Could Shorter Courses of Antibiotics Treat Sepsis?

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Why treat with shorter courses?

Antibiotic use far exceeds any other hospital setting

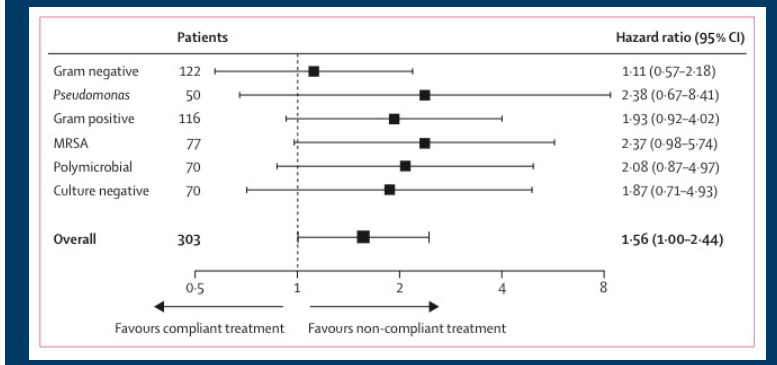
Driver for AMR

Overuse associated with worse outcomes

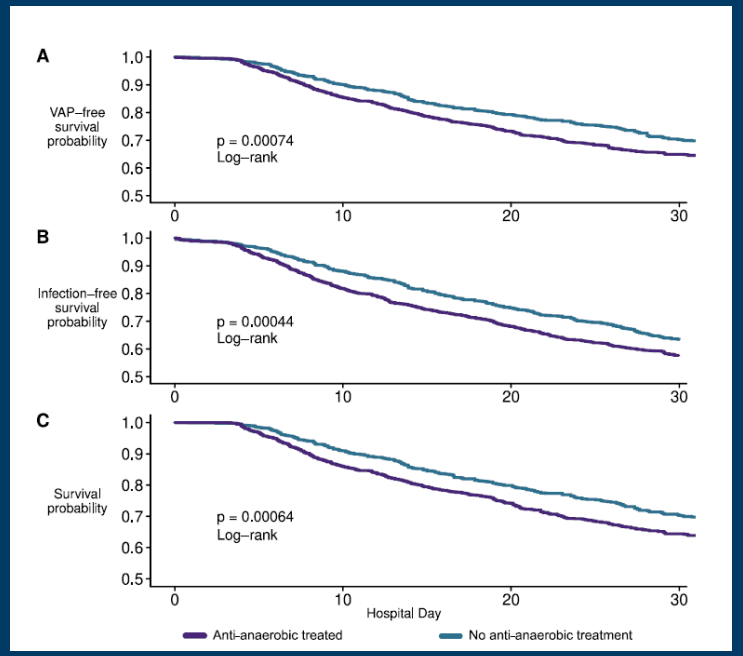
Table 5.6 Percentage of all antibiotic prescribing attributed to piperacillin/tazobactam, carbapenems and colistin in secondary care by speciality, expressed as DDDs per admissions, England, 2020

Specialist Group	DDDs per admission	Piperacillin/ tazobactam	Carbapenems	Colistin
Intensive Care Unit	54.96	6.6%	5.7%	0.1%
AE/Non-specific Out-Patient Department	6.95	1.4%	0.6%	0.2%
Geriatrics	2.71	4.6%	1.8%	0.0%
General Medicine	1.44	4.4%	2.0%	0.2%
General Surgery	2.34	3.2%	1.5%	0.0%
Specialist Medicine	2.44	4.6%	3.6%	3.5%
Other	3.09	2.9%	1.8%	0.0%
Orthopaedics	1.94	3.0%	1.7%	0.0%
Obstetrics and Gynaecology	1.44	1.0%	0.5%	0.0%
Paediatrics	1.10	2.4%	2.5%	5.3%
Specialist Surgery	0.66	3.4%	2.9%	1.5%

ESPAUR 2020-2021



Kett Lancet Infect Dis 2011



Chanderraj Eur Respir 2022

Surviving sepsis guidelines - 2026

37 ✓ ⊕◯◯◯ For adults with sepsis or septic shock, we **suggest** de-escalation of antimicrobial therapy over no de-escalation when no pathogens are identified on final culture results.

