelets, red blood cells, or fresh frozen plasma infusions compared with placebo (platelet infusion: 1/16 [6%] with rFVIIa *v* 3/9 [33%] with placebo; RR 0.19, 95% CI 0.02 to 1.55; packed red blood cells infusions 5/16 [31%] with rFVIIa *v* 3/9 [33%] with placebo; RR 0.94, 95% CI 0.29 to 3.04; fresh frozen plasma infusions 4/16 [25%] with rFVIIa *v* 2/9 [22%] with placebo; RR 1.13, 95% CI 0.25 to 4.98).

Harms: In the RCT no clinical evidence of thromboembolic complications was observed in either group. [23]

Comment: The RCT is likely to have been underpowered to detect a clinically important difference between groups.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

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 immunoglobulin to standard intravenous fluids: One RCT added. [21] The RCT found insufficient evidence in assessing the addition of intravenous immunoglobulin to standard intravenous fluids in children with secondary dengue infection. Categorisation unchanged (Unknown effectiveness).

REFERENCES

1. World Health Organization. Dengue hemorrhagic fever: diagnosis, treatment, prevention and control. Geneva: WHO 1997.
2. Pinheiro FP, Corber SJ. Global situation of dengue and dengue haemorrhagic fever, and its emergence in the Americas. *World Health Stat Q* 1997;50:161–168.[PubMed]
3. Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev* 1998;11:480–494.[PubMed]
4. Guzman MG, Kouri G. Dengue: an update. *Lancet Infect Dis* 2002;2:33–42.[PubMed]
5. Githeko AK, Lindsay SW, Confalonieri UE, et al. Climate change and vector-borne diseases: a regional analysis. *Bull World Health Organ* 2000;78:1136–1147.[PubMed]
6. Cardosa MJ. Dengue haemorrhagic fever: questions of pathogenesis. *Curr Opin Infect Dis* 2000;13:471–475.[PubMed]
7. Morens DM. Antibody-dependent enhancement of infection and the pathogenesis of viral disease. *Clin Infect Dis* 1994;19:500–512.[PubMed]
8. Vaughn DW, Green S, Kalayanarooj S, et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. *J Infect Dis* 2000;181:2–9.[PubMed]
9. Rigau-Perez JG, Clark GG, Gubler DJ, et al. Dengue and dengue hemorrhagic fever. *Lancet* 1998;352:971–977.[PubMed]
10. Dung NM, Day NPJ, Tam DTH, et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. *Clin Infect Dis* 1999;29:787–794.[PubMed]
11. Ngo NT, Cao XT, Kneen R, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis* 2001;32:204–213.[PubMed]
12. Wills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005;353:877–889.[PubMed]
13. Halstead SB, O'Rourke EJ. Editorial response: resuscitation of patients with dengue hemorrhagic fever/dengue shock syndrome. *Clin Infect Dis* 1999;29:795–796.[PubMed]
14. Tassniyom S, Vasanawathana S, Dhiensiri T, et al. Failure of carbazochrome sodium sulfonate (AC-17) to prevent dengue vascular permeability or shock: a randomized, controlled trial. *J Pediatr* 1997;131:525–528.[PubMed]
15. Funahara Y, Sumarmo, Shirahata A, et al. Protection against marked plasma leakage in dengue haemorrhagic fever by infusion of carbazochrome sodium sulfonate (AC-17). *Southeast Asian J Trop Med Public Health* 1987;18:356–361.[PubMed]

