Supplementary table 1. Characteristics of included studies

Study	Study design	Setting	Number of children	Intervention	Control	Co-interventions
Maitland 2011 [8]	RCT	Kenya Tanzania Uganda	3,141	20 to 40 mls/kg of 5% albumin or 0.9% saline over the first hour, followed by maintenance fluids	Intravenous maintenance fluids alone (2.5 to 4.0 mls/kg/hr)	Antibiotics, antimalarials, antipyretics, anticonvulant drugs, hypoglycemia treatment and blood transfusion
Santhanam 2008 [14]	RCT	India	147	20 to 40 mls/kg of Ringers lactate over 15 minutes followed by dopamine if therapeutic goal not achieved after 15 minutes	20 mls/kg over 20 minutes up to 60 mls/kg over 1 hour followed by dopamine if therapeutic goal not achieved at 1 hour	Antibiotics, anticonvulsant drugs, intubation, ventilation support, treatment of hypoglycemia, hypocalcemia and asthma
Carcillo 2009 [15]	Prospective cohort	USA	187 (a subgroup)	Received PALS/APLS - recommended resuscitation (20 to 40 mls/kg) or recovered quickly	Did not receive PALS/APLS - recommended resuscitation	Inotropic therapy
Han 2003 [17]	Retrospective records review	USA	91	Received PALS/APLS recommended resuscitation (>60 mls/kg normal saline) or recovered	Did not receive PALS/APLS recommended resuscitation	Antibiotics, inotropic/vasopressor support and hydrocortisone therapy
Carcillo 1991 [16]	Prospective cohort	USA	34	> 40 mls/kg total fluids (normal saline, Ringers lactate, 5% albumin or blood products)	<20 mls/kg total fluids or 20 to 40 mls/kg total fluids	Antibiotics, vasopressor and/or inotropic support and assisted ventilation
Oliveira 2008 [18]	Retrospective records review	Brazil	90	>40 mls/kg in the first hour (colloids, crystalloids, or packed red blood cells)	<20 mls/kg in the first hour	Antibiotics and inotropic support

Supplementary table 1. Characteristics of included studies (continued)

Study	Study design	Definition of severe febrile illness	Definition of circulatory impairment	Our classification	Overall mortality
Maitland 2011 [8]	Randomized controlled trial	Febrile illness with impaired consciousness and/or respiratory distress	One or more of: capillary refilling time ≥3 secs, severe tachycardia, temperature gradient or weak pulse	Some circulatory impairment (IC) (Subgroup of severely impaired circulation (SIC))	9.5% (42%)
Santhanam 2008 [14]	Randomized controlled trial	Children with septic shock	Tachycardia with signs of decreased perfusion including: decreased peripheral pulses compared with central pulses, altered alertness, flash capillary refill or capillary refill >2 secs, mottled or cool extremities, or decreased urine output	Some circulatory impairment (IC)	18%
Carcillo 2009 [15]	Prospective cohort	Infants and children with trauma and non-trauma diagnoses (including septic shock)	Prolonged capillary refill time (>3 seconds or mottled extremities) and/or hypotension (systolic blood pressure less than the fifth percentile for age according to PALS/APLS criteria)	Some circulatory impairment (IC)	12.5%
Han 2003 [17]	Retrospective records review	Infants and children with septic shock	Decreased perfusion, including decreased mental status, prolonged capillary refill time (>3 seconds), diminished peripheral pulses, or mottled extremities and hypotension (systolic blood pressure less than the fifth percentile for age)	Severe circulatory impairment (SIC)	29%
Carcillo 1991 [16]	Prospective cohort	Children with septic shock	Blood pressure <2 SDs below the mean for age, combined with three of the following four criteria for decreased perfusion: decreased peripheral pulses; mottled or cool extremities; tachycardia (heart rate >180 bpm for patients <5 years of age; and >160 bpm for patients ≥5 years of age); or urine output <1 mls/kg per hour (or <20 mls/hr in children weighing >20 kg)	Severe circulatory impairment (SIC)	51%
Oliveira 2008 [18]	Retrospective records review	Children with sepsis and septic shock	Decreased perfusion (decreased peripheral pulses, mottled or cool extremities, capillary refill time <1 second or >3 seconds), hypotension (systolic blood	Severe circulatory impairment (SIC)	47%

	pressure less than the fifth percentile for age, using the PALS formula), altered mental status, or oliguria (<1 mls/kg per hour)

bpm: Beats per minute; PALS: Pediatric Advanced Life Support; APLS: Advanced Pediatric Life Support; SD: Standard deviation;
IC: Severe febrile illness and any sign of impaired circulation;
SIC: Severe febrile illness and signs of severely impaired circulation;
IC but not SIC: Severe febrile illness and impaired circulation but not severely impaired circulation