2021 STATEMENT

✓ ⊕◯◯◯ For adults with sepsis or septic shock, we **suggest** daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation.

Remark: De-escalation involves discontinuing unnecessary antimicrobial therapy or narrowing the spectrum of antimicrobial agents where appropriate.

39 ✓ ⊕◯◯◯ For adults with an initial diagnosis of sepsis or septic shock and adequate source control, we **suggest** using shorter over longer duration of antimicrobial therapy.

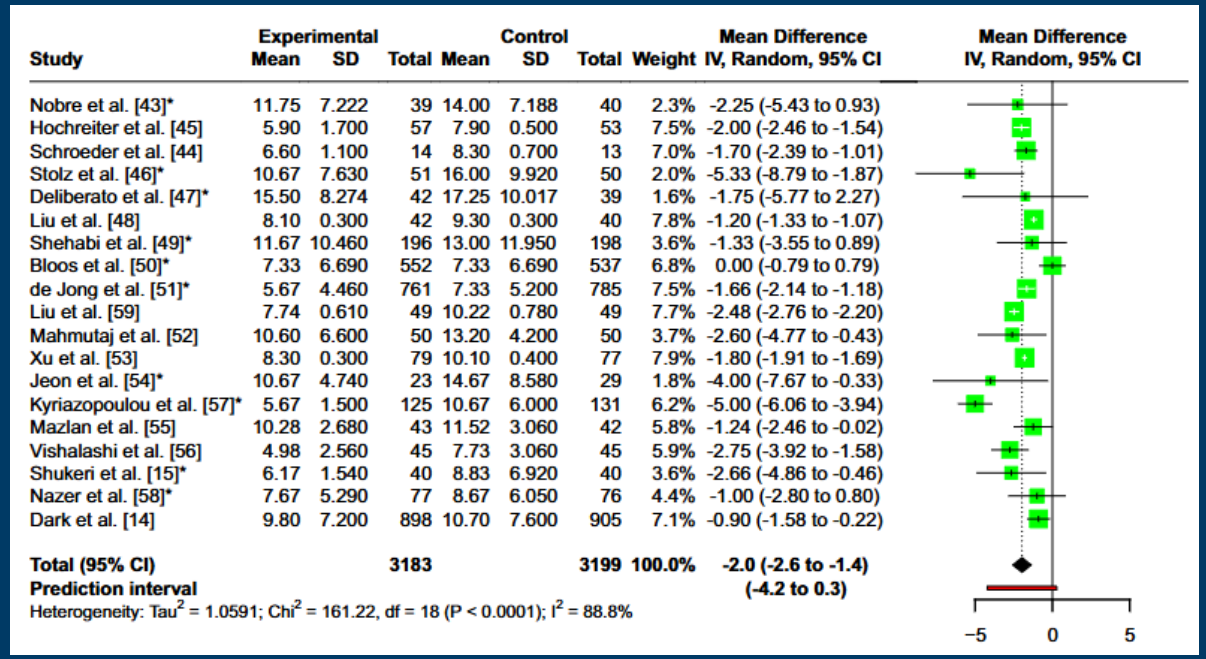
40 ✓ ⊕⊕◯◯ For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we **suggest** using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobial therapy over clinical evaluation alone.

Could Shorter Courses of Antibiotics Treat Sepsis?

