

## THIS EPISODE IN BRIEF

The treatment trials reward restraint: 7 days of antibiotics matched 14 for bloodstream infection (BALANCE), a MAP target of 80 to 85 raised mortality at 65 or older (OPTPRESS), and vasopressors first matched fluids first (ARISE FLUIDS). A capillary refill protocol shortened organ support without changing mortality (ANDROMEDA-SHOCK-2), and antibiotic urgency tracked shock more than immune status (Gupta).

On recognition, the one randomized ward-alert trial (SCREEN) lowered adjusted mortality with a qSOFA trigger and a required response. Machine-learning outcome gains (CHARTwatch, TREWS, COMPOSER) come from nonrandomized designs, Epic's updated model still fires many alerts per true case, and nearly a third of infected patients who deteriorated stayed below a NEWS2 of 5 in their first 4 ED hours (Nielsen).

**About this episode.** A one-off episode on twelve references: treatment (1 to 6) and recognition, response and prediction (7 to 12). Eleven papers and four editorials read in full; CEPEC, without results yet, from its registration.

## 7 days

of antibiotics noninferior to 14 for bloodstream infection (BALANCE)

## NNH 10

for death with a MAP target of 80 to 85 at age 65 or older (OPTPRESS)

## 0.85

adjusted risk ratio for death with electronic ward screening (SCREEN)

## AT A GLANCE

| #                                                  | Study                                                             | Design                                    | Result in one line                                                                           | Signal            |
|----------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------|----------------------------------------------------------------------------------------------|-------------------|
| ANTIBIOTICS: TIMING AND DURATION                   |                                                                   |                                           |                                                                                              |                   |
| 1                                                  | <b>Gupta: antibiotic timing</b><br>Clin Infect Dis 2026           | Cohort, 9 US hospitals, 39,842 stays      | Higher mortality with a 1 to 3 h delay in septic shock only; immune status did not modify it | Confirms practice |
| 2                                                  | <b>BALANCE: 7 vs 14 days</b><br>N Engl J Med 2025                 | Noninferiority RCT, 74 hospitals, 3,608   | Death 14.5% vs 16.1%; noninferior within a 4-point margin                                    | Change practice   |
| EARLY RESUSCITATION: FLUID, PERFUSION AND PRESSURE |                                                                   |                                           |                                                                                              |                   |
| 3                                                  | <b>ARISE FLUIDS: pressors vs fluids</b><br>N Engl J Med 2026      | RCT, 51 sites, 963 ED patients            | Days alive and out of hospital 76 vs 76; less pulmonary edema                                | Confirms practice |
| 4                                                  | <b>ANDROMEDA-SHOCK-2: CRT protocol</b><br>JAMA 2025               | RCT, 86 ICUs, 1,467 patients              | Win ratio 1.16 (95% CI 1.02 to 1.33); death 26.5% vs 26.6%                                   | Consider locally  |
| 5                                                  | <b>OPTPRESS: MAP 80 to 85 at 65+</b><br>Intensive Care Med 2025   | RCT, 29 hospitals, 516, stopped early     | 90-day death 39.3% vs 28.6%; NNH about 10                                                    | Confirms practice |
| 6                                                  | <b>CEPEC: MAP band platform</b><br>ClinicalTrials.gov NCT06605144 | Adaptive platform RCT, recruiting         | Four MAP bands from 56 to 75; results after 2029                                             | Watch             |
| FINDING SEPSIS: SCORES AND SCREENS                 |                                                                   |                                           |                                                                                              |                   |
| 7                                                  | <b>Nielsen: below NEWS2 5</b><br>Am J Emerg Med 2023              | ED cohort, 1 centre, 2,055 patients       | 29.8% of serious outcomes had NEWS2 under 5                                                  | Confirms practice |
| 8                                                  | <b>SCREEN: ward qSOFA alert</b><br>JAMA 2025                      | Stepped-wedge RCT, 43 wards, 60,055       | Adjusted RR 0.85 (95% CI 0.77 to 0.93); crude 3.2% vs 3.1%                                   | Consider locally  |
| MACHINE-LEARNING EARLY WARNING                     |                                                                   |                                           |                                                                                              |                   |
| 9                                                  | <b>CHARTwatch: deterioration model</b><br>CMAJ 2024               | Controlled before-after, 13,649 stays     | aRR 0.74 (0.55 to 1.00); vs control wards 0.79 (0.50 to 1.24)                                | Watch             |
| 10                                                 | <b>TREWS: confirmed sepsis alerts</b><br>Nat Med 2022             | Cohort, 5 hospitals, 6,877 patients       | Prompt confirmation: adjusted mortality 3.3 points lower                                     | Watch             |
| 11                                                 | <b>COMPOSER: deep-learning ED alert</b><br>NPJ Digit Med 2024     | Before-after, 2 EDs, 6,217 patients       | Mortality 9.5% vs 11.4% modelled; bundle compliance up 5 points                              | Watch             |
| 12                                                 | <b>Epic Sepsis Model v2</b><br>JAMA Netw Open 2026                | Validation, 4 systems, 227,091 encounters | AUROC 0.82 to 0.92; PPV 0.13 to 0.26 at 60% sensitivity                                      | Consider locally  |

