



The Role of Fluid Resuscitation in Dengue Shock Syndrome: A Comprehensive Systematic Review of Randomized Controlled Trials and Primary Studies

¹ Devy Widiya Grafitasari

¹ Widodo General Hospital, Ngawi Regency, Central Java, Indonesia

Corresponding Email : devywidia.dw@gmail.com

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ABSTRACT

Introduction: Dengue shock syndrome (DSS) represents the most severe manifestation of dengue virus infection, characterized by acute endothelial hyperpermeability leading to profound intravascular volume depletion. Despite the absence of specific antiviral therapy, parenteral fluid replacement remains the cornerstone of management. However, WHO recommendations regarding fluid type, volume, and de-escalation strategies rest upon limited and ageing evidence.

Methods: This systematic review, conducted in accordance with PRISMA 2020 guidelines, synthesized evidence from 24 primary studies (5 randomized controlled trials, 19 observational studies) encompassing >11,000 patients. Eligibility included RCTs, cohort, case-control, and cross-sectional studies evaluating intravenous or oral fluid therapy in children and adults with dengue hemorrhagic fever, DSS, or severe dengue. Fourteen prespecified outcome domains were extracted. Methodological quality was assessed

using Cochrane RoB 2, Newcastle-Ottawa Scale, and ROBINS-I, with GRADE certainty rating per outcome.

Results: Isotonic crystalloid demonstrated non-inferiority to synthetic colloid for initial resuscitation in moderate paediatric DSS (RR 1.08, 95% CI 0.78-1.47). Cumulative fluid volume at 24 hours discriminated mechanical ventilation requirement with AUC 0.871 (threshold 181 mL/kg), and colloid-to-crystalloid ratio with AUC 0.781 (threshold 1.6). Liberal-colloid maintenance strategy increased respiratory compromise odds 8.84-fold ($p < 0.001$) and respiratory support odds 8.16-fold ($p < 0.001$) while reducing recurrent shock (RR 0.13, $p = 0.043$). Ventilated children exhibited 22.4% mortality versus 0.1% in non-ventilated. Dengue-associated acute kidney injury occurred in 4.8-35.1%, with fatality 22.4% versus 5.7% without renal injury.

Discussion: The evidence supports reconceptualizing DSS fluid therapy from volume-maximizing to volume-titrating paradigm. Colloid physiological advantages in surrogate haemodynamic endpoints do not translate into survival benefit, and prolonged colloid exposure is positively harmful, particularly where respiratory support is unavailable.

Conclusion: Isotonic crystalloid constitutes first-line resuscitation for moderate DSS. Cumulative volume and colloid proportion are modifiable, dose-dependent determinants of respiratory failure, renal injury, and mortality. Adequately powered multicentre RCTs in paediatric and adult DSS with protocolised de-resuscitation represent the highest research priority.

Keywords: Dengue shock syndrome; severe dengue; fluid resuscitation; crystalloid; colloid.

INTRODUCTION

Background

Dengue is the most rapidly expanding arthropod-borne viral disease of humans, endemic in more than one hundred countries across tropical and subtropical latitudes, with a geographical range that continues to widen under the combined pressures of urbanisation, human mobility and climate-driven expansion of the *Aedes* vector into previously unaffected territories including southern Europe and the southern United States. Infection with any of the four antigenically related dengue virus serotypes produces a clinical spectrum ranging from subclinical infection through undifferentiated febrile illness to life-threatening syndromes characterised by capillary leakage, haemorrhage and organ failure. Although the overwhelming majority of infections resolve without specific therapy, a small proportion progress to the dengue vascular permeability syndrome, the most consequential clinical manifestation of dengue and the pathophysiological substrate of dengue shock syndrome.^{41,42}

The cardinal and pathognomonic feature of dengue shock syndrome (DSS) is a transient but intense increase in systemic microvascular permeability, temporally concentrated around the day of defervescence, which permits protein-rich plasma to escape from the intravascular into the interstitial and serosal compartments. The consequence is acute intravascular volume depletion superimposed upon haemoconcentration, with progressive narrowing of pulse pressure, reduction in stroke volume index and cardiac index, and ultimately decompensated hypotensive shock. Prospective haemodynamic characterisation of adults with dengue using non-invasive cardiac output monitoring and bedside ultrasonography has demonstrated that mean arterial pressure falls significantly by day six of fever, that pulse pressure narrows between days four and seven, and that stroke volume index and cardiac index decline between days four and fifteen and days five and eight respectively; critically, that work also established that hypovolaemic shock and cardiogenic shock occur in approximately equal proportions among adults with dengue shock, intravascular

hypovolaemia preceding defervescence and myocardial dysfunction supervening on the day of defervescence and persisting for up to two weeks thereafter.¹²

Mechanistic studies have progressively clarified the endothelial basis of this leakage. In a prospective cohort of adults with dengue shock in Vietnam, biomarkers of hyperinflammation (interleukin-6, ferritin), endothelial activation (angiopoietin-1, angiopoietin-2, soluble Tie-2, vascular cell adhesion molecule-1) and endothelial glycocalyx degradation (hyaluronan, heparan sulfate, endocan, syndecan-1) were each associated with organ-failure severity, and interleukin-6 correlated most strongly with the severity of pulmonary vascular leak, while angiopoietin-2 and syndecan-1 predicted intensive-care admission and death. These findings establish that the leaking endothelium of dengue is not a passive sieve but an actively inflamed and enzymatically denuded barrier, an observation with direct consequences for the pharmacological logic of colloid therapy, since an intact glycocalyx is a prerequisite for the oncotic retention on which colloid efficacy depends.¹³

In the continuing absence of a licensed antiviral agent or an effective endothelial-stabilising therapy, and with vaccination affording only partial and serotype-dependent protection, the clinical management of DSS rests entirely upon judicious volume replacement. Fluid resuscitation is therefore not an adjunct but the definitive intervention, and its correct execution is the principal determinant of survival. Where fluid therapy is delivered competently, case fatality in paediatric DSS falls below one per cent; where it is delivered late, insufficiently or excessively, mortality rises steeply. National mortality audits illustrate the stakes: a two-year nationwide review of dengue deaths in Malaysia found that DSS contributed to more than seventy per cent of all fatalities across every age stratum, that half of decedents had multi-organ involvement, and that death occurred at a median of three days after admission, that is, squarely within the window in which fluid decisions are made.^{23,41,42}

The paradox at the centre of this field is that the same intervention which is indispensable is also, beyond a threshold, injurious. Because DSS leakage is self-limiting and reverses over twenty-four to forty-eight hours, fluid administered during the leakage phase is progressively reabsorbed during the recovery phase; volume that was appropriate at hour two may be lethal at hour twenty-

four. The resulting complications, namely pulmonary oedema, pleural and peritoneal effusion, respiratory compromise requiring non-invasive or invasive ventilatory support, intra-abdominal hypertension and obstructive physiology, and acute kidney injury, are iatrogenic in origin and, in principle, preventable. Extensive evidence in general critical care confirms that fluid accumulation is independently associated with mortality, acute kidney injury, prolonged mechanical ventilation and prolonged intensive-care stay in both adults and children, with each one per cent increase in percentage fluid overload conferring approximately a six per cent increase in the adjusted odds of death.^{38,39,40,46}

Research objectives

The general objective of this systematic review was to synthesise, appraise and integrate all available randomised and non-randomised primary clinical evidence concerning the role of fluid resuscitation in dengue shock syndrome and severe dengue, in order to define an evidence-based framework for fluid type, volume, sequencing and de-escalation. The specific objectives were as follows.

- To determine whether isotonic crystalloid solutions are inferior, equivalent or superior to synthetic colloid solutions for initial resuscitation of dengue shock syndrome, with respect to resuscitation failure requiring rescue colloid, and to identify the severity strata in which any differential effect is concentrated.^{1,2,3}
- To quantify the comparative effect of specific fluid preparations, namely Ringer lactate, 0.9% sodium chloride, dextran 70, gelatin and 6% hydroxyethyl starch, on physiological recovery endpoints including haematocrit normalisation, cardiac index restoration, blood pressure recovery and time to initial clinical recovery.^{1,2,3}
- To establish whether cumulative resuscitation volume and the colloid-to-crystalloid infusion ratio behave as dose-dependent determinants of adverse outcome, and to identify quantitative thresholds of clinical utility.^{4,5,6}
- To determine the association between fluid resuscitation strategy and the incidence of respiratory compromise, requirement for nasal continuous positive airway pressure or

mechanical ventilation, recurrent shock, acute kidney injury, haemorrhagic complications, transfusion requirement, adverse fluid reactions, metabolic derangement, length of stay, cost, and mortality.^{4,5,6,7,15,18}

- To appraise the methodological quality and risk of bias of the constituent evidence base, to rate the certainty of evidence for each outcome domain using the GRADE approach, and to define the residual research gap with sufficient precision to inform trial design.¹⁻²⁴

Significance and anticipated benefits of the review

The theoretical benefit of this review lies in reconciling two apparently contradictory bodies of evidence, namely the demonstrable physiological superiority of colloid solutions in restoring intravascular volume across a leaking endothelium, and the demonstrable clinical harm associated with their prolonged or high-proportion use. By separating surrogate haemodynamic endpoints from patient-important outcomes, the review clarifies why a fluid that performs better on the monitor may perform worse for the patient, and situates dengue within the broader critical-care literature on colloid safety and fluid stewardship.^{3,5,27,32}

The clinical and practical benefits are more immediate. Dengue is overwhelmingly a disease of resource-constrained health systems in which epidemics arrive in surges, in which paediatric and adult patients are frequently managed by non-specialists in district hospitals, and in which respiratory support capacity is limited or absent. Evidence that a liberal-colloid strategy multiplies the odds of requiring nasal continuous positive airway pressure or mechanical ventilation by a factor approaching eight has direct operational consequences for such settings, because the complication generated by the fluid choice may exceed the capacity of the facility to treat it. Equally, the identification of an actionable cumulative-volume threshold provides front-line clinicians with a concrete, bedside-computable quantity around which to organise vigilance, and provides hospital quality committees with an auditable process measure.^{5,4,6}

For health policy and guideline development, the review provides a consolidated evidence table against which WHO and national dengue management algorithms may be re-examined, particularly in respect of the circumstances under which synthetic colloids are recommended and the duration for which they should be continued. For research funders and trialists, the review

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specifies the precise gaps, namely the absence of contemporary randomised comparisons in adults, the absence of randomised evaluations of restrictive versus liberal cumulative-volume strategies, and the absence of trials incorporating protocolised de-resuscitation, that must be addressed before management can claim a genuinely evidence-based foundation.^{5,42,48}

Hypotheses

The following hypotheses were formulated a priori and tested against the assembled evidence.

H1 (null hypothesis of fluid-type equivalence for resuscitation failure). Isotonic crystalloid and synthetic colloid solutions do not differ significantly in the proportion of patients with moderately severe dengue shock syndrome who require rescue colloid after initial resuscitation.

H2 (alternative hypothesis of physiological superiority of colloid). Colloid solutions produce significantly more rapid normalisation of haematocrit, restoration of cardiac index and recovery of blood pressure than crystalloid solutions, with the magnitude of advantage inversely proportional to admission pulse pressure.

H3 (alternative hypothesis of dose-dependent volume harm). Cumulative resuscitation volume administered during the first twenty-four hours is significantly and independently associated with respiratory failure requiring mechanical ventilation, deterioration in glomerular filtration and mortality, and this association exhibits a definable threshold.

H4 (alternative hypothesis of colloid-proportion harm). A higher colloid-to-crystalloid infusion ratio and a longer duration of colloid exposure are significantly associated with respiratory compromise and requirement for respiratory support, independent of baseline severity.

H5 (alternative hypothesis of differential colloid safety). Individual colloid preparations differ significantly in adverse-reaction profile despite equivalent haemodynamic efficacy, such that colloid selection is a safety rather than an efficacy decision.

Research gap

Notwithstanding the pivotal position of fluid therapy in dengue management, four specific evidentiary gaps persist and are addressed by this review. The first is chronological and demographic: the entire randomised evidence base for fluid type in DSS consists of three double-blind trials conducted in Vietnamese children and published between 1999 and 2005, enrolling 50,

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230 and 512 participants respectively. No adequately powered randomised comparison of resuscitation fluids in DSS has been published in the two decades since, and none has been conducted in adults, despite the epidemiological transition in several endemic countries towards an adult-predominant severe-dengue burden and despite national audits showing that dengue deaths now occur primarily in adults.^{1,2,3,23}

The second gap is conceptual: existing randomised trials addressed the question of which fluid, but not the questions of how much fluid, for how long, and when to stop. Because the leakage phase of DSS is self-limiting and followed by obligatory reabsorption, the dose and duration questions are arguably more consequential than the type question, yet the evidence bearing upon them is exclusively observational, has emerged only within the last two years, and derives predominantly from a single Vietnamese tertiary paediatric intensive care unit. The correspondingly large and rigorous body of general critical-care evidence on fluid stewardship, de-resuscitation and the four phases of fluid therapy has not been systematically integrated into the dengue-specific literature.^{4,5,6,48}

The third gap is methodological: fluid exposure has been operationalised inconsistently across studies, variously as total volume in millilitres per kilogram, as bolus number, as colloid-to-crystalloid ratio, as duration of colloid infusion, or as categorical management strategy, which precludes straightforward pooling and obscures dose-response relationships. Similarly, fluid overload has been defined by at least thirty-five distinct criteria in the paediatric critical-care literature, an inconsistency which propagates directly into the dengue evidence base and which no dengue-specific review has previously catalogued.^{39,38}

The fourth gap is inferential: because clinicians administer more fluid to sicker patients, every observational association between cumulative volume and adverse outcome is exposed to confounding by indication. Only two studies in the dengue literature have made a serious attempt to address this, one through inverse probability weighting for baseline severity and one through propensity-score matching, and no previous review has systematically distinguished those analyses which adjusted for severity from those which did not. Consequently the field has lacked a

defensible answer to the central practical question of whether excess fluid causes respiratory failure or merely marks the patients destined to develop it.^{5,9,4}

Novelty

This review is novel in five respects. First, it is to our knowledge the first systematic review to integrate the classical randomised fluid-type evidence in DSS with the large observational fluid-dose evidence published in 2024 and 2025, thereby addressing fluid type, fluid volume and colloid proportion within a single analytical framework rather than in isolation. Second, it adopts a design-restricted inclusion strategy in which randomised, cohort, case-control, cross-sectional, prospective and retrospective designs alone populate the primary evidence tables, while systematic reviews and meta-analyses are deliberately excluded from those tables and reserved for contextual triangulation in the Discussion, thereby eliminating the double-counting of primary data that has affected previous narrative treatments of this topic.¹⁻²⁴

Third, the review extracts and tabulates fourteen prespecified outcome domains, extending well beyond the mortality-and-fluid-type dyad that has dominated prior synthesis to encompass recurrent shock, respiratory support requirement, renal trajectory, haemorrhage and transfusion, adverse fluid reactions, metabolic and lactate-derived indices, organ dysfunction, resource utilisation and cost. Fourth, it presents an explicit dose-response and threshold analysis, collating for the first time in a single table the quantitative discriminatory performance and optimal cut-points reported for cumulative fluid volume and colloid-to-crystalloid ratio. Fifth, it applies dual risk-of-bias instrumentation, RoB 2 for randomised evidence and the Newcastle-Ottawa Scale with ROBINS-I domain judgements for non-randomised evidence, together with GRADE certainty rating per outcome, and interprets each finding in explicit relation to whether severity confounding was addressed.^{4,5,6,9}

METHODS

Protocol, reporting standard and review design

This study was designed and executed as a systematic review of primary clinical studies and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question was framed in the PICOS format and

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specified in advance of literature interrogation, together with eligibility criteria, outcome domains, risk-of-bias instrumentation and the intended synthesis strategy. The review was conceived as a design-restricted synthesis: only primary study designs were permitted to populate the evidence tables, and secondary syntheses were used exclusively for contextual interpretation. No amendments were made to the prespecified outcome list after data extraction commenced.¹⁻⁵

Table 1. PICOS framework and review question

Element	Specification
Population (P)	Children and adults with laboratory-supported or clinically defined dengue infection meeting criteria for dengue haemorrhagic fever, dengue shock syndrome (WHO 1997) or severe dengue (WHO 2009), managed in emergency, ward, high-dependency or intensive-care settings; and, for prevention-of-shock outcomes, ambulatory patients with suspected dengue at risk of plasma leakage.
Intervention / Exposure (I)	Any parenteral or oral fluid resuscitation strategy, characterised by (a) fluid type: Ringer lactate, Ringer acetate, 0.9% sodium chloride, dextran 70, modified gelatin, 6% hydroxyethyl starch, albumin, or oral rehydration; (b) cumulative volume administered (mL/kg or L) within a defined time window; (c) colloid-to-crystalloid infusion ratio; (d) duration of colloid exposure; or (e) protocolised versus non-protocolised fluid management.
Comparator (C)	An alternative fluid type, an alternative cumulative volume stratum, an alternative colloid-to-crystalloid ratio stratum, an alternative management strategy (conservative-colloid, intermediate-colloid, liberal-colloid), standard care, or an internal reference group defined by outcome status.
Outcomes (O)	Fourteen prespecified domains (Table 4), including all-cause mortality, resuscitation failure requiring rescue colloid, time to haemodynamic recovery, haematocrit and cardiac-index normalisation, recurrent shock, cumulative fluid volume and ratio thresholds, respiratory compromise and

	ventilatory support, acute kidney injury and renal trajectory, haemorrhage and transfusion, adverse fluid reactions, metabolic and lactate-derived indices, organ dysfunction, resource utilisation and cost, and prevention of shock or hospitalisation.
Study design (S)	INCLUDED: randomised controlled trials; cohort studies (prospective or retrospective); case-control studies; cross-sectional studies; other observational analytic designs. EXCLUDED from evidence tables: systematic reviews, meta-analyses, network meta-analyses, narrative and scoping reviews, guidelines, editorials, case reports, case series, animal and in-vitro studies, and modelling or simulation studies.
Review question	In patients with dengue shock syndrome or severe dengue, what is the effect of fluid resuscitation strategy - defined by fluid type, cumulative volume, colloid proportion and duration - on mortality, resuscitation success, haemodynamic recovery, recurrent shock, respiratory and renal complications, haemorrhage, adverse reactions and resource utilisation?

