WHEN TO STOP ANTIBIOTICS?

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A BALANCING ACT

Antibiotics are an important therapy for infection

Antibiotics carry multiple side-effects

- often covert, often significant

.. so give when needed .. in most patients there is NO need to rush ..

… and don’t carry on for longer than necessary

ARE ANTIBIOTICS BAD?

- obvious side-effects (rashes, liver & renal dysfunction ..)
- overgrowth of multi-drug resistant bacteria & fungi
- immunomodulatory
- alter healthy (protective) microbiota
- compromize mitochondrial function
- Jarisch-Herxheimer reaction - release of bacterial products (especially with bacteriocidals)

JAMA Internal Medicine | Original Investigation

Association of Adverse Events With Antibiotic Use in Hospitalized Patients

Pranita D. Tamma, MD, MHS; Edina Avdic, PharmD, MBA; David X. Li, BS; Kathryn Dzintars, PharmD; Sara E. Cosgrove, MD, MS

MAIN OUTCOMES AND MEASURES Medical records of 1488 patients were examined for 30 days after antibiotic initiation for the development of the following antibiotic-associated ADEs: gastrointestinal, dermatologic, musculoskeletal, hematologic, hepatobiliary, renal, cardiac, and neurologic; and 90 days for the development of *Clostridium difficile* infection or incident multidrug-resistant organism infection, based on adjudication by 2 infectious diseases trained clinicians.

RESULTS

A total of 298 (20%) patients experienced at least 1 antibiotic-associated ADE. Furthermore, 56 (20%) non–clinically indicated antibiotic regimens were associated with an ADE, including 7 cases of *C difficile* infection. Every additional 10 days of antibiotic therapy conferred a 3% increased risk of an ADE. The most common ADEs were gastrointestinal, renal, and hematologic abnormalities, accounting for 78 (42%), 45 (24%), and 28 (15%) 30-day ADEs, respectively.

JAMA Intern Med. 2017;177(9):1308-1315.

PNEUMONIA NEEDS A LONG COURSE OF TREATMENT ...

.. DOES IT?

Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study

Rachida el Moussaoui, Corianne A J M de Borgie, Peterhans van den Broek, Willem N Hustinx, Paul Bresser, Guido E L van den Berk, Jan-Werner Poley, Bob van den Berg, Frans H Krouwels, Marc J M Bonten, Carla Weenink, Patrick M M Bossuyt, Peter Speelman, Brent C Opmeer, Jan M Prins

Conclusions Discontinuing amoxicillin treatment after three days is not inferior to discontinuing it after eight days in adults admitted to hospital with mild to moderate-severe community acquired pneumonia who substantially improved after an initial three days' treatment.

BMJ 2006; 332:1755

BACTERIAL MENINGITIS NEEDS A LONG COURSE OF TREATMENT ...

.. DOES IT?

5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study

*Elizabeth Molyneux, Shaikh Qamaruddin Nizami, Samir Saha, Khanh Truong Huu, Matloob Azam, Zulfiqar Ahmad Bhutta, Ramadan Zaki, Martin Willi Weber, Shamim Ahmad Qazi, for the CSF 5 Study Group**

Interpretation In children beyond the neonatal age-group with purulent meningitis caused by *S pneumoniae*, *H influenzae* type b, or *N meningitidis* who are stable by day 5 of ceftriaxone treatment, the antibiotic can be safely discontinued.

	5-day treatment group (n=496)	10-day treatment group (n=508)	Total	Risk difference (%; 95% CI)
Overall outcomes for all children				
			33	0·3 (–1·9 to 2·5)
meningitis	8 (2%)	13 (3%)	21	–0·95 (–2·7 to 8·2)
Relapse of meningitis	2 (0%)	0	2	–0·4 (–0·15 to 0·96)
Deaths related to meningitis only*	9 (2%)	6 (1%)	15	0·63 (–0·87 to 2·1)
Deaths due to any reason after cure (until follow-up at 6 months after enrolment)	22 (4%)	19 (4%)	41†	0·69 (–1·8 to 3·1)
Survival with sequelae	129 (26%)	138 (27%)	267	–1·2 (–6·6 to 4·3)

Lancet 2011; 377: 1837–45

Three Days of Intravenous Benzyl Penicillin Treatment of Meningococcal Disease in Adults

Rod Ellis-Pegler,[1] Lesley Galler,[2] Sally Roberts,[3] Mark Thomas,[1] and Andrew Woodhouse[1]

Departments of [1]Infectious Diseases, [2]Critical Care Medicine, and [3]Microbiology, Auckland Hospital, Auckland, New Zealand

- 58 patients (>15 y.o)
- 21% septic shock, 10% severe sepsis
- Rx 12 MU benzylpenicillin/day for 3 days

Patients received a mean (± SD) of 3.0 ± 0.5 days of treatment. No patients relapsed. Five patients died. All but 1 death occurred during benzyl penicillin treatment, and the only posttreatment death was not due to meningococcal disease. Three days of intravenous benzyl penicillin is sufficient treatment for adults with meningococcal disease. The usual recommendations for duration of treatment are excessive.