Signals: **CHANGE PRACTICE** **CONSIDER LOCALLY** **CONFIRMS PRACTICE** **WATCH** Click a title to jump to its card

# The studies

## ANTIBIOTICS: TIMING AND DURATION

### 1. Time to antibiotics: shock sets the urgency, with no extra penalty for immunocompromise

**CONFIRMS PRACTICE** Gupta et al, Clin Infect Dis 2026;83:447-455 • Retrospective cohort, 9 US hospitals, 39,842 hospitalizations • Certainty: Low • [Article](#)

**Bottom line.** Among 39,842 ED hospitalizations with suspected sepsis, antibiotics at 1 to 3 hours instead of within the first hour were associated with higher in-hospital mortality in septic shock, both without immunocompromise (OR 1.41, 95% CI 1.12 to 1.76) and with it (OR 1.21, 95% CI 1.002 to 1.47). Without shock there was no association, even at 3 to 6 hours, and immune status did not modify the timing effect (interaction  $P = .27$ ).

**Population:** Adults with suspected sepsis in 9 Mass General Brigham EDs, 2015 to 2024 (cultures and IV antibiotics within 6 h, organ dysfunction or shock within 3 h); 48% immunocompromised by adapted FDA criteria, 2,283 severe • **Exposure:** ED arrival to first IV antibiotic, 1 to 3 h vs 0 to 1 h (primary) and 3 to 6 h vs 0 to 3 h • **Outcome:** Adjusted in-hospital mortality

#### RESULTS

- All suspected sepsis, 1 to 3 h vs 0 to 1 h: OR 1.33 (95% CI 1.12 to 1.59) without immunocompromise and 1.08 (95% CI 0.94 to 1.25) with it. Severity modified the effect strongly ( $P = .0015$ ).
- Sepsis without shock: OR 1.22 (95% CI 0.93 to 1.60) and 0.94 (95% CI 0.76 to 1.16); at 3 to 6 h vs 0 to 3 h, 1.14 and 1.04, all crossing 1. Severe immunocompromise in shock: OR 1.29 (95% CI 0.59 to 2.82).
- Antibiotics were already fast: median 2.27 h without immunocompromise, 2.17 h with it and 1.95 h when severe.

#### CAVEATS

- Observational timing data carry confounding by indication: clearer and sicker presentations get faster antibiotics.
- The severe subgroup is small with a wide interval, and immune status came from diagnosis codes.
- With death or discharge to hospice as the outcome, every timing association weakened and lost significance. One health system, community-onset ED sepsis only.

**How it fits.** Consistent with SSC 2026, which asks for antimicrobials within an hour for possible septic shock and allows up to 3 hours, after rapid assessment, for possible sepsis without shock, and with earlier work showing timing matters most in shock. It questions blanket one-hour targets for every immunocompromised patient; neutropenic fever guidance still sets one hour. No accompanying commentary was found.