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Dengue shock syndrome	Severe dengue	Children and adults
I (Intervention/Exposure)	Fluid resuscitation	Intravenous fluids	Colloid therapy
C (Comparison)	Isotonic crystalloid	Synthetic colloid	Conservative vs liberal strategy
O (Outcome)	Respiratory failure	Acute kidney injury	Mortality

The Boolean MeSH keywords inputted on databases for this research are: (*"Dengue shock syndrome" OR "Severe dengue" OR "Children and adults"*) AND (*"Fluid resuscitation" OR "Intravenous fluids" OR "Colloid therapy"*) AND (*"Isotonic crystalloid" OR "Synthetic colloid" OR "Conservative vs liberal strategy"*) AND (*"Respiratory failure" OR "Acute kidney injury" OR "Mortality"*)

Eligibility criteria

Eligibility criteria were applied hierarchically, first to design, then to population, then to exposure characterisation, and finally to outcome reporting. A study was required to satisfy every inclusion criterion and to breach no exclusion criterion. Studies which reported dengue outcomes but did not characterise fluid therapy in any quantitative or categorical manner, and in which no prespecified outcome could be extracted, were excluded at full-text stage.

Table 2. Inclusion and exclusion criteria

Domain	Inclusion criteria	Exclusion criteria
Design	Randomised controlled trial; prospective cohort; retrospective cohort; case-control; cross-sectional; other analytic observational design; secondary analysis of a randomised trial or cohort.	Systematic review; meta-analysis; network meta-analysis; narrative or scoping review; clinical practice guideline; editorial or commentary; case report; case series; animal, in-vitro or bench study; mathematical modelling or simulation study; economic simulation.
Population	Children and/or adults with dengue haemorrhagic fever, dengue shock syndrome or severe dengue; ambulatory suspected dengue for prevention-of-shock outcomes; patient-level clinical data reported.	Non-dengue shock states as the sole population; mixed critical-illness cohorts in which dengue patients could not be identified; healthy volunteers; seroprevalence-only or vector-only studies.

Exposure	Fluid therapy characterised by type, cumulative volume, colloid-to-crystalloid ratio, duration of colloid exposure, or protocolised management strategy; or fluid-related complication used as exposure or outcome.	No characterisation of fluid therapy whatsoever and no extractable fluid-related outcome; pharmacological interventions unrelated to volume replacement reported without any fluid data.
Outcomes	At least one prespecified outcome domain (Table 4) reported with a numerical estimate, effect measure, or descriptive proportion permitting extraction.	Outcomes reported only as unquantified narrative statements; abstract-only records without extractable numerical data.
Publication	Peer-reviewed journal article, any language, any publication year, indexed in the searched sources with a resolvable record identifier.	Preprints; conference abstracts without full publication; theses; records without a verifiable persistent identifier.

Study selection and data extraction

Records retrieved from each query were compiled, de-duplicated across queries, and screened at title and abstract level against the design and population criteria. Records surviving this stage were assessed at full-text or full-abstract level against the exposure and outcome criteria. Data were extracted onto a standardised extraction template comprising bibliographic identifiers (first author, publication year, journal), geographical setting and number of centres, study design and time frame, population age stratum and case definition, sample size, fluid intervention or exposure and its comparator, all reported prespecified outcomes with their effect estimates and confidence intervals or p-values, adjustment strategy, and reported limitations. Where a single patient cohort generated multiple publications addressing different outcomes, each publication was retained as a distinct analytical unit but the shared provenance was recorded explicitly in order to prevent inferential double-counting; this circumstance applies to the linked series of analyses from the

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tertiary paediatric intensive-care cohort in southern Vietnam covering 2013 to 2022, which contributed the fluid-load analysis, the mechanical-ventilation risk score, the lactate-to-bicarbonate analysis, the lactate-to-albumin analysis, the hypophosphataemia analysis and the obesity analysis.^{4,6,7,8,9,10}

Prespecified outcome domains

Fourteen outcome domains were specified before extraction, organised into four families: mortality and resuscitation success; physiological and haemodynamic recovery; fluid-attributable organ complications; and resource utilisation, safety and prevention.

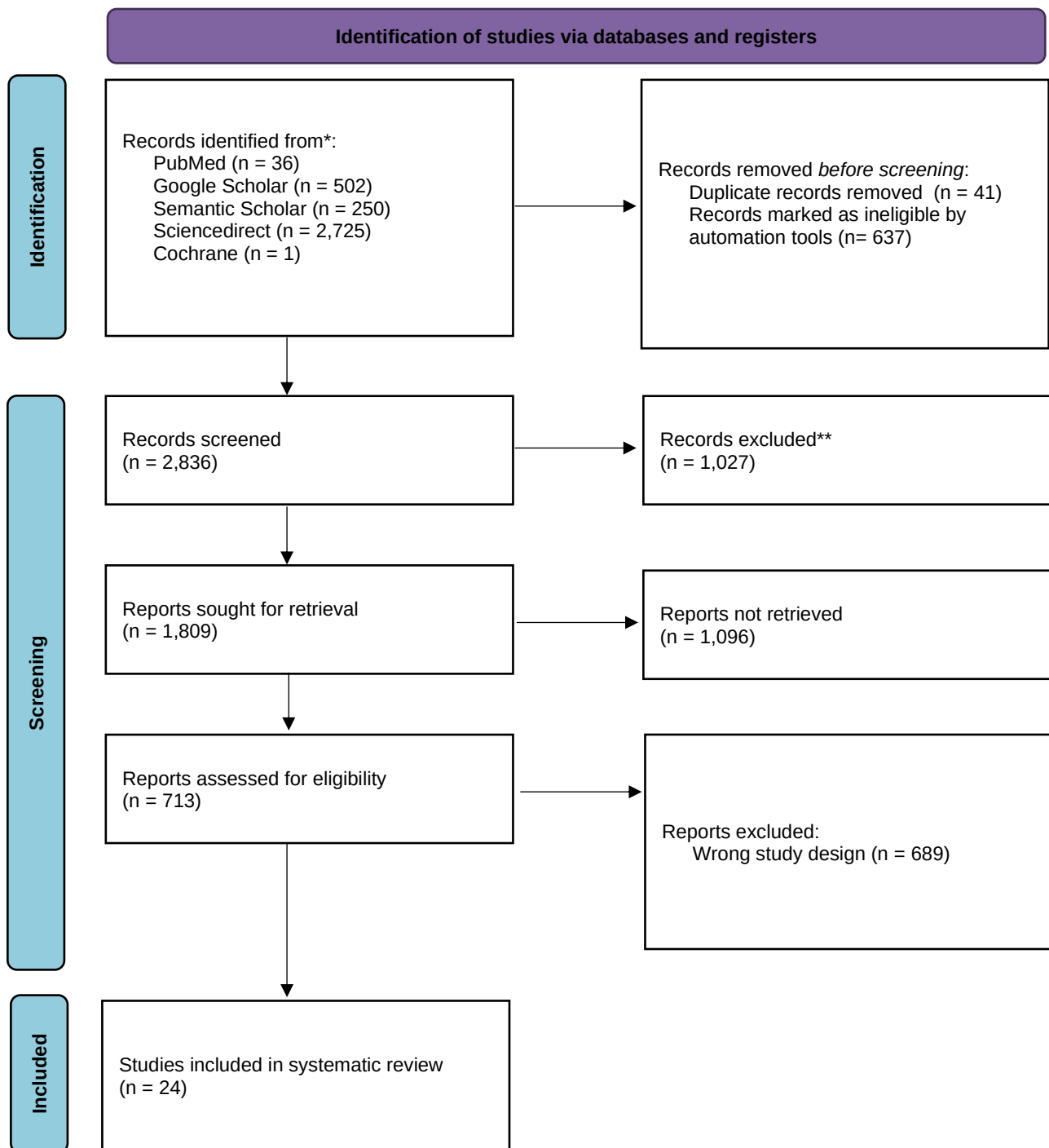
Table 3. Prespecified outcome domains and operational definitions

No.	Outcome domain	Operational definition
O1	All-cause mortality	In-hospital, 28-day or study-period death from any cause; case-fatality proportion; and multivariable predictors of death including fluid-related covariates.
O2	Resuscitation failure / rescue-colloid requirement	Requirement for rescue colloid at any time after administration of the allocated study fluid; failure of allocated regimen to restore haemodynamic stability.
O3	Time to initial haemodynamic recovery	Interval from commencement of resuscitation to initial clinical recovery or to first attainment of haemodynamic stability.
O4	Haematocrit and cardiac-performance normalisation	Rate and completeness of haematocrit normalisation; restoration of cardiac index, stroke volume index, blood pressure and pulse pressure.
O5	Recurrent shock	One or more further episodes of shock after initial stabilisation during the same admission.
O6	Cumulative fluid volume and colloid-to-crystalloid ratio	Total intravenous volume administered within a defined window (typically 24 h), expressed in mL/kg or L; colloid-to-crystalloid infusion ratio; discriminatory performance and optimal thresholds.

O7	Respiratory compromise and ventilatory support	Respiratory distress attributable to fluid accumulation; requirement for nasal continuous positive airway pressure, non-invasive or invasive mechanical ventilation; duration of ventilation.
O8	Acute kidney injury and renal trajectory	Acute kidney injury by AKIN or KDIGO criteria; change in estimated glomerular filtration rate; requirement for renal replacement therapy; renal insufficiency at discharge.
O9	Haemorrhage, coagulopathy and transfusion	Clinically significant bleeding; severe bleeding; derangement of coagulation indices; requirement for blood component transfusion.
O10	Adverse fluid reactions	Allergic or anaphylactoid reaction, urticaria, pruritus, rash, or other reaction attributable to the administered fluid.
O11	Metabolic, lactate-derived and biochemical outcomes	Serum lactate and lactate-derived ratios; metabolic acidosis; electrolyte and phosphate derangement; transaminase elevation.
O12	Organ dysfunction and multi-organ failure	Sequential Organ Failure Assessment score; hepatic dysfunction and acute liver failure; encephalopathy; multi-organ dysfunction; obstructive shock physiology.
O13	Resource utilisation, length of stay and cost	Duration of hospital and intensive-care stay; duration of vasoactive support; intensive-care admission; direct cost of fluid strategy.
O14	Prevention of shock, intravenous fluid requirement and hospitalisation	Progression to shock or severe dengue; requirement for intravenous fluid; hospital admission among ambulatory patients.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Dengue shock syndrome" OR "Severe dengue" OR "Children and adults") AND ("Fluid resuscitation" OR "Intravenous fluids" OR "Colloid therapy") AND ("Respiratory failure" OR "Acute kidney injury" OR "Mortality")	36
Google Scholar	("Dengue shock syndrome" OR "Severe dengue" OR "Children and adults") AND ("Fluid resuscitation" OR "Intravenous fluids" OR "Colloid therapy") AND ("Isotonic crystalloid" OR "Synthetic colloid" OR "Conservative vs liberal strategy") AND ("Respiratory failure" OR "Acute kidney injury" OR "Mortality")	502
Semantic Scholar	("Dengue shock syndrome" OR "Severe dengue" OR "Children and adults") AND ("Fluid resuscitation" OR "Intravenous fluids" OR "Colloid therapy") AND ("Isotonic crystalloid" OR "Synthetic colloid" OR "Conservative vs liberal strategy") AND ("Respiratory failure" OR "Acute kidney injury" OR "Mortality")	250
Science-direct	("Dengue shock syndrome" OR "Severe dengue" OR "Children and adults") AND ("Fluid resuscitation" OR "Intravenous fluids" OR "Colloid therapy") AND ("Respiratory failure" OR "Acute kidney injury" OR "Mortality")	2,725
Cochrane	("Dengue shock syndrome" OR "Severe dengue" OR "Children and adults") AND ("Fluid resuscitation" OR "Intravenous fluids" OR "Colloid therapy") AND ("Isotonic crystalloid" OR "Synthetic colloid" OR "Conservative vs liberal strategy") AND ("Respiratory failure" OR "Acute kidney injury" OR "Mortality")	1



Article search flowchart

Risk-of-bias assessment

Randomised controlled trials were appraised using the Cochrane Risk of Bias 2 (RoB 2) tool across its five domains, namely bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result, with an overall judgement derived according to the tool algorithm. Non-randomised studies were appraised using the Newcastle-Ottawa Scale (NOS), with separate item sets for cohort and cross-sectional designs, generating a score out of nine; NOS judgements were supplemented by explicit domain-level consideration of confounding, selection of participants, classification of exposure, and missing data drawn from the ROBINS-I framework, since confounding by indication is the dominant threat to validity in this literature. Colour coding is applied throughout: green denotes low risk or high quality, amber denotes moderate risk, some concerns or unclear, and red denotes high risk or low quality.¹⁻²⁴

Table 4. Risk of bias in randomised controlled trials (Cochrane RoB 2)

Study (first author, year)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall judgement
Dung NM, 1999	Low	Low	Low	Low	Moderate	Some concerns (small sample, n=50; no registered protocol)
Ngo NT, 2001	Low	Low	Low	Low	Low	Low risk of bias

Study (first author, year)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall judgement
Wills BA, 2005	Low	Low	Low	Low	Low	Low risk of bias
Nasir NH, 2017	Low	Moderate	Moderate	Moderate	Moderate	Some concerns (open-label pilot, underpowered)
Lye DC, 2017	Low	Moderate	Low	Low	Low	Some concerns (open-label design)

D1-D5 = RoB 2 domains. Colour key: green = low risk; amber = some concerns / moderate; red = high risk.

Table 5. Risk of bias and methodological quality in non-randomised studies (Newcastle-Ottawa Scale with ROBINS-I domain judgements)

Study (first author, year)	Design	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	NOS total	Dominant ROBINS-I concern
Vo LT, 2025 (fluid load)	Retrospective cohort	4	2	3	9 - High	Low: confounding

Study (first author, year)	Design	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	NOS total	Dominant ROBINS-I concern
						addressed by multivariable modelling and mixed-effects analysis
Trieu HT, 2025	Retrospective multicentre cohort	4	2	3	9 - High	Low: inverse probability weighting applied for baseline severity
Nguyen Tat T, 2024 (ML risk score)	Retrospective cohort	4	2	2	8 - High	Moderate: internal validation only, no external cohort
Nguyen Tat T, 2024 (L/B ratio)	Retrospective cohort	3	2	3	8 - High	Moderate: single centre; residual confounding by severity
Nguyen Tat T, 2025 (LAR)	Retrospective secondary	3	2	2	7 - High	Moderate: secondary

Study (first author, year)	Design	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	NOS total	Dominant ROBINS-I concern
	analysis					analysis of parent cohort; overlapping population
Vo LT, 2025 (hypophosphataemia)	Retrospective cohort	3	2	2	7 - High	Moderate: very small sample (n=57) despite propensity matching
Nguyen TH, 2023 (obesity)	Retrospective cohort	3	2	2	7 - High	Moderate: nutritional misclassification possible
Yacoub S, 2017	Prospective observational cohort	4	1	3	8 - High	Moderate: fluid volume analysed as continuous covariate without severity weighting
Thanachartwet V, 2016	Prospective observational	4	1	3	8 - High	Moderate: few shock events

Study (first author, year)	Design	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	NOS total	Dominant ROBINS-I concern
	cohort					(n=17) limiting precision
McBride A, 2024	Prospective observational cohort	4	2	3	9 - High	Low: prespecified biomarker analysis with control groups
Vidal C, 2025	Retrospective multicentre cohort	3	2	3	8 - High	Moderate: high comorbidity burden and co-infection confounding
Mallhi TH, 2015 (AKI)	Retrospective cohort	3	2	2	7 - High	Moderate: nephrotoxic co-exposure incompletely adjusted
Mallhi TH, 2017 (mortality/LOS)	Retrospective cross-sectional	3	1	2	6 - Moderate	Moderate: cross-sectional design precludes temporality
Diptyanusa A, 2019	Retrospective	3	2	2	7 - High	Moderate:

Study (first author, year)	Design	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	NOS total	Dominant ROBINS-I concern
	cohort					referral-centre selection bias
Wang C, 2023	Retrospective multicentre cohort	3	2	3	8 - High	Moderate: adult severe dengue only; fluid data limited
Bodinayake CK, 2021	Prospective surveillance cohort	4	1	3	8 - High	Moderate: platelet-threshold enrolment criterion restricts generalisability
Thomas L, 2011	Prospective observational with retrospective classification	3	1	2	6 - Moderate	Moderate: retrospective outcome reclassification
Woon YL, 2016	Retrospective national mortality review	3	0	2	5 - Moderate	High: decedents only, no surviving comparator

Study (first author, year)	Design	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	NOS total	Dominant ROBINS-I concern
						group
Talukdar S, 2021	Prospective observational cohort	4	2	3	9 - High	Low: prespecified predictor model with internal validation

NOS = Newcastle-Ottawa Scale. Colour key applied to NOS total: green = high quality (7-9); amber = moderate quality (4-6); red = low quality (0-3). L/B = lactate-to-bicarbonate; LAR = lactate-to-albumin ratio; ML = machine learning; AKI = acute kidney injury; LOS = length of stay.

