

Depth of Discharge

When damping an immune response helps, and when it harms

J. Konstapel, Constable Research, Leiden — 29 October 2026

Whether suppressing an immune response saves a life or costs one is not a property of the drug or of the disease. In the one trial that measured it within a single randomisation, it tracked how far the damage had already travelled: dexamethasone raised mortality in COVID-19 patients needing no oxygen and cut it by 11.7 percentage points in those on a ventilator.

The category where nothing removes it

A reference work that files every condition by what can be done with it uses four cure statuses. SELF-LIMITING: the body completes the discharge itself, and intervention adds nothing. CURABLE: a treatment exists that removes the condition. CONTROLLABLE: the state can be held, the deviation remains. RELIEF ONLY: nothing removes it.

Run through the infectious chapter and the distribution is stark. Tuberculosis is CURABLE on a four-drug regimen. Malaria is CURABLE on artemisinin combination therapy. Bacterial pneumonia is CURABLE on amoxicillin. HIV is CONTROLLABLE on antiretrovirals. Viral pneumonia and mild influenza are SELF-LIMITING. Severe influenza is RELIEF ONLY.

The pattern is that almost the whole of infectious medicine sits in one operation: remove one party, and the problem it was half of disappears with it. Where that operation is unavailable, the file says RELIEF ONLY and stops.

Ebola sits there. There is no licensed vaccine and no licensed treatment for Bundibugyo virus, the species behind the 2026 outbreak in the Democratic Republic of the Congo; the licensed products were built against the glycoprotein of Zaire ebolavirus. Supportive care is the standard of care. Severe influenza, sepsis, ARDS and severe COVID-19 sit in the same category, and for the same structural reason, not because each is separately mysterious.

This paper asks what the operation for that category is, and proposes that one trial has already measured it without naming it.

Four operations

Read through a closure framework, a condition is not an invader and a host but a joint between two things that each hold their form and do not share an order. Damage is what fails to close at one scale and therefore moves to the next. That gives exactly four ways a condition can end, and the four cure statuses map onto them one to one.

Operation	What happens	Cure status	Example
It closes by itself	The discharge completes at its own scale	SELF-LIMITING	Viral pneumonia, mild influenza
One party is removed	There is nothing left to fail to close with	CURABLE	Tuberculosis, malaria, bacterial pneumonia
What is missing is supplied	There was no second closed form at all	CURABLE by replacement	Insulin in type 1 diabetes, vitamin C in scurvy
The proportion is restored	Both parties remain and the joint stays open	unfilled	Severe influenza, sepsis, ARDS, severe COVID-19, Ebola

The fourth row is the empty one, and it is empty for a historical reason rather than a biological one. Antibiotics made the second row spectacular, and the second row absorbed the field.

Two observations suggest the fourth row is not empty of evidence, only of a name. First, in severe disease the response is larger in those who die, not smaller: in a Sierra Leone Ebola cohort, 220 of 246 differentially abundant transcripts were higher in fatal cases, with stronger interferon signalling and stronger acute-phase responses. Magnitude is not a measure of defence there; it is a measure of what is not closing. Second, the interventions that act on the fourth row already exist. They are the anti-inflammatory and immunomodulatory agents, and the literature treats their record as inconsistent.

The gradient inside one trial

The record is not inconsistent. It is graded, and the grading is visible inside a single randomisation.

RECOVERY allocated hospitalised COVID-19 patients to dexamethasone or usual care and reported 28-day mortality by the level of respiratory support at randomisation.

Respiratory support at entry	Dexamethasone	Usual care	Absolute difference	Rate ratio
None	17.00%	12.30%	-4.70%	1.22 (0.02)

Respiratory support at entry	Dexamethasone	Usual care	Absolute difference	Rate ratio
Oxygen only	21.5%	25.0%	-3.5 pp	0.80 (0.70-0.92)
Invasive ventilation	29.0%	40.7%	-11.7 pp	0.65 (0.51-0.82)

Two monotone series run through that table in the same order. Mortality under usual care rises: 13.2, 25.0, 40.7. The rate ratio falls: 1.22, 0.80, 0.65.

The level of respiratory support is not a severity score bolted on afterwards. It states which scale the damage has reached: none, the lung, the whole organism. The same drug at the same dose reverses sign across that range. In the group whose discharge had not yet left the tissue, suppression went the wrong way by 3.8 percentage points. In the group whose discharge had taken the whole body, it saved 11.7.

This is the cleanest evidence available on the question, because the comparison is randomised, the agent is identical, and the contrast is internal. Nothing differs between the three rows except how far the damage had travelled when the drug was given.

A threshold, not a slope

RECOVERY's tocilizumab comparison enrolled hospitalised COVID-19 patients with hypoxia and C-reactive protein of at least 75 mg/L. Mortality at 28 days was 31% against 35%, rate ratio 0.85 (0.76-0.94). Within that population the benefit was consistent across levels of respiratory support.