### 2. Seven days of antibiotics for bloodstream infection is noninferior to fourteen, in ICU and ward patients alike

**CHANGE PRACTICE** BALANCE Investigators, N Engl J Med 2025;392:1065-1078 • Noninferiority RCT, 74 hospitals, 7 countries, 3,608 patients • Certainty: High • [Article](#)

**Bottom line.** In 3,608 hospitalized patients with bloodstream infection, 55% of them in ICU, 7 days of adequate antibiotics was noninferior to 14 days for 90-day mortality: 14.5% vs 16.1%, difference -1.6 percentage points (95.7% CI -4.0 to 0.8) against a 4-point margin. Per-protocol and modified intention-to-treat analyses agreed, relapse was similar (2.6% vs 2.2%), and the 7-day group gained a median 5 antibiotic-free days by day 28.

**Population:** Hospitalized adults with a pathogenic bacterium in blood culture; excluded severe immunosuppression, *Staphylococcus aureus* or *S. lugdunensis*, fungemia, contaminants and foci needing prolonged therapy • **Intervention:** 7 days of adequate antibiotics • **Comparison:** 14 days; agent, dose and route at clinician discretion, allocation concealed until day 7 • **Outcome:** Death from any cause at 90 days

#### RESULTS

- Case mix: community onset 75.4%; urinary source 42.2%, intra-abdominal 18.8%, lung 13.0%; monomicrobial gram-negative 71.0%.

- Per-protocol -2.0 points (95% CI -4.5 to 0.6). ICU death 9.0% vs 9.6%; hospital death 9.3% vs 10.3%. C difficile 1.7% vs 2.0%; resistant organism infection or colonization 9.5% vs 8.5% (difference 1.1, 95% CI -0.8 to 2.9).
- Robustness (our Wald approximation): about 56 additional deaths in the 7-day arm would have been needed to push the upper bound past the margin.

#### CAVEATS

- Open label, and 23.1% of the 7-day group was treated longer than allowed; nonadherence in a noninferiority trial biases toward similarity. Median delivered durations were 8 and 14 days.
- The excluded groups (S aureus, neutropenia, transplant, endovascular and undrained infection) are where duration decisions are hardest.
- Adverse events, C difficile and resistance were infrequent, so modest differences cannot be excluded.

*How it fits.* Earlier trials (604, 503 and 248 patients) were gram-negative only, used 10-point margins and enrolled few ICU patients; BALANCE extends the result to critically ill patients and gram-positive organisms. Fowler's accompanying NEJM editorial calls it a landmark, notes the shorter course did not reduce antibiotic-related adverse events, and flags limited applicability where transplant, immunocompromised or multidrug-resistant cases dominate.

## EARLY RESUSCITATION: FLUID, PERFUSION AND PRESSURE

### 3. Fluids first or vasopressors first in early septic shock: the same days alive and out of hospital

**CONFIRMS PRACTICE** ARISE FLUIDS Investigators, N Engl J Med 2026;395:1387-1398 • Open-label RCT, 51 sites, 963 ED patients • Certainty: Moderate • [Article](#)

**Bottom line.** In 963 ED patients with septic shock who had received 1 to 2 litres, stopping further fluid and starting vasopressors early gave the same median days alive and out of hospital at day 90 as a fluid-first approach: 76 vs 76, difference 0.0 days (95% CI -2.7 to 2.7). The vasopressor arm received about 1.1 litres less over 24 hours and had less pulmonary edema; 90-day mortality was 16.4% vs 14.4% (RR 1.14, 95% CI 0.85 to 1.54).

**Population:** ED adults with suspected infection, SBP under 90 or MAP under 65 after at least 1,000 ml, lactate above 2, within 6 h of arrival and before more than 2,000 ml • **Intervention:** Stop fluids and start vasopressors for 6 to 24 h, with 250 ml boluses only for defined triggers • **Comparison:** Up to 1,000 ml then 500 ml boluses (30 ml/kg within 3 h recommended), later vasopressors • **Outcome:** Days alive and out of hospital to day 90

#### RESULTS

- Separation: fluid over 24 h 1,140 vs 2,248 ml (difference -1,108 ml, 95% CI -1,395 to -850); vasopressor within 24 h 86.5% vs 67.6%, median start 0.4 vs 1.4 h; peripheral vasopressor 71.9% vs 55.4%; ICU admission 76.5% vs 67.8%.
- Pulmonary edema 0.6% vs 5.0% (RR 0.12, 95% CI 0.03 to 0.39): about 23 patients treated vasopressor-first to avoid one event (our calculation). 28-day death 12.9% vs 10.0% (RR 1.29, 95% CI 0.91 to 1.85).