Supplementary table 2. Summary of findings and quality of evidence

Bolus fluids compared to maintenance fluids alone in children with severe febrile illness and severely impaired circulation (SIC)

Patient or population: Children with severe febrile illness and severely impaired circulation
Settings: Hospitals (East Africa, USA, Brazil)
Intervention: Bolus fluid resuscitation (albumin or normal saline) followed by maintenance fluids
Comparison: Maintenance fluids alone[1]

Outcomes	Study design	Assumed risk **Maintenance fluids alone**	Corresponding risk (95% CI) **Bolus followed by maintenance fluids**	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Mortality	RCT	**20 per 100**	**48 per 100** (17 to 138)	**RR 2.40** (0.84 to 6.88)	65 (1 study)	⊕⊕⊖⊖ **Low**[2,3,4,5]	Maitland 2011 [8]
	Prospective cohort	**60 per 100**	**11 per 100** (2 to 73)	**RR 0.19** (0.03 to 1.21)	34 (1 study)	⊕⊖⊖⊖ **Very low**[6,7]	Carcillo 1991 [16]
	Retrospective cohort	**73 per 100**	**33 per 100** (NA)	**RR 0.45** (NA)	90 (1 study)	⊕⊖⊖⊖ **Very low**[8,9,10]	Oliveira 2008 [18]
	Retrospective cohort	**38 per 100**	**8 per 100** (2 to 30)	**RR 0.20** (0.05 to 0.78)	91 (1 study)	⊕⊖⊖⊖ **Very low**[11,12]	Han 2003 [17]

The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] All children received antibiotics, maintenance fluids and supportive care according to standard guidelines;
[2] This data represents a sub-group of patients from the large FEAST trial in East Africa [8]. These 65 patients had signs of a febrile illness and fulfilled the ETAT definition of shock;
[3] No serious risk of bias: Randomization and allocation concealment were adequate to reduce the risk of selection bias. Study staff were unblinded to the intervention;
[4] Downgraded by 1 for serious indirectness: Children with severe hypotension were excluded;
[5] Downgraded by 1 for serious imprecision: This subgroup of patients from the FEAST trial is severely underpowered to detect clinically important differences between the interventions;
[6] This study retrospectively examined health records of children with septic shock admitted to pediatric intensive care in Washington USA, and compares three groups receiving >40 mls/kg in the first hour, 20-40 mls/kg, and <20 mls/kg. Here we present > 40mls/ kg vs <40 mls/kg;
[7] Downgraded by 1 for serious imprecision: This trial is severely underpowered to confidently detect clinically important differences;
[8] This study retrospectively compared mortality in children with septic shock who received >40 mls/kg during the first hour of treatment with those receiving <20 mls/kg;
[9] Downgraded by 1 for serious indirectness: This study was conducted in a pediatric intensive care unit in Sao Paulo, Brazil, and over 80% had a severe pre-existing chronic disease such as malignancy;
[10] Downgraded by 1 for serious imprecision: The data were only presented as percentages and 95% CI could not be calculated. A P-value of <0.05 is stated by the authors;

[11] This study retrospectively examined the health records of children presenting with septic shock in the USA, requiring transport to a children hospital;
[12] Downgraded by 1 for risk of bias: This study compares 'appropriate fluid therapy' in line with ACCM/PALS guidelines with 'inadequate fluid therapy'. The 'appropriate therapy' group includes those where fluid was given in line with ACCM/PALS guidelines AND those who recovered quickly irrespective of how much fluid was given.

Supplementary table 3. Bolus fluids compared to maintenance fluids alone in children with severe febrile illness and severely impaired circulation (SIC)

