Successful stewardship in hospital settings

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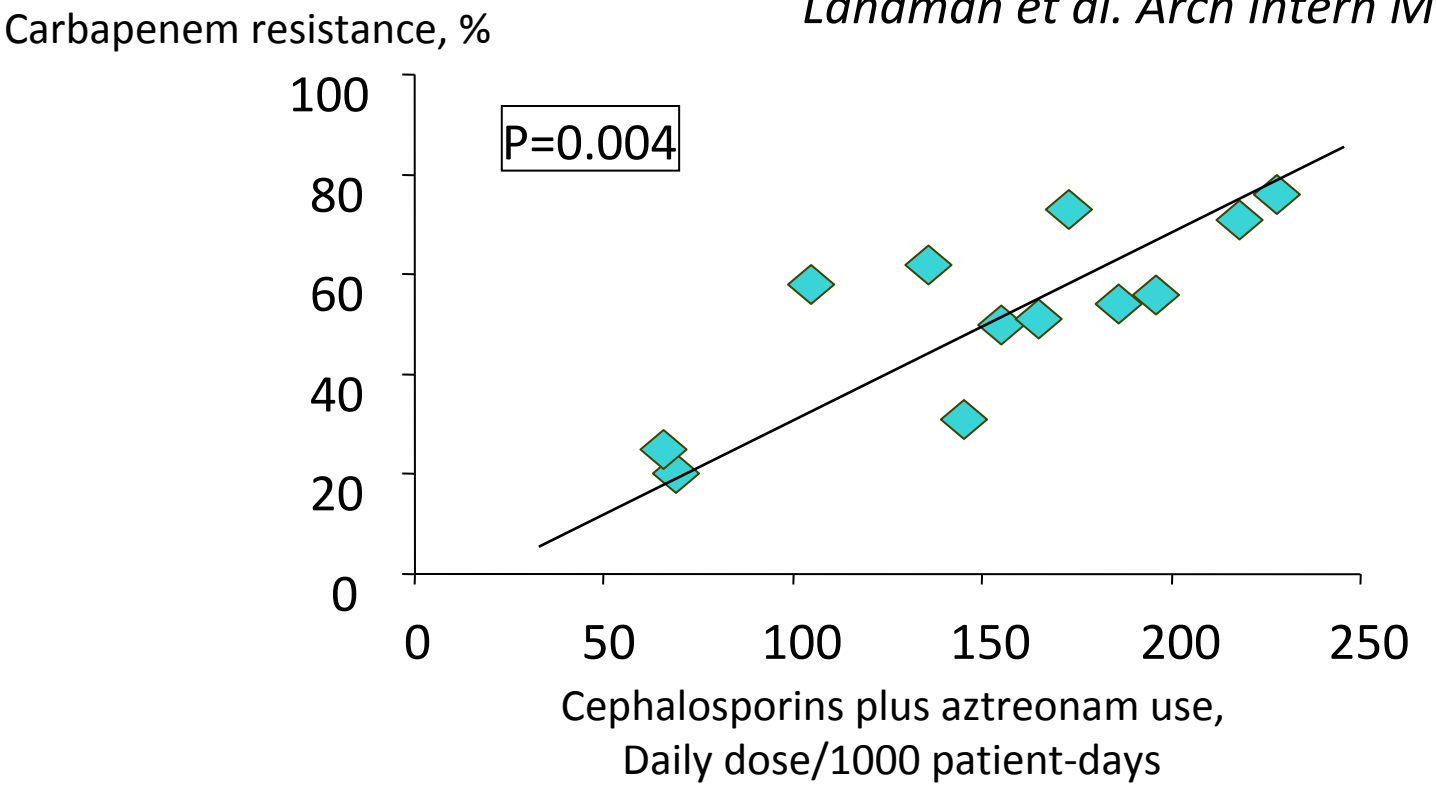
Conflicts of interest

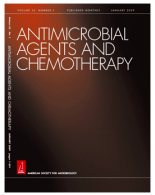
- Personal fees
  - Bayer HealthCare, MSD, Biomérieux, Faron
- Grants
  - Bayer HealthCare, Curetis, Faron, Maquet