#### CAVEATS

- Open label; the authors note pulmonary edema reporting may be biased.
- The 90-day mortality interval runs from a 15% relative reduction to a 54% increase, and point estimates favoured the fluids arm at every time point, so harm from the vasopressor-first strategy cannot be excluded.
- Many patients were excluded for treatment limits, cardiac failure or more than 2 litres already given, and most of the separation in fluid arose in the first 6 hours.

*How it fits.* Consistent with CLOVERS and CLASSIC, and the first of the three to randomize before the 30 ml/kg dose that SSC 2026 keeps as a conditional recommendation. Iwashyna's NEJM editorial offers two readings of the three trials: the strategies tested were not tailored enough, or, with prompt source control and monitoring, the range of reasonable approaches is wide. Antibiotics here started at a median of under an hour.

## 4. A capillary refill time protocol shortens organ support in early septic shock, with no change in mortality

**CONSIDER LOCALLY** ANDROMEDA-SHOCK-2 Investigators, JAMA 2025;334:1988-1999 • Open-label RCT, 86 ICUs, 19 countries, 1,467 patients • Certainty: **Moderate** • [Article](#)

**Bottom line.** Within 4 hours of septic shock, a 6-hour tiered protocol targeting a capillary refill time (CRT) of 3 seconds or less beat usual care on a hierarchical composite of death, duration of vital support and hospital stay: win ratio 1.16 (95% CI 1.02 to 1.33). The gain came from shorter vital support; 28-day mortality was the same (26.5% vs 26.6%, HR 0.99, 95% CI 0.81 to 1.21).

**Population:** Septic shock with lactate 2 or more on norepinephrine after at least 1,000 ml; median 1,500 ml given and norepinephrine 0.23 vs 0.21 mcg/kg/min at entry • **Intervention:** CRT rechecked after each step and hourly once normal. Tier 1: pulse pressure and diastolic pressure guide fluid (if responsive) or norepinephrine. Tier 2: echo, further fluid, a 1-hour MAP 80 to 85 test in chronic hypertension, a 1-hour dobutamine test • **Comparison:** Usual care • **Outcome:** Hierarchical composite at 28 days

### RESULTS

- Wins 48.9% vs 42.1%; vital support decided the largest share of pairs (47.5%; wins 26.4% vs 21.1%). Vital support-free days 16.5 vs 15.4 (proportional OR 1.28, 95% CI 1.06 to 1.54), reported without formal testing after the mortality gate failed.
- At 6 h: CRT normalized in 85.9% vs 61.7%; fluid 595 vs 847 ml (difference -251 ml); dobutamine 12.3% vs 5.3%. 36.4% had a normal CRT throughout and received no protocol intervention.

### CAVEATS

- Unblinded, and stopping vasopressors, extubation and kidney replacement were clinician decisions; the winning tier is the most judgment-sensitive.
- Dedicated trained staff ran the protocol at the bedside, so protocol and extra reassessment cannot be separated.
- Separation was modest, and a bundle cannot show which step helped; the diastolic pressure step normalized CRT in few patients.

*How it fits.* Follows ANDROMEDA-SHOCK (CRT vs lactate, 424 patients). Machado and Semler's JAMA editorial favours adopting selected elements, ranks CRT above lactate or central venous saturation as a perfusion target, and suggests much of the effect may be better-targeted fluid. The protocol's MAP test lasts one hour and is reversed if CRT does not respond, unlike the sustained high target in OPTPRESS.

## 5. A MAP target of 80 to 85 raised mortality in older patients with septic shock

**CONFIRMS PRACTICE** Endo et al, Intensive Care Med 2025;51:883-892 • Open-label RCT, 29 Japanese hospitals, 516 patients, stopped early • Certainty: **Moderate** • [Article](#)

**Bottom line.** In 516 patients aged 65 or older with septic shock, a MAP target of 80 to 85 for up to 72 hours increased 90-day mortality against a target of 65 to 70: 39.3% vs 28.6%, risk difference 10.7 percentage points (95% CI 2.6 to 18.9), about one extra death for every 10 patients treated. No subgroup benefited, including patients with chronic hypertension, and the trial stopped early.