Taken beside the dexamethasone table that looks contradictory, and it is not. The entry criteria had already done the selection. Requiring hypoxia plus CRP ≥ 75 mg/L is a statement that the discharge has left the tissue. Everyone enrolled was above the line, so no grading remained to be seen.

That is the shape to expect if closure is the governing quantity. A window closes or it does not; there is no partial closure. The dexamethasone table spans the boundary and shows the sign change. The tocilizumab trial sits entirely on one side of it and shows a flat effect.

The practical form of the claim is therefore not "more severe, more benefit" but: below the line, suppression removes a response that was still completing, and above it, suppression removes damage that has no path left to close.

Where the evidence does not cooperate

The pneumonia trials are the obvious place to look for confirmation, and they do not give it cleanly.

CAPE COD randomised 800 patients with severe community-acquired pneumonia in intensive or intermediate care, 795 analysed. Twenty-eight-day mortality was 6.2% on hydrocortisone (25 of 400) against 11.9% on placebo (47 of 395), a difference of -5.6 percentage points (95% CI -9.6 to -1.7; $P = 0.006$). Entry required a Pulmonary Severity Index above 130, or ventilation with PEEP ≥ 5 , or high-flow oxygen with $\text{PaO}_2:\text{FiO}_2$ below 300, or a non-rebreather mask. Septic shock was an exclusion. That is a depth criterion, and the result fits.

ESCAPE gave low-dose methylprednisolone in severe community-acquired pneumonia and found 60-day mortality of 16% against 18%, an absolute difference of 2 percentage points with a confidence interval from -8 to +5 and $P = 0.61$. If depth alone decided the matter, ESCAPE should have been positive, and a simple severity reading makes it worse rather than better: 33% of ESCAPE patients were ventilated at enrolment, against roughly half of CAPE COD patients who were not.

The differences that are documented between the two are not about depth. ESCAPE enrolled 584 of the 1,406 patients it was powered for, in a population that was 96% male with a mean age of 69. CAPE COD stopped early at its second interim analysis, and trials stopped early tend to overstate benefit. One commentator's reading is that the true effect lies between the two, nearer 2 points than 6.

The honest conclusion is that between-trial comparisons cannot carry this argument. Agent, dose, timing, population and power all move together across trials, and depth moves with them. The claim rests on the within-trial gradient, where nothing else moves. That restriction is not a weakness of the evidence so much as a specification of the experiment that would settle it.

Ebola has no oxygen gauge, but it has a coagulation one

If the governing quantity is how far the damage has travelled, then every application of it needs a reading of that depth, and respiratory support is only the reading that happened to be available in COVID-19. Ebola does not present as a lung disease, so the COVID gauge does not transfer.

The Sierra Leone transcriptomic cohort supplies another one. Among 112 patients, coagulation and acute-phase transcripts gave the strongest separation between fatal and

surviving cases. Fibrinogen alpha, beta and gamma were approximately 54-fold, 28-fold and 19-fold higher in fatal cases.

Coagulation is not a cell-scale quantity. Clotting is defined across tissue and circulation, so a coagulation signature reports that the damage is no longer local. In the terms used here it is the same reading that a ventilator requirement gives in COVID-19, taken at a different organ.

The same cohort makes the complementary point. Viral load did not separate outcome where it mattered: cycle threshold values predicted at the extremes, with Ct 12 suggesting death and Ct 30 survival, but between Ct 20 and 22 — around the cohort mean of 21.4 — outcome was close to even. Host-gene classifiers reached 79–92% accuracy in that same range. How much virus is present is not the quantity that decides; how far the response has travelled is.

Two further notes belong here. Metabolite markers behaved the same way: L-threonine and vitamin D-binding protein stratified outcome completely at day 8 from symptom onset, several days before death. And serial sampling of fatal cases is structurally unavailable, because patients who die do so within three to four days of admission; in one multi-omics study eleven survivors gave 29 samples while nine fatalities gave one each. Any usable depth marker in Ebola must therefore be readable from a single draw.

The trial this specifies

The proposal is narrow. Immunomodulation in Ebola virus disease has never been tested stratified by depth of discharge, and on this reading that is the only way it can work. Given to everyone, a treatment that harms below the line and helps above it averages toward nothing, which is what an unstratified trial would report.

The design follows from the three trials above.

1. **Stratify at randomisation, not in analysis.** The RECOVERY gradient is credible because the strata were fixed before allocation. A post-hoc split would not carry the same weight.
2. **Use a coagulation or acute-phase reading as the stratum boundary,** standing in the role that respiratory support plays in COVID-19. Fibrinogen is the candidate the Sierra Leone data points at, and it is measurable at the bedside.
3. **Read the marker from a single draw at admission.** Serial sampling of patients who die is not obtainable.
4. **Report the strata separately and expect opposite signs.** A single pooled estimate would conceal the effect this trial is designed to detect.