Antibiotic Use and Carbapenem-Resistant *A. baumannii*

Landman et al. Arch Intern Med 2002



Emergence of Imipenem-Resistant Gram-Negative Bacilli in Intestinal Flora of Intensive Care Patients



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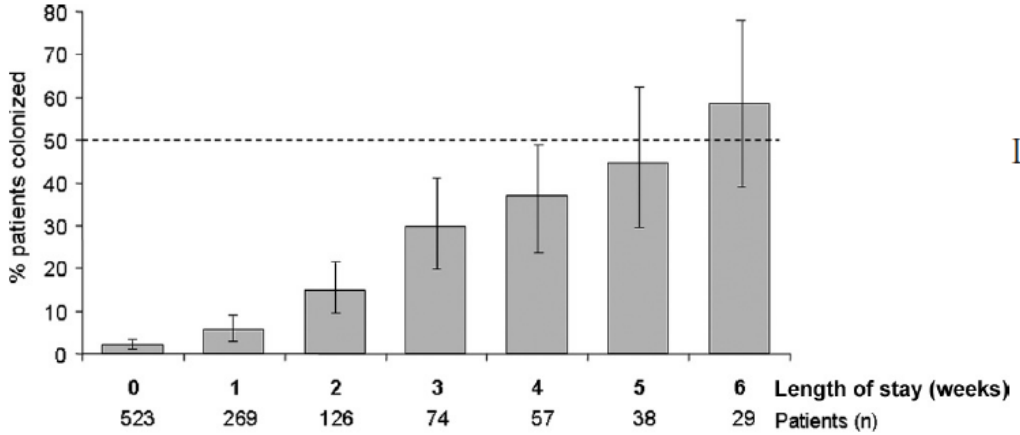

FIG 1 Rates of intestinal colonization by imipenem-resistant gram-negative bacilli in intensive care patients. Bars indicate observed rates ± standard deviation (SD) (error bars).

Days of imipenem exposure	Univariate	Multivariate
0	1.0	1.0
1 to 3	4.4 (1.1–20.5)	5.9 (1.5–25.7)
4 to 21	6.0 (1.7–23.3)	7.8 (2.4–29.8)

Antimicrobial Agents and Chemotherapy 2013

Which measures?

- In hospital settings (in the ICU), easy because pathogens are frequently isolated
- De-escalation
  - Narrowing the antimicrobial spectrum
  - Using alternative to carbapenems
  - Switching to monotherapy
  - Shortening the duration of treatment

Narrowing the antimicrobial spectrum

According to the targeted pathogen

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

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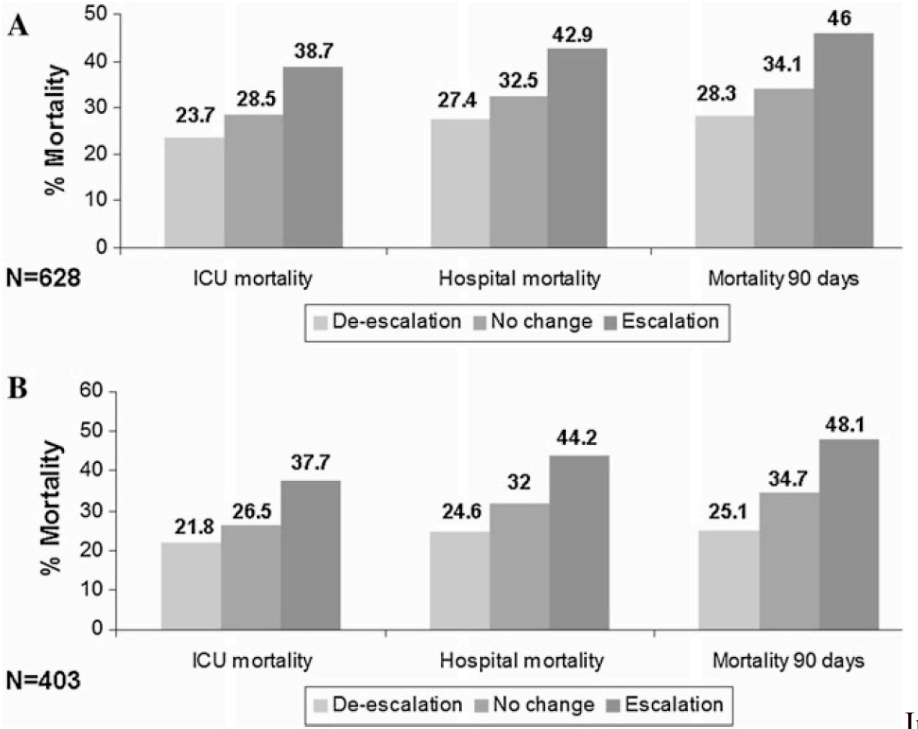