**Population:** Septic shock at 65 or older, randomized within 3 h of vasopressor start; median age 78, 53% with chronic hypertension • **Intervention:** MAP 80 to 85 for 72 h or until off vasopressors • **Comparison:** MAP 65 to 70; both arms added vasopressin once norepinephrine reached 0.1 mcg/kg/min • **Outcome:** 90-day all-cause mortality

### RESULTS

- Death attributed to sepsis 30.0% vs 17.8%; 28-day death 30.4% vs 21.6%. About 2.5 fewer days free of kidney replacement, ventilation and catecholamines.
- More vasopressor exposure over 72 h: median norepinephrine 15.6 vs 9.6 mg and vasopressin 34.0 vs 11.8 units; vasopressors ran a median 65 vs 42 h. Fluid volumes were similar.
- Fragility index 6 (our calculation, Fisher exact test).

### CAVEATS

- Stopped at 518 of 836 planned patients after an interim analysis, which tends to exaggerate effect size.

- Open label, a fixed block size of 10, cuff pressures in principle, and an all-Japanese population.
- Control mortality (28.6%) was well below the 45% assumed in planning.

**How it fits.** Earlier trials, including SEPSISPAM and the 65 trial, found no consistent benefit from higher targets. OPTPRESS adds a mortality signal in the opposite direction in older patients, with no benefit in chronic hypertension, the group where earlier studies suggested a higher target might help.

## 6. CEPEC: a Canadian adaptive platform, now recruiting, that compares MAP targets from 56 to 75

**WATCH** CEPEC, ClinicalTrials.gov NCT06605144, record updated September 2026 • Adaptive Bayesian platform RCT, open label, recruiting; no results • Certainty: **Not applicable** • [Registry record](#)

**Bottom line.** CEPEC is a recruiting, Canadian-led adaptive platform for routine ICU supportive care, sponsored by the Université de Sherbrooke. Its vasopressor domain is designed to randomize patients with hypotension to one of four MAP bands (56 to 60, 61 to 65, 66 to 70 or 71 to 75), lets clinicians limit randomization to two or more adjacent bands where they have equipoise, and aims to identify which patients do better at lower or higher pressures.

**Population:** Patients on, or needing, vasopressors for hypotension with MAP under 75 and an expected ICU stay over 24 h, within 24 h of eligibility; excludes acute brain or spinal cord injury, recent transplant and expected organ donors • **Intervention:** Randomized MAP band • **Outcome:** Composite of mortality, persistent organ dysfunction, hospital days and discharge disposition to day 30

### RESULTS

- Other domains: platelet transfusion thresholds before procedures (the Canadian arm of T4P, five thresholds from under 10 to under 50, primary 90-day mortality) and bolus vs continuous enteral feeding (feasibility).
- Started March 2025; estimated enrollment 5,500; primary completion estimated December 2029. Sites in New Brunswick, Ontario and Quebec are recruiting, with Auckland and the UK planned.

### CAVEATS

- No results yet; this card describes a design.
- Open label with clinician-chosen bands, which helps enrollment and complicates interpretation at the extremes.
- A composite primary outcome will need its components read separately when results arrive.

**How it fits.** A natural next step after the 65 trial and OPTPRESS, both in older patients. CEPEC asks whether the best band varies between patients.

## FINDING SEPSIS: SCORES AND SCREENS

## 7. Nearly a third of infected ED patients who died or reached ICU stayed below a NEWS2 of 5 in their first 4 hours

**CONFIRMS PRACTICE** Nielsen et al, Am J Emerg Med 2023;68:144-154 • Secondary analysis of a single-centre prospective ED cohort, 2,055 patients • Certainty: **Low** • [Article](#)

**Bottom line.** Of 2,055 ED patients treated for suspected bacterial infection at one Danish hospital, 198 (9.6%) died in hospital or went to ICU, and 59 of them (29.8%) never reached a NEWS2 of 5 in their first 4 hours. In that low-score group, diabetes (OR 2.23, 95% CI 1.23 to 4.05), a SOFA score of 2 or more (OR 2.57, 95% CI 1.37 to 4.79) and a DNACPR order (OR 3.70, 95% CI 1.75 to 7.79) independently predicted the outcome.