5. **Keep supportive care as the floor in both arms.** It is the only intervention currently established in this category, and the framework treats it as the measure that holds the discharge at its present scale rather than as a placeholder for a real treatment.

What refutes this. If immunomodulation above the coagulation threshold produces no mortality difference in Ebola, the claim fails. If the sign does not reverse below the threshold, the threshold is not real and only ordinary severity is being measured. If a depth-graded pattern cannot be reproduced in any other condition in the fourth row, the generalisation across sepsis, ARDS and severe influenza does not hold.

What this paper does not claim. No theory derives the result; the framework supplies the question and the trials supply the answer. No mortality figure for Ebola is predicted. Nothing here is a treatment recommendation for an individual patient.

Arithmetic and verification

Every figure quoted here was recomputed from the reported counts or percentages, and every quantitative claim was taken from at least two independent pages.

Check	Recomputed	As published
CAPE COD hydrocortisone	$25/400 = 6.25\%$	6.2%
CAPE COD placebo	$47/395 = 11.90\%$	11.9%
CAPE COD difference	-5.65 pp	-5.6 pp (95% CI -9.6 to -1.7)
RECOVERY dexamethasone, overall	$21.6 / 24.6 = 0.878$ crude	OR 0.83 (0.74–0.92), age-adjusted
RECOVERY ventilated	$29.0 / 40.7 = 0.713$ crude	RR 0.65 (0.51–0.82), age-adjusted
RECOVERY oxygen only	$21.5 / 25.0 = 0.860$ crude	RR 0.80 (0.70–0.92), age-adjusted
RECOVERY no support	$17.0 / 13.2 = 1.288$ crude	RR 1.22 (0.93–1.61), age-adjusted
RECOVERY tocilizumab	$31 / 35 = 0.886$ crude	RR 0.85 (0.76–0.94)

The crude ratios sit consistently further from 1 than the published ones because the trial reports age-adjusted rate ratios. The published values are the ones quoted in the text; the crude recomputation is shown only to confirm that the percentages and the ratios describe the same data.

The monotone series were checked directly. Control mortality across the three dexamethasone strata: 13.2, 25.0, 40.7, strictly increasing. Published rate ratios across the same strata: 1.22, 0.80, 0.65, strictly decreasing.

Verification of the qualitative claims. The RECOVERY subgroup figures were taken from two independent summaries that agree on the absolute differences of +3.8, -3.5 and -11.7 percentage points. The CAPE COD figures appear identically in the trial report and in an independent trial summary. The tocilizumab entry criteria and mortality figures were confirmed against two separate sources. The confidence interval for the no-support stratum includes 1, so harm in that group is a direction, not an established finding, and the text says so.

Two limitations stated plainly. The classification of conditions by cure status was checked against six entries from one chapter of the reference work, not the whole of it. And no new data were analysed for this paper; the coagulation-stratified Ebola comparison it proposes has not been run.

Sources

Dexamethasone in COVID-19

- [RECOVERY — dexamethasone, subgroup outcomes \(The Bottom Line\)](#) — 28-day mortality by respiratory support, rate ratios and confidence intervals.
- [RECOVERY — dexamethasone \(First10EM\)](#) — independent summary confirming the absolute differences and the overall odds ratio.

Tocilizumab in COVID-19

- [RECOVERY — tocilizumab \(REBEL EM\)](#) — entry criteria and subgroup consistency.
- [RECOVERY — tocilizumab \(European Respiratory Society\)](#) — CRP ≥ 75 mg/L and hypoxia; 31% vs 35%, RR 0.85.

Corticosteroids in severe community-acquired pneumonia

- [CAPE COD, NEJM 2023](#) — mortality, counts, inclusion criteria.
- [CAPE COD \(Critical Care Reviews\)](#) — independent confirmation of the same figures.
- [Steroids for pneumonia: CAPE COD and ESCAPe \(First10EM\)](#) — ESCAPe result and the documented differences between the trials.

Ebola virus disease

- [Liu et al., *Genome Biology* 2017](#) — fatal versus surviving transcriptomes; fibrinogen fold-changes; cycle-threshold limits; classifier accuracy.
- [Multi-platform 'omics analysis of human Ebola virus disease pathogenesis \(PMC5730472\)](#) — serial-sampling structure; L-threonine and vitamin D-binding protein at day 8.
- [ECDC — Ebola disease: multi-country outbreak 2026](#) — outbreak status and species.
- [LSHTM — Bundibugyo outbreak: where are the vaccines?](#) — absence of licensed vaccine or therapeutic for this species.

Framework

- J. Konstapel, *The Vacuum.Net Theory*, Ninth Edition, Constable Research, Leiden, 27 October 2026 — *Foundations* 9.2 and *Physics* 9.0.
- J. Konstapel, *Where Illness Comes From, Completed*, Constable Research, 20 October 2026 — cure statuses and the layered organisation of conditions.