Clinical Infectious Diseases 2003; 37:658–62

Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study

N Nathan, T Borel, A Djibo, D Evans, S D[illegible] Corty, M Guillerm, K P Alberti, L Pinoges, P J Guerin, D Legros

one dose given in peripheral clinics in Niger

	Overall		Chloramphenicol		Ceftriaxone		Difference % (90% CI)
	n (%)	Total	n (%)	Total	n (%)	Total	
Per-protocol analysis							
Treatment failure at 72 h	16 (5%)	308	8 (5%)	148	8 (5%)	160	−0·4% (−4·6 to 3·8)
Death at 72 h	11 (4%)	308	5 (3%)	148	6 (4%)	160	0·4% (−3·1 to 3·8)
Second injection between 24 h and 48 h	20 (7%)	298	9 (6%)	144	11 (7%)	154	0·8% (−3·9 to 5·7)
Neurological sequelae at 72 h	23 (8%)	297	9 (6%)	143	14 (9%)	154	2·8% (−2·3 to 7·9)

Table 2: Proportion of primary and secondary endpoints

Lancet 2005; 366: 308–313

S AUREUS BACTERAEMIA NEEDS A LONG COURSE OF TREATMENT ...

.. DOES IT?

Cannula-associated *Staphylococcus aureus* bacteraemia: outcome in relation to treatment

M. G. THOMAS*[1] and A. J. MORRIS*[2]

There was no relationship between the duration of treatment and the rate of relapse of deep-seated infection ($P = 0.24$). This observation held true regardless of whether the duration of treatment was analysed as ≤7 versus ≥8, ≤10 versus ≥11, or ≤14 versus ≥15 days ($P = 0.62$, 0.87 and 0.16, respectively).

- 276 patients
- 8 week follow-up

Other large studies have also failed to show an association between the duration of therapy for *S. aureus* bacteraemia and the risk of relapse.[8,18,22]

Available evidence, however, indicates that when there is a prompt clinical response to treatment it need not routinely exceed 7 days.

Internal Medicine Journal 2005; 35: 319–330

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial

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Michel Wolff, MD
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Sylvie Chevret, MD
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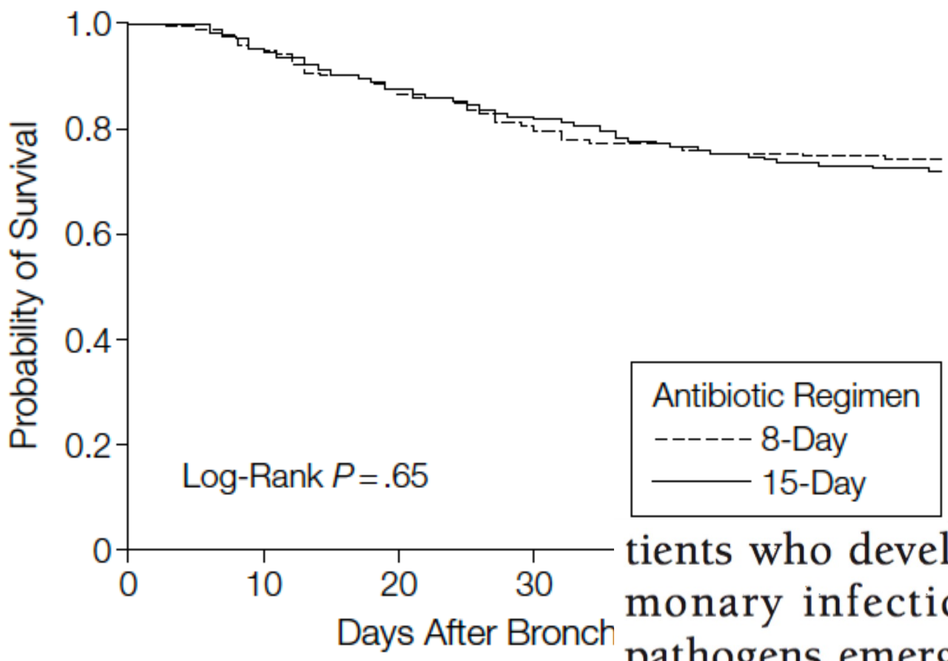
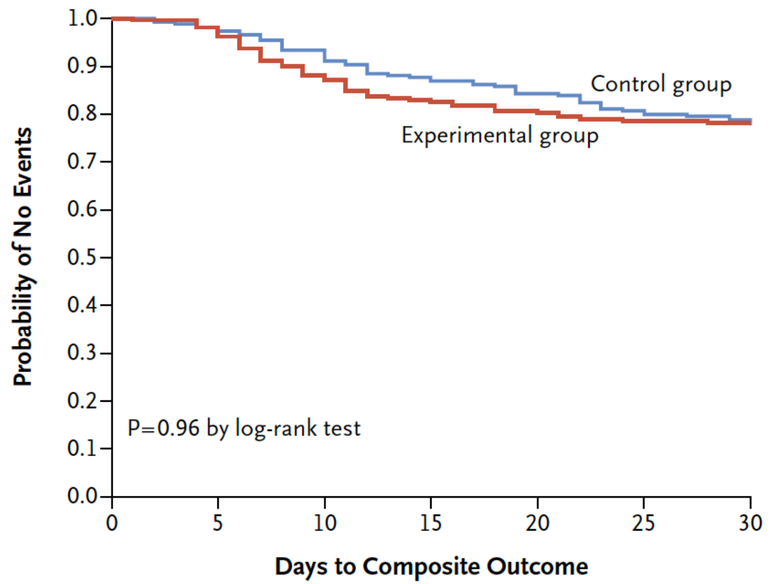