Quality assessment						Summary of findings				
Bolus fluids compared to maintenance fluids alone in children with severe febrile illness and any sign of impaired circulation (IC)										
						Number of patients		Effect size		
Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**No bolus**	**Bolus**	**Relative risk (95% CI)**	**Absolute effect**	**Quality**
Outcome: Mortality										
Randomised control trial‡ [8]	No serious risk of bias[1]	No serious inconsistency	Serious[2]	Serious[3]	Undetected	3/15 (20%)	24/50 (48%)	RR 2.40 (0.84 to 6.88)	28 more per 100 (from 3 fewer to 100 more)	⨁⨁⊖⊖ Low
Prospective cohort study† [16]	Serious[4]	No serious inconsistency	No serious indirectness	Serious[5]	Undetected	15/25 (60%)	1/9 (11%)	RR 0.19 (0.03 to 1.21)	49 fewer per 100 (from 58 fewer to 13 more)	⨁⊖⊖⊖ Very low
Retrospective cohort study¶ [18]	Serious[6]	No serious inconsistency	Serious[7]	Serious[8]	Undetected	73%††	33%††	RR 0.45 95% CI not estimatable	Not estimatable	⨁⊖⊖⊖ Very low
Retrospective cohort study‡‡ [17]	Serious[9]	No serious inconsistency	No serious indirectness	Serious[10]	Undetected	24/64 (37.5%)	2/27 (7.4%)	RR 0.20 (0.05 to 0.78)	30 fewer per 100 (from 8 fewer to 36 fewer)	⨁⊖⊖⊖ Very low

CI: Confidence interval;

‡This data represents a sub-group of patients from the large FEAST trial in East Africa [8]. These 65 patients had signs of a febrile illness and fulfilled the ETAT definition of shock. The intervention comprised bolus fluid resuscitation (40 mls/kg albumin or normal saline) followed by maintenance fluids (2.5 to 4.0 mls/kg). The control (no bolus) group received maintenance fluids alone (2.5 to 4.0 mls/kg);

[1]No serious risk of bias: Randomization and allocation concealment were adequate to reduce the risk of selection bias. Study staff were unblinded to the intervention;

[2]Downgraded by 1 for serious indirectness: Children with severe hypotension were excluded;

[3]Downgraded by 1 for serious imprecision: This subgroup of patients from the FEAST trial is severely underpowered to detect clinically important differences between the interventions;

†This study retrospectively examined health records of children with septic shock admitted to pediatric intensive care in Washington USA, and compares three groups receiving >40 mls/kg in the first hour, 20-40 mls/kg, and <20 mls/kg. Here we present > 40mls/ kg vs <40 mls/kg;

[4]Adequate baseline characteristics were not presented;

[5]Downgraded by 1 for serious imprecision: This trial is severely underpowered to confidently detect clinically important differences;

¶This study retrospectively compared mortality in children with septic shock who received >40 mls/kg during the first hour of treatment with those receiving <20 mls/kg;

[6]Downgraded by 1 for risk of bias: The study compared survivors and non-survivors. The survivors were more likely to have had higher fluid volumes and were also significantly younger;

[7]Downgraded by 1 for serious indirectness: This study was conducted in a pediatric intensive care unit in Sao Paulo, Brazil, and over 80% had a severe pre-existing chronic disease such as malignancy;

[8]Downgraded by 1 for serious imprecision: The data were only presented as percentages and 95% CI could not be calculated. A P-value of <0.05 is stated by the authors;

†† A total of 45 children with septic shock died – however the number of deaths in the treatment groups was unclear (reported as 33%, >40 mls/kg and 73%, <20 mls/kg during the first hour of treatment);

‡‡ This study retrospectively examined the health records of children presenting with septic shock in the USA, requiring transport to a children hospital;

[9]Downgraded by 1 for risk of bias: This study compares 'appropriate fluid therapy' in line with ACCM/PALS guidelines with 'inadequate fluid therapy'. The 'appropriate therapy' group includes those where fluid was given in line with ACCM/PALS guidelines AND those who recovered quickly irrespective of how much fluid was given;

[10]Downgraded by 1 for serious imprecision: Small sample size (N=91 patients). Small number of events (N=26 deaths).

Patient or population: Children with severe febrile illness and some circulatory impairment
Settings: Hospitals (East Africa, India, USA)
Intervention: Bolus fluid resuscitation (albumin or normal saline) followed by maintenance fluids
Comparison: Maintenance fluids alone[1]