- Yes! (UK standard of care 8 days)
- By what method?
- How short?
- Infection specific vs sepsis as a syndrome

Biomarker-guided durations

- Generally procalcitonin, limited evidence for CRP
- Durations NOT initiation
- 2-day reduction in duration initial course



Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Nobre et al. [43]*	11.75	7.222	39	14.00	7.188	40	2.3%	-2.25 (-5.43 to 0.93)
Hochreiter et al. [45]	5.90	1.700	57	7.90	0.500	53	7.5%	-2.00 (-2.46 to -1.54)
Schroeder et al. [44]	6.60	1.100	14	8.30	0.700	13	7.0%	-1.70 (-2.39 to -1.01)
Stolz et al. [46]*	10.67	7.630	51	16.00	9.920	50	2.0%	-5.33 (-8.79 to -1.87)
Deliberato et al. [47]*	15.50	8.274	42	17.25	10.017	39	1.6%	-1.75 (-5.77 to 2.27)
Liu et al. [48]	8.10	0.300	42	9.30	0.300	40	7.8%	-1.20 (-1.33 to -1.07)
Shehabi et al. [49]*	11.67	10.460	196	13.00	11.950	198	3.6%	-1.33 (-3.55 to 0.89)
Bloos et al. [50]*	7.33	6.690	552	7.33	6.690	537	6.8%	0.00 (-0.79 to 0.79)
de Jong et al. [51]*	5.67	4.460	761	7.33	5.200	785	7.5%	-1.66 (-2.14 to -1.18)
Liu et al. [59]	7.74	0.610	49	10.22	0.780	49	7.7%	-2.48 (-2.76 to -2.20)
Mahmutaj et al. [52]	10.60	6.600	50	13.20	4.200	50	3.7%	-2.60 (-4.77 to -0.43)
Xu et al. [53]	8.30	0.300	79	10.10	0.400	77	7.9%	-1.80 (-1.91 to -1.69)
Jeon et al. [54]*	10.67	4.740	23	14.67	8.580	29	1.8%	-4.00 (-7.67 to -0.33)
Kyriazopoulou et al. [57]*	5.67	1.500	125	10.67	6.000	131	6.2%	-5.00 (-6.06 to -3.94)
Mazlan et al. [55]	10.28	2.680	43	11.52	3.060	42	5.8%	-1.24 (-2.46 to -0.02)
Vishalashi et al. [56]	4.98	2.560	45	7.73	3.060	45	5.9%	-2.75 (-3.92 to -1.58)
Shukeri et al. [15]*	6.17	1.540	40	8.83	6.920	40	3.6%	-2.66 (-4.86 to -0.46)
Nazer et al. [58]*	7.67	5.290	77	8.67	6.050	76	4.4%	-1.00 (-2.80 to 0.80)
Dark et al. [14]	9.80	7.200	898	10.70	7.600	905	7.1%	-0.90 (-1.58 to -0.22)
Total (95% CI)			**3183**			**3199**	**100.0%**	**-2.0 (-2.6 to -1.4)**
Prediction interval								**(-4.2 to 0.3)**

Heterogeneity: $Tau^2 = 1.0591$; $Chi^2 = 161.22$, df = 18 ($P < 0.0001$); $I^2 = 88.8\%$

Biomarker-guided durations

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis

The ADAPT-Sepsis Randomized Clinical Trial

Paul Dark, MD, PhD; Anower Hossain, PhD; Daniel F. McAuley, MD; David Brealey, MD; Gordon Carlson, MD;

- Population: critically ill adults with suspected sepsis
- Intervention: Procalcitonin or C-reactive protein
- Comparator: Standard of care
- Outcome: 28-day mortality (non-inferiority), 28-day antibiotics (superiority)

Outcomes	Daily PCT-guided protocol (n = 918)	Daily CRP-guided protocol (n = 924)	Standard care (n = 918)
Primary outcomes			
Effectiveness			
Total antibiotic treatment duration to 28 d after randomization, mean (SD), d [No.]	9.8 (7.2) [898]	10.6 (7.7) [892]	10.7 (7.6) [905]
Safety			
28-d All-cause mortality, No./total (%)[b]	184/879 (20.9)	184/874 (21.1)	170/878 (19.4)
Secondary outcomes			
Antibiotic treatment duration for initial sepsis period, mean (SD), days [No.]	7.0 (5.7) [893]	7.4 (6.0) [889]	8.1 (6.1) [902]