**Population:** Adults with suspected bacterial infection given antibiotics within 24 h of ED arrival, Slagelse Hospital, October 2017 to March 2018 • **Exposure:** Worst NEWS2 in the first 4 h, split at 5 • **Outcome:** In-hospital death or ICU transfer

### RESULTS

- Low-score patients with a serious outcome were older (median 77 vs 72), more often had urinary (37.3% vs 17.3%) or abdominal (20.3% vs 8.6%) sources, and none met qSOFA 2 or more. Positive blood cultures 5.1% vs 24.5%.
- Median time to IV antibiotics 6.7 h in the low-score group vs 4.2 h with NEWS2 5 or more. Model AUROC 0.72 and 0.70.

**CAVEATS**

- Single centre, only 59 events in the key group, and lactate missing for most patients.
- NEWS2 was taken from the first 4 hours only; serial scoring might have caught later deterioration.
- Associations only; a DNACPR order likely marks frailty and goals of care.

**How it fits.** A score threshold works as a floor for escalation and leaves a gap: older patients with urinary and abdominal infection whose vital signs look reassuring. SSC 2021 already advised against using qSOFA alone as a screening tool.

## 8. Electronic qSOFA screening on hospital wards lowered adjusted 90-day mortality in a stepped-wedge trial

**CONSIDER LOCALLY** Arabi et al, JAMA 2025;333:763-773 • Stepped-wedge cluster RCT, 43 wards, 5 Saudi hospitals, 60,055 patients • Certainty: **Moderate** • [Article](#)

**Bottom line.** Revealing a qSOFA alert (2 of 3 criteria within 12 hours) to ward nurses and physicians, with training, a required nurse assessment, physician documentation and feedback dashboards, lowered adjusted 90-day in-hospital mortality: aRR 0.85 (95% CI 0.77 to 0.93), number needed to screen 206. Crude mortality was 3.2% vs 3.1%, so the benefit depends on adjustment for calendar period and COVID-19.

**Population:** All adults admitted to 43 medical, surgical and oncology wards, 2019 to 2021 • **Intervention:** Revealed alert with a nurse and physician response loop, training and audit • **Comparison:** Silent alert, calculated and not shown • **Outcome:** 90-day in-hospital mortality

**RESULTS**

- Alerts fired in 14.6% of screened patients; 73% were acknowledged and physicians judged 34.8% to be sepsis. Within 12 h, lactate testing rose (aRR 1.30) and IV fluid orders doubled (aRR 2.17); new antibiotic orders did not change, since 81.3% already had antibiotics.
- Vasopressor use (aRR 0.86) and new multidrug-resistant organisms fell, while code blue calls (aOR 1.24), new kidney replacement therapy (aOR 1.20) and C difficile (aOR 1.30) rose.

**CAVEATS**

- Stepped-wedge designs are confounded by time, and COVID-19 waves arrived mid-trial; screening periods had more COVID-19 cases (11.8% vs 5.2%).
- Among alerted patients, mortality did not differ (aRR 1.04, 95% CI 0.93 to 1.16), so the mechanism is unclear.
- One health system on one EMR, and the intervention bundled training, a mandated response and feedback with the alert.

**How it fits.** The first large randomized evidence for sepsis alerts. Angus's accompanying JAMA editorial says the design shows whether the intervention worked and little about why, points to the absent effect among alerted patients, and favours further evaluations before wide adoption. The trigger was qSOFA, which SSC 2021 advised against as a sole screening tool.

## MACHINE-LEARNING EARLY WARNING

## 9. CHARTwatch: a deterioration model on a Toronto medicine unit, linked to fewer non-palliative deaths

**WATCH** Verma et al, CMAJ 2024;196:E1027-E1037 • Nonrandomized controlled before-after study, 1 academic GIM unit, 13,649 admissions • Certainty: **Low** • [Article](#)

**Bottom line.** At St. Michael's Hospital in Toronto, a machine-learning model predicting death or transfer to ICU, step-up or palliative care, paged to physicians and charge nurses with a high-risk pathway, was associated with fewer non-palliative in-hospital deaths on general internal medicine: 1.6% vs 2.1% before (aRR 0.74, 95% CI 0.55 to 1.00). Against untreated subspecialty wards, the difference-in-differences estimate was not significant (RR 0.79, 95% CI 0.50 to 1.24).