Synthesis strategy and certainty of evidence

A formal quantitative meta-analysis with pooled effect estimation was considered and rejected on methodological grounds. Three specific sources of irreducible heterogeneity precluded pooling: first, fluid exposure was operationalised in mutually non-convertible metrics across studies, encompassing allocated fluid type, cumulative volume in millilitres per kilogram, colloid-to-crystalloid ratio, duration of colloid infusion and categorical management strategy; second, the outcome of respiratory compromise was ascertained variously as clinical respiratory distress, requirement for nasal continuous positive airway pressure, requirement for invasive ventilation, or a composite of these; third, the underlying populations spanned moderately severe paediatric shock, profound paediatric shock, adult ward-level severe dengue and adult intensive-care severe dengue, in which the baseline risk of every outcome differs by an order of magnitude. Pooling across these strata would have produced a statistically precise but clinically uninterpretable summary estimate.¹⁻

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Synthesis was therefore conducted as a structured, tabular and narrative integration organised by outcome domain, in which effect estimates are reported as extracted, with their

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original confidence intervals or p-values, and grouped by design and severity stratum. Within each outcome domain, evidence was appraised for direction of effect, statistical significance, consistency across studies, adequacy of adjustment for baseline severity, and dose-response gradient where applicable. Certainty of evidence for each domain was rated using the GRADE approach, starting from high for bodies of randomised evidence and from low for bodies of observational evidence, with downgrading for risk of bias, indirectness, imprecision and inconsistency, and upgrading of observational evidence for large magnitude of effect and demonstrable dose-response gradient.

RESULTS

Characteristics of included studies

The 24 included primary studies comprised five randomised controlled trials and nineteen observational studies, the latter consisting of eleven retrospective cohort or cross-sectional analyses and eight prospective observational cohorts. Aggregate enrolment exceeded eleven thousand patients with dengue. Geographical distribution was heavily concentrated in the Asia-Pacific dengue belt, with Vietnam contributing the entire randomised fluid-type evidence base and the largest observational series, and with additional contributions from Malaysia, Myanmar, Thailand, Sri Lanka, Singapore, Pakistan, China, Saudi Arabia, Brazil, Martinique and Reunion Island. Fifteen studies enrolled children exclusively or predominantly, seven enrolled adults exclusively, and two enrolled both.¹⁻²⁴

Table 6. Characteristics of included randomised controlled trials

First author, year	Country	Design	Sample size	Population	Intervention arms	Primary outcome
Dung NM, 1999	Vietnam	Double-blind RCT, 4 arms	50	Children with dengue shock syndrome	Dextran 70 vs gelafundin 35,000 (gelatin) vs	Restoration of cardiac index, blood pressure and haematocrit

					Ringer lactate vs 0.9% saline	normalisation
Ngo NT, 2001	Vietnam	Double-blind RCT, 4 arms	230	Children with dengue shock syndrome, first hour of resuscitation	Dextran vs gelatin vs Ringer lactate vs 0.9% saline	Clinical response and recovery time in the first hour
Wills BA, 2005	Vietnam	Double-blind RCT, stratified by shock severity	512 (383 moderate; 129 severe)	Children with dengue shock syndrome	Moderate shock: Ringer lactate vs 6% dextran 70 vs 6% hydroxyethyl starch. Severe shock: dextran vs starch	Requirement for rescue colloid at any time after study fluid
Nasir NH, 2017	Malaysia	Open-label RCT (pilot / feasibility)	138	Ambulatory patients aged >12 y with suspected dengue and	Fluid chart plus 200 mL cup and home-care card vs home-care	Hospitalisation, intravenous fluid requirement, total oral fluid intake

				platelets <150 x 10 ⁹ /L	card alone	
Lye DC, 2017	Singapore and Malaysia	Open-label multicentre RCT (5 hospitals)	372 (188 vs 184)	Adults >=21 y with dengue and platelets <=20 x 10 ⁹ /L	Prophylactic platelet transfusion plus supportive care (bed rest, fluid therapy, antipyretics) vs supportive care alone	Clinical bleeding by day 7 or discharge

Table 7. Characteristics of included observational studies

First author, year	Country	Design and period	Sample size	Population	Fluid exposure or comparison examined	Key outcomes reported
Vo LT, 2025	Vietnam	Retrospective cohort, tertiary paediatric ICU, 2013-2022	1,278	Children with dengue shock syndrome with complete fluid data	Cumulative intravenous fluid volume in first 24 h; colloid-to-crystalloid infusion ratio	Mechanical ventilation; renal function trajectory to 48 h; thresholds

Trieu HT, 2025	Malaysia, Myanmar, Vietnam	Retrospective cohort, 7 hospitals	691 (547 stabilised within 2 h)	Children with dengue shock syndrome	Crystalloid-only vs mixed crystalloid/colloid initial resuscitation; conservative vs intermediate vs liberal colloid strategy over first 6 h	Respiratory compromise; NCPAP/ventilation; recurrent shock; length of stay; cost
Nguyen Tat T, 2024	Vietnam	Retrospective cohort, 2013-2022	1,278	Children with dengue shock syndrome	Large cumulative fluid infusion and higher colloid-to-crystalloid ratio as model covariates	Mechanical ventilation risk score; mortality in ventilated vs non-ventilated
Nguyen Tat T, 2024	Vietnam	Retrospective cohort, 2013-mid 2022	492	PICU-admitted children with dengue shock syndrome	Cumulative fluid infused in first 24 h as multivariable predictor	28-day in-hospital mortality; lactate and lactate-to-bicarbonate ratio
Nguyen Tat T, 2025	Vietnam	Retrospective secondary analysis,	524	Children with dengue shock syndrome	Fluid-related severity covariates within machine-learning models	Composite of death, ventilation, acute liver failure,

		2013-2022				encephalitis
Vo LT, 2025	Vietnam	Retrospective cohort with propensity-score matching, 2022	57	Mechanically ventilated children with dengue shock syndrome	Severe hypophosphataemia during PICU stay (fluid/metabolic consequence)	In-hospital mortality; duration of ventilation and vasopressor support
Nguyen TH, 2023	Vietnam	Retrospective cohort	858	PICU-admitted children with dengue shock syndrome	Obesity as a determinant of plasma-leak severity and fluid requirement	Mortality; mechanical ventilation; paediatric acute liver failure
Yacoub S, 2017	Vietnam	Prospective observational cohort, paediatric and adult ICU	102 (22 no shock; 48 single shock; 32 recurrent shock)	Patients with dengue admitted to ICU within 12 h	Total intravenous fluid administered during ICU admission; daily echocardiography and lactate	Recurrent shock; respiratory distress; stroke volume index; lactate
Thanachartwet V,	Thailand	Prospective	162 (17 with shock)	Hospitalised adults with	Non-invasive cardiac output	Type of circulatory

2016		observational cohort, 2013-2015		confirmed dengue	monitoring and inferior vena cava ultrasonography to guide fluid assessment	shock; haemodynamic and preload parameters over illness course
McBride A, 2024	Vietnam	Prospective observational cohort, 2019-2022	135 dengue shock; 37 septic shock; 25 controls	Adults ≥ 16 y with dengue shock	Supportive intravenous fluid therapy with serial lung ultrasound for pulmonary vascular leak	SOFA score; ICU admission; mortality; pulmonary vascular leak severity
Vidal C, 2025	Reunion Island (France)	Retrospective multicentre cohort, 5 ICUs, 2017-2022	137 ICU cases (of 2,817 hospitalised)	Adults with laboratory-confirmed severe dengue in ICU	Circulatory failure management including catecholamine requirement and VA-ECMO	In-hospital mortality; organ failures; predictors of death
Mallhi TH, 2015	Pakistan	Retrospective cohort, 2008-2013	667	Hospitalised dengue patients	Fluid-relevant complications: dengue haemorrhagic fever, multi-organ dysfunction,	Acute kidney injury by AKIN criteria; renal insufficiency at discharge;

					nephrotoxic drug exposure	mortality
Mallhi TH, 2017	Pakistan	Retrospective cross-sectional, tertiary care	667	Confirmed dengue inpatients	Determinants of prolonged hospitalisation including haemoconcentration >20%	Prolonged hospital stay >3 days; in-hospital mortality
Diptyanusa A, 2019	Thailand	Retrospective cohort, 2012-2017	1,484 (71 with AKI)	Hospitalised adults with dengue	Haemodynamic and volume-related determinants of renal injury	Acute kidney injury by KDIGO criteria; dialysis; mortality
Wang C, 2023	China (Guangdong)	Retrospective multicentre cohort, 2013-2019	242 (85 with AKI)	Adults with severe dengue	Respiratory distress and volume-related covariates as determinants of renal injury	Acute kidney injury; severe AKI requiring RRT; mortality; length of stay
Bodinayake CK, 2021	Sri Lanka	Prospective surveillance cohort, 2017-	1,064 (70 children; 994 adults)	Hospitalised febrile patients with confirmed dengue and platelets	Inpatient versus potential ambulatory fluid management; progression through WHO severity	Dengue haemorrhagic fever; dengue shock syndrome; severe dengue;

		2018		$\leq 100,000/\mu\text{L}$	categories	mortality
Thomas L, 2011	Martinique (France)	Prospective observational study with retrospective classification	715	Adults presenting to emergency department with febrile dengue	Intravenous saline infusion in patients with dehydration- type severe presentation without plasma leakage	Response to intravenous fluid within 24 h; severity classification; organ failure
Woon YL, 2016	Malaysia	Retrospective national mortality review, 2013- 2014	322 dengue deaths	All nationally notified dengue deaths	Timing of medical contact and hospitalisation relative to fluid- responsive phase	Cause of death; contribution of dengue shock syndrome; organ involvement
Talukdar S, 2021	Thailand	Prospective observational cohort, 2018- 2020	667 (318 with plasma leakage)	Dengue patients aged ≥ 15 y	Prediction of plasma leakage to permit timely and appropriate fluid administration	Plasma leakage; plasma-leak score performance

ICU = intensive care unit; PICU = paediatric intensive care unit; NCPAP = nasal continuous positive airway pressure; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment; VA-ECMO = veno-arterial extracorporeal membrane oxygenation; AKIN = Acute Kidney Injury Network; KDIGO = Kidney Disease Improving Global Outcomes. Studies from the tertiary paediatric ICU in southern Vietnam covering 2013-2022 derive from an overlapping patient cohort and are reported as separate analytical units addressing distinct outcomes.

All-cause mortality

Mortality in dengue shock syndrome is critically dependent on the setting, the severity stratum and, decisively, on whether respiratory failure supervenes. Across the three double-blind randomised trials of resuscitation fluid conducted in Vietnamese children, mortality was extraordinarily low and did not differ by allocated fluid: all 230 children in the four-arm first-hour comparison survived, and only one death occurred among 512 children in the three-fluid comparison, corresponding to a case fatality below 0.2 per cent. This near-uniform survival is the single most important contextual fact in the field, because it means that no randomised trial in dengue shock syndrome has ever been powered for mortality, and that fluid-type recommendations rest necessarily upon surrogate endpoints.^{2,3}

Observational cohorts in which respiratory failure occurs reveal a radically different mortality landscape. In a cohort of 1,278 children with dengue shock syndrome managed in a tertiary paediatric intensive care unit, fatality among the 170 children who required mechanical ventilation was 22.4 per cent, against 0.1 per cent among those who did not, a differential of more than two hundred fold. Since cumulative fluid volume and colloid proportion were themselves independent predictors of ventilation in the same cohort, this gradient establishes the mechanism by which fluid strategy influences survival: not directly, but through the generation of respiratory failure. In a separate analysis of 492 children from the same institution, multivariable modelling identified three independent clinical predictors of 28-day in-hospital mortality, namely severe bleeding, the cumulative amount of fluid infused in the first twenty-four hours, and a vasoactive-inotropic score exceeding thirty; cumulative fluid volume therefore enters the mortality model directly and not merely as a marker of severity.^{6,7}

Among adults the mortality burden is substantially higher and is driven by multi-organ failure rather than by haemorrhage. In five intensive care units on Reunion Island, 137 adults with severe dengue experienced 25 per cent in-hospital mortality, with circulatory failure in 62 per cent, hepatic failure in 50 per cent, renal failure in 59 per cent, and independent predictors of death comprising catecholamine use (odds ratio 4.71, 95% confidence interval 1.58-14.07, $p=0.005$) and admission respiratory rate (odds ratio 1.10 per unit, 95% CI 1.03-1.17, $p=0.004$). The prognostic weight attached to respiratory rate at admission is notable, since it is the earliest clinical signal of the pulmonary consequences of plasma leakage and of the volume administered to counteract it. National mortality audit in Malaysia found that dengue shock syndrome contributed to more than seventy per cent of 322 dengue deaths, that more than half of decedents had multi-organ involvement, and that death occurred at a median of three days after admission.^{14,23}

Table 8. All-cause mortality by study

First author, year	Design	n	Mortality observed	Fluid-related determinant of death	Statistical significance
Ngo NT, 2001	RCT	230	0 deaths (0%)	No difference between dextran, gelatin, Ringer lactate, saline	Not applicable (no events)
Wills BA, 2005	RCT	512	1 death (<0.2%)	No difference between Ringer lactate, dextran 70, hydroxyethyl starch	Not applicable (single event)
Dung NM, 1999	RCT	50	No deaths reported	No difference across four regimens	Not applicable
Lye DC, 2017	RCT	372	No deaths	One serious	Adverse

			reported	adverse event of fluid overload in transfusion arm	events 6.26x higher with transfusion, p=0.0064
Nguyen Tat T, 2024 (ML score)	Retrospective cohort	1,278	22.4% in ventilated vs 0.1% in non-ventilated	Large cumulative fluid infusion and high colloid-to-crystalloid ratio predicted ventilation	Marked between-group differential; model C-statistic high
Nguyen Tat T, 2024 (L/B)	Retrospective cohort	492	26 deaths (5.3%)	Cumulative fluid infused in first 24 h an independent multivariable predictor	Independent predictor in multivariable model
Vo LT, 2025 (hypophosphataemia)	Retrospective cohort	57 ventilated	16 deaths (28%)	Severe hypophosphataemia not associated with death but with prolonged support	Mortality association not significant; support duration significant
Nguyen TH, 2023 (obesity)	Retrospective cohort	858	Not the primary endpoint	Obesity associated with ventilation need but not with death	Ventilation OR 2.3 (1.31-4.06), p<0.01; mortality NS

Vidal C, 2025	Retrospective cohort (adults, ICU)	137	25% in-hospital mortality	Catecholamine use and admission respiratory rate predicted death	OR 4.71 (1.58-14.07), p=0.005; OR 1.10 (1.03-1.17), p=0.004
McBride A, 2024	Prospective cohort (adults)	135	5 deaths	Interleukin-6, ferritin, angiopoietin-2 and syndecan-1 predicted death	IL-6 OR 4.49, p=0.005; Ang-2 OR 8.06, p=0.002; syndecan-1 OR 6.51, p<0.001
Mallhi TH, 2015	Retrospective cohort	667	1.2% overall; all deaths occurred in the AKI subgroup	Acute kidney injury the common pathway to death	All fatalities had AKI
Mallhi TH, 2017	Retrospective cross-sectional	667	Case fatality 1.1%	Multi-organ dysfunction, AKI, respiratory failure	Multi-organ dysfunction p<0.001; respiratory failure

					p=0.007
Wang C, 2023	Retrospective cohort (adults)	242	22.4% with AKI vs 5.7% without AKI	Respiratory distress an independent determinant of AKI	p<0.001 for mortality difference
Diptyanusa A, 2019	Retrospective cohort (adults)	1,484	12.7% within the AKI subgroup	Severe dengue and haemodynamic compromise	Significant in multivariable analysis
Woon YL, 2016	National mortality review	322 deaths	All decedents	Dengue shock syndrome contributed to >70% of deaths	Descriptive; DSS leading cause across age groups
Bodinayake CK, 2021	Prospective cohort	1,064	2 deaths (0.2%)	Very low mortality with protocolised inpatient fluid management	Descriptive

RCT = randomised controlled trial; ML = machine learning; L/B = lactate-to-bicarbonate ratio; AKI = acute kidney injury; NS = not significant; OR = odds ratio; DSS = dengue shock syndrome.