Dark JAMA 2025

Biomarker-guided durations

- Population - Paediatrics with IV antibiotics for suspected serious bacterial infections
- Intervention – Procalcitonin-guided stopping (if <0.25ng/ml) or oral switch (if decrease of >80%)
- Control - Standard of care including CRP
- Outcome – co-primaries:
  - Duration of intravenous antibiotics
  - Composite safety – readmission/restart IV abx/mortality

Procalcitonin-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection in the UK (BATCH): a pragmatic, multicentre, open-label, two-arm, individually randomised, controlled trial

Cherry-Ann Waldron, Philip Pallmann*, Simon Schoenbuchner, Debbie Harris, Lucy Brookes-Howell, Céu Mateus, Jolanta Bernatoniene,*

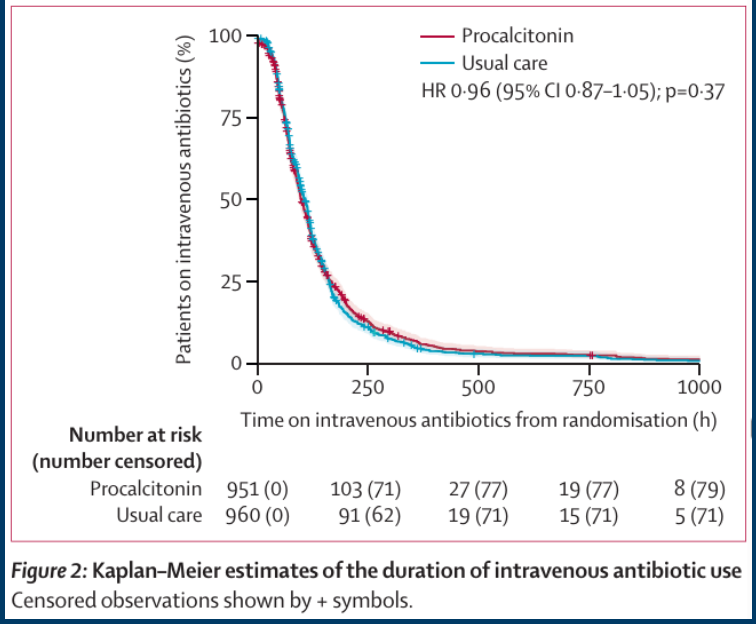


Figure 2: **Kaplan–Meier estimates of the duration of intravenous antibiotic use**
Censored observations shown by + symbols.

	Adherence
Procalcitonin test availability	
At all clinical reviews	360/948 (38%)
At any clinical review	775/948 (82%)
At first clinical review	583/949 (61%)
Procalcitonin test was considered	
At all clinical reviews	226/939 (24%)
At any clinical review	618/928 (67%)
At first clinical review	438/939 (47%)
Algorithm adhered to	
At all clinical reviews	153/940 (16%)
At any clinical review	527/922 (57%)
At first clinical review	352/939 (37%)

Data are n/N (%).

Table 4: **Adherence in the procalcitonin group**

Waldron Lancet Child Adolesc Health 2025

Fixed durations – infection specific vs sepsis

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Duration of Antibiotic Treatment in Community-Acquired Pneumonia A Multicenter Randomized Clinical Trial

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

ORIGINAL ARTICLE

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

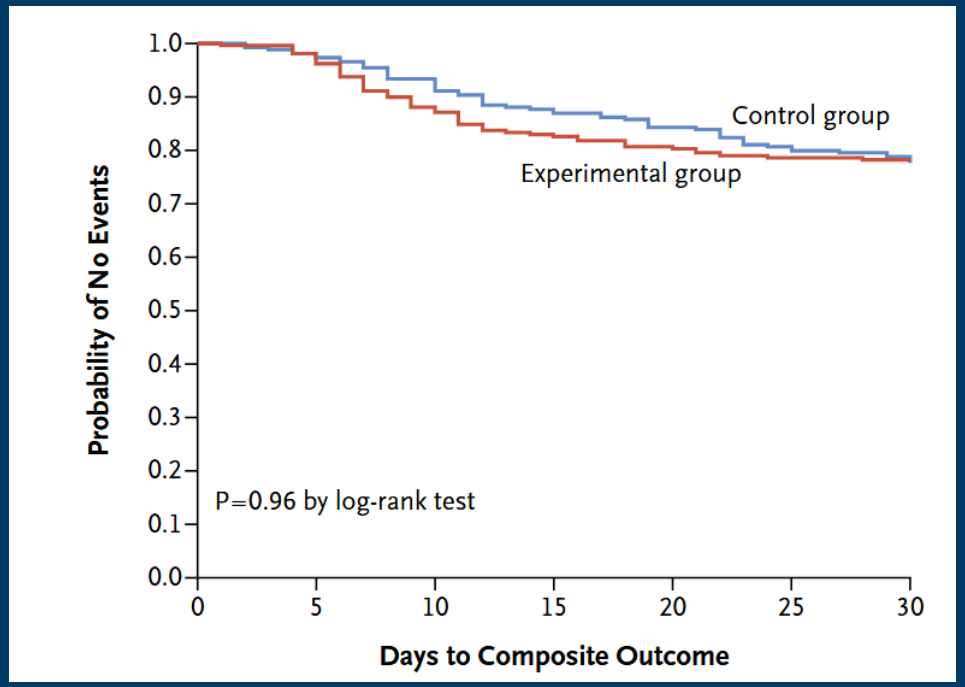
1. Uranga JAMA Int Med 2016
2. Yahav Clin Infect Dis 2019
3. Sawyer NEJM 2015

Fixed duration

ORIGINAL ARTICLE

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans,



- Population: 518 patients, complicated intra-abdominal infection with source control
- Intervention: 4 days antibiotics
- Control: 2 days after resolution of fever, WCC, ileus, max 10 days
- Outcome: Composite of surgical-site infection, recurrent intra-abdominal infection, death 30 days
  - 22% in both groups

Sawyer NEJM 2015

Fixed duration

Individualised, short-course antibiotic treatment versus usual long-course treatment for ventilator-associated pneumonia (REGARD-VAP): a multicentre, individually randomised, open-label, non-inferiority trial

Yin Mo, Suchart Booraphun, Andrew Yunkai Li, Pornanan Domthong, Gyan Kayastha, Yie Hui Lau, Ploenchan Chetchotisakd, Direk Limmathurotsakul, Paul Anantharajah Tambyah, Ben S Cooper, on behalf of the REGARD-VAP investigators

- Population - ICU patients with suspected ventilator-associated pneumonia
- Intervention – 'fitness criteria', stop abx within 3 days if culture negative, within 5 days is culture positive, all within 7 days
- Control – duration at least 8 days
- Outcome – Composite of death or pneumonia recurrence at 60 days

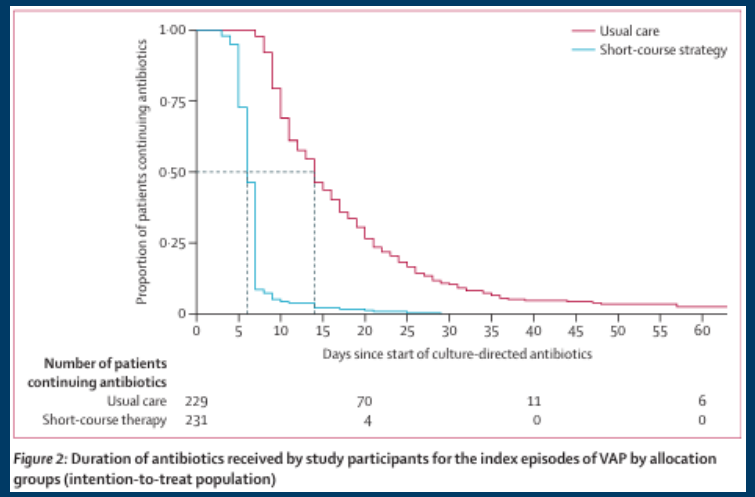
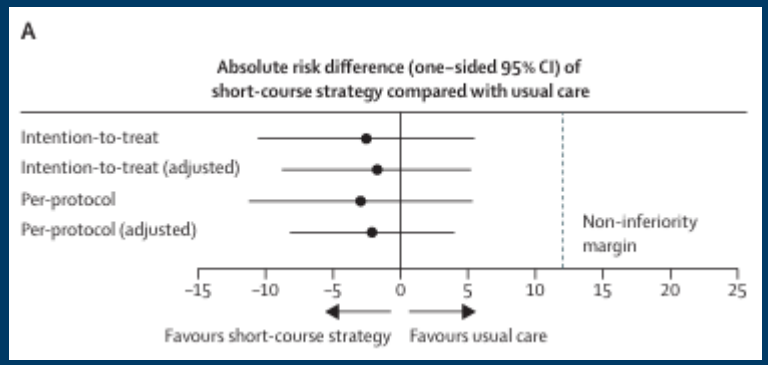


Figure 2: Duration of antibiotics received by study participants for the index episodes of VAP by allocation groups (intention-to-treat population)



Mo Lancet Resp Med 2024

What is the lower limit?

JAMA Pediatrics

RCT: Short-Course Therapy for Urinary Tract Infections in Children: the SCOUT Randomized Clinical Trial

POPULATION

639 Female, 25 Male

Children with urinary tract infection (UTI) exhibiting clinical improvement after 5 d of antimicrobials

Age range: 2 m to 10 y

INTERVENTION

664 Children with data on primary outcome

328 Standard course
5 d of Prescribed oral antimicrobials plus 5 more days of the same antimicrobial

336 Short course
5 d of Prescribed oral antimicrobials plus 5 days of matching placebo

SETTINGS / LOCATIONS

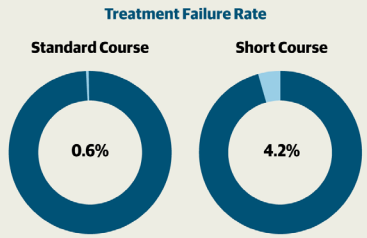
2 Children's hospitals with their associated EDs and outpatient clinics

PRIMARY OUTCOME

Treatment failure, defined as UTI between day 6 visit and day 11-14 visit

FINDINGS

Treatment failure rates were lower for the standard course compared with the short course, though both groups had overall low rates



2 of 328 Had primary outcome (0.6%)
14 of 336 Had primary outcome (4.2%)

Zaoutis T, Shaikh N, Fisher BT, et al. Short-course therapy for urinary tract infections in children: the SCOUT randomized clinical trial. *JAMA Pediatr.* Published online June 26, 2023. doi:10.1001/jamapediatrics.2023.1979

2 days versus 5 days of postoperative antibiotics for complex appendicitis: a pragmatic, open-label, multicentre, non-inferiority randomised trial

Elisabeth M L de Wijkerslooth, Evert-Jan G Boerma, Charles C van Rossem, Joost van Rosmalen, Coen I M Baeten, Frédérique H Beverdam,

	2-day group	5-day group	Risk difference (95% CI)
			Univariable
Intention-to-treat			
Intra-abdominal abscess, surgical-site infection, or mortality	51 (10%)	41 (8%)	2·0% (–1·6 to 5·6)
Intra-abdominal abscess	43 (9%)	36 (7%)	1·4% (–1·9 to 4·8)
Surgical-site infection	10 (2%)	5 (1%)	1·0% (–0·6 to 2·6)
Mortality	1 (<1%)	--	0·2% (–0·5 to 0·9)
Total	n=502	n=503	--

Zaoutis JAMA Paeds 2023

de Wijkerslooth Lancet 2023

Emerging evidence in this space

- Suspected sepsis
- Three interventions:
  - PCT and PCR diagnostic
  - Fluid management
  - Immune modulation

- Suspected sepsis
- Fixed, 5-day course of antibiotics

- Women with UTI
- 4 different durations

Summary

- High pressure to initiate antibiotics in sepsis
- Optimising duration could improve antibiotic stewardship
- PCT-guided does reduce duration by 1-2 days
- Response-guided duration is recommended by SSC
- Further evidence for fixed durations emerging