Outcomes	Study design	Assumed risk **Maintenance fluids alone**	Corresponding risk (95% CI) **Bolus followed by maintenance fluids**	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Mortality at 48 hours	RCT	**73 per 1000**	**106 per 1000** (82 to 135)	**RR 1.45** (1.13 to 1.86)	3,141 (1 study)	⊕⊕⊕⊕ **High**[2,3,4,5,6]	Maitland 2011 [8]
Mortality at 72 hours	RCT	**18 per 100**	**18 per 100** (9 to 35)	**RR 0.99** (0.49 to 1.98)	147 (1 study)	⊕⊕⊖⊖ **Low**[7,8,9]	Santhanam 2008 [14]
Mortality	Prospective cohort	**14 per 100**	**12 per 100** (5 to 27)	**RR 0.84** (0.37 to 1.91)	187 (1 study)	⊕⊖⊖⊖ **Very low**[10,11]	Carcillo 2009 [15]
Mortality at 4 weeks	RCT	**87 per 1000**	**121 per 1000** (97 to 152)	**RR 1.39** (1.11 to 1.74)	3,141 (1 study)	⊕⊕⊕⊕ **High**[4,5,6]	Maitland 2011 [8]
Neurologic sequelae at 4 weeks	RCT	**20 per 1000**	**21 per 1000** (12 to 35)	**RR 1.03** (0.61 to 1.75)	2,983 (1 study)	⊕⊕⊕⊖ **Moderate**[4,5,12]	Maitland 2011 [8]
Pulmonary edema, increased intracranial pressure	RCT	**16 per 1000**	**24 per 1000** (14 to 41)	**RR 1.46** (0.85 to 2.53)	3,141 (1 study)	⊕⊕⊕⊖ **Moderate**[4,5,12]	Maitland 2011 [8]
Severe anaemia: mortality at 48 hours	RCT	**90 per 1000**	**155 per 1000** (105 to 227)	**RR 1.71** (1.16 to 2.51)	987 (1 study)	⊕⊕⊕⊖ **Moderate**[13]	Maitland 2011 [8]
Non-severe anaemia: mortality at 48 hours	RCT	**6 per 100**	**8 per 100** (6 to 12)	**RR 1.31** (0.93 to 1.84)	2,067 (1 study)	⊕⊕⊕⊖ **Moderate**[14]	Maitland 2011 [8]

The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] All children received antibiotics, maintenance fluids and supportive care according to standard guidelines;
[2] The FEAST inclusion criteria were: One or more of: capillary refill >2 secs, lower limb temp gradient, weak pulse, tachycardia;
[3]The bolus was initially 20 mls/kg over 1 hour but this was increased to 40 mls/kg part-way through the trial following a preliminary analysis which showed increased mortality with the bolus;
[4] No serious risk of bias: Randomization and allocation concealment were adequate to reduce the risk of selection bias. Study staff were unblinded to the intervention;

[5] No serious indirectness: Children with severe hypotension, severe malnutrition, gastroenteritis, or shock due to trauma surgery or burns were excluded;
[6] No serious imprecision: The result is clinically important and statistically significant;
[7]Children with septic shock in hospital in India were randomized to 20 to 40 mls/kg over 15 mins or 20 mls/kg over 20 mins up to a maximum of 60 mls/kg over an hour;
[8] Downgraded by 1 for serious indirectness: The comparison in this trial is not easily related to the comparison in FEAST;
[9] Downgraded by 1 for serious imprecision: The trial is underpowered to confidently rule out differences;
[10] This non-randomized study compares children with shock who received resuscitation in line with PALS guidelines early, and those that didn't. This subgroup excludes trauma cases, but includes cardiac, neurological, respiratory, sepsis and gastroenteritis as causes of shock;
[11] Downgraded by 1 for serious indirectness as the fluid volumes administered are not presented;
[12] Downgraded by 1 for serious imprecision: The 95% CI includes a relative risk of 1 (no effect) and appreciable benefit and harm;
[13] Severe anaemia, hemoglobin <5 g/dl: Downgraded by 1 for serious imprecision (95% CI includes appreciable harm) and few events (n=131 deaths);
[14] Non-severe anaemia, hemoglobin ≥5 g/dl: Downgraded by 1 for serious imprecision (95% CI includes 1 (no effect)) and few events (n=157 deaths).

Supplementary table 5. Bolus fluids compared to maintenance fluids alone in children with severe febrile illness and any sign of impaired circulation (IC)