Resuscitation failure and rescue-colloid requirement

The requirement for rescue colloid after administration of an allocated study fluid is the most methodologically satisfactory efficacy endpoint available in dengue shock syndrome, because it is objective, occurs frequently enough to permit adequate power, and directly operationalises the clinical question of whether the initial fluid choice sufficed. The largest randomised trial in this field adopted this endpoint as primary and produced a decisive negative result. Among 383 children with moderately severe shock, the relative risk of requiring rescue colloid with Ringer lactate

compared with either colloid was 1.08 (95% confidence interval 0.78-1.47, $p=0.65$), an estimate whose confidence interval excludes any clinically meaningful disadvantage for crystalloid. Among 129 children with severe shock randomised between the two colloids, the relative risk with dextran compared with starch was 1.13 (95% CI 0.74-1.74, $p=0.59$), and in the combined analysis 0.88 (95% CI 0.66-1.17, $p=0.38$).³

The interpretive weight of this triad of null results is considerable. It establishes that for the great majority of children presenting with dengue shock, an inexpensive, universally available, non-allergenic isotonic crystalloid achieves the same resuscitation success as a costly synthetic colloid. Since the same trial found no differences in bleeding manifestations, coagulation derangements or severity of fluid overload between fluid groups, the case for crystalloid as first-line therapy in moderately severe shock is not merely economic but comprehensive. The corollary is equally important: the negative result does not extend to profound shock, in which no crystalloid arm was randomised on ethical grounds, and in which the appropriate comparison remains between colloids.³

Evidence from the earlier four-arm trials complements this finding by identifying the subgroup in which colloid may retain genuine advantage. In 230 children resuscitated in the first hour, no fluid demonstrated overall superiority, but recovery times were longest in the Ringer lactate group, and comparison of pooled colloid against pooled crystalloid suggested benefit for children presenting with the lowest pulse pressures. Pulse pressure at presentation, rather than fluid allocation, was the most significant determinant of clinical response. This observation has been operationally translated in subsequent practice into severity-stratified fluid selection, and constitutes the principal surviving indication for first-line colloid.²

Table 9. Resuscitation failure and rescue-colloid requirement

First author, year	Comparison	Effect estimate	95% CI / p-value	Interpretation
Wills BA, 2005	Ringer lactate vs either colloid, moderate shock	RR 1.08	0.78-1.47; $p=0.65$	No significant difference; crystalloid non-

	(n=383)			inferior
Wills BA, 2005	Dextran 70 vs 6% hydroxyethyl starch, severe shock (n=129)	RR 1.13	0.74-1.74; p=0.59	No significant difference between colloids
Wills BA, 2005	Dextran 70 vs 6% hydroxyethyl starch, combined analysis (n=512)	RR 0.88	0.66-1.17; p=0.38	No significant difference between colloids
Ngo NT, 2001	Dextran vs gelatin vs Ringer lactate vs saline, first hour (n=230)	No clear advantage of any fluid; longest recovery with Ringer lactate	Descriptive; pulse pressure the dominant determinant	Colloid advantage confined to lowest pulse- pressure stratum
Dung NM, 1999	Colloids (dextran 70, gelatin) vs crystalloids (Ringer lactate, saline) (n=50)	Colloids restored cardiac index and blood pressure and normalised haematocrit more rapidly	Directional finding in small sample	Physiological superiority of colloid without outcome benefit
Trieu HT, 2025	Crystalloid-only vs mixed crystalloid/colloid initial resuscitation (n=691)	547/691 (79%) stabilised within 2 h irrespective of regimen	Descriptive	Most children stabilise rapidly with either approach

RR = relative risk; CI = confidence interval.

Time to initial haemodynamic recovery

Time to initial recovery is the endpoint on which colloid solutions perform most favourably, and the divergence between this outcome and rescue-colloid requirement is the central paradox of the fluid-type literature. In the three-fluid randomised comparison, treatment with Ringer lactate resulted in a marginally longer time to initial recovery than treatment with either colloid solution, and in less rapid improvement in haematocrit, yet produced no difference in any other measure of treatment response and no difference in the primary endpoint. The marginal nature of the temporal advantage, coupled with its failure to propagate into any patient-important outcome, is precisely why the trial concluded in favour of crystalloid for moderately severe shock.³

The four-arm first-hour trial reached a congruent conclusion from the opposite direction: no fluid regimen showed clear overall advantage, but the longest recovery times occurred in the Ringer lactate group. Taken together with the finding that admission pulse pressure was the dominant determinant of clinical response, the temporal data support a threshold model rather than a linear model of colloid benefit, in which the modest kinetic advantage of colloid becomes clinically consequential only where the physiological reserve is smallest, that is, in profound shock with markedly narrowed pulse pressure. In adult sepsis, comparable time-to-stability endpoints have likewise failed to separate colloid from crystalloid regimens, with a randomised comparison of a balanced gelatine regimen against a balanced crystalloid regimen finding haemodynamic stability at 4.7 versus 5.8 hours ($p=0.3716$) despite a significantly more favourable fluid balance in the gelatine arm.^{2,3,29}

Table 10. Time to initial haemodynamic recovery

First author, year	Comparison	Finding	Interpretation
Wills BA, 2005	Ringer lactate vs colloid, moderate shock	Marginally longer time to initial recovery with Ringer	Kinetic disadvantage of crystalloid is real but clinically marginal

		lactate; no difference in other response measures	
Ngo NT, 2001	Four fluid regimens, first hour of resuscitation	Longest recovery times in the Ringer lactate group; no fluid clearly superior overall	Colloid advantage restricted to narrow-pulse-pressure presentations
Dung NM, 1999	Colloid vs crystalloid	Dextran 70 gave the most rapid normalisation of haematocrit and restoration of cardiac index	Dextran the most kinetically efficient colloid in this small trial
Trieu HT, 2025	Initial resuscitation regimens, 7 hospitals	547 of 691 children (79%) achieved stability within 2 hours	Rapid stabilisation is the norm and is not regimen-dependent

Haematocrit normalisation and cardiac performance

Physiological restoration endpoints demonstrate the clearest and most reproducible superiority of colloid solutions in dengue shock syndrome. In the four-arm double-blind comparison in 50 children, colloids, namely dextran 70 and the protein digest gelafundin 35,000, restored cardiac index and blood pressure and normalised haematocrit more rapidly than the crystalloids Ringer lactate and 0.9% saline, with dextran 70 producing the most rapid haematocrit normalisation and cardiac-index restoration without adverse effects. The larger three-fluid trial confirmed the haematocrit finding, reporting less rapid improvement in haematocrit with Ringer lactate than with either colloid. The mechanistic coherence of these observations is complete: an iso-oncotic

macromolecular solution retains intravascular water more effectively than an isotonic salt solution across a permeable barrier, and the haematocrit is the most direct available bedside index of that retention.^{1,3}

Prospective haemodynamic phenotyping in adults establishes why physiological restoration alone is an inadequate therapeutic target. Using non-invasive cardiac output monitoring and inferior vena cava ultrasonography in 162 hospitalised adults with dengue, stroke volume index and cardiac index declined significantly between days four and fifteen and days five and eight after fever onset respectively, and a significant proportion of patients with dengue shock exhibited an inferior vena cava diameter below 1.5 centimetres with a collapsibility index above 50 per cent between days four and five. Critically, hypovolaemic shock accounted for 9 of 17 shock episodes (52.9 per cent) and cardiogenic shock for 8 (47.1 per cent), with median time to shock onset at six days after fever onset, the day of defervescence. Approximately half of dengue shock is therefore not a volume-deficient state at all, and in that half the administration of further volume, whether colloid or crystalloid, addresses the wrong physiology.¹²

Echocardiographic data from a prospective intensive-care cohort of 102 patients reinforce this conclusion and add a temporal dimension. Patients who went on to develop recurrent shock had significantly higher enrolment pulse rate (median 114 versus 100 versus 100 beats per minute, $p=0.002$), significantly lower stroke volume index (median 21.6 versus 22.8 versus 26.8 mL/m², $p<0.001$) and significantly higher lactate (4.2 versus 2.9 versus 2.2 mmol/L, $p=0.001$) than those with a single shock episode or no shock. Yet on study days three to five, it was higher stroke volume index together with worse left ventricular function, expressed as a higher left myocardial performance index, that was associated with respiratory distress. The same physiological variable therefore signals under-resuscitation early and over-resuscitation late, which is the strongest available argument for serial rather than single-point haemodynamic assessment.¹¹

Table 11. Haematocrit normalisation, cardiac performance and preload indices

First author, year	Modality	Principal quantitative finding	Interpretation
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Dung NM, 1999	Serial haematocrit and cardiac index	Colloids restored cardiac index and blood pressure and normalised haematocrit more rapidly than crystalloids; dextran 70 fastest	Confirms oncotic mechanism; establishes surrogate superiority of colloid
Wills BA, 2005	Serial haematocrit	Less rapid haematocrit improvement with Ringer lactate than with either colloid	Surrogate advantage reproduced in a large sample
Ngo NT, 2001	Pulse pressure and clinical response	Pulse pressure at presentation was the most significant determinant of clinical response, exceeding fluid allocation	Severity, not fluid choice, dominates early physiology
Thanachartwet V, 2016	Non-invasive cardiac output monitoring and IVC ultrasonography (n=162)	Stroke volume index and cardiac index significantly reduced days 4-15 and 5-8 ($p<0.05$); IVC diameter <1.5 cm with collapsibility $>50\%$ days 4-5 ($p<0.05$); hypovolaemic shock 52.9%, cardiogenic shock 47.1%	Half of dengue shock is cardiogenic, not volume-responsive
Yacoub S, 2017	Daily echocardiography over 5 days	Recurrent-shock group: pulse 114 vs 100 vs 100/min ($p=0.002$); SVI	Serial assessment distinguishes under- from over-resuscitation

	(n=102)	21.6 vs 22.8 vs 26.8 mL/m ² (p<0.001); lactate 4.2 vs 2.9 vs 2.2 mmol/L (p=0.001). Higher SVI and worse LV function on days 3-5 associated with respiratory distress	
McBride A, 2024	Serial lung ultrasound and endothelial biomarkers (n=135 adults)	IL-6 correlated most strongly with pulmonary vascular leak severity (R=0.41, p<0.001); Ang-2 correlated with leak (R=0.33, p<0.001)	Leak severity is inflammation-driven and quantifiable at the bedside

IVC = inferior vena cava; SVI = stroke volume index; LV = left ventricular; IL-6 = interleukin-6; Ang-2 = angiotensin-2.

Recurrent shock

Recurrent shock affects approximately thirty per cent of patients with dengue shock syndrome and identifies a phenotype at substantially elevated risk of fluid overload, respiratory distress and death. The only comparative evidence on the influence of fluid strategy upon recurrence derives from the seven-hospital retrospective cohort, in which a liberal-colloid general management strategy, defined as continuous colloid infusion for more than four hours in clinically stable patients, was associated with a marked reduction in recurrent shock episodes relative to a conservative crystalloid-only strategy, with a risk ratio of 0.13 (p=0.043). This corresponds to an approximate eighty-seven per cent relative reduction and is the single most favourable result reported for liberal colloid use anywhere in the dengue literature.^{5,11}

The finding must nonetheless be interpreted together with the harms accrued in the same comparison, since the identical management contrast that reduced recurrent shock increased the odds of respiratory compromise by a factor of 8.84 (p<0.001) and the odds of requiring nasal

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continuous positive airway pressure or ventilation by a factor of 8.16 ($p < 0.001$), while also incurring significantly higher cost. Expressed as a clinical judgement, prolonged colloid infusion in stable patients trades a common, generally survivable and readily re-treatable complication, namely a further shock episode, for a less common but far more dangerous and resource-intensive complication, namely respiratory failure requiring positive-pressure support. In settings without reliable access to non-invasive or invasive ventilation, that trade is unfavourable, which is precisely the conclusion drawn by the investigators.⁵

Predictive rather than interventional evidence indicates that recurrence can be anticipated at admission. Admission lactate significantly predicted subsequent recurrent shock ($p = 0.004$) and correlated positively with the total intravenous fluid volume received ($\rho = 0.323$, $p = 0.001$) and with admission alanine and aspartate aminotransferase ($\rho = 0.764$ and $\rho = 0.773$ respectively, both $p < 0.001$). The correlation between admission lactate and total fluid volume is bidirectionally informative: patients with higher lactate receive more fluid, which both confounds observational fluid-outcome associations and offers a practical means of stratifying who requires escalated haemodynamic surveillance from the outset.¹¹

Table 12. Recurrent shock

First author, year	Exposure or predictor	Effect estimate and significance	Interpretation
Trieu HT, 2025	Liberal-colloid strategy (colloid >4 h) vs conservative crystalloid-only strategy in stable patients (n=547)	RR 0.13; $p = 0.043$	Significant reduction in recurrence, offset by an 8-fold rise in respiratory compromise and support requirement
Yacoub S, 2017	Admission venous lactate as predictor of recurrent shock	$p = 0.004$ for prediction; lactate correlated with total	Recurrence is predictable at admission and is confounded with fluid volume

	(n=102)	intravenous fluid received (rho=0.323, p=0.001)	
Yacoub S, 2017	Stroke volume index at enrolment, recurrent vs single vs no shock	21.6 vs 22.8 vs 26.8 mL/m ² ; p<0.001	Recurrent-shock phenotype is haemodynamically identifiable at enrolment
Yacoub S, 2017	Enrolment pulse rate, recurrent vs single vs no shock	114 vs 100 vs 100 beats/min; p=0.002	Simple bedside vital signs stratify recurrence risk
Thanachartwet V, 2016	Serial IVC and cardiac-output monitoring (n=162 adults)	Myocardial dysfunction persisted from defervescence to 2 weeks after fever onset	Late recurrence may be cardiogenic rather than hypovolaemic

RR = risk ratio; IVC = inferior vena cava.

Cumulative fluid volume, colloid-to-crystalloid ratio and dose-response thresholds

The most consequential quantitative findings of this review concern fluid dose rather than fluid type. In a retrospective cohort of 1,278 children with dengue shock syndrome and complete fluid data, the total intravenous fluid volume administered during the first twenty-four hours of paediatric intensive care admission discriminated the subsequent need for mechanical ventilation with an area under the receiver operating characteristic curve of 0.871 (95% confidence interval 0.836-0.905, p<0.001), and the colloid-to-crystalloid infusion ratio discriminated the same outcome with an area under the curve of 0.781 (95% CI 0.743-0.819, p<0.001). The optimal cut-point for cumulative infusion was 181 millilitres per kilogram, and for the colloid-to-crystalloid ratio was

1.6. An area under the curve exceeding 0.87 for a single continuous clinical variable is a level of discrimination rarely achieved by any biomarker in critical care, and it is achieved here by a quantity that is entirely within the prescriber control.⁴

Multivariable analysis in the same cohort identified excessive fluid resuscitation and a higher proportion of colloid solutions during the first twenty-four hours as independent predictors of mechanical ventilation, alongside female sex, severe bleeding and severe transaminitis. The resulting predictive model demonstrated a concordance statistic of 89 per cent with strong calibration and a Brier score of 0.04. Importantly, a more pronounced decline in glomerular filtration rate was observed in children who required ventilation than in those who did not, linking the volume-respiratory axis to the volume-renal axis within a single cohort and a single time frame.⁴

The dose-response character of these relationships is what elevates them above ordinary observational association. Three of the Bradford Hill criteria are satisfied within this evidence: a biological gradient, in that risk rises continuously with volume and with colloid proportion and a threshold can be identified; temporality, in that fluid exposure in the first twenty-four hours precedes ventilation and renal decline measured subsequently; and coherence, in that the mechanism, namely reabsorption of extravasated fluid into a recovering circulation with consequent pulmonary oedema, is independently established. The principal residual threat remains confounding by indication, and the two studies that addressed severity most rigorously, one by inverse probability weighting and one by multivariable adjustment with formal calibration, both retained significant fluid-outcome associations after adjustment.^{4,5,6}

Table 13. Cumulative fluid volume, colloid proportion and quantitative thresholds

First author, year	Fluid metric	Discrimination (AUC, 95% CI)	Optimal threshold	Adjusted association with outcome
Vo LT, 2025	Total intravenous fluid volume, first 24 h of PICU	0.871 (0.836-0.905), p<0.001	181 mL/kg	Excessive fluid resuscitation an independent

	admission			multivariable predictor of mechanical ventilation
Vo LT, 2025	Colloid-to-crystalloid infusion ratio, first 24 h	0.781 (0.743-0.819), p<0.001	Ratio 1.6	Higher colloid proportion an independent multivariable predictor of mechanical ventilation
Vo LT, 2025	Model incorporating volume and ratio	C-statistic 89%; Brier score 0.04	Not applicable	Strong calibration on internal validation
Nguyen Tat T, 2024 (ML)	Large cumulative fluid infusion; higher colloid-to-crystalloid ratio	Random forest and support vector machine models highest discrimination	Not reported as single cut-point	Both retained as significant features on SHAP analysis
Nguyen Tat T, 2024 (L/B)	Cumulative amount of fluid infused, first 24 h	Not applicable (predictor within mortality model)	Not applicable	Independent multivariable predictor of 28-day in-hospital mortality
Trieu HT, 2025	Duration of colloid infusion (conservative <1 h; intermediate 1-4 h; liberal >4 h)	Not applicable (categorical strategy)	4 h of continuous colloid	Liberal strategy: respiratory compromise OR 8.84, p<0.001; NCPAP/ventilation OR 8.16, p<0.001, after

				inverse probability weighting
Yacoub S, 2017	Total intravenous fluid administered during ICU admission	Not applicable	Not applicable	Respiratory distress OR 1.03 per unit volume (95% CI 1.01-1.06), p=0.001

AUC = area under the receiver operating characteristic curve; PICU = paediatric intensive care unit; SHAP = Shapley Additive Explanations; NCPAP = nasal continuous positive airway pressure; OR = odds ratio; ML = machine learning; L/B = lactate-to-bicarbonate.