Total cohort
N = 628

Initial treatment adequate
N = 403

Intensive Care Med (2014) 40:32–40

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

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Factors associated with mortality in multivariable analysis

	Total cohort ($n = 628$)		Cohort with adequate empirical antimicrobial therapy ($n = 403$)	
	Adjusted by PS OR (95 % CI)	p	Adjusted by PS OR (95 % CI)	p
SOFA day of culture results	1.11 (1.04–1.23)	<0.001	1.18 (1.16–1.29)	<0.001
Septic shock	1.70 (1.03–2.84)	0.043		
Inadequate empirical treatment	2.03 (1.06–3.84)	0.030		
De-escalation	0.55 (0.32–0.98)	0.022	0.57 (0.38–0.94)	0.019

Intensive Care Med (2014) 40:32–40

Impact of de-escalation of beta-lactam antibiotics on the emergence of antibiotic resistance in ICU patients: a retrospective observational study

Intensive Care Med (2016) 42:1029–1039

Liesbet De Bus[1*], Wouter Denys[1], Julie Catteeuw[1], Bram Gadeyne[1], Karel Vermeulen[2], Jerina Boelen[1], Geert Claeys[3], Jan J. De Waele[1], Johan Decruyenaere[1] and Pieter O. Depuydt[1,4]

Patient outcome	Treatment				*p* value	
	Total ($n = 344$)	Continuation ($n = 221$; 64%)	De-escalation ($n = 85$; 25%)	Escalation ($n = 38$; 11%)	De-escalation vs. continuation	Escalation vs. continuation
Antibiotic treatment duration in the ICU for the infection under study (days)	6 (5–9)	5 (4–7)	8 (6–10)	11 (8–19)	<0.001	<0.001
Total antibiotic consumption in the ICU (days)	10 (5–20)	7 (4–15)	12 (7–22)	24 (13–39)	<0.001	<0.001
Subsequent nosocomial infection during ICU stay (% of patients)	127 (36.9 %)	73 (33.0 %)	33 (38.8 %)	21 (55. 3%)	0.34	0.008
LOS in ICU following start of the infection under study (days)	9 (6–17)	8 (5–15)	11 (6–19)	17 (10–23)	0.001	<0.001
ICU mortality	76 (22.1 %)	47 (21.3 %)	19 (22.4 %)	10 (26.3 %)	0.84	0.49
Hospital mortality	117 (34 %)	73 (33 %)	28 (32.9 %)	16 (42.1 %)	0.99	0.28
Emergence of pathogens resistant to the initial BL therapy	112 (32.6 %)	68 (30.8 %)	29 (34.1 %)	15 (39.5 %)	0.57	0.29

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Karine Bézulier
François Antonini
Julien Textoris
Claude Martin