Quality assessment						Summary of findings				
						Number of patients		Effect size		
Outcomes **Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**No bolus**	**Bolus**	**Relative risk (95% CI)**	**Absolute effect**	**Quality**
Mortality at 48 hours, RCT‡ [8]	No serious risk of bias[1]	No serious inconsistency	No serious indirectness[2]	No serious imprecision[3]	Undetected	76/1044 (7.3%)	221/2097 (10.5%)	RR 1.45 (1.13 to 1.86)	33 more per 1000 (from 9 more to 63 more)	⊕⊕⊕⊕ High
Mortality at 72 hours, RCT† [14]	No serious risk of bias[4]	No serious inconsistency	Serious[5]	Serious[6]	Undetected	13/73 (17.8%)	13/74 (17.6%)	RR 0.99 (0.49 to 1.98)	0 fewer per 100 (from 9 fewer to 17 more)	⊕⊕⊖⊖ Low
Mortality Prospective cohort ¶ [15]	Serious[7]	No serious inconsistency	Serious[8]	Serious[9]	Undetected	18/128 (14.1%)	7/59 (11.9%)	RR 0.84 (0.37 to 1.91)	2 fewer per 100 (from 9 fewer to 13 more)	⊕⊖⊖⊖ Very low
Mortality at 4 weeks, RCT [8]	No serious risk of bias[1]	No serious inconsistency	No serious indirectness[2]	No serious imprecision[3]	Undetected	91/1044 (8.7%)	254/2097 (12.1%)	RR 1.39 (1.11 to 1.74)	34 more per 1000 (from 10 more to 65 more)	⊕⊕⊕⊕ High
Neurologic sequelae at 4 weeks, RCT [8]	No serious risk of bias[1]	No serious inconsistency	No serious indirectness[2]	Serious[10]	Undetected	20/997 (2.0%)	41/1986 (2.1%)	RR 1.03 (0.61 to 1.75)	1 more per 1000 (from 8 fewer to 15 more)	⊕⊕⊖⊖ Moderate
Pulmonary edema, increased intracranial pressure, RCT [8]	No serious risk of bias[1]	No serious inconsistency	No serious indirectness[2]	Serious[10]	Undetected	17/1044 (1.6%)	50/2097 (2.4%)	RR 1.46 (0.85 to 2.53)	7 more per 1000 (from 2 fewer to 25 more)	⊕⊕⊖⊖ Moderate
Severe anaemia: mortality at 48 hours, RCT [8]	No serious risk of bias[1]	No serious inconsistency	No serious indirectness[2]	Serious[11]	Undetected	30/332 (9%)	101/655 (15.4%)	RR 1.71 (1.16 to 2.51)	64 more per 1000 (from 14 more to 136 more)	⊕⊕⊖⊖ Moderate
Non-severe anaemia: mortality at 48 hours, RCT [8]	No serious risk of bias[1]	No serious inconsistency	No serious indirectness[2]	Serious[12]	Undetected	43/683 (6.3%)	114/1384 (8.2%)	RR 1.31 (0.93 to 1.84)	20 more per 1000 (from 4 fewer to 53 more)	⊕⊕⊖⊖ Moderate

RCT: Randomised controlled trial;
‡Children were randomized to a fluid bolus (20 to 40 mls/kg albumin or normal saline over 1 hour) or maintenance fluids (2.5 to 4.0 mls/kg/hour);
[1]No serious risk of bias: Randomization and allocation concealment were adequate to reduce the risk of selection bias. Study staff were unblinded to the intervention;
[2]No serious indirectness: Children with severe hypotension, severe malnutrition, gastroenteritis, or shock due to trauma surgery or burns were excluded;
[3]No serious imprecision: The result is clinically important and statistically significant;
†Children with septic shock in hospital in India were randomized to 20 to 40 mls/kg over 15 mins or 20 mls/kg over 20 mins up to a maximum of 60 mls/kg over an hour;
[4]Low risk of selection bias (random sequence generation and allocation concealment adequate); low risk of reporting bias;
[5]Downgraded by 1 for serious indirectness: The comparison in this trial is not easily related to the comparison in FEAST trial [8];
[6]Downgraded by 1 for serious imprecision: The trial is underpowered to confidently rule out differences;
¶ This non-randomized study compares children with shock who received resuscitation in line with PALS guidelines early, and those that didn't. This subgroup excludes trauma cases, but includes cardiac, neurological, respiratory, sepsis and gastroenteritis as causes of shock;
[7]High risk for selection bias and confounding: 'Received recommended APLS/PALS fluid therapy' was defined as those who recovered regardless of fluid therapy plus those who didn't recover but received >20 mg/kg of fluids. Children who didn't receive recommended APLS/PALS treatment were significantly younger and had significantly longer capillary refill times, lower blood pressure, and higher oxygen requirements;
[8]Downgraded by 1 for serious indirectness as the fluid volumes administered are not presented;
[9]Downgraded by 1 for serious imprecision: Small sample size (N=187 patients) and small number of events (N=25 deaths due to sepsis);
[10]Downgraded by 1 for serious imprecision: The 95% CI includes a relative risk of 1 (no effect) and appreciable benefit and harm;
[11]Severe anaemia, hemoglobin <5 g/dl: Downgraded by 1 for serious imprecision (95% CI includes appreciable harm) and few events (n=131 deaths);
[12]Non-severe anaemia, hemoglobin ≥5 g/dl: Downgraded by 1 for serious imprecision (95% CI includes 1 (no effect)) and few events (n=157 deaths).