Respiratory compromise and ventilatory support

Respiratory compromise is the dominant fluid-attributable complication of dengue shock syndrome and the principal mechanism through which fluid strategy influences survival. The most informative comparative data derive from the seven-hospital retrospective cohort of 691 children, in which mixed crystalloid-colloid initial resuscitation, compared with crystalloid alone during the first two hours, was significantly associated with respiratory compromise (hazard ratio 2.08, p=0.022), with requirement for nasal continuous positive airway pressure or ventilation (odds ratio 2.34, p<0.045) and with additional days in hospital after shock onset (risk ratio 1.33, p=0.032), after adjustment for baseline severity by inverse probability weighting. Among the 547 children who stabilised within two hours, the liberal-colloid maintenance strategy increased the odds of respiratory compromise 8.84-fold (p<0.001) and of respiratory support 8.16-fold (p<0.001) relative to a conservative crystalloid-only strategy.⁵

Cohort data quantify both the incidence and the lethality of this complication. Among 1,278 children with dengue shock syndrome, 170 (13.3 per cent) required mechanical ventilation, and case fatality within that group was 22.4 per cent against 0.1 per cent in the non-ventilated group. Obesity independently increased the odds of severe respiratory failure requiring ventilation 2.3-fold (95% confidence interval 1.31-4.06, p<0.01) in a cohort of 858 children, without affecting mortality or acute liver failure, which is consistent with a mechanism operating through increased plasma-leak burden and reduced respiratory reserve rather than through generalised disease severity. In

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prospective intensive-care data, total intravenous fluid administered during the admission was associated with respiratory distress with an odds ratio of 1.03 per unit volume (95% CI 1.01-1.06, $p=0.001$), and higher stroke volume index with worse left ventricular function on days three to five predicted the same outcome.^{4,6,10,11}

In adult severe dengue, admission respiratory rate was an independent predictor of in-hospital death (odds ratio 1.10 per breath per minute, 95% CI 1.03-1.17, $p=0.004$), and among the same 137 intensive-care patients circulatory failure occurred in 62 per cent with six patients requiring veno-arterial extracorporeal membrane oxygenation. Pulmonary vascular leak assessed by daily lung ultrasound in 135 adults with dengue shock correlated most strongly with interleukin-6 ($R=0.41$, $p<0.001$) and with angiopoietin-2 ($R=0.33$, $p<0.001$), establishing that the pulmonary compartment is both the earliest and the most quantifiable site of leak and therefore the appropriate target for bedside surveillance during resuscitation.^{13,14}

Table 14. Respiratory compromise and ventilatory support

First author, year	Exposure	Effect estimate and significance	Interpretation
Trieu HT, 2025	Mixed crystalloid/colloid vs crystalloid-only initial resuscitation (n=691)	Respiratory compromise HR 2.08, $p=0.022$; NCPAP/ventilation OR 2.34, $p<0.045$	Adding colloid at the outset doubles respiratory risk after severity adjustment
Trieu HT, 2025	Liberal-colloid (>4 h) vs conservative-colloid strategy in stable patients (n=547)	Respiratory compromise OR 8.84, $p<0.001$; NCPAP/ventilation OR 8.16, $p<0.001$	Prolonged colloid exposure is the strongest identified determinant of respiratory failure
Vo LT,	Cumulative fluid	AUC 0.871 (0.836-	Volume is a highly

2025	volume, first 24 h	0.905), $p < 0.001$; threshold 181 mL/kg	discriminating, modifiable determinant of ventilation
Vo LT, 2025	Colloid-to-crystalloid ratio, first 24 h	AUC 0.781 (0.743- 0.819), $p < 0.001$; threshold 1.6	Colloid proportion independently predicts ventilation
Nguyen Tat T, 2024 (ML)	Composite fluid and clinical covariates (n=1,278)	170/1,278 (13.3%) ventilated; fatality 22.4% vs 0.1%	Ventilation marks a two- hundred-fold mortality differential
Nguyen TH, 2023	Obesity in children with dengue shock syndrome (n=858)	OR 2.3 (1.31- 4.06), $p < 0.01$ for severe respiratory failure requiring ventilation	Obesity is an identifiable pre- treatment risk amplifier
Yacoub S, 2017	Total intravenous fluid during ICU admission (n=102)	OR 1.03 per unit volume (1.01- 1.06), $p = 0.001$	Dose-dependent relationship confirmed prospectively
Yacoub S, 2017	Higher SVI and higher left myocardial performance index, days 3-5	Associated with respiratory distress	Late-phase over-resuscitation is echocardiographically detectable
Vidal C, 2025	Admission respiratory rate in adult severe dengue (n=137)	OR 1.10 per breath/min (1.03- 1.17), $p = 0.004$ for death	Respiratory rate is an early independent mortality signal
McBride A, 2024	Interleukin-6 and angiopoietin-2 vs	IL-6 $R = 0.41$, $p < 0.001$; Ang-2	Leak severity is biologically graded and ultrasound-

	pulmonary vascular leak (n=135)	R=0.33, p<0.001	quantifiable
Wang C, 2023	Respiratory distress as determinant of acute kidney injury (n=242)	OR 4.15 (1.79-9.63)	Respiratory and renal complications are mechanistically linked

HR = hazard ratio; OR = odds ratio; AUC = area under the curve; NCPAP = nasal continuous positive airway pressure; SVI = stroke volume index; ML = machine learning.

Acute kidney injury and renal trajectory

Dengue-associated acute kidney injury occupies an ambiguous position between consequence of shock and consequence of its treatment, and the assembled evidence supports contributions from both. Reported incidence varies widely with the case definition and case mix, from 4.8 per cent among 1,484 hospitalised adults in Thailand assessed by KDIGO criteria, through 14.2 per cent among 667 inpatients in Pakistan assessed by AKIN criteria, to 35.1 per cent among 242 adults with severe dengue in southern China, of whom 13.2 per cent reached stage 3. Prognostic weight is uniformly heavy: in the Chinese cohort, fatality was 22.4 per cent with acute kidney injury against 5.7 per cent without ($p<0.001$) with a median hospital stay of thirteen versus nine days ($p<0.001$); in the Pakistani cohort, all fatalities occurred among patients with acute kidney injury and 48.4 per cent of survivors with renal injury retained renal insufficiency at discharge.^{15,17,18}

The determinants identified across these cohorts are informative about mechanism. Multivariable analysis in the Pakistani cohort identified dengue haemorrhagic fever (odds ratio 8.0, 95% confidence interval 3.64-17.59, $p<0.001$), multi-organ dysfunction (odds ratio 17.9, 95% CI 9.14-35.12, $p<0.001$), rhabdomyolysis (odds ratio 7.9, 95% CI 3.04-20.49), diabetes mellitus (odds ratio 4.7, $p=0.034$), late hospitalisation (odds ratio 2.1, $p=0.033$) and nephrotoxic drug exposure (odds ratio 2.9, $p=0.006$). The Chinese cohort identified respiratory distress (odds ratio 4.15, 95% CI 1.79-9.63), high international normalised ratio (odds ratio 6.44, 95% CI 1.89-21.95), hypertension, nephrotoxic drugs and haematuria. Two of these determinants, namely late hospitalisation and respiratory distress, connect renal injury directly to the fluid axis: the former

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reflects delayed volume replacement in the leakage phase, and the latter reflects fluid accumulation in the recovery phase.^{15,18}

The most direct evidence linking fluid dose to renal trajectory within a dengue population comes from linear mixed-effects modelling of renal function over the first forty-eight hours in 1,278 children, in which a more pronounced decline in glomerular filtration rate occurred in those requiring mechanical ventilation, that is, in those who had received the largest cumulative volumes and the highest colloid proportions. Because both the pulmonary and the renal outcome share the same upstream exposure within the same cohort and the same time window, the most parsimonious interpretation is that excessive volume replacement injures the kidney through venous congestion and increased renal interstitial pressure, in addition to any direct effect of the colloid molecule itself.⁴

Table 15. Acute kidney injury and renal trajectory

First author, year	Population	AKI incidence	Independent determinants	Renal and survival outcomes
Vo LT, 2025	Children with DSS (n=1,278)	Renal function modelled as continuous outcome	Ventilation requirement (itself driven by fluid volume and colloid ratio)	Significantly steeper decline in glomerular filtration rate in ventilated children
Mallhi TH, 2015	Hospitalised dengue (n=667), Pakistan	95/667 (14.2%); AKIN-I 76.8%, AKIN-II 16.8%, AKIN-III	DHF OR 8.0 (3.64-17.59); MODS OR 17.9 (9.14-35.12); rhabdomyolysis OR 7.9 (3.04-20.49); diabetes OR 4.7; late hospitalisation	Renal insufficiency at discharge in 48.4%; all deaths occurred in AKI group; longer stay OR 1.3, p=0.044

		6.4%	OR 2.1; nephrotoxic drugs OR 2.9	
Diptyanusa A, 2019	Hospitalised adults (n=1,484), Thailand	71/1,484 (4.8%) by KDIGO	Older age, male sex, diabetes, obesity, severe dengue, bacterial co-infection	Dialysis in 14.1% of AKI cases; mortality 12.7% in AKI group
Wang C, 2023	Adults with severe dengue (n=242), China	85/242 (35.1%); severe (stage 3) 32/242 (13.2%)	Hypertension OR 2.03 (1.10-3.76); nephrotoxic drugs OR 1.90 (1.00- 3.60); respiratory distress OR 4.15 (1.79-9.63); high INR OR 6.44 (1.89- 21.95); haematuria OR 2.12 (1.14- 3.95)	Fatality 22.4% vs 5.7% (p<0.001); stay 13 vs 9 days (p<0.001)
Mallhi TH, 2017	Dengue inpatients (n=667)	Not primary endpoint	AKI among factors associated with death (p<0.001)	Prolonged stay in 49.2%; mean stay 4.88 +/- 2.74 days
Vidal C, 2025	Adult ICU severe dengue (n=137)	Renal failure in 59%	Multi-organ failure predominant	In-hospital mortality 25%
Wills BA,	Children	Not reported	No difference in	No signal of colloid-

2005	with DSS (n=512), RCT	as an endpoint	fluid-overload severity between fluid groups	attributable renal harm in this trial
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AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; KDIGO = Kidney Disease Improving Global Outcomes; DHF = dengue haemorrhagic fever; MODS = multi-organ dysfunction syndrome; INR = international normalised ratio; DSS = dengue shock syndrome; OR = odds ratio.

Haemorrhage, coagulopathy and transfusion

The theoretical concern that synthetic colloids might aggravate the haemostatic derangement of dengue, whether through haemodilution, interference with platelet function and factor VIII/von Willebrand complex activity, or impairment of fibrin polymerisation, was directly addressed by the three-fluid randomised trial and was not substantiated: bleeding manifestations, coagulation derangements and severity of fluid overload were similar across all fluid-treatment groups, including dextran 70 and hydroxyethyl starch. Similarly, dextran 70 was reported to normalise haematocrit and restore cardiac index most rapidly without adverse effects in the earlier four-arm trial. Within the dengue population, therefore, the randomised evidence does not support a clinically significant colloid-attributable coagulopathy at the doses used for initial resuscitation.^{1,3}

Severe bleeding nonetheless remains one of the most powerful determinants of adverse outcome in dengue shock syndrome, entering multivariable models both for mechanical ventilation and for mortality. In 1,278 children, severe bleeding was an independent predictor of the need for mechanical ventilation alongside excessive fluid resuscitation and high colloid proportion; in 492 children, severe bleeding was an independent predictor of 28-day mortality alongside cumulative fluid volume and a vasoactive-inotropic score exceeding thirty. The co-occurrence of bleeding and volume overload in the same predictive models is clinically important because these two complications pull fluid decisions in opposite directions, the former demanding volume and blood component replacement and the latter demanding restraint.^{4,7}

The role of prophylactic platelet transfusion as an adjunct to fluid-based supportive care was tested in a multicentre open-label randomised trial of 372 adults with dengue and platelet counts of

20,000 per microlitre or below. Clinical bleeding by day seven or discharge occurred in 40 of 187 patients (21 per cent) in the transfusion group and 48 of 182 (26 per cent) in the supportive-care-only group, with a risk difference of -4.98 per cent (95% confidence interval -15.08 to 5.34) and a relative risk of 0.81 (95% CI 0.56-1.17, $p=0.16$). Adverse events were significantly more frequent with transfusion, occurring in thirteen versus two patients, with a relative risk of 6.26 (95% CI 1.43-27.34, $p=0.0064$), and included one serious adverse event of fluid overload and one of transfusion-related acute lung injury. This result is directly relevant to fluid stewardship because it demonstrates that a volume-adding prophylactic intervention conferred no haemostatic benefit while adding volume-related harm.²⁰

Table 16. Haemorrhage, coagulopathy and transfusion

First author, year	Comparison or exposure	Effect estimate and significance	Interpretation
Wills BA, 2005	Ringer lactate vs dextran 70 vs hydroxyethyl starch (n=512)	Bleeding manifestations, coagulation derangements and fluid-overload severity similar across all groups	No colloid-attributable coagulopathy at resuscitation doses in dengue
Dung NM, 1999	Dextran 70 and gelatin vs crystalloids (n=50)	Dextran 70 most rapid haematocrit and cardiac-index restoration without adverse effects	Small-sample safety signal favourable
Lye DC, 2017	Prophylactic platelet transfusion plus	Bleeding 21% vs 26%; RR 0.81 (0.56-	No haemostatic benefit from a volume-adding

	supportive care vs supportive care alone (n=372 adults)	1.17), p=0.16; risk difference -4.98% (- 15.08 to 5.34)	prophylactic intervention
Lye DC, 2017	Adverse events, transfusion vs control	13 vs 2 events; RR 6.26 (1.43-27.34), p=0.0064, including fluid overload and TRALI	Volume-adding adjuncts carry measurable respiratory and volume risk
Nguyen Tat T, 2024 (ML)	Severe bleeding as model covariate (n=1,278)	Independent predictor of need for mechanical ventilation	Bleeding and volume overload coexist as competing drivers
Nguyen Tat T, 2024 (L/B)	Severe bleeding as model covariate (n=492)	Independent predictor of 28-day in-hospital mortality	Haemorrhage remains an independent lethal pathway
Vidal C, 2025	Haemorrhagic events in adult ICU severe dengue (n=137)	Thrombocytopenia in 78% but haemorrhagic events uncommon; death driven by multi- organ failure	In adults, organ failure rather than bleeding dominates mortality
Woon YL, 2016	Contribution to dengue deaths (n=322)	Severe bleeding contributed to 29.7% of deaths vs DSS >70% and severe organ involvement 69%	Shock outweighs haemorrhage as a cause of death

RR = relative risk; TRALI = transfusion-related acute lung injury; ML = machine learning; L/B = lactate-to-bicarbonate; DSS = dengue shock syndrome.

Adverse fluid reactions

Where two fluids are equally efficacious, the choice between them becomes a safety decision, and on this criterion the randomised evidence in dengue shock syndrome is unambiguous. In the three-fluid trial, only minor differences in efficacy were detected between dextran 70 and 6% hydroxyethyl starch, but significantly more recipients of dextran than of starch experienced adverse reactions. On this basis the trial concluded that although the two colloids perform similarly in children with severe shock, starch may be preferable for that group specifically because of the adverse-reaction burden associated with dextran. This is the clearest example in the dengue fluid literature of a management recommendation determined by tolerability rather than by effect.³

The earlier four-arm trials did not detect adverse effects attributable to dextran 70 or to gelatin, but were considerably smaller, with 50 and 230 participants respectively, and were consequently underpowered for uncommon reactions. Read together, the three trials indicate an adverse-reaction gradient that becomes detectable only at sample sizes above several hundred, which has the practical implication that reassuring safety data from small single-centre series should not be relied upon when selecting a synthetic colloid. It should be noted that the dengue-specific evidence does not extend to the renal and mortality signals attributed to hydroxyethyl starch in adult critical illness, since no dengue trial has been powered for those endpoints; the apparent within-dengue preference for starch over dextran on tolerability grounds must therefore be qualified by the broader critical-care safety literature discussed in Section 4.^{1,2,3,27,32}

Table 17. Adverse fluid reactions

First author, year	Fluids compared	Adverse-reaction finding	Consequence for fluid selection
Wills BA, 2005	6% dextran 70 vs 6% hydroxyethyl starch (n=512)	Significantly more adverse reactions with dextran than	Starch preferred over dextran for severe shock on tolerability grounds

		with starch, at equivalent efficacy	
Wills BA, 2005	Ringer lactate vs either colloid	No excess of bleeding, coagulopathy or fluid-overload severity in any arm	Crystalloid carries no efficacy penalty and no safety penalty in moderate shock
Dung NM, 1999	Dextran 70, gelafundin 35,000, Ringer lactate, 0.9% saline (n=50)	No adverse effects attributed to dextran 70	Underpowered for uncommon reactions
Ngo NT, 2001	Dextran, gelatin, Ringer lactate, saline (n=230)	No fluid-specific adverse-effect signal reported; all patients survived	Underpowered for uncommon reactions
Lye DC, 2017	Platelet transfusion as volume-adding adjunct (n=372)	Urticaria (3), maculopapular rash (1), pruritus (1), chest pain (1), anaphylaxis (1), TRALI (1), fluid overload (1)	Illustrates the adverse-event cost of unnecessary volume-adding therapy

TRALI = transfusion-related acute lung injury.