De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial

Intensive Care Med (2014) 40:1399–1408

Duration	De-escalation group ($n = 59$)	Continuation group ($n = 57$)	P
Duration of ICU stay (days)			
From inclusion to discharge	15.2 ± 15.0 9 [1–79]	11.8 ± 12.6 8 [1–60]	0.71
From admission to discharge	29.1 ± 50.0 13 [1–375]	18.1 ± 15.7 12 [3–67]	0.11
Number of ICU-free days[a]	13.2 ± 10.6 18 [0–23]	15.0 ± 11.3 21 [0–25]	0.21
Ventilator-free days[a]	18.9 ± 11.6 23 [6–29]	19.3 ± 11.8 26 [6–29]	0.55
Catecholamine-free days[a]	22.3 ± 10.3 28 [21–29]	21.6 ± 11.2 28 [16–29]	0.93
Number of antibiotic days	14.1 ± 13.4 9 [7–15]	9.9 ± 6.6 7.5 [6–13]	0.04
Number of companion antibiotic days	2.3 ± 0.8 2.0 [2.0–3.0]	3.2 ± 1.7 3.0 [2.8–3.0]	<0.00
Number of antibiotic days for the initial episode	7.9 ± 5.2	8.0 ± 4.3	0.94
Number of antipseudomonal agent-free days[a]	23.6 ± 9.2 29 [24–29]	20.1 ± 9.6 24 [15–28]	<0.001
Number of carbapenem-free days[a]	25.6 ± 7.3 29 [26–29]	23.5 ± 8.4 29 [19–29]	0.17
Number of anti-MRSA drug-free days[a]	25.8 ± 7.1 29 [27–29]	24.1 ± 8.4 29 [21–29]	0.30

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Narrowing of antimicrobial spectrum

- Is not associated with worse outcome
- Is not associated with fewer acquisition of MDR pathogens (but short-term follow-up…what about long-term?)
- Is associated with longer duration of antimicrobial treatment
  - Initial treatment not taken into account ?
  - Silly reasoning ? (« If I give narrow-spectrum antibiotic, I will treat a little bit longer as a security measure »)

Alternative to carbapenems?

In patients infected with ESBL strains

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Clinical Infectious Diseases 2012;54(2):167–74

MAJOR ARTICLE

β-Lactam/β-Lactam Inhibitor Combinations for the Treatment of Bacteremia Due to Extended-Spectrum β-Lactamase–Producing *Escherichia coli*: A Post Hoc Analysis of Prospective Cohorts

Jesús Rodríguez-Baño,[1,2] María Dolores Navarro,[1] Pilar Retamar,[1] Encarnación Picón,[1] Álvaro Pascual,[1,3] and the Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group[a]

Table 4. Cox Regression Analysis of Associations Between Different Variables and Mortality in the Definitive Therapy Cohort

	Crude Analysis		Adjusted Analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Male sex	1.2 (.46–2.29)	.9	…	…
Age[a]	1.00 (.97–1.02)	.9	…	…
Nosocomial BSI	0.99 (.45–2.22)	.9	…	…
Charlson index[a]	1.02 (.88–1.28)	.7	…	…
Neutropenia	1.78 (.88–13.32)	.5	…	…
High-risk source[b]	2.07 (.94–4.54)	.06	…	…
Pitt score[a]	1.49 (1.26–1.78)	<.001	1.38 (1.12–1.70)	.002
Severe sepsis or shock[c]	3.64 (1.66–7.99)	.001	2.10 (.87–5.05)	.09
Empirical therapy with BLBLI	0.56 (.18–1.73)	.3	…	…
Inappropriate empirical therapy	1.76 (.78–3.93)	.1	…	…
Definitive therapy with BLBLI[d]	0.66 (.24–1.76)	.4	0.76 (.28–2.07)	.5

Alternatives to carbapenems: for whom?

- Patients infected with ESBL strains
- Empirical treatment: carbapenems
- De-escalation possible, even in the most severe patients, but only according to MIC
  - Cefepime if MIC<1 mg/L
  - Pip/taz if MIC<4 mg/L
  - Ceftazidime if MIC<1 mg/L

Monotherapy or combination therapy?