**Population:** GIM admissions from the ED, excluding COVID-19, influenza and comfort care; cardiology, respirology and nephrology units as controls • **Intervention:** Real-time model with text pages and emails for high-risk patients (hourly from January 2021) and a pathway of physician review within 1 h, more vital signs and palliative care prompts • **Comparison:** November 2016 to June 2020 vs November 2020 to June 2022 • **Outcome:** Non-palliative in-hospital death

### RESULTS

- High-risk alerted patients, after vs before: non-palliative death 7.1% vs 10.3% (aRR 0.69, 95% CI 0.46 to 1.02). Overall deaths 3.4% vs 3.7%, not different.
- In the 24 h after a high-risk alert, antibiotics rose from 28.9% to 49.4%, steroids from 10.4% to 17.0% and median vital sign checks from 3 to 5. Sensitivity 53% and PPV 31% at the chosen threshold.

### CAVEATS

- Not randomized; the before period ended as COVID-19 arrived, and the comparator analysis does not exclude chance.
- The primary outcome excludes deaths with palliative care, and palliative transfers rose slightly, so changes in end-of-life care can move it.
- Single centre; the developers have a commercial interest after the tool was acquired by a start-up.

*How it fits.* A general deterioration tool, built and run in Ontario without remote nurse monitoring, which the authors argue aids generalizability. Like SCREEN, it changed bedside processes: here more antibiotics, steroids and vital sign checks, and in SCREEN more lactate testing and fluid orders.

## 10. TREWS: prompt confirmation of a sepsis alert was associated with lower mortality across five hospitals

**WATCH** Adams et al, Nat Med 2022;28:1455-1460 • Prospective cohort, 5 Maryland and DC hospitals, 6,877 alerted septic patients • Certainty: **Low** • [Article](#)

**Bottom line.** Across 590,736 monitored encounters in two academic and three community hospitals, 6,877 septic patients were alerted by TREWS before any antibiotic. Patients whose alert a clinician evaluated and confirmed within 3 hours had lower adjusted in-hospital mortality than those whose alert was not confirmed in that window: adjusted absolute reduction 3.3 percentage points (95% CI 1.7 to 5.1), about 18% relative.

**Population:** Septic patients alerted no more than 1 h before triage or admission, with first antibiotics after the alert and within 24 h, not admitted directly to ICU • **Exposure:** Alert evaluated and confirmed within 3 h (61%) vs not (39%) • **Outcome:** Adjusted in-hospital mortality

### RESULTS

- Unadjusted mortality 14.6% vs 19.2%. In a high-risk cohort identified by a model applied prospectively, the absolute reduction was larger (4.5 points) and the relative reduction smaller (13.2%).
- Each hour from alert to antibiotics: adjusted OR 1.08 (95% CI 1.02 to 1.15) within 6 h, close to earlier door-to-antibiotic studies. In a companion paper, 89% of alerts were evaluated and 82% of sepsis cases were flagged.

**CAVEATS**

- The comparison is between alerts acted on promptly and alerts that were not, so confounding by clinician and by how clear the picture was is likely; there is no unalerted control group.
- Patients already on antibiotics or never alerted were excluded, so the study says little about overall effect.
- The relative reduction is 18.7% in the abstract and 18.2% in the results; the developers have a commercial interest.

*How it fits.* The design supports one claim: acting quickly on an accurate alert is associated with better outcomes. Whether switching the alert on lowers mortality needs a controlled comparison.

## 11. COMPOSER: a nurse-facing deep-learning alert in two EDs, followed by lower sepsis mortality

**WATCH** Boussina et al, NPJ Digit Med 2024;7:14 • Before-after quasi-experimental study, 2 UC San Diego EDs, 6,217 septic patients • Certainty: Low • [Article](#)

**Bottom line.** After a deep-learning model began triggering a nurse-facing advisory in two EDs, in-hospital mortality among septic patients was 9.5% against a modelled counterfactual of 11.4%, an absolute reduction of 1.9% (95% CI 0.3% to 3.5%), with sepsis bundle compliance up 5.0 points. The model withholds a score on unfamiliar data, labelling it indeterminate, to cut false alarms.