Metabolic, lactate-derived and biochemical outcomes

Lactate and lactate-derived indices have emerged as the most practical bedside markers of resuscitation adequacy in paediatric dengue shock syndrome, and their performance characteristics are well quantified. For prediction of 28-day in-hospital mortality among 492 children, serum lactate achieved an area under the curve of 0.876 (95% confidence interval 0.807-0.944) with an

optimal cut-point of 4.2 millimoles per litre, and the lactate-to-bicarbonate ratio achieved 0.867 (95% CI 0.80-0.934) with an optimal cut-point of 0.25, both $p < 0.001$. When combined with the identified clinical predictors, the lactate-to-bicarbonate model yielded a higher odds ratio (8.66, 95% CI 1.96-38.3, $p < 0.01$) than the lactate-based model (1.35, 95% CI 1.15-1.58, $p < 0.001$).⁷

In a subsequent secondary analysis of 524 children, the lactate-to-albumin ratio outperformed both serum lactate and the lactate-to-bicarbonate ratio for the composite endpoint of in-hospital death, mechanical ventilation, dengue-associated acute liver failure and encephalitis, achieving an area under the curve of 0.82 (95% CI 0.76-0.87) against 0.72 (95% CI 0.65-0.78) for lactate and 0.68 (95% CI 0.62-0.74) for the lactate-to-bicarbonate ratio, all comparisons $p < 0.001$, with an optimal lactate-to-albumin cut-point of 1.25. The superiority of an albumin-normalised index is mechanistically interesting in the context of fluid therapy, since serum albumin in dengue reflects the magnitude of protein loss across the leaking endothelium and therefore encodes leak severity in addition to tissue hypoperfusion.⁸

Fluid and electrolyte derangement generated during resuscitation has independent prognostic consequences. Among 57 mechanically ventilated children with dengue shock syndrome, 21 (37 per cent) developed severe hypophosphataemia during intensive-care admission; after propensity-score matching for age, serum calcium, metabolic acidosis and creatinine, severe hypophosphataemia was not associated with mortality but was significantly correlated with prolonged mechanical ventilation and prolonged vasopressor requirement. Prospective data also demonstrate that admission lactate correlates strongly with transaminase elevation ($\rho = 0.764$ for alanine aminotransferase and $\rho = 0.773$ for aspartate aminotransferase, both $p < 0.001$) and with total intravenous fluid received ($\rho = 0.323$, $p = 0.001$), indicating that metabolic, hepatic and volume derangements co-segregate.^{9,11}

Table 18. Metabolic, lactate-derived and biochemical outcomes

First author, year	Marker	Discrimination (AUC, 95% CI)	Optimal cut-point	Outcome predicted

Nguyen Tat T, 2024	Serum lactate	0.876 (0.807-0.944), $p<0.001$	4.2 mmol/L	28-day in-hospital mortality
Nguyen Tat T, 2024	Lactate-to-bicarbonate ratio	0.867 (0.80-0.934), $p<0.001$	0.25	28-day in-hospital mortality
Nguyen Tat T, 2024	L/B combined with clinical predictors vs lactate model	OR 8.66 (1.96-38.3), $p<0.01$ vs OR 1.35 (1.15-1.58), $p<0.001$	Not applicable	28-day in-hospital mortality
Nguyen Tat T, 2025	Lactate-to-albumin ratio	0.82 (0.76-0.87), $p<0.001$	1.25	Composite of death, ventilation, acute liver failure, encephalitis
Nguyen Tat T, 2025	Serum lactate (same cohort)	0.72 (0.65-0.78)	Not reported	Same composite endpoint
Nguyen Tat T, 2025	Lactate-to-bicarbonate ratio (same cohort)	0.68 (0.62-0.74)	0.20	Same composite endpoint
Vo LT, 2025	Severe hypophosphataemia in ventilated children (n=57)	Present in 21/57 (37%)	Not applicable	Prolonged ventilation and vasopressor duration; not mortality
Yacoub S, 2017	Admission lactate (n=102)	$p=0.004$ for prediction of recurrent shock	Not reported	Recurrent shock; correlated with total fluid ($\rho=0.323$) and transaminases

				(rho=0.764/0.773)
Nguyen Tat T, 2024 (ML)	Severe transaminitis as model covariate (n=1,278)	Independent predictor	Not applicable	Mechanical ventilation requirement

AUC = area under the curve; L/B = lactate-to-bicarbonate; OR = odds ratio; ML = machine learning.

Organ dysfunction and multi-organ failure

Multi-organ dysfunction is the final common pathway of dengue shock and is quantitatively linked to both inadequate and excessive volume replacement. In a prospective cohort of 135 adults with dengue shock, median Sequential Organ Failure Assessment score at admission was 7, thirty-four patients required intensive-care admission and five died; interleukin-6 and ferritin were associated with admission organ-failure score with beta coefficients of 0.70 and 0.45 respectively (both $p < 0.001$), and all patients who died had pre-mortem ferritin of at least 100,000 nanograms per millilitre. All four glyocalyx degradation biomarkers were positively associated with organ-failure score, and syndecan-1 alone predicted intensive-care admission (odds ratio 2.02, $p < 0.001$) and death (odds ratio 6.51, $p < 0.001$).¹³

In adult intensive care on Reunion Island, hepatic failure occurred in 50 per cent and renal failure in 59 per cent of 137 patients with severe dengue, neurological presentations in 9 per cent, myocarditis in 9 per cent and distributive shock in 12 per cent, with mortality attributed primarily to multiple organ failure rather than to haemorrhagic complications. Among children, obesity was significantly associated with respiratory failure requiring ventilation but not with dengue-associated paediatric acute liver failure or with mortality, indicating that the hepatic and respiratory pathways to organ failure are dissociable. National mortality review in Malaysia found multi-organ involvement in more than half of 322 decedents and severe organ involvement contributing to 69 per cent of deaths.^{10,14,23}

A distinct and under-recognised organ-failure phenotype arising directly from volume overload is dengue obstructive shock syndrome, in which the combination of severe plasma leakage

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into the thoracic and abdominal cavities and positive-pressure mechanical ventilation raises intrathoracic pressure sufficiently to impair venous return and cardiac output. Although documented in only two reported patients, and therefore excluded from the primary evidence tables as a case report, this entity is conceptually important because it represents the terminal expression of the fluid-overload cascade and because its management inverts the usual reflex: both patients recovered following judicious fluid administration guided by repeated point-of-care ultrasonography, plasma exchange and continuous renal replacement therapy, rather than further volume expansion.⁴⁹

Table 19. Organ dysfunction and multi-organ failure

First author, year	Population	Organ dysfunction findings	Interpretation
McBride A, 2024	135 adults with dengue shock	Median SOFA 7; 34 required ICU; 5 deaths. IL-6 beta 0.70 and ferritin beta 0.45 vs SOFA (both $p < 0.001$); syndecan-1 predicted ICU admission (OR 2.02, $p < 0.001$) and death (OR 6.51, $p < 0.001$); all decedents had ferritin $\geq 100,000$ ng/mL	Organ failure is inflammation- and glycocalyx-driven, not purely haemodynamic
Vidal C, 2025	137 adults, 5 ICUs	Circulatory failure 62% (distributive 12%, myocarditis 9%); hepatic failure 50%; renal failure 59%; neurological 9%; 6 patients required VA-ECMO; mortality 25%	Adult severe dengue is a multi-organ disease; haemorrhage uncommon
Nguyen	858	Obesity associated with	Respiratory and hepatic

TH, 2023	children with DSS	ventilation (OR 2.3, 1.31-4.06, $p<0.01$) but not with acute liver failure or death	organ-failure pathways are dissociable
Nguyen Tat T, 2025	524 children with DSS	17% met the composite endpoint of death, ventilation, acute liver failure or encephalitis	Composite organ-failure burden is substantial and predictable
Mallhi TH, 2015	667 dengue inpatients	Multi-organ dysfunction the strongest determinant of AKI (OR 17.9, 9.14-35.12, $p<0.001$)	Renal injury is embedded within multi-organ failure
Mallhi TH, 2017	667 dengue inpatients	Multi-organ dysfunction independently associated with prolonged stay (OR 2.1) and with death ($p<0.001$)	Organ failure drives both mortality and resource use
Woon YL, 2016	322 dengue deaths	Multi-organ involvement in >50%; severe organ involvement contributed to 69% of deaths; DSS to >70%	Shock and organ failure are the dominant lethal mechanisms

SOFA = Sequential Organ Failure Assessment; ICU = intensive care unit; IL-6 = interleukin-6; VA-ECMO = veno-arterial extracorporeal membrane oxygenation; DSS = dengue shock syndrome; AKI = acute kidney injury; OR = odds ratio.

Resource utilisation, length of stay and cost

Fluid strategy has directly measurable economic and logistical consequences. In the seven-hospital cohort, mixed crystalloid-colloid initial resuscitation was significantly associated with additional days in hospital after shock onset relative to crystalloid alone (risk ratio 1.33, $p=0.032$), and the liberal-colloid strategy incurred significantly higher costs than the conservative crystalloid-

only strategy in addition to its eightfold increase in respiratory-support requirement. Since synthetic colloids are intrinsically more expensive than isotonic crystalloids, and since the complications they generate consume high-dependency capacity, the cost differential compounds across the acquisition price of the fluid, the length of stay, and the requirement for respiratory support.⁵

Duration of organ support constitutes the other major resource consequence. Among 57 mechanically ventilated children with dengue shock syndrome, median duration of ventilation was five days (interquartile range 3-6) and median vasopressor duration three days (interquartile range 1-5), with severe hypophosphataemia significantly prolonging both. In adults, acute kidney injury lengthened hospital stay from a median of nine to thirteen days ($p<0.001$) in a Chinese multicentre cohort, and acute kidney injury was significantly associated with prolonged stay in a Pakistani cohort (odds ratio 1.3, $p=0.044$) in which 49.2 per cent of 667 patients stayed longer than three days and mean stay was 4.88 plus or minus 2.74 days.^{9,16,18}

At the level of health-system organisation, the burden of hospitalisation for dengue is substantially in excess of the burden of severe disease, which creates an opportunity for fluid-based triage. Prospective surveillance of 1,064 hospitalised patients with confirmed dengue in Sri Lanka found that although 80 per cent of children and 54.7 per cent of adults developed dengue haemorrhagic fever during admission, only 8.6 per cent of children and 2.2 per cent of adults developed dengue shock syndrome, and mortality was 0.2 per cent. The investigators concluded that developing an algorithm to triage patients to ambulatory rather than inpatient management should be a future goal in order to optimise the use of health-care resources in endemic countries.²¹

Table 20. Resource utilisation, length of stay and cost

First author, year	Finding	Effect estimate and significance	Resource implication
Trieu HT, 2025	Days in hospital after shock onset, mixed crystalloid/colloid vs crystalloid alone	RR 1.33; $p=0.032$	Colloid at the outset prolongs admission

Trieu HT, 2025	Cost of liberal-colloid vs conservative-colloid strategy	Significantly higher for liberal strategy	Higher acquisition cost compounded by complication cost
Vo LT, 2025 (hypophosphataemia)	Duration of support in ventilated children (n=57)	Median ventilation 5 days (IQR 3-6); vasopressors 3 days (IQR 1-5); both prolonged by severe hypophosphataemia	Metabolic derangement extends organ-support demand
Wang C, 2023	Length of stay with vs without acute kidney injury (adults)	13 vs 9 days; p<0.001	Renal injury adds four hospital days
Mallhi TH, 2017	Prolonged hospitalisation >3 days (n=667)	49.2% of patients; mean stay 4.88 +/- 2.74 days; DHF OR 2.3, MODS OR 2.1	Half of admissions exceed three days
Mallhi TH, 2015	Length of stay with acute kidney injury	OR 1.3; p=0.044	Renal injury independently prolongs stay
Bodinayake CK, 2021	Severity distribution among 1,064 hospitalised dengue patients	DSS in 8.6% of children and 2.2% of adults; mortality 0.2%	Substantial scope for ambulatory triage of low-risk patients
Nasir NH, 2017	Hospital admission with	10.0% vs 17.6%;	Signal of

	vs without a structured oral fluid chart	p=0.192 (not significant)	admission reduction requiring adequately powered confirmation
Vidal C, 2025	ICU utilisation for severe dengue	137 ICU admissions per 72,434 confirmed infections (1.8 per 1,000)	ICU demand is low per infection but concentrated in epidemics

RR = risk ratio; OR = odds ratio; IQR = interquartile range; DHF = dengue haemorrhagic fever; MODS = multi-organ dysfunction syndrome; DSS = dengue shock syndrome; ICU = intensive care unit.

Prevention of shock, intravenous fluid requirement and hospitalisation

Upstream fluid interventions in the ambulatory phase offer the theoretical possibility of preventing shock altogether, and one randomised evaluation of this strategy has been conducted. In a pilot randomised trial of 138 ambulatory patients aged over twelve years with suspected dengue and thrombocytopenia, provision of a structured fluid chart and a 200 millilitre cup in addition to a dengue home-care card produced fewer hospital admissions (7 of 70, 10.0 per cent, versus 12 of 68, 17.6 per cent, $p=0.192$), fewer patients requiring intravenous fluid (9 of 70, 12.9 per cent, versus 15 of 68, 22.1 per cent, $p=0.154$) and greater daily oral intake (approximately 3,000 versus 2,500 millilitres, $p=0.521$). None of these differences attained statistical significance, and the study was explicitly designed and reported as a feasibility exercise requiring a larger definitive trial.¹⁹

Observational evidence indicates both that progression to shock is uncommon among hospitalised dengue patients and that a substantial subgroup of apparently severe presentations is volume-responsive without plasma leakage. In a prospective emergency-department study of 715 adults with confirmed dengue in Martinique, severe illness was documented in 332 cases (46.4 per

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cent), of which dengue haemorrhagic fever or dengue shock syndrome accounted for 104 (31.3 per cent) and acute organ failure for 56 (16.9 per cent); however 171 patients (51.5 per cent of severe cases) presented with presyncope, intense weakness, prolonged gastrointestinal symptoms and hypotension without evidence of plasma leakage, and improved markedly within twenty-four hours with saline infusion. The investigators concluded that many patients who appear seriously ill on presentation will respond to intravenous fluids.²²

Timely identification of plasma leakage is the pivotal determinant of whether fluid therapy is initiated at the appropriate moment. A prospective cohort of 667 dengue patients aged fifteen years or above, of whom 318 (47.7 per cent) developed plasma leakage, identified three independent predictors, namely body mass index of 25 kilograms per square metre or above (odds ratio 1.784, 95% confidence interval 1.040-3.057, $p=0.035$), platelet count below 100,000 per cubic millimetre on fever days three to four (odds ratio 2.151, 95% CI 1.269-3.647, $p=0.004$) and aminotransferase of 100 units per litre or above on fever days three to four (odds ratio 2.189, 95% CI 1.231-3.891, $p=0.008$), yielding a three-point score in which a score of one or more had 88.8 per cent sensitivity and a score of three had 93.4 per cent specificity, with an area under the curve of 0.677 (95% CI 0.616-0.739).²⁴

Table 21. Prevention of shock, intravenous fluid requirement and hospitalisation

First author, year	Intervention or predictor	Effect estimate and significance	Interpretation
Nasir NH, 2017	Structured fluid chart plus 200 mL cup vs home-care card alone (n=138, RCT)	Admission 10.0% vs 17.6%, $p=0.192$; intravenous fluid 12.9% vs 22.1%, $p=0.154$; oral intake ~3,000 vs ~2,500 mL, $p=0.521$	Consistent direction of benefit but underpowered; definitive trial required

Thomas L, 2011	Intravenous saline in severe-appearing dengue without plasma leakage (n=715 adults)	171/332 severe cases (51.5%) had dehydration-type presentation improving markedly within 24 h with saline	A large fraction of severe presentations are simple volume-responsive states
Talukdar S, 2021	Three-item plasma-leak score (BMI ≥ 25 ; platelets $< 100,000/\text{mm}^3$; AST or ALT ≥ 100 U/L on fever days 3-4)	ORs 1.784 (1.040-3.057), 2.151 (1.269-3.647), 2.189 (1.231-3.891); AUC 0.677 (0.616-0.739); sensitivity 88.8% at score ≥ 1 ; specificity 93.4% at score 3	Permits pre-emptive rather than reactive fluid planning
Bodinayake CK, 2021	Progression among 1,064 hospitalised confirmed dengue patients	DHF in 80% of children and 54.7% of adults; DSS in 8.6% and 2.2%; severe dengue in 14.3% and 11.4%; mortality 0.2%	Progression to shock is uncommon; triage algorithms warranted
Woon YL, 2016	Timing of recognition among 322 dengue deaths	Only 34% suspected of dengue at initial presentation; 22.4% had no warning signs; median 1 day to first	Failure of early recognition precedes failure of fluid therapy

		medical contact	
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RCT = randomised controlled trial; BMI = body mass index; AST = aspartate aminotransferase; ALT = alanine aminotransferase; AUC = area under the curve; DHF = dengue haemorrhagic fever; DSS = dengue shock syndrome; OR = odds ratio.