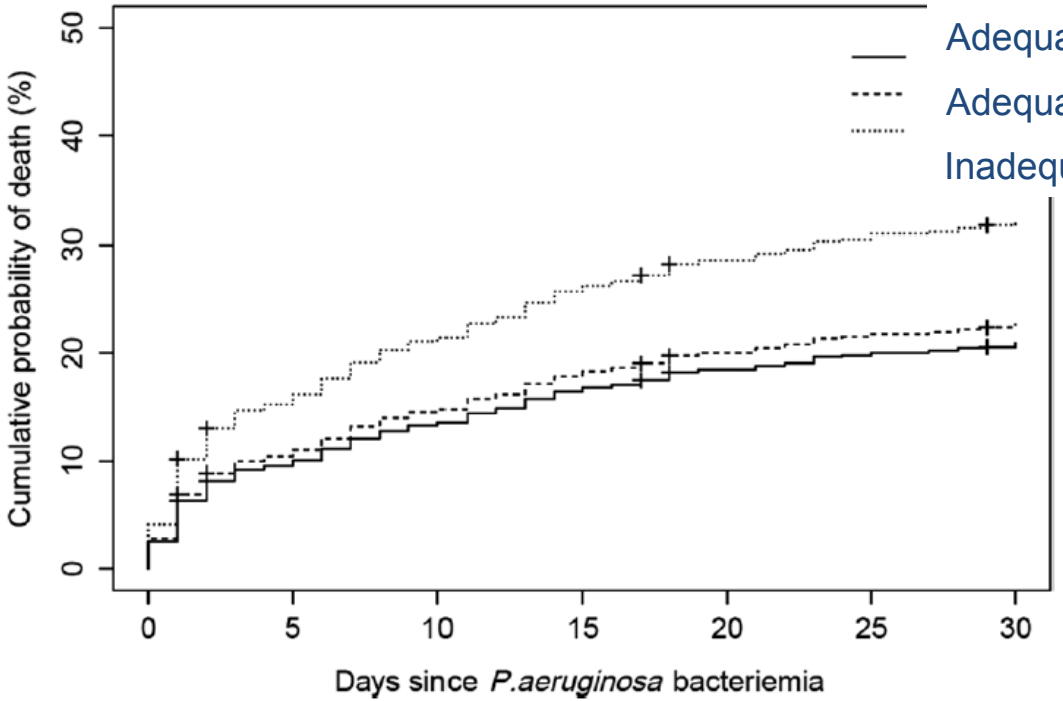
Appropriateness of Antibiotic Therapy in Patients Receiving or not an AG as Empirical Therapy

Microorganism	Combination No./total no. (%)	Beta-lactam No./total no. (%)	OR (95% CI)	P
Non-ESBL *E. coli*	242/248 (98)	2,454/2,489 (99)	0.6 (0.2-1.7)	0.3
ESBL *E. coli*	21/28 (75)	62/122 (51)	2.9 (1.1-8.2)	0.02
Non-ESBL *Klebsiella*	62/63 (98)	393/420 (94)	4 (0.7-177)	0.2
ESBL K. pneumoniae	18/20 (90)	38/63 (60)	2 (1.2-4.2)	0.01
P. mirabilis	10/10 (100)	116/118 (98)		1
Salmonella spp.	15/15 (100)	108/109 (99)		1
AmpC organisms	78/82 (95)	258/326 (79)	5.1 (1.8-20)	0.001
P. aeruginosa	133/143 (93)	201/319 (63)	7.8 (3.8-16)	<.0001
Other NF-GNB	24/51 (47)	53/105 (51)	0.9 (0.4-1.8)	0.7
Miscellaneous	18/18 (100)	105/114 (92)		0.4

Martinez JA, et al. AAC 2010;54:3590-6

Effect of Adequate Single-Drug vs Combination Antimicrobial Therapy on Mortality in *Pseudomonas aeruginosa* Bloodstream Infections: A Post Hoc Analysis of a Prospective Cohort

Peña C, et al. Clin Infect Dis 2013;57:208-16



N = 593

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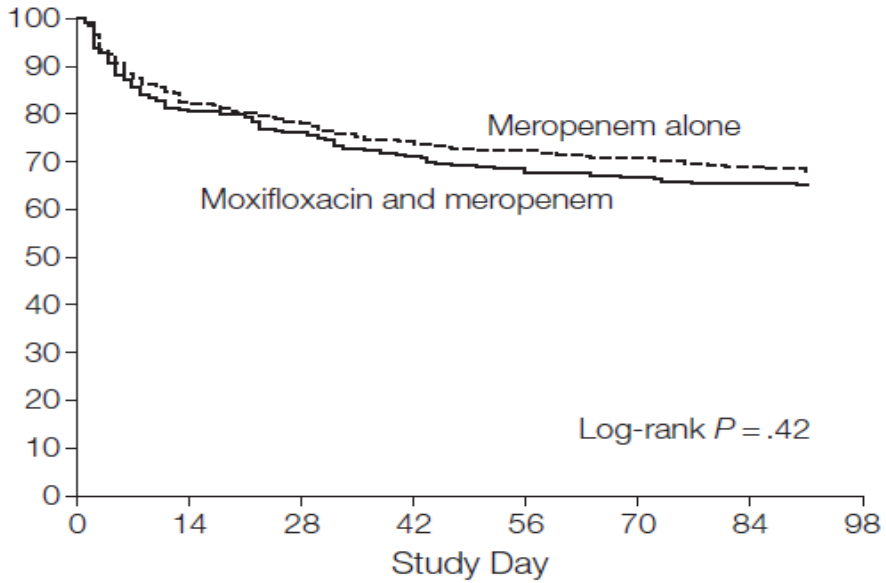
Empirical Treatment With Moxifloxacin and Meropenem vs Meropenem in Patients With Severe Sepsis: A Randomized Trial

Brunkhorst FM, et al. JAMA. 2012;307:2390-9

A Overall survival in intent-to-treat analysis



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Mono or combination therapy?

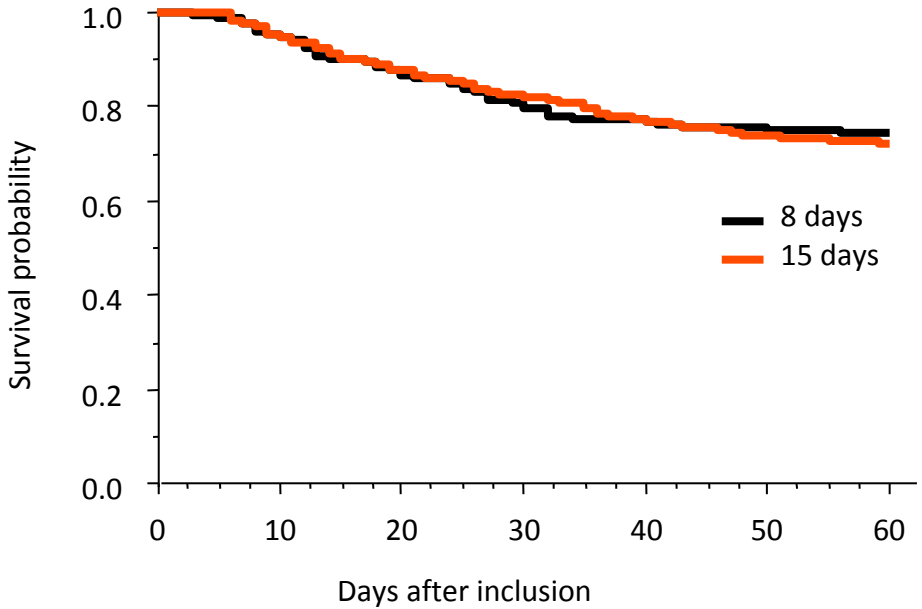
- Combination therapy for empirical treatment
  - Increase the likelihood of appropriateness of treatment
  - Use aminoglycosides
- Monotherapy after 48-72 hrs.
  - No benefice to continue combination therapy once the pathogen is isolated and susceptible to the pivotal antibiotic

Shortening duration of treatment

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

A Randomized Trial

JAMA. 2003;290:2588-2598

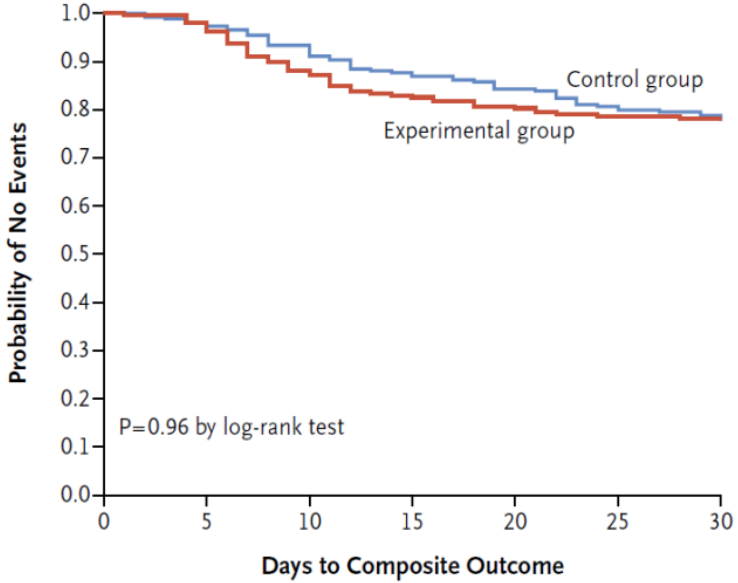


Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

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

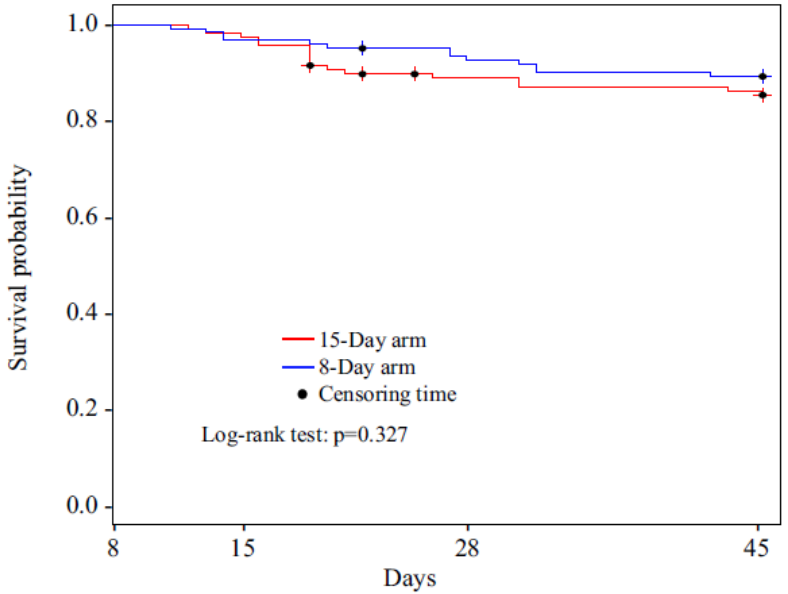
4 vs. 8 days

Primary outcome:
Surgical-site infection, recurrent intraabominal infection or death



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

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



Number at risk (number censored)				
8-Day arm	120 (0)	118 (0)	111 (1)	107 (100)
15-Day arm	116 (0)	114 (0)	101 (3)	97 (92)

Intensive Care Med

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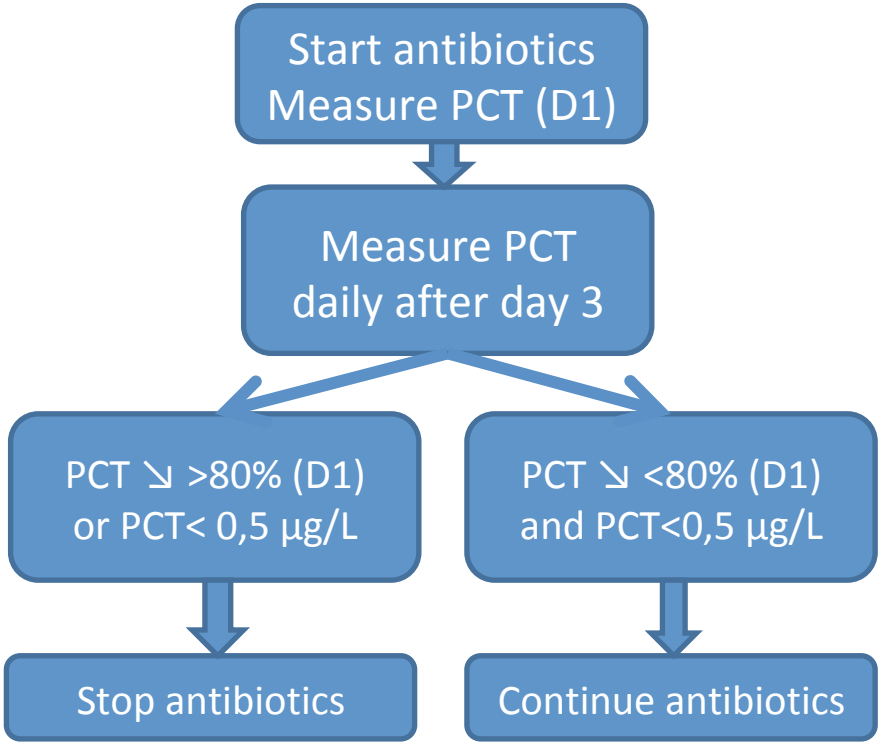
Use of procalcitonin to shorten duration of treatment

- Biomarker associated with bacterial infection severity and prognosis
- No increase or rapid decrease associated with clinical and bacteriological cure, and good outcome



Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis

Lancet Infect Dis 2017

	Control (n=3372)	Procalcitonin group (n=3336)	Adjusted OR or difference (95% CI), p value*	$p_{interaction}$
Overall				
Initiation of antibiotics	2894 (86%)	2351 (70%)	0·27 (0·24 to 0·32), p<0·0001	..
Duration of antibiotics, days†	9·4 (6·2)	8·0 (6·5)	−1·83 (−2·15 to −1·5), p<0·0001	..
Total exposure of antibiotics, days‡	8·1 (6·6)	5·7 (6·6)	−2·43 (−2·71 to −2·15), p<0·0001	..
30-day mortality	336 (10%)	286 (9%)	0·83 (0·7 to 0·99), p=0·037	..
Treatment failure	841 (25%)	768 (23%)	0·90 (0·80 to 1·01), p=0·068	..
Setting-specific outcomes				
Intensive care unit	1233	1214	..	..
Initiation of antibiotics	1224 (99%)	1116 (92%)	0·02 (0·01 to 0·05), p<0·0001	<0·0001
Duration of antibiotics, days†	9·5 (7·4)	8·8 (7·8)	−1·23 (−1·82 to −0·65), p<0·0001	<0·0001
Total exposure of antibiotics, days‡	9·5 (7·4)	8·1 (7·9)	−1·44 (−1·99 to −0·88), p<0·0001	<0·0001
30-day mortality	273 (22%)	229 (19%)	0·84 (0·69 to 1·02), p=0·081	0·619
Length of ICU stay, days	14·8 (16·2)	15·3 (17·5)	0·56 (−0·82 to 1·93), p=0·427	0·849
Length of hospital stay, days	26·3 (26·9)	25·8 (23·9)	−0·33 (−2·28 to 1·62), p=0·739	0·641

Conclusion

- Antimicrobial stewardship can be successfully conducted in the hospital setting, but should not be restrained to one measure and should mix all of them
  - Change to narrow spectrum antibiotics when susceptibility is obtained
  - Spare carbapenems agents in ESBL infection (first obtain the MIC)
  - Monotherapy after 48-72 hrs.
  - Shorten duration of treatment (including stopping unduly antibiotics, i.e. treat bacterial infection and only bacterial infection)
- The true impact of these measures on MDR acquisition (patient level) and ecology (hospital, national level) remains to be determined