De-escalation of antibiotic therapy

ESGAP
ESCMID STUDY GROUP FOR ANTIBIOTIC POLICIES
European Society of Clinical Microbiology and Infectious Diseases

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Istanbul, Oct 7th 2016

De-escalation: concept

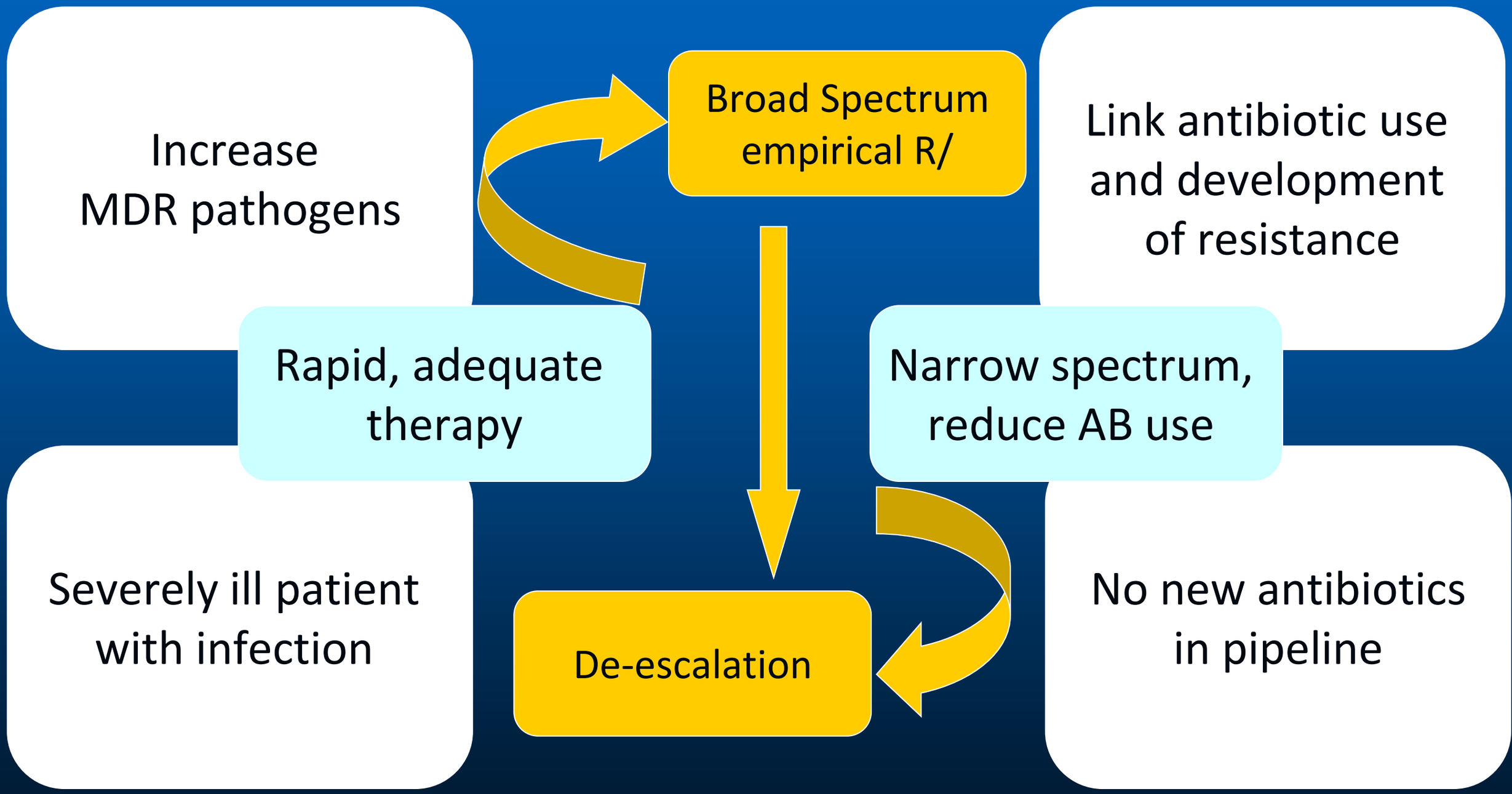

figure: Liesbeth de Bus

De-escalation: concept

GUIDELINES

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

Streamlining or de-escalation of empirical antimicrobial therapy on the basis of culture results and elimination of redundant combination therapy can more effectively target the causative pathogen, resulting in **decreased antimicrobial exposure** and **substantial cost savings**

A-II → good evidence, but no RCT's (2007)

De-escalation: concept

Intensive Care Med (2013) 39:165–228
DOI 10.1007/s00134-012-2769-8

GUIDELINES

R. P. Dellinger
Mitchell M. Levy
Andrew Rhodes
Djillali Annane
Herwig Gerlach
Steven M. Opal
Jonathan E. Sevransky
Charles L. Sprung
Ivor S. Douglas
Roman Jaeschke
Tiffany M. Osborn
Mark E. Nunnally
Sean R. Townsend
Konrad Reinhart
Ruth M. Kleinpell
Derek C. Angus
Clifford S. Deutschman
Flavia R. Machado
Gordon D. Rubenfeld
Steven Webb
Richard J. Beale
Jean-Louis Vincent
Rui Moreno
The Surviving Sepsis Campaign Guidelines Committee
including The Pediatric Subgroup*

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

Antimicrobial regimen should be reassessed daily for potential de-escalation

Grade 1B → strong recommendation, but no RCT's (2012)

De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock (Review)

Silva BNG, Andriolo RB, Atallah ÁN, Salomão R

THE COCHRANE COLLABORATION®

Authors conclusions (2012)

- *"*We did not include any study"
- There is <u>no adequate evidence</u> that de-escalation of antimicrobial agents is effective and safe in patients with sepsis, severe sepsis and septic shock

De-escalation: definitions

Narrow the spectrum

Reduce the amount of antibiotics

Stop ‘safety’ antibiotics (MRSA)

Stop if infection is unlikely

Therapy aimed at ‘causative pathogen’

‘Switching’

The de-escalation paradigm

Hit hard with appropriate antibiotic(s) administered adequately - early, IV, high dose, PK/PD

De-escalate when possible:
change to NARROWER SPECTRUM

This is not exactly right!

Elaboration of a consensual definition of de-escalation all

E. Weiss, J.-R. Zahar, P. Lesprit, E. Ruppe, M. Leone, J. Chastre, J.-C. Lucet, C. Paugam-Burtz, C. Brun-Buisson, J.-F. Timsit on behalf of the 'De-escalation' Study Group

- It is not just about the spectrum! but also on the impact on bystander microbiota and on colonisation resistance: both have to be considered (84% agreement)

- potential ecological effects = not only spectrum but also route, PK/PD, and *in vivo* inactivation

CMI *2015*

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E. Weiss, J.-R. Zahar, P. Lesprit, E. Ruppe, M. Leone, J. Chastre, J.-C. Lucet C. Paugam-Burtz, C. Brun-Buisson, J.-F. Timsit on behalf of the 'De-escalation' Study Group

- no consensus was reached on the delay within which DE should be performed and on whether or not the shortening of antibiotic therapy duration should be included in DE definition

- work also underlines the difficulties of reaching a consensus on the relative ecological impact of each individual drug and on the timing of DE

CMI *2015*

De-escalation: goals?

Reduce selection of MDR bacteria

Reduce colonisation with MDR bacteria