**Population:** Adult ED patients meeting Sepsis-3 within 12 h, January 2021 to April 2023 • **Intervention:** Risk score for sepsis in the next 4 h firing an Epic advisory to the nurse, who could notify the physician • **Comparison:** 705-day before period vs 145-day after period, Bayesian structural time series • **Outcome:** In-hospital mortality

**RESULTS**

- About 235 alerts a month, 1.65 per nurse. Nurses chose to notify the physician in about 55% of acknowledged alerts, and those patients received antibiotics sooner.
- The 72-hour SOFA rise was 4% smaller. ICU transfer and ICU-free days did not change, and the mortality drop was significant at the safety-net hospital only.

**CAVEATS**

- Five months of after data, no concurrent control, and one academic centre with a major interest in sepsis and clinical informatics.
- The counterfactual depends on model assumptions, and effects on alerted patients without sepsis, such as antibiotic use, were not measured.
- The developers co-founded a start-up focused on commercializing decision support tools.

*How it fits.* Like TREWS, an outcome signal for an ML sepsis alert from a nonrandomized design. Its nurse-first routing echoes the required nurse assessment in SCREEN.

## 12. Epic Sepsis Model v2: better discrimination than v1, with low PPV and wide variation between sites

**CONSIDER LOCALLY** Wong et al, JAMA Netw Open 2026;9:e260181 • Prospective validation, 4 US health systems, 227,091 encounters • Certainty: Moderate • [Article](#)

**Bottom line.** In the first multicentre external validation of Epic's updated gradient-boosted sepsis model, run live and fine-tuned at each site, encounter-level AUROC ranged from 0.82 to 0.92, better than the original model at every site. At a threshold catching 60% of cases, PPV was 0.13 to 0.26, and clinicians would review 21 to 35 alerts for each sepsis case arising in the next 12 hours.

**Population:** Adult ED and inpatient encounters at Michigan, OHSU, Emory and MetroHealth, 2023 to 2025; 3.3% met Sepsis-3 •

**Index test:** ESM v2 score every 15 minutes • **Reference:** Sepsis-3 EHR criteria, and clinician recognition by first antibiotic, lactate or culture order

**RESULTS**

- Against clinician recognition, AUROC fell slightly to 0.80 to 0.90, with a median lead time of 1.4 to 7.1 h.

- Weakest at tertiary centres and for hospital-onset sepsis. At one site, 30% of sepsis cases had no reliable early score because no CBC was available in the first hour. Original model at the same threshold: AUROC 0.65 to 0.84, PPV 0.07 to 0.14.

## CAVEATS

- Accuracy only; patient outcomes were not measured.
- Evaluated after deployment, so alerts may have shaped the orders that define the reference label.
- Every site fine-tuned the model, so base-model performance is unknown.

*How it fits.* Epic reports about 731 hospitals on v2. The authors call for local validation, alert silencing and a workflow for false positives with any proprietary model; the authors note its discrimination is generally lower than reported for frontier models such as COMPOSER and TREWS.

**Across the twelve.** The treatment papers reward restraint and reassessment: shorter antibiotic courses, lower pressure targets in older patients, and fluid given to patients whose perfusion responds. Every alert study that measured care processes found changes, with more lactate, fluid, antibiotics or monitoring. The outcome evidence rests on one stepped-wedge trial that needed adjustment and on before-after or responder comparisons. In journal club, ask what each alert made people do, and for whom.

*Journal Watcher special episode, Sepsis 2026, October 2026. Twelve references: eleven papers read in full from the publisher or PubMed Central, and CEPEC from its ClinicalTrials.gov record. Accompanying editorials read for BALANCE, ARISE FLUIDS, ANDROMEDA-SHOCK-2 and SCREEN. Fragility index, NNH, NNT and robustness counts are our calculations. Statements about the 2026 Surviving Sepsis Campaign guidelines come from a separate check of the guideline. Prepared with AI assistance; check the original papers before acting on any summary.*

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