Certainty of evidence

Certainty was rated per outcome domain using the GRADE approach. Randomised evidence for fluid-type comparisons in moderately severe paediatric shock was rated moderate, downgraded from high for indirectness because all trials were conducted in Vietnamese children between 1999 and 2005 and their applicability to adults and to contemporary practice is uncertain. Observational evidence on cumulative volume and colloid proportion, although beginning at low certainty by design, was upgraded to moderate on account of large effect magnitude, demonstrable dose-response gradient and adequate adjustment for baseline severity in the two most rigorous analyses. Outcomes for which certainty remained low or very low are those in which the evidence rests on single small cohorts or on underpowered pilot randomisation.¹⁻²⁴

Table 22. GRADE summary of findings

No.	Outcome domain	Summary of principal finding	Certainty	Reason for rating
O1	All-cause mortality	No difference by fluid type in randomised trials (mortality <0.2%); cumulative fluid volume an independent multivariable predictor of 28-day mortality; ventilated children 22.4% vs 0.1% fatality; adult ICU mortality	Moderate	Randomised data uninformative (no events); observational data consistent, large effect, dose-response

		25%		
O2	Resuscitation failure / rescue colloid	Crystalloid non-inferior to colloid in moderate shock (RR 1.08, 0.78-1.47); colloids equivalent to each other	Moderate	Large adequately powered blinded RCT; downgraded for indirectness (paediatric, single country, 2005)
O3	Time to haemodynamic recovery	Marginally longer with Ringer lactate than colloid; no propagation to patient-important outcomes	Moderate	Consistent across three RCTs; surrogate endpoint
O4	Haematocrit and cardiac performance	Colloid normalises haematocrit and restores cardiac index faster; half of adult dengue shock is cardiogenic rather than hypovolaemic	Moderate	Coherent mechanism; RCT plus prospective physiological cohorts
O5	Recurrent shock	Liberal-colloid strategy reduces recurrence (RR 0.13, p=0.043) but at eightfold respiratory cost	Low	Single non-randomised comparison; wide uncertainty; competing harm
O6	Cumulative volume and colloid ratio	Volume AUC 0.871 (threshold 181 mL/kg); ratio AUC 0.781 (threshold 1.6); both independent predictors	Moderate	Observational upgraded for very large effect, dose-response and calibration

		of ventilation		
O7	Respiratory compromise and ventilation	Mixed initial resuscitation HR 2.08; liberal colloid OR 8.84 for compromise and 8.16 for support; volume OR 1.03 per unit	Moderate	Multiple concordant cohorts; severity-adjusted; very large effect
O8	Acute kidney injury and renal trajectory	AKI in 4.8-35.1%; fatality 22.4% vs 5.7%; steeper GFR decline in ventilated (high-volume) children	Low	Heterogeneous definitions; fluid exposure indirectly measured in most cohorts
O9	Haemorrhage and transfusion	No colloid-attributable coagulopathy in RCT; prophylactic platelet transfusion ineffective (RR 0.81) and harmful (adverse events RR 6.26)	Moderate	Direct randomised evidence for both questions
O10	Adverse fluid reactions	Significantly more reactions with dextran 70 than hydroxyethyl starch at equivalent efficacy	Moderate	Prespecified safety comparison in adequately powered RCT
O11	Metabolic and lactate-derived outcomes	Lactate AUC 0.876 (cut-point 4.2 mmol/L); L/B 0.867 (0.25); LAR 0.82	Low	Single-institution overlapping cohorts; internal validation only

		(1.25) superior for composite endpoint		
O12	Organ dysfunction	SOFA correlates with IL-6, ferritin and glycocalyx markers; adult multi-organ failure the dominant lethal pathway	Low	Observational; mechanistic rather than interventional
O13	Resource use, stay and cost	Mixed initial resuscitation RR 1.33 for hospital days; liberal colloid significantly costlier; AKI adds 4 days	Low	Single comparative cohort for cost; heterogeneous stay definitions
O14	Prevention of shock and hospitalisation	Fluid chart reduced admission 17.6% to 10.0% (p=0.192, NS); plasma-leak score AUC 0.677; half of severe presentations volume-responsive without leak	Very low	Underpowered pilot randomisation; modest predictive discrimination

RR = relative or risk ratio; HR = hazard ratio; OR = odds ratio; AUC = area under the curve; GFR = glomerular filtration rate; L/B = lactate-to-bicarbonate; LAR = lactate-to-albumin ratio; SOFA = Sequential Organ Failure Assessment; IL-6 = interleukin-6; AKI = acute kidney injury; NS = not statistically significant; RCT = randomised controlled trial; ICU = intensive care unit.

DISCUSSION

Principal findings and their integration

This systematic review of 24 primary studies enrolling more than eleven thousand patients establishes five principal findings that together support a reconceptualisation of fluid therapy in dengue shock syndrome. First, isotonic crystalloid is non-inferior to synthetic colloid for initial resuscitation of moderately severe paediatric dengue shock, with a relative risk of rescue-colloid requirement of 1.08 (95% confidence interval 0.78-1.47), and should therefore constitute first-line therapy. Second, colloid retains a genuine but strictly physiological advantage confined to surrogate endpoints, namely faster haematocrit normalisation, faster cardiac-index restoration and marginally shorter time to initial recovery, with the benefit concentrated in patients presenting with the narrowest pulse pressure. Third, cumulative resuscitation volume behaves as a dose-dependent hazard with an identifiable threshold, discriminating the need for mechanical ventilation with an area under the curve of 0.871 above 181 millilitres per kilogram in the first twenty-four hours. Fourth, colloid proportion and duration are independently harmful, with a liberal-colloid strategy multiplying the odds of respiratory compromise by 8.84 and of respiratory support by 8.16. Fifth, colloid selection within the class is a tolerability rather than an efficacy decision, since dextran 70 caused significantly more adverse reactions than hydroxyethyl starch at equivalent effect.^{1,2,3,4,5}

The integration of these findings resolves the apparent contradiction at the centre of the field. Colloid solutions do exactly what their pharmacology predicts: they retain water intravascularly across a permeable barrier and therefore restore measured haemodynamic variables faster than crystalloid. The reason this does not translate into clinical benefit is that the leakage phase of dengue is self-terminating. Every millilitre of colloid retained in the intravascular space during the leakage phase, and every millilitre of colloid that has escaped into the interstitium and drags water after it, must be handled by the circulation and the kidneys during the reabsorption phase twenty-four to forty-eight hours later. The physiological advantage is therefore front-loaded and the physiological cost is back-loaded, and because trials measure the advantage in hours and the cost in days, the advantage is systematically easier to detect than the cost. It is precisely this asymmetry that the recent observational literature on cumulative volume has begun to correct.^{3,4,5}

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The therapeutic trade-off is quantifiable and should be made explicit at the bedside. In the seven-hospital comparison, prolonged colloid use in stable children reduced recurrent shock with a risk ratio of 0.13 while increasing the odds of needing respiratory support by a factor of 8.16. Recurrent shock is common, generally detectable, and re-treatable with a further bolus; respiratory failure requiring positive-pressure ventilation is less common but carries, in the largest available paediatric series, a 22.4 per cent case fatality. Expressed in terms of expected harm rather than relative risk, trading recurrent shock for ventilatory dependence is an unfavourable exchange in almost any dengue-endemic setting, and is categorically unfavourable where non-invasive or invasive respiratory support is not reliably available. The investigators own conclusion, that prolonged use of colloid solutions may be inappropriate especially in settings without access to respiratory support, follows directly.^{5,6}

Pathophysiological interpretation: the endothelial glycocalyx and the limits of oncotic logic

The pharmacological premise of colloid therapy is that a macromolecular solute exerts oncotic pressure across a semi-permeable membrane and therefore retains water within the vascular lumen. This premise requires an intact endothelial glycocalyx, since it is the glycocalyx and not the endothelial cell layer that constitutes the effective oncotic barrier in the revised Starling model. Prospective biomarker profiling in adults with dengue shock demonstrates that this barrier is not intact: hyaluronan, heparan sulfate, endocan and syndecan-1 were all positively associated with organ-failure severity, and syndecan-1 independently predicted intensive-care admission (odds ratio 2.02, $p<0.001$) and death (odds ratio 6.51, $p<0.001$). Glycocalyx shedding of this magnitude implies that the retention of infused macromolecules is progressively lost as disease severity increases, which explains the counter-intuitive observation that colloid performs least well where it is most needed.¹³

The same dataset locates the driver of leakage upstream of the endothelium in the inflammatory compartment. Interleukin-6 and ferritin were associated with admission organ-failure score with beta coefficients of 0.70 and 0.45 respectively (both $p<0.001$), with intensive-care admission and with mortality, and interleukin-6 correlated most strongly with the severity of pulmonary vascular leak ($R=0.41$, $p<0.001$). Angiopoietin-2, a marker of endothelial destabilisation

through Tie-2 antagonism, correlated with pulmonary leak ($R=0.33$, $p<0.001$) and independently predicted death (odds ratio 8.06, $p=0.002$). These observations imply that the definitive solution to dengue leakage is not a better fluid but an intervention that closes the barrier, and they identify anti-interleukin-1 and anti-interleukin-6 agents and Tie-2 agonists as rational candidates for therapeutic trials. Preliminary uncontrolled experience with the interleukin-1 receptor antagonist anakinra in 45 children with hyperinflammatory severe dengue reported 80 per cent survival with improvement in fluid requirements following initiation, although mortality was 100 per cent in the four children with ferritin above 100,000 nanograms per millilitre.^{13,51}

A second pathophysiological consideration further constrains the oncotic argument. Prospective non-invasive haemodynamic phenotyping in adults established that only 52.9 per cent of dengue shock episodes were hypovolaemic and 47.1 per cent were cardiogenic, with myocardial dysfunction appearing on the day of defervescence and persisting for up to two weeks. In the cardiogenic half of dengue shock, volume expansion of any composition is physiologically inappropriate and may precipitate pulmonary oedema at volumes far below the 181 millilitres per kilogram threshold derived from mixed populations. This finding provides the strongest available justification for serial bedside echocardiography or non-invasive cardiac output monitoring in dengue shock that does not respond promptly to initial resuscitation, and for the corresponding shift from protocol-driven to physiology-driven fluid titration.^{12,11}

Comparison with the wider critical-care fluid literature

The dengue-specific findings of this review are congruent with, and are strengthened by, an extensive body of secondary evidence in general critical care, which is discussed here in accordance with the protocol under which systematic reviews and meta-analyses were excluded from the primary evidence tables but retained for contextual triangulation. Cochrane synthesis of 69 studies enrolling 30,020 critically ill participants found that starches, dextrans, albumin or fresh frozen plasma probably make little or no difference to mortality compared with crystalloids, and that starches probably slightly increase the need for blood transfusion (relative risk 1.19, 95% confidence interval 1.02-1.39) and renal replacement therapy (relative risk 1.30, 95% CI 1.14-1.48). An earlier systematic review of 26 unconfounded trials reported an increased absolute mortality risk

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of 4 per cent with colloids, and meta-analysis of 38 trials found that hydroxyethyl starch was associated with increased mortality (relative risk 1.09, 95% CI 1.02-1.17), renal failure (relative risk 1.27, 95% CI 1.09-1.47) and renal replacement therapy (relative risk 1.32, 95% CI 1.15-1.50) after exclusion of trials subsequently retracted for misconduct.^{27,30,32}

Direct randomised evidence in adult sepsis reinforces this pattern. Assignment to 6% hydroxyethyl starch 130/0.42 rather than Ringer acetate increased 90-day mortality (51 per cent versus 43 per cent; relative risk 1.17, 95% CI 1.01-1.36, $p=0.03$) and renal replacement therapy (22 per cent versus 16 per cent; relative risk 1.35, 95% CI 1.01-1.80, $p=0.04$). The CRISTAL trial of 2,857 patients with hypovolaemic shock found no difference in 28-day mortality between colloids and crystalloids (relative risk 0.96, 95% CI 0.88-1.04) with a lower 90-day mortality in the colloid arm (relative risk 0.92, 95% CI 0.86-0.99) that the investigators themselves designated exploratory. Network meta-analyses in sepsis have consistently placed balanced crystalloids and albumin above low-molecular-weight starch and saline for survival, and a recent network meta-analysis of 28 trials and 8,770 patients ranked balanced crystalloids highest for reduction of 28-day and 90-day mortality, renal replacement therapy and transfusion.^{33,34,35,36,37}

The specific dengue observation that starch may be preferable to dextran on tolerability grounds must therefore be read within, and not in isolation from, this wider evidence. Within dengue, at resuscitation doses, in children, and with mortality events too few to analyse, starch appeared the safer of the two colloids. In adult critical illness, at cumulative doses, starch is the colloid most consistently associated with renal harm. The reconciliation is dose and duration: the dengue trial administered starch as a bolus for initial resuscitation of a self-limiting leak, whereas the critical-care trials administered it as a maintenance resuscitation fluid over days in sepsis. This is a further, and perhaps the most clinically important, argument for the position that colloid in dengue should be used briefly or not at all, and that the operative question is not which colloid but for how long.^{3,27,32,33}

Evidence on fluid accumulation is likewise convergent and considerably larger than the dengue-specific literature. Meta-analysis of 44 paediatric studies enrolling 7,507 children found that fluid overload was associated with in-hospital mortality (odds ratio 4.34, 95% confidence interval

3.01-6.26), with prolonged mechanical ventilation (odds ratio 2.14, 95% CI 1.25-3.66) and with acute kidney injury (odds ratio 2.36, 95% CI 1.27-4.38), and that after adjustment for illness severity each one per cent increase in percentage fluid overload conferred a 6 per cent increase in the adjusted odds of death (adjusted odds ratio 1.06, 95% CI 1.03-1.10). A larger and more recent synthesis of 120 studies enrolling 44,682 children reproduced these estimates almost exactly, and in adults, meta-analysis of 31 observational studies and 31,076 patients found that mortality risk increased by a factor of 1.19 per litre of positive fluid balance. The dengue-specific volume thresholds identified in this review are therefore not anomalous but are the local expression of a general principle.^{38,39,40}

Dose, duration and de-escalation: fluid therapy as a prescribed quantity

The most actionable implication of this review is that cumulative volume and colloid proportion should be treated as prescribed and audited quantities with defined ceilings, rather than as open-ended responses to persistent tachycardia. The threshold analysis provides concrete anchors: cumulative infusion above 181 millilitres per kilogram in the first twenty-four hours and a colloid-to-crystalloid ratio above 1.6 identify children at markedly elevated risk of requiring mechanical ventilation, with areas under the curve of 0.871 and 0.781 respectively. These are not merely statistical cut-points but plausible operational triggers: crossing either should prompt formal reassessment of the leak phase, bedside echocardiographic or ultrasonographic evaluation of preload and pulmonary interstitial fluid, and explicit consideration of transition from resuscitation to de-resuscitation.⁴

The conceptual framework that best accommodates these findings is the four-phase model of fluid therapy comprising resuscitation, optimisation, stabilisation and evacuation, together with the four determinants of drug, dosing, duration and de-escalation, articulated as fluid stewardship in analogy with antimicrobial stewardship. Dengue shock syndrome is arguably the ideal disease in which to apply this framework, because its leak phase has a predictable duration of twenty-four to forty-eight hours, its reabsorption phase is obligatory rather than optional, and its complications are therefore temporally anticipable in a way that those of sepsis are not. The corollary is that fluid

prescription in dengue should carry an explicit anticipated end point in time as well as in volume, and that the transition to active fluid removal should be planned rather than reactive.^{48,4,5}

Evidence from paediatric intensive care indicates that both the degree and the rate of fluid accumulation matter independently. In a cohort of 1,017 children, peak percentage fluid overload was associated with intensive-care mortality (odds ratio 1.05 per per-cent, 95% confidence interval 1.02-1.09, $p=0.001$), with major adverse kidney events within thirty days (odds ratio 1.05, 95% CI 1.02-1.08, $p=0.001$), with duration of mechanical ventilation and with length of stay, and the rate of accumulation was independently associated with the same outcomes. Applied to dengue, where fluid is administered at high rates over short intervals, this suggests that bolus rate as well as cumulative total warrants attention, and that the common practice of repeated rapid boluses for persistent tachycardia during the reabsorption phase may be actively harmful.⁴⁶

It must nonetheless be acknowledged that the negative consequences of insufficient fluid have not disappeared and remain the historical reason for liberal practice. National mortality audit in Malaysia found that only 34 per cent of eventual dengue decedents were suspected of having dengue at initial presentation and that 22.4 per cent had no warning signs, with death occurring at a median of three days after admission. Late recognition, not over-resuscitation, was the dominant failure in that series. The correct interpretation of the present review is therefore not that less fluid is always better, but that fluid should be given promptly and adequately during the leak phase and then stopped decisively, which is a more demanding clinical discipline than either liberal or restrictive practice alone.^{23,22}

Adults versus children: an evidence base misaligned with the epidemiology

A structural misalignment exists between where the evidence was generated and where the disease burden now lies. All randomised evidence on resuscitation fluid in dengue shock syndrome derives from Vietnamese children studied between 1999 and 2005, whereas national mortality data show that dengue deaths now occur primarily in adults, with 72.5 per cent of 322 Malaysian dengue deaths occurring in the 15 to 59 year age group and diabetes and hypertension common comorbidities among adult and elderly decedents. Adult severe dengue in intensive care carries a mortality of 25 per cent, with a median age of 63 years, comorbidity-driven multi-organ failure, co-

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infection in 33 per cent of cases, and an initial diagnosis other than dengue in 38 per cent. None of these features characterises the trial populations from which fluid recommendations are derived.^{2,3,14,23}

The physiological differences are equally material. Approximately half of adult dengue shock is cardiogenic, myocardial dysfunction persists for up to two weeks after fever onset, and myocarditis was documented in 9 per cent of adult intensive-care cases with six patients requiring veno-arterial extracorporeal membrane oxygenation. Age-related reduction in ventricular compliance, prevalent hypertension and diabetes, and diminished renal reserve all reduce tolerance of volume loading relative to a healthy eight-year-old child. Extrapolating a paediatric volume threshold of 181 millilitres per kilogram to a comorbid adult would be indefensible, and no adult-specific threshold currently exists. This is the single largest gap in the field.^{12,14}

The corresponding gap in adult management is partially bridged by evidence that a substantial proportion of severe-appearing adult dengue is not plasma-leak shock at all. In 715 adults presenting to an emergency department, 171 of 332 severe cases (51.5 per cent) had presyncope, weakness, prolonged gastrointestinal symptoms and hypotension attributable to dehydration and electrolyte loss without evidence of plasma leakage, and improved markedly within twenty-four hours with saline infusion. Distinguishing this volume-responsive dehydration phenotype from true plasma-leak shock is therefore an essential adult triage task, since the former requires straightforward crystalloid replacement whereas the latter requires cautious, ceiling-bounded, closely monitored resuscitation.²²

Confounding by indication and the limits of observational inference

The central inferential challenge in this literature is that clinicians administer more fluid to sicker patients, so that any association between cumulative volume and adverse outcome may reflect severity rather than causation. Three features of the assembled evidence mitigate but do not eliminate this concern. First, the two most rigorous analyses adjusted explicitly for baseline severity, one by inverse probability weighting across seven hospitals and one by multivariable modelling with formal calibration and Brier scoring, and both retained significant fluid-outcome associations after adjustment. Second, the exposure-outcome relationship exhibits a dose-response

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gradient with an identifiable threshold, which is difficult to generate by confounding alone. Third, the temporal ordering is correct, with fluid exposure measured in the first twenty-four hours and outcomes ascertained subsequently.^{4,5}

Two further considerations strengthen the causal reading. The colloid-to-crystalloid ratio is not a severity marker in the same sense as total volume, because it reflects a categorical clinician preference regarding fluid composition rather than the quantity demanded by the patient physiology, and it nonetheless independently predicted mechanical ventilation with an area under the curve of 0.781. Additionally, the duration-of-colloid comparison in the seven-hospital cohort was restricted to the 547 children who had already achieved haemodynamic stability within two hours, that is, to a group in whom continued colloid was by definition not required by ongoing instability; within this severity-homogeneous group the odds of respiratory compromise rose 8.84-fold with liberal colloid. This design feature substantially weakens the confounding-by-indication explanation for that particular finding.^{4,5}

Residual confounding nevertheless persists in the remainder of the evidence. Unmeasured severity, site-level differences in respiratory-support availability which may influence both fluid practice and the ascertainment of respiratory outcomes, secular changes in practice across the 2013 to 2022 study period, and the overlapping provenance of six analyses from a single Vietnamese cohort all constrain inference. The appropriate epistemic position is that the volume-harm relationship is highly probable, quantitatively consistent, mechanistically coherent and supported by convergent general critical-care evidence, but that it has never been tested in a randomised comparison of restrictive against liberal cumulative-volume strategies in dengue, and therefore cannot be regarded as established with the certainty attaching to the fluid-type question.^{4,5,6,38,39}

Implications for clinical practice

Several practice implications follow with sufficient consistency to be stated. Isotonic crystalloid, preferably a balanced solution, should be used for initial resuscitation of moderately severe dengue shock, with colloid reserved for profound shock with markedly narrowed pulse pressure, for failure of crystalloid resuscitation, and for the shortest interval necessary. Where colloid is required, the dengue-specific tolerability data favour 6% hydroxyethyl starch over dextran

70, but the wider critical-care evidence on starch-associated renal harm argues strongly for limiting exposure to the initial resuscitation period and against continuation into maintenance therapy. Cumulative volume should be recorded, totalled and reviewed at defined intervals, with formal reassessment triggered on approach to 180 millilitres per kilogram in the first twenty-four hours in children.^{1,2,3,4,5,27,32}

Monitoring should be serial and physiological rather than single-point and protocolar. Admission lactate identifies patients at elevated risk of recurrent shock and correlates with subsequent total fluid requirement; the lactate-to-albumin ratio above 1.25 and the lactate-to-bicarbonate ratio above 0.25 provide additional discrimination for composite adverse outcomes and mortality respectively. Serial echocardiography and inferior vena cava assessment permit identification of the cardiogenic phenotype and of the transition from hypovolaemia to congestion, and daily lung ultrasound quantifies pulmonary interstitial and pleural fluid accumulation before clinical respiratory distress becomes apparent. In settings where these modalities are unavailable, respiratory rate, oxygen requirement and serial abdominal girth remain informative, and admission respiratory rate independently predicted mortality in adult severe dengue.^{7,8,11,12,13,14}

Two additional practice points deserve emphasis. First, volume-adding adjuncts of unproven benefit should be avoided: prophylactic platelet transfusion in adults with dengue and platelet counts of 20,000 per microlitre or below did not reduce bleeding (relative risk 0.81, 95% confidence interval 0.56-1.17) and increased adverse events more than sixfold (relative risk 6.26, 95% CI 1.43-27.34, $p=0.0064$) including fluid overload and transfusion-related acute lung injury. Second, obesity should be treated as a pre-treatment risk amplifier, since obese children with dengue shock had 2.3-fold higher odds of requiring mechanical ventilation (95% CI 1.31-4.06, $p<0.01$) without a corresponding increase in mortality or acute liver failure, implying that they warrant lower volume ceilings and earlier respiratory surveillance rather than more intensive general therapy.^{20,10}

In resource-limited district settings the practical hierarchy is clear. Where respiratory support is unavailable or unreliable, colloid should not be continued beyond initial resuscitation under any circumstances, because the complication generated may exceed the capacity of the facility to treat it. Conversely, where recognition is the limiting factor, as suggested by the finding

that only 34 per cent of eventual dengue decedents were suspected of dengue at first presentation, investment in earlier identification and in plasma-leak prediction, for which a validated three-item score achieving 88.8 per cent sensitivity is available, will yield greater benefit than refinement of fluid composition.^{5,23,24}

Strengths of this review

This review has several methodological strengths. Its inclusion strategy was design-restricted a priori so that only primary studies populate the evidence tables, which eliminates the double-counting of source data that occurs when systematic reviews and their constituent trials are tabulated together; secondary syntheses were retained exclusively for contextual triangulation in this Discussion, where their function is to test the external coherence of the dengue-specific findings rather than to contribute effect estimates. Fourteen outcome domains were prespecified and each is reported in a dedicated table, which extends the scope of synthesis well beyond the mortality-and-fluid-type dyad that has characterised previous treatments. Dual risk-of-bias instrumentation was applied, with RoB 2 for randomised evidence and the Newcastle-Ottawa Scale supplemented by ROBINS-I domain judgements for non-randomised evidence, and GRADE certainty was rated for every outcome.¹⁻²⁴

A further strength is the explicit integration of the classical fluid-type randomised evidence with the fluid-dose observational evidence published in 2024 and 2025. Because these two literatures address different questions with different designs, they have generally been discussed separately, with the consequence that the practical question of how much fluid has received less attention than the more tractable question of which fluid. Their combination in a single analytical framework, together with a dedicated dose-response and threshold table, is to our knowledge new. Finally, every reference is accompanied by a resolvable Consensus record link, permitting the reader to verify the existence, authorship, journal and year of each cited study independently, which addresses directly the reproducibility concerns that attach to reference lists in narrative and systematic reviews alike.¹⁻²⁴

Research priorities

Four research priorities follow from this review, in descending order of importance. The first is a multicentre randomised trial of restrictive versus liberal cumulative-volume strategies in dengue shock syndrome, using a prespecified volume ceiling in the region of 180 millilitres per kilogram in the first twenty-four hours for children, a composite primary endpoint of death or requirement for respiratory support, and mandatory reporting of cumulative volume in standardised units. The second is a randomised trial of resuscitation fluid in adult dengue shock, which has never been conducted, stratified by shock phenotype using non-invasive cardiac output monitoring or echocardiography so that the hypovolaemic and cardiogenic halves of adult dengue shock are analysed separately. The third is a randomised evaluation of protocolised de-resuscitation, comprising defined triggers for cessation of maintenance fluid and for active fluid removal during the reabsorption phase. The fourth is a randomised comparison of ultrasound-guided fluid titration, incorporating inferior vena cava assessment and daily lung ultrasound, against standard clinically guided management.^{4,5,11,12,13}

Two methodological reforms would substantially increase the value of future research. Fluid exposure should be reported in a standardised core set comprising cumulative volume in millilitres per kilogram at fixed time points, colloid proportion, bolus number and rate, and cumulative fluid balance as a percentage of admission weight, so that dose-response relationships become poolable across studies. Fluid overload should be defined by a single consensus criterion in dengue research, given the thirty-five definitions currently in circulation in paediatric critical care. In parallel, the identification of interleukin-6, angiopoietin-2 and the Tie-2 axis as drivers of pulmonary vascular leak provides a rational basis for trials of endothelial-stabilising and immunomodulatory therapy, which if successful would reduce the leak that fluid therapy exists to compensate and would thereby render the entire fluid-type debate substantially less consequential.^{4,39,13,51}

CONCLUSION AND RECOMMENDATIONS

Conclusion

Fluid resuscitation remains the only definitive therapy for dengue shock syndrome, and its correct execution is the principal modifiable determinant of survival. The evidence assembled in this systematic review of 24 primary studies supports four conclusions. First, isotonic crystalloid is

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non-inferior to synthetic colloid for initial resuscitation of moderately severe dengue shock in children, with a relative risk of rescue-colloid requirement of 1.08 (95% confidence interval 0.78-1.47), and should therefore be first-line therapy; the physiological advantages of colloid, namely more rapid haematocrit normalisation and cardiac-index restoration, are real, reproducible, confined to surrogate endpoints, and concentrated in patients presenting with the narrowest pulse pressure. Second, cumulative resuscitation volume is a dose-dependent, threshold-bearing and modifiable determinant of harm, discriminating the need for mechanical ventilation with an area under the curve of 0.871 above 181 millilitres per kilogram in the first twenty-four hours, and entering multivariable models for 28-day mortality as an independent predictor.^{1,2,3,4,7}

Third, the proportion and duration of colloid exposure are independently harmful: mixed crystalloid-colloid initial resuscitation doubled the hazard of respiratory compromise (hazard ratio 2.08, $p=0.022$) and prolonged colloid infusion in already-stabilised children multiplied the odds of respiratory compromise by 8.84 and of respiratory support by 8.16 (both $p<0.001$), while reducing recurrent shock (risk ratio 0.13, $p=0.043$) - a trade-off that is unfavourable wherever respiratory support is not reliably available. Fourth, the clinical consequence of these complications is severe: case fatality among ventilated children with dengue shock syndrome was 22.4 per cent against 0.1 per cent in the non-ventilated, and dengue-associated acute kidney injury carried a fatality of 22.4 per cent against 5.7 per cent without renal injury. Fluid therapy in dengue shock syndrome is therefore best conceived not as volume maximisation but as time-limited, ceiling-bounded, physiology-guided volume titration followed by decisive de-escalation.^{4,5,6,18}

These conclusions are held with moderate certainty for the fluid-type and volume-threshold findings and with low or very low certainty for the renal, metabolic, organ-dysfunction, resource and prevention domains. The most consequential residual uncertainty is that no randomised trial has yet compared restrictive with liberal cumulative-volume strategies in dengue, and that no randomised trial of resuscitation fluid has ever been conducted in adults, in whom mortality is an order of magnitude higher, approximately half of shock is cardiogenic rather than hypovolaemic, and the disease burden is increasingly concentrated.¹⁻²⁴

Recommendations for clinical practice

- Use isotonic crystalloid, preferably a balanced solution, as first-line resuscitation for moderately severe dengue shock syndrome in children, and reserve colloid for profound shock with markedly narrowed pulse pressure or for documented failure of crystalloid resuscitation.^{2,3}
- Where colloid is indicated, prefer 6% hydroxyethyl starch to dextran 70 on tolerability grounds within dengue, but restrict exposure to the initial resuscitation period only, and do not continue synthetic colloid as a maintenance fluid.^{3,27,32,33}
- Record and total cumulative fluid volume prospectively, and trigger formal multidisciplinary reassessment on approach to 180 millilitres per kilogram within the first twenty-four hours in children, or to a colloid-to-crystalloid ratio approaching 1.6.⁴
- Do not continue colloid infusion in patients who have achieved haemodynamic stability, and do not continue it at all beyond initial resuscitation in facilities without reliable access to non-invasive or invasive respiratory support.⁵
- Institute serial rather than single-point monitoring, using admission and repeat lactate with derived ratios, serial echocardiography or inferior vena cava assessment where available, and daily lung ultrasound to detect pulmonary interstitial accumulation before clinical respiratory distress appears.^{7,8,11,12,13}
- Identify and manage the cardiogenic phenotype distinctly: shock that persists or recurs after adequate initial volume replacement, particularly around and after defervescence, should prompt assessment of myocardial function rather than further volume loading.^{11,12}
- Plan the transition from resuscitation to de-resuscitation explicitly, with defined triggers for cessation of maintenance fluid and for active fluid removal during the obligatory reabsorption phase at twenty-four to forty-eight hours.^{48,4}
- Treat obesity, severe bleeding, severe transaminitis, high vasoactive-inotropic score and elevated admission lactate as pre-treatment risk amplifiers warranting lower volume ceilings and earlier respiratory and renal surveillance.^{4,6,7,10,11}

- Avoid volume-adding adjuncts of unproven benefit, including prophylactic platelet transfusion in adults with dengue and thrombocytopenia in the absence of clinically significant bleeding.²⁰
- Strengthen early recognition and plasma-leak prediction, using validated simple criteria based on body mass index, platelet count and aminotransferase level on fever days three to four, since late recognition remains a dominant contributor to dengue mortality.^{23,24}

Recommendations for research

- Conduct a multicentre randomised controlled trial of restrictive versus liberal cumulative-volume strategy in paediatric dengue shock syndrome, with a prespecified volume ceiling and a composite primary endpoint of death or requirement for respiratory support.^{4,5}
- Conduct the first randomised trial of resuscitation fluid in adult dengue shock syndrome, stratified by shock phenotype determined by non-invasive cardiac output monitoring or echocardiography.^{12,14}
- Randomise protocolised de-resuscitation against usual care during the reabsorption phase, with prespecified triggers for fluid cessation and active removal.^{48,46}
- Randomise ultrasound-guided fluid titration, incorporating inferior vena cava and lung ultrasound, against standard clinically guided management.^{11,12,13}
- Adopt a standardised core outcome and exposure set for dengue fluid research, comprising cumulative volume in millilitres per kilogram at fixed time points, colloid proportion, bolus number and rate, and cumulative fluid balance as a percentage of admission weight, together with a single consensus definition of fluid overload.^{39,4}
- Advance trials of endothelial-stabilising and immunomodulatory therapy targeting the interleukin-1, interleukin-6 and Tie-2 axes, which if effective would reduce the plasma leak that fluid therapy exists to compensate.^{13,51}
- Extend the geographical base of primary evidence to Latin American, African and South Asian settings, and to district-hospital as well as tertiary-centre practice, in order to establish

the external validity of volume thresholds derived predominantly from a single tertiary Vietnamese paediatric cohort.^{4,6,7,8}

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