16. Panpanich R, Sornchai P, Kanjanaratanakorn K. Corticosteroids for treating dengue shock syndrome. In: The Cochrane Library, Issue 2, 2008. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.
17. Tassniyom S, Vasanawathana S, Chirawatkul A, et al. Failure of high-dose methylprednisolone in established dengue shock syndrome: a placebo-controlled, double-blind study. *Pediatrics* 1993;92:111–115.[PubMed]
18. Sumarmo, Talogo W, Asrin A, et al. Failure of hydrocortisone to affect outcome in dengue shock syndrome. *Pediatrics* 1982;69:45–49.[PubMed]
19. Min M, Tin U, Aye M, et al. Hydrocortisone in the management of dengue shock syndrome. *Southeast Asian J Trop Med Public Health* 1975;6:573–579.[PubMed]
20. Pongpanich B, Bhanchet P, Phanichyakarn P, et al. Studies on dengue hemorrhagic fever. Clinical study: an evaluation of steroids as a treatment. *J Med Assoc Thai* 1973;56:6–14.[PubMed]
21. Dimaano EM, Saito M, Honda S, et al. Lack of efficacy of high-dose intravenous immunoglobulin treatment of severe thrombocytopenia in patients with secondary dengue virus infection. *Am J Trop Med Hygiene* 2007;77:1135–1138.
22. Frias MV. The use of intravenous immunoglobulin in dengue shock syndrome: a randomized double-blind placebo-controlled trial [dissertation]. Manila, The Philippines: University of the Philippines College of Medicine 1999.
23. Chuansumrit A, Wangruangsatid S, Lektrakul Y, et al. Control of bleeding in children with Dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind, placebo-controlled study. *Blood Coag Fibrinolysis* 2005;16:549–555.
24. Wills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005;353:877–889.[PubMed]

Marissa M Alejandria
Associate Professor
Section of Infectious Diseases
Departments of Medicine and Clinical Epidemiology College of Medicine, University of the Philippines Manila
The Philippines

Competing interests: MA declares that she has no competing interests.

Disclaimer

TABLE 1 **WHO grading of severity of dengue haemorrhagic fever.** [1]

Grade	Description
Grade I	Fever accompanied by non-specific constitutional symptoms; the only haemorrhagic manifestation is a positive tourniquet test, easy bruising, or both
Grade II	Spontaneous bleeding in addition to the manifestations of Grade I, usually in the form of skin and other haemorrhages
Grade III	Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin, and restlessness
Grade IV	Profound shock with undetectable blood pressure or pulse

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TABLE GRADE evaluation of interventions for dengue fever or dengue shock sydrome in children

Important outcomes	Symptom severity, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
What are the effects of supportive treatments for dengue haemorrhagic fever or dengue shock syndrome in children?									
3 (655) [10] [11] [24]	Symptom severity	Crystalloids *v* colloids	4	0	0	–1	0	Moderate	Directness point deducted for delayed measurement of outcome
1(383) [24]	Symptom severity	Ringer's lactate *v* colloids (moderately severe shock)	4	0	0	0	0	High	
1(129) [24]	Symptom severity	Dextran *v* starch solutions (severe shock)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (172) [15] [14]	Symptom severity	Carbazochrome *v* placebo	4	–3	–1	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, no intention-to-treat analysis, and methodological flaws. Consistency point deducted for conflicting results. Directness point deducted for baseline differences of population (uncertainty about duration of illness or age of participants)
at least 2 RCTs (at least 89 children) [16]	Symptom severity	Corticosteroids *v* no treat-ment	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 partici-pants in comparator groups
4 (284) [16]	Mortality	Corticosteroids *v* placebo or no treatment	4	–3	–1	–2	0	Very low	Quality points deducted for methodological weakness-es (open label trial with unclear randomisation and allocation concealment, and disparities in reporting of results in text article and table of results). Consis-tency point deducted for conflicting results. Directness points deducted for baseline differences between groups and disparity in numbers of participants in comparator groups
1 (31) [21]	Symptom severity	Intravenous immunoglobulin (IVIG) *v* no IVIG	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (216) [22]	Mortality	Intravenous immunoglobulin *v* placebo	4	0	0	0	0	High	
1 (25) [23]	Symptom severity	Recombinant activated factor VII (rFVIIa)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Type of evidence: 4 = RCT; 2 = Observational
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio