# Should Adults with Vasopressor-Dependent Septic Shock Receive Corticosteroids? A Structured Pro and Con Appraisal of Two Discordant Trials

Mosrur Ahmed

*Assistant Professor, Rahman Institute of Pharmaceutical Sciences and Research, Guwahati, Assam, India.*

Email; laskar.mosrur94@gmail.com

Received: 08 February 2026; Revised: 18 April 2026; Accepted: 24 April 2026; Published: 10 June 2026

**Abstract**

**Background:** Corticosteroids have been studied as adjunctive therapy in septic shock for more than fifty years, yet uncertainty persists. Two adequately powered randomised trials published within weeks of one another reported conflicting effects on mortality while agreeing on every other major endpoint. Guidelines make only a weak recommendation, and practice varies widely between units.

**Methods:** We adopted a structured pro and con format. After a neutral presentation of the trial evidence, the strongest available case for routine corticosteroid use and the strongest available case against it are each set out in turn, followed by explicit rebuttals from the opposing side. A final adjudication distinguishes what the two positions agree on from what divides them, appraises five candidate explanations for the discordance, and states what would settle the question.

**Results:** The larger trial randomised 3,800 mechanically ventilated patients to hydrocortisone 200 mg daily by infusion and found no difference in 90-day mortality. The smaller trial randomised 1,241 vasopressor-dependent patients to hydrocortisone with fludrocortisone and reported 90-day mortality of 43.0 per cent against 49.1 per cent. Both reported faster shock reversal and earlier liberation from mechanical ventilation. Pooled analyses give a 28-day mortality risk ratio of about 0.88, with consistent estimates for the dual regimen. A meta-research study of 38 systematic reviews found that 39 per cent reported benefit and 61 per cent no evidence of effect, with discordance confined to reviews posing broad questions; reviews restricted to hydrocortisone with fludrocortisone were consistent.

**Conclusion:** The two sides disagree about mortality and about almost nothing else. The most defensible position is that corticosteroids shorten shock in everyone and may improve survival in a subgroup not yet reliably identified, which supports a short, monitored course in vasopressor-dependent shock rather than either routine universal use or categorical avoidance.

**Keywords:** Septic Shock, Corticosteroids, Hydrocortisone, Fludrocortisone, Critical Care, Evidence Appraisal.

## 1. WHY THIS QUESTION WILL NOT SETTLE

Sepsis affects tens of millions of people annually and causes millions of deaths, and corticosteroids have been proposed as adjunctive therapy for more than half a century [1]. Few questions in critical care have been examined by more randomised trials, and few remain as unresolved.

The modern impasse has a specific origin. Two adequately powered randomised trials, both enrolling adults with septic shock and both administering 200 mg of hydrocortisone daily for seven days, reported conflicting effects on mortality [1]. They were published within weeks of one another. Neither has been discredited. Both are cited, routinely and in good faith, by clinicians who reach opposite conclusions at the bedside.

This paper does not attempt to arbitrate by weight of citation. It adopts instead a structured pro and con format, on the view that a question this durable is better served by hearing each side at its strongest than by a synthesis that smooths the disagreement away. We present the trial evidence neutrally, then the case

for routine use, then the case against, then each side's reply to the other, and only then an adjudication. Readers who find themselves persuaded by whichever section they read most recently will have had the experience the format is designed to produce.

## 2. METHOD OF THIS APPRAISAL

This is a structured narrative appraisal, not a systematic review; no protocol was registered and no formal screening was conducted. We searched for randomised trials, patient-level and aggregate meta-analyses, guideline recommendations and meta-research on corticosteroids in adult septic shock. No primary data were collected and no individual patient records were accessed, so institutional review board approval, informed consent and trial registration do not apply.

The arguments attributed below to the pro and con positions are constructed by the authors from the published literature. They are not the stated positions of any named investigator, and no author holds either position as a personal conviction. The adjudication in the penultimate section represents our own reading and is identified as such.

### 2.1. The Evidence, Presented Neutrally

Figure 1 and Table 1 set the two landmark trials side by side. The larger randomised 3,800 patients with septic shock who were receiving mechanical ventilation to hydrocortisone 200 mg daily by continuous infusion for seven days or placebo, and found no difference in 90-day mortality [2]. The smaller randomised 1,241 patients with vasopressor-dependent septic shock to hydrocortisone 50 mg six-hourly together with fludrocortisone 50 µg daily for seven days, or placebo, and reported 90-day mortality of 43.0 per cent against 49.1 per cent, with more vasopressor-free and organ-failure-free days [3,4].

Three earlier trials frame these. A 2002 trial of hydrocortisone with fludrocortisone in 299 patients reported reduced 28-day mortality [3]. A trial of 499 patients receiving hydrocortisone alone found no overall mortality difference but quicker shock reversal [3]. And a trial of a fixed hydrocortisone regimen in community-acquired pneumonia with cardiovascular or respiratory failure reported a low probability of reducing 90-day mortality [5].

What is striking, and is central to the adjudication below, is how narrow the disagreement is. Both landmark trials reported earlier shock reversal and earlier liberation from mechanical ventilation with glucocorticoids [1]. Both reported more hyperglycaemia. They differ on mortality, and on essentially nothing else that they set out to measure (Figure 2).

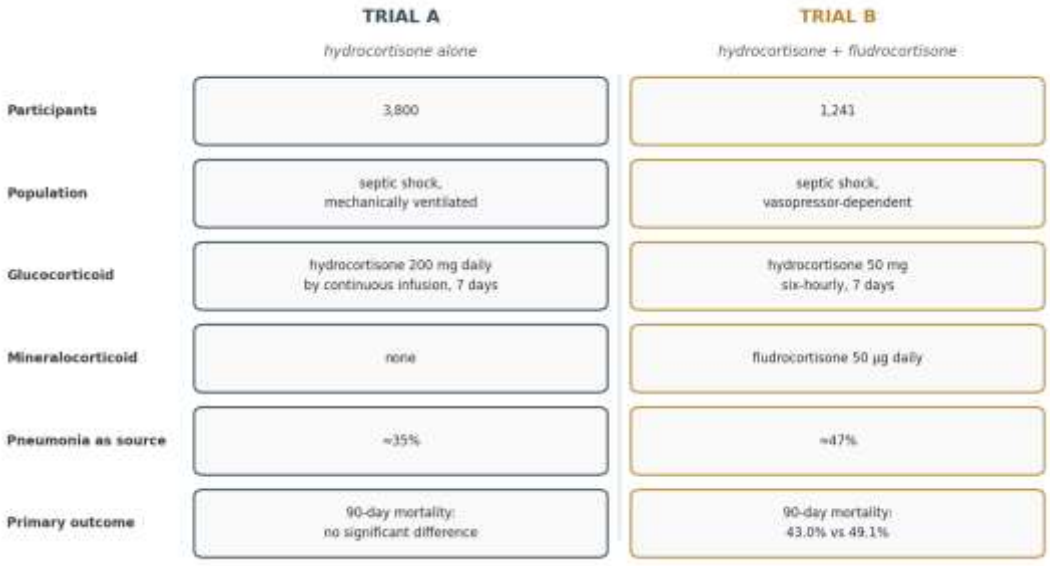


Figure 1. The two landmark trials compared. Trial A administered hydrocortisone alone; Trial B added fludrocortisone. Data sources: references [1–4].

Table 1. Randomised evidence on corticosteroids in septic shock.

| Trial | n | Regimen | Principal finding |
|---|---|---|---|
| Early dual-regimen trial (2002) | 299 | Hydrocortisone with fludrocortisone | Reduced 28-day mortality |
| Hydrocortisone-alone trial | 499 | Hydrocortisone alone | No overall mortality difference; quicker shock reversal |
| Large hydrocortisone trial | 3,800 | Hydrocortisone 200 mg daily by infusion, 7 days | No difference in 90-day mortality; faster shock resolution |
| Dual-regimen trial | 1,241 | Hydrocortisone 50 mg six-hourly plus fludrocortisone 50 µg daily, 7 days | 90-day mortality 43.0% vs 49.1%; more vasopressor- and organ-failure-free days |
| Pneumonia platform comparison | — | Fixed hydrocortisone 50 mg six-hourly, 7 days | Low probability of reducing 90-day mortality in this population |

*Trials are identified by regimen and size rather than by acronym, to keep the comparison rather than the brand in view. Full identification is given in references [2–5].*

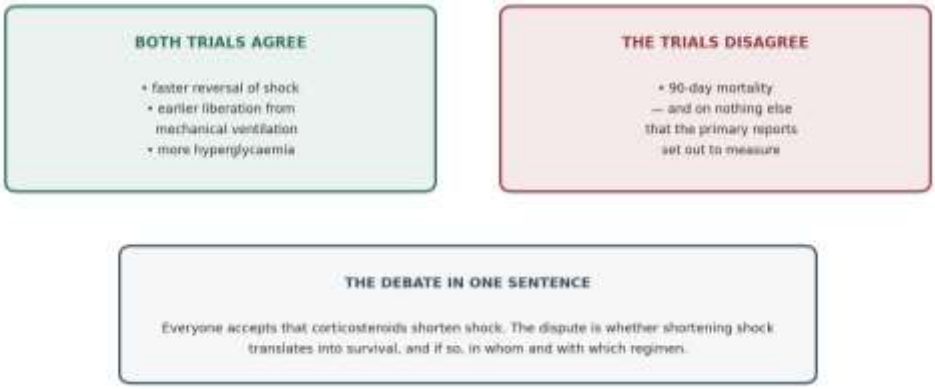


Figure 2. What the two trials agree on, and the single point on which they differ.

## 3. PRO THE CASE FOR GIVING CORTICOSTEROIDS

The pro position does not rest on either single trial. It rests on the pooled estimate, on the consistency of that estimate where the question is posed narrowly, and on the favourable balance of a cheap, short, familiar intervention.

### 3.1. The pooled estimate favours treatment

A meta-analysis of 18 randomised trials reported a 28-day mortality risk ratio of 0.88 (95% CI 0.79–0.98), with mortality of 31.0 per cent against 35.5 per cent and moderate heterogeneity [6]. The effect was most pronounced for regimens delivering 201–300 mg daily, where heterogeneity was absent, and for combination therapy including fludrocortisone [6]. An absolute reduction of four to five percentage points in a condition with mortality above 30 per cent is not a trivial quantity, and it is larger than the effect of several interventions that critical care regards as settled.

### 3.2. The dual regimen is consistently positive

Where the question is narrowed to hydrocortisone with fludrocortisone, the signal stops wobbling. A systematic review and meta-analysis of that regimen pooled 2,050 patients from three studies using similar seven-day schedules without tapering, and reported reduced 28-day mortality (risk ratio 0.88, 95% CI 0.78–0.99) with no heterogeneity, lower long-term mortality (risk ratio 0.90, 95% CI 0.83–0.98) and a higher rate of shock reversal [7]. A meta-research study of 38 systematic reviews found that discordant conclusions occurred exclusively among reviews evaluating broad, non-specific corticosteroid strategies,

while conclusions for hydrocortisone plus fludrocortisone were consistent in finding benefit [8] (Figure 3, Figure 4).

The pro reading of this is straightforward. The field has been arguing about an average taken across regimens that are not the same treatment. Once the mineralocorticoid is specified, the evidence coheres.

### 3.3. The agreed benefits are real benefits

Both landmark trials found faster shock reversal and earlier liberation from mechanical ventilation [1]. These are not trivial process measures. Less time on vasopressors and fewer ventilator days mean less sedation, less delirium, less immobility and earlier discharge from intensive care, and they matter to patients independently of whether mortality moves.

### 3.4. The balance of benefit and harm is favourable

Hydrocortisone is inexpensive, universally available, familiar to every intensivist, and given for seven days. In the dual-regimen synthesis, adverse events other than hyperglycaemia were similar between groups [7]. An intervention with a plausible mortality benefit, definite shortening of shock, a well-characterised and manageable principal adverse effect, and negligible cost has a favourable expected value even under uncertainty.

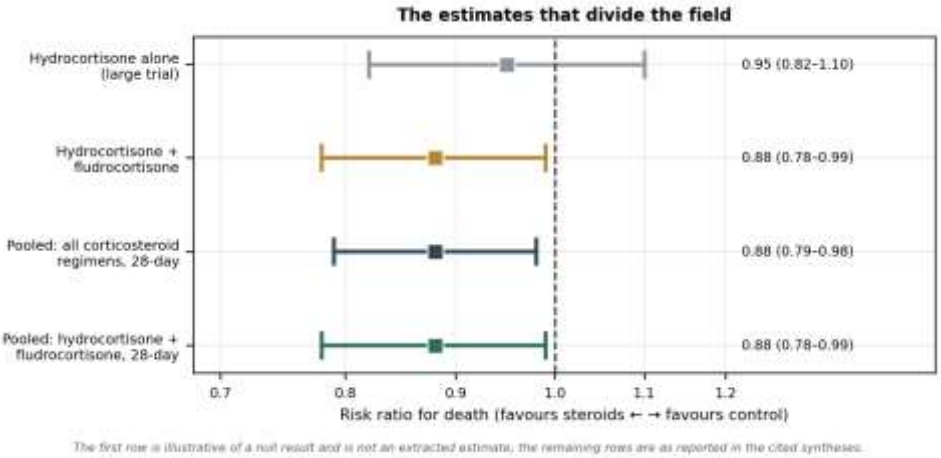


Figure 3. Mortality estimates across regimens and syntheses. The first row is illustrative of a null single-trial result; the remaining rows are as reported in the cited syntheses. Data sources: references [2,3,6,7].

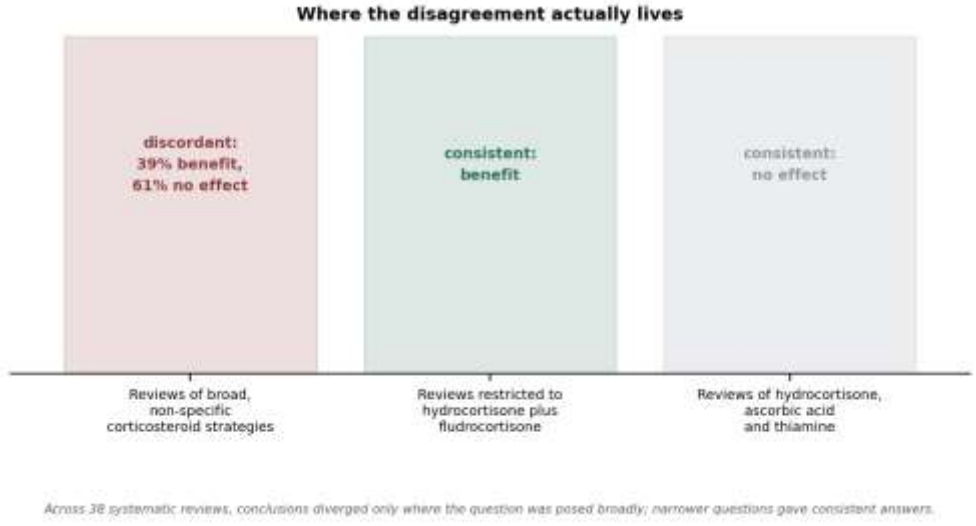


Figure 4. Where the disagreement lives. Across 38 systematic reviews, conclusions diverged only where the clinical question was posed broadly. Data source: reference [8].

Table 2. The pro case in summary.

| Argument | Evidence | Strength |
|---|---|---|
| Pooled mortality favours treatment | 28-day mortality risk ratio 0.88 (0.79–0.98) across 18 trials; 31.0% vs 35.5% | Moderate |
| The dual regimen is consistently positive | Risk ratio 0.88 (0.78–0.99) with no heterogeneity across 2,050 patients; reviews of this regimen do not diverge | Moderate to strong |
| Shock reversal and ventilator liberation | Agreed by both landmark trials | Strong |
| Favourable harm profile | Adverse events other than hyperglycaemia similar between groups | Moderate |
| Cost and availability | Inexpensive, familiar, seven-day course | Strong |

## 4. CON THE CASE AGAINST ROUTINE USE

The con position does not claim that corticosteroids are useless. It claims that the mortality benefit is not established, that the case rests on subgroup and regimen-specific reasoning applied after the fact, and that a treatment of unproven survival benefit should not become routine in a population this heterogeneous.

### 4.1. The largest and most rigorous single trial was null

The 3,800-patient trial is the largest randomised comparison in this field and found no difference in 90-day mortality [2]. Its size gave it precision that no other trial approaches, and a null result from the best-powered study is the single most informative datum available. Pooled estimates that dilute it with smaller and older trials of varying quality are not obviously an improvement on it.

### 4.2. Most systematic reviews find no effect

The meta-research study that the pro side cites also reports that among 38 systematic reviews with short-term mortality meta-analyses, 15 (39 per cent) found benefit and 23 (61 per cent) found no evidence of effect [8]. That is the majority position in the synthesised literature, and it should be stated as such rather than set aside as an artefact of question framing.

The same study observed that reviews including populations of sepsis with or without shock more frequently reported benefit than those restricted to septic shock — 62 per cent against 22 per cent — and that no single methodological or clinical factor consistently explained the discordance [8]. The con reading is that the positive signal is strongest where the population is least well defined, which is the opposite of what a real treatment effect usually looks like.

### 4.3. Shock reversal is a surrogate

That corticosteroids raise blood pressure and shorten vasopressor requirement has never been in dispute; it follows from their pharmacology. Critical care has an extensive history of interventions that improved haemodynamics and did not improve survival, and in some cases worsened it. Treating faster shock reversal as evidence of benefit is precisely the inference that history counsels against.

### 4.4. The subgroup reasoning arrived after the result

The claim that pneumonia identifies the responsive subgroup derives from an exploratory subgroup analysis in which the dual regimen reduced 90-day mortality in patients with community-acquired pneumonia (38.5 per cent against 51.3 per cent) while showing no difference in those without (46.4 per cent against 47.7 per cent) [9]. Pneumonia was the presumed source in about 47 per cent of that trial and about 35 per cent in the other [9]. This is a coherent story, but it is a story assembled to explain a discordance that was already known, and a platform trial of a fixed hydrocortisone regimen in pneumonia with cardiovascular or respiratory failure reported a low probability of mortality benefit [5].

### 4.5. The harms are under-characterised

Hyperglycaemia is consistently increased [7], and in a population already at risk of dysglycaemia-associated harm that is not a trivial finding. Neuromuscular weakness, delayed wound healing, secondary infection and longer-term consequences of a seven-day glucocorticoid course are inconsistently ascertained across trials, and a treatment whose survival benefit is unproven has a lower threshold for harm than one whose benefit is established.

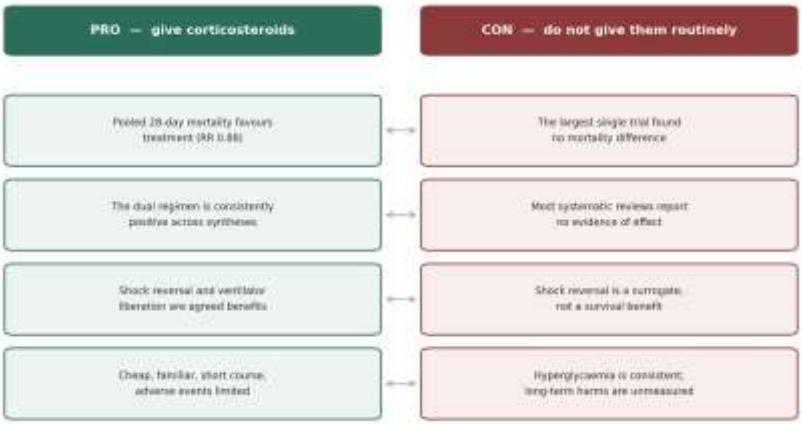


Figure 5. The principal claims on each side, paired against their opposing arguments.

Table 3. The con case in summary.

| Argument | Evidence | Strength |
|---|---|---|
| The largest trial was null | 3,800 patients; no difference in 90-day mortality | Strong |
| Most reviews find no effect | 23 of 38 systematic reviews report no evidence of effect | Moderate to strong |
| Benefit is strongest where the population is least defined | 62% of reviews including sepsis ± shock report benefit, against 22% restricted to septic shock | Moderate |
| Shock reversal is a surrogate | Pharmacologically expected; historical precedent for haemodynamic benefit without survival benefit | Moderate |
| Subgroup reasoning is post hoc | Pneumonia subgroup identified after the discordance was known; platform evidence in pneumonia unsupportive | Moderate |
| Harms are incompletely measured | Hyperglycaemia consistent; other harms inconsistently ascertained | Moderate |

### 4.6. Rebuttals

Each side is now given the opportunity to answer the other's strongest point. We have restricted each reply to the arguments that we judge it can actually answer, and have not manufactured replies where none is available.

Table 4. The exchange in summary.

| Point at issue | Pro position | Con position |
|---|---|---|
| Weight of the largest trial | Precise about hydrocortisone alone; silent on the dual regimen | The best-powered evidence available and it was null |
| Counting reviews | Reviews are not independent observations | The majority finding should not be dismissed |

| | | |
|---|---|---|
| Shock reversal | A benefit in its own right | A surrogate with a poor historical record |
| The mineralocorticoid | Explains the discordance and is supported by regimen-specific syntheses | Never tested head to head against hydrocortisone alone |
| Precision of the pooled estimate | Confidence interval excludes no effect | Fragile to one further null trial |

## 5. ADJUDICATION

Three observations seem to us to survive the exchange.

### 5.1. The disagreement is narrower than it appears

Both sides accept that corticosteroids shorten shock and shorten mechanical ventilation. Both accept that hyperglycaemia increases. Both accept that the mortality question is unresolved at the level of the individual trial. What divides them is whether an unresolved mortality question, in the presence of agreed secondary benefits and a modest harm profile, licenses routine use. That is a question about decision thresholds under uncertainty rather than about the evidence itself, and framing it as an evidential dispute has prolonged it.

### 5.2. Five explanations compete, and none has been demonstrated

Figure 6 and Table 5 set out the candidates: the addition of the mineralocorticoid; the differing proportion of pneumonia as the source of sepsis; differences in baseline severity between the cohorts; the dosing schedule of bolus against continuous infusion; and chance. They are not mutually exclusive, and the meta-research evidence explicitly reports that no single methodological or clinical factor consistently explained the discordance across the review literature [8]. Any account that presents one of these as established overstates the position.


Figure 6. Five candidate explanations for the discordance between the two landmark trials.

Table 5. Candidate explanations appraised.

| Explanation | What supports it | What would test it | Standing |
|---|---|---|---|
| The mineralocorticoid | Regimen-specific syntheses are consistent where broad ones are not | Randomised comparison of hydrocortisone against hydrocortisone plus fludrocortisone | Plausible, untested |

| | | | |
|---|---|---|---|
| Source of sepsis | Pneumonia commoner in the positive trial; benefit concentrated in that subgroup | Prospective enrichment by source of infection | Plausible, post hoc |
| Baseline severity | Higher control-arm mortality in the positive trial | Prespecified interaction analysis by severity | Plausible |
| Dosing schedule | Bolus and infusion differ in receptor exposure | Randomised comparison of schedule at equal total dose | Speculative |
| Chance | Two trials of this size can differ by this much | Further adequately powered trials | Cannot be excluded |

### 5.3. Our reading

Stated plainly, and identified as our own judgement rather than as a finding: the most parsimonious account consistent with all of the evidence is that corticosteroids shorten shock in essentially everyone with vasopressor-dependent septic shock, and improve survival in some subgroup that has not yet been reliably identified. On that account both landmark trials are correct — the larger one because its population diluted the responsive subgroup, the smaller one because its population concentrated it — and the pooled estimate of about 0.88 is the average of a real effect in some patients and none in others.

If that account is right, the clinical implication is neither routine universal use nor categorical avoidance. It is a short, monitored course in the patients in whom shock is the immediate problem, with an explicit acknowledgement that the survival benefit is uncertain, and with the discipline to stop when the indication resolves.

### 5.4. A Position for Practice under Uncertainty

Figure 7 and Table 6 set out a position that both sides of this debate could implement without abandoning their view, which is the most that can honestly be offered while the question is open. Guidelines currently make a weak recommendation for low-dose hydrocortisone in vasopressor-dependent septic shock [10], and the approach below is consistent with that.

Four points deserve emphasis. The indication is persisting shock despite adequate fluid resuscitation and ongoing vasopressor requirement, not sepsis as such; the evidence in sepsis without shock is weaker and the meta-research suggests that broadening the population is where spurious benefit appears [8]. Hyperglycaemia should be actively monitored, since it is the one adverse effect on which the trials agree. The course should stop at seven days or when vasopressors are no longer needed, since no trial supports longer. And the indication, regimen and stop date should be recorded, so that a unit can audit its own practice against whichever trial eventually resolves the question.

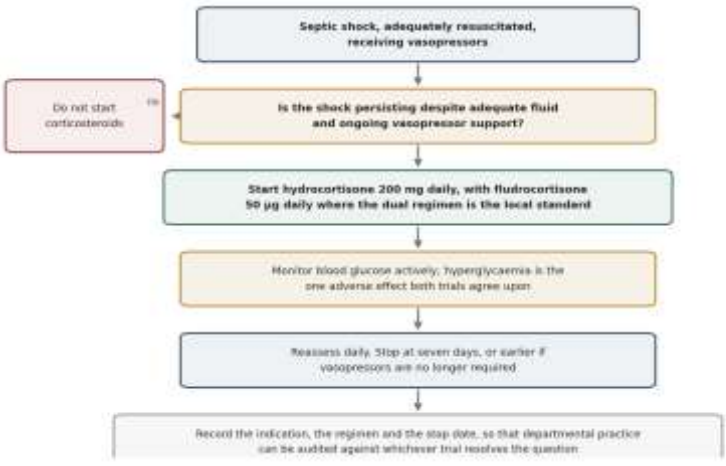


Figure 7. A practical position consistent with both sides of the debate and with current guideline recommendations. This is the authors' synthesis and is not a guideline.

Table 6. Practical position, with the basis and the residual uncertainty for each element.

| Element | Position | Basis | Residual uncertainty |
|---|---|---|---|
| Indication | Vasopressor-dependent septic shock persisting after adequate fluid resuscitation | Guideline recommendation; trial populations | Whether the responsive subgroup is narrower still |
| Regimen | Hydrocortisone 200 mg daily; add fludrocortisone where the dual regimen is local standard | Regimen-specific syntheses; trial protocols | The mineralocorticoid has not been tested head to head |
| Monitoring | Active blood glucose monitoring | Hyperglycaemia agreed across trials | Threshold for intervention not defined by these trials |
| Duration | Seven days, or until vasopressors are discontinued | Trial protocols used seven days without tapering | Optimal duration untested |
| What to tell the family | Shock will probably shorten; survival benefit is uncertain | The agreed and disputed findings respectively | None; this is what the evidence states |
| Documentation | Record indication, regimen and stop date | Enables local audit against future evidence | None |

Table 7. What would settle the question.

| Question | Trial that would answer it | Priority |
|---|---|---|
| Is the mineralocorticoid the active component? | Randomised comparison of hydrocortisone plus fludrocortisone against hydrocortisone alone, powered for mortality | Highest |
| Is pneumonia the responsive subgroup? | Prospective enrichment by source of infection, with prespecified interaction analysis | High |
| Does dosing schedule matter? | Randomised comparison of six-hourly bolus against continuous infusion at equal total dose | Moderate |
| Can responders be identified biologically? | Predictive enrichment using a prespecified biomarker or transcriptomic endotype | High |
| What are the medium-term harms? | Extended follow-up of existing cohorts for weakness, infection and functional outcome | Moderate |

## 6. LIMITATIONS

This is a structured narrative appraisal and not a systematic review. No protocol was registered, no screening was documented, and the evidence cited was selected to represent each position at its strongest rather than to be exhaustive.

The pro and con positions are constructions. Real investigators hold more nuanced views than the advocacy format permits, and a reader should not attribute either position to any author of the trials discussed. The

format's advantage is that it prevents the premature synthesis that a conventional review encourages; its cost is that it sharpens both positions beyond what their proponents would recognise.

We have relied on aggregate reporting of trial results and on published syntheses rather than on reanalysis of patient-level data. Where we quote percentages and risk ratios these are as reported in the cited sources, and readers making clinical decisions should consult the primary reports.

The adjudication and the practical position are our judgements, identified as such. They have not been prospectively evaluated, and the account we favour — a real effect concentrated in an unidentified subgroup — is a hypothesis that would itself require the enrichment trials listed in Table 7 to confirm.

Finally, the debate is confined to adults with septic shock. Paediatric populations, sepsis without shock, and corticosteroid use for other indications in critical illness are outside the scope of this appraisal and the conclusions should not be extended to them.

## 7. CONCLUSION

Two adequately powered trials of the same daily dose of hydrocortisone in septic shock reported conflicting effects on mortality and concordant effects on everything else. Half a century of research has not settled which is right, and a further half decade of meta-analysis has largely reproduced the disagreement at a higher level of aggregation.

What the exchange above suggests is that the two positions are closer than the literature's tone implies. Nobody disputes that corticosteroids shorten shock. Nobody claims the mortality question is closed. The disagreement is about what to do when a cheap, short, familiar treatment has definite secondary benefits, a manageable principal harm, and an unresolved effect on survival — and that is a question about how a clinician should act under uncertainty, not a question the next meta-analysis will answer.

The trial that would answer it is not difficult to specify: hydrocortisone with fludrocortisone against hydrocortisone alone, powered for mortality. That it has not been done, after twenty years in which the mineralocorticoid has been the leading explanation for the field's central discordance, is the most striking observation this appraisal has to offer.

**Declarations**

**Ethical approval:** Not applicable.

**Funding:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Conflicts of interes:** The authors declare that there are no conflicts of interest regarding the publication of this paper.

**Data availability:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author contributions:**

| Name of Author | C | M | So | Va | Fo | I | R | D | O | E | Vi | Su | P | Fu |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mosrur Ahmed | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

## 8. REFERENCES

1. R. Pirracchio, D. Annane, A. K. Waschka, F. Lamontagne, Y. M. Arabi, and P. E. Bollaert, 'Patient-level meta-analysis of low-dose hydrocortisone in adults with septic shock', NEJM Evid, vol. 2, no. 6, 2023. doi.org/10.1056/EVIDoa2300034
2. B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, and R. Bellomo, 'Adjunctive glucocorticoid therapy in patients with septic shock', N Engl J Med, vol. 378, no. 9, pp. 797-808, 2018. doi.org/10.1056/NEJMoa1705835

3. N. J. Meyer and H. C. Prescott, 'Fludrocortisone with hydrocortisone in sepsis: new evidence in an ongoing debate', Intensive Care Med, vol. 50, no. 12, pp. 2143-2145, 2024. doi.org/10.1007/s00134-024-07699-8
4. D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J. P. Quenot, and S. Siami, 'Hydrocortisone plus fludrocortisone for adults with septic shock', N Engl J Med, vol. 378, no. 9, pp. 809-818, 2018. doi.org/10.1056/NEJMoa1705716
5. L. Wang, Y. Chen, J. Zhang, H. Liu, and M. Zhao, 'Corticosteroids for sepsis and septic shock: a meta-analysis of 18 RCTs with dose-stratified and fludrocortisone subgroup evaluation', BMC Anesthesiol, vol. 25, 2025. doi.org/10.1186/s12871-025-03388-1
6. L. Wang, Y. Chen, J. Zhang, H. Liu, and M. Zhao, 'Corticosteroids for sepsis and septic shock: a meta-analysis of 18 RCTs with dose-stratified and fludrocortisone subgroup evaluation', BMC Anesthesiol, vol. 25, 2025. doi.org/10.1186/s12871-025-03388-1
7. R. Yamamoto, I. Nahara, M. Toyosaki, T. Fukuda, Y. Masuda, and S. Fujishima, 'Hydrocortisone with fludrocortisone for septic shock: a systematic review and meta-analysis', Acute Med Surg, vol. 7, no. 1, 2020. doi.org/10.1002/ams2.563
8. D. Annane, V. Sébille, C. Charpentier, P. E. Bollaert, B. François, and J. M. Korach, 'Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock', JAMA, vol. 288, no. 7, pp. 862-871, 2002. doi.org/10.1001/jama.288.7.862
9. C. L. Sprung, D. Annane, D. Keh, R. Moreno, M. Singer, and K. Freivogel, 'Hydrocortisone therapy for patients with septic shock', N Engl J Med, vol. 358, no. 2, pp. 111-124, 2008. doi.org/10.1056/NEJMoa071366
10. D. Annane, E. Bellissant, P. E. Bollaert, J. Briegel, D. Keh, and Y. Kupfer, 'Corticosteroids for treating sepsis in children and adults', Cochrane Database Syst Rev, vol. 12, 2019. doi.org/10.1002/14651858.CD002243.pub4
11. B. Rochwerg, S. J. Oczkowski, R. Siemieniuk, T. Agoritsas, E. Belley-Cote, and D. 'aragon, 'Corticosteroids in sepsis: an updated systematic review and meta-analysis', Crit Care Med, vol. 46, no. 9, pp. 1411-1420, 2018. doi.org/10.1097/CCM.0000000000003262
12. F. Fang, Y. Zhang, J. Tang, L. D. Lunsford, T. Li, and R. Tang, 'Association of corticosteroid treatment with outcomes in adult patients with sepsis: a systematic review and meta-analysis', JAMA Intern Med, vol. 179, no. 2, pp. 213-223, 2019. doi.org/10.1001/jamainternmed.2018.5849
13. M. Singer, C. S. Deutschman, C. W. Seymour, M. Shankar-Hari, D. Annane, and M. Bauer, 'The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)', JAMA, vol. 315, no. 8, pp. 801-810, 2016. doi.org/10.1001/jama.2016.0287
14. K. E. Rudd, S. C. Johnson, K. M. Agesa, K. A. Shackelford, D. Tsoi, and D. R. Kievlan, 'Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study', Lancet, vol. 395, pp. 200-211, 2020. doi.org/10.1016/S0140-6736(19)32989-7
15. D. Annane, S. M. Pastores, B. Rochwerg, W. Arlt, R. A. Balk, and A. Beishuizen, 'Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency in critically ill patients', Crit Care Med, vol. 45, no. 12, pp. 2078-2088, 2017. doi.org/10.1097/CCM.0000000000002737
16. A. Téblick, S. Vander Perre, L. Pauwels, S. Derde, T. Van Oudenhove, and L. Langouche, 'The role of pro-opiomelanocortin in the ACTH-cortisol dissociation of sepsis', Crit Care, vol. 25, 2021. doi.org/10.1186/s13054-021-03475-y
17. E. Boonen, H. Vervenne, P. Meersseman, R. Andrew, L. Mortier, and P. E. Declercq, 'Reduced cortisol metabolism during critical illness', N Engl J Med, vol. 368, no. 16, pp. 1477-1488, 2013. doi.org/10.1056/NEJMoa1214969
18. N. Heming, S. Sivanandamoorthy, P. Meng, R. Bounab, and D. Annane, 'Immune effects of corticosteroids in sepsis', Front Immunol, vol. 9, 2018. doi.org/10.3389/fimmu.2018.01736
19. D. B. Antcliffe, K. L. Burnham, F. Al-Beidh, S. Santhakumaran, S. J. Brett, and C. J. Hinds, 'Transcriptomic signatures in sepsis and a differential response to steroids: from the VANISH

randomized trial', Am J Respir Crit Care Med, vol. 199, no. 8, pp. 980-986, 2019. doi.org/10.1164/rccm.201807-1419OC

20. H. R. Wong, S. J. Atkinson, N. Z. Cvijanovich, N. Anas, G. L. Allen, and N. J. Thomas, 'Combining prognostic and predictive enrichment strategies to identify children with septic shock responsive to corticosteroids', Crit Care Med, vol. 44, no. 10, pp. e1000-1003, 2016. doi.org/10.1097/CCM.0000000000001833
21. C. W. Seymour, J. N. Kennedy, S. Wang, C. H. Chang, C. F. Elliott, and Z. Xu, 'Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis', JAMA, vol. 321, no. 20, pp. 2003-2017, 2019. doi.org/10.1001/jama.2019.5791
22. F. Lamontagne, B. Rochwerg, L. Lytvyn, G. H. Guyatt, M. H. Møller, and D. Annane, 'Corticosteroid therapy for sepsis: a clinical practice guideline', BMJ, vol. 362, 2018. doi.org/10.1136/bmj.k3284
23. B. Gibbison, J. A. López-López, J. Higgins, T. Miller, G. D. Angelini, and S. L. Lightman, 'Corticosteroids in septic shock: a systematic review and network meta-analysis', Crit Care, vol. 21, 2017. doi.org/10.1186/s13054-017-1659-4
24. D. Keh, E. Trips, G. Marx, S. P. Wirtz, E. Abduljawwad, and S. Bercker, 'Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS randomized clinical trial', JAMA, vol. 316, no. 17, pp. 1775-1785, 2016. doi.org/10.1001/jama.2016.14799
25. J. L. Vincent, 'The coming era of precision medicine for intensive care', Crit Care, vol. 21, no. 3, 2017. doi.org/10.1186/s13054-017-1910-z
26. J. Ioannidis, 'The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses', Milbank Q, vol. 94, no. 3, pp. 485-514, 2016. doi.org/10.1111/1468-0009.12210