Notably, among patients who developed recurrent pulmonary infections, multiresistant pathogens emerged significantly less frequently in those who had received 8 days of antibiotics (42.1% vs 62.3% of recurrent infections; $P = .04$).

JAMA. 2003;290:2588-2598

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, C.H. Cook, P.J. O'Neill, J.E. Mazuski, R. Askari, M.A. Wilson, L.M. Napolitano, N. Namias, P.R. Miller, E.P. Dellinger, C.M. Watson, R. Coimbra, D.L. Dent, S.F. Lowry,* C.S. Cocanour, M.A. West, K.L. Banton, W.G. Cheadle, P.A. Lipsett, C.A. Guidry, and K. Popovsky



No. at Risk							
Control group	260	255	243	228	219	210	205
Experimental group	258	253	227	214	208	203	202

4 vs 8 days

N Engl J Med 2015;372:1996-2005.

Effect of C-Reactive Protein–Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia

A Randomized Clinical Trial

Elodie von Dach, PhD; Werner C. Albrich, MD; Anne-Sophie Brunel, MD; Virginie Prendki, MD; Clémence Cuvelier, MD; Domenica Flury, MD; Angèle Gayet-Ageron, MD, PhD; Benedikt Huttner, MD; Philipp Kohler, MD; Eva Lemmenmeier, MD; Shawna McCallin, PhD; Anne Rossel, MD; Stephan Harbarth, MD; Laurent Kaiser, MD; Pierre-Yves Bochud, MD; Angela Huttner, MD

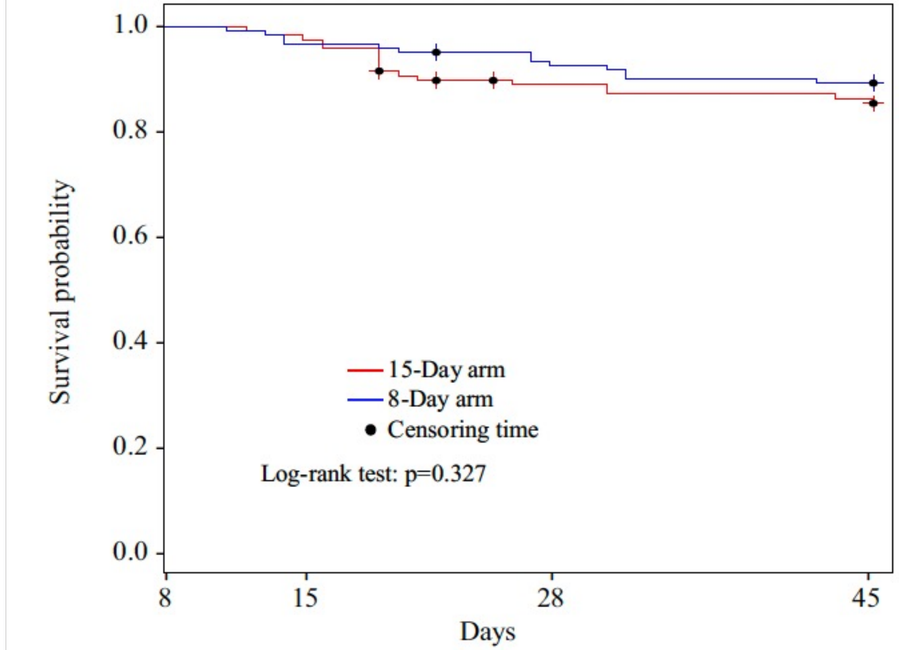
Outcome	Antibiotic therapy duration group, No. (%)		
	CRP-guided (n = 169)	7 d (n = 169)	14 d (n = 165)
Primary outcome			
Clinical response through day 30			
Clinical success	160 (97.6)	155 (93.4)	154 (94.5)

CONCLUSIONS AND RELEVANCE Among adults with uncomplicated gram-negative bacteremia, 30-day rates of clinical failure for CRP-guided antibiotic treatment duration and fixed 7-day treatment were noninferior to fixed 14-day treatment.

JAMA. 2020;323(21):2160-2169.

Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial

Philippe Montravers[1,18*], Florence Tubach[2], Thomas Lescot[3], Benoit Veber[4], Marina Esposito-Farèse[5], Philippe Seguin[6], Catherine Paugam[7], Alain Lepape[8], Claude Meistelman[9], Joel Cousson[10], Antoine Tesniere[11], Gaetan Plantefeve[12], Gilles Blasco[13], Karim Asehnoune[14], Samir Jaber[15], Sigismond Lasocki[16], Herve Dupont[17] and For the DURAPOP Trial Group



Primary and secondary outcomes	15-day arm (n=116)	8-day arm (n=120)
Primary outcome		
Antibiotic-free days on Day28, median [IQR][a]	12 [6—13]	15 [6—20]
Secondary outcome		
Length of ICU stay between Day0 and Day45, median [IQR][b]	12 [7—20]	13 [7.75—25]
Length of hospital stay between Day0 and Day45, median [IQR][c]	30 [20—45]	30.5 [18.75—45]
Secondary outcomes		
Organ failure on Day15, n (%)[d]	17/96 (18)	15/90 (17)
Organ failure on Day28, n (%) [e]	4/60 (5)	3/63 (6)
Emergence of MDR bacteria in both surveillance samples and clinical isolates confounded, n (%)[g]	52/104 (50)	46/108 (43)
Emergence of fungi, n (%)[g]	27/106 (25)	22/107 (21)

Conclusion: Short-course antibiotic therapy in critically ill ICU patients with PIAI reduces antibiotic exposure. Continuation of treatment until day 15 is not associated with any clinical benefit.

Intensive Care Med (2018) 44:300–310

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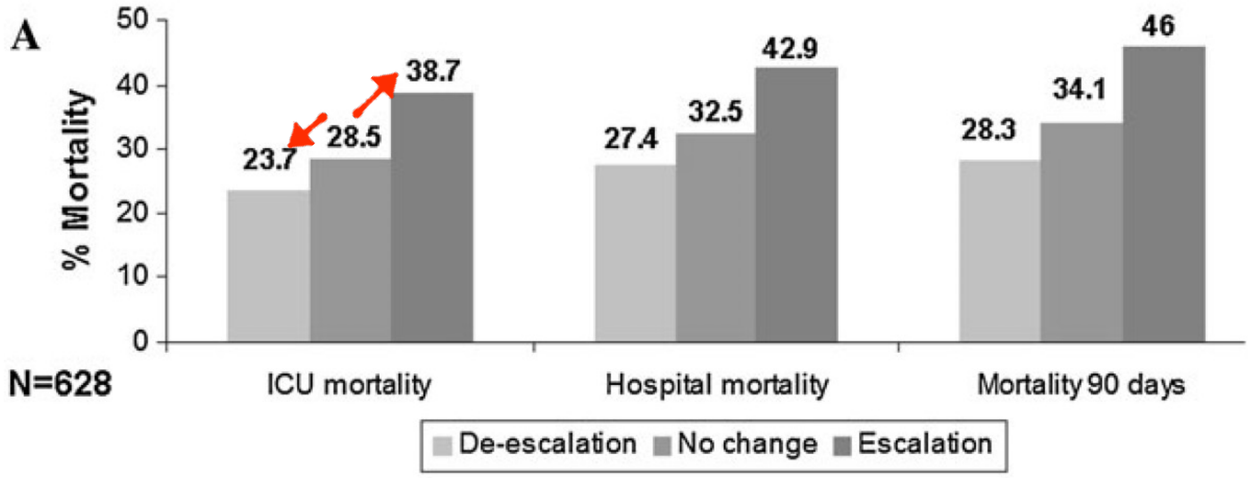
De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock



Intensive Care Med (2014) 40:32–40

no change" (empirical therapy was maintained without modification), "escalation of therapy" (the switch to or addition of an antibiotic with a broader spectrum), and "de-escalation" (switch to or interruption of a drug class resulting in a less broad spectrum of coverage).

WHAT I DO ...

- Standard course of therapy for MOST infections = 4-5 days
- Monotherapy usually sufficient (rarely use aminoglycosides)
- Prolonged course only if:
  - inadequate source control
  - deep-seated infection e.g. osteomyelitis, endocarditis
- If patient hasn't improved after 4-5 days then query whether:
  - receiving right antibiotic?
  - inadequate source control?
  - actually has a bacterial infection?

THANK YOU FOR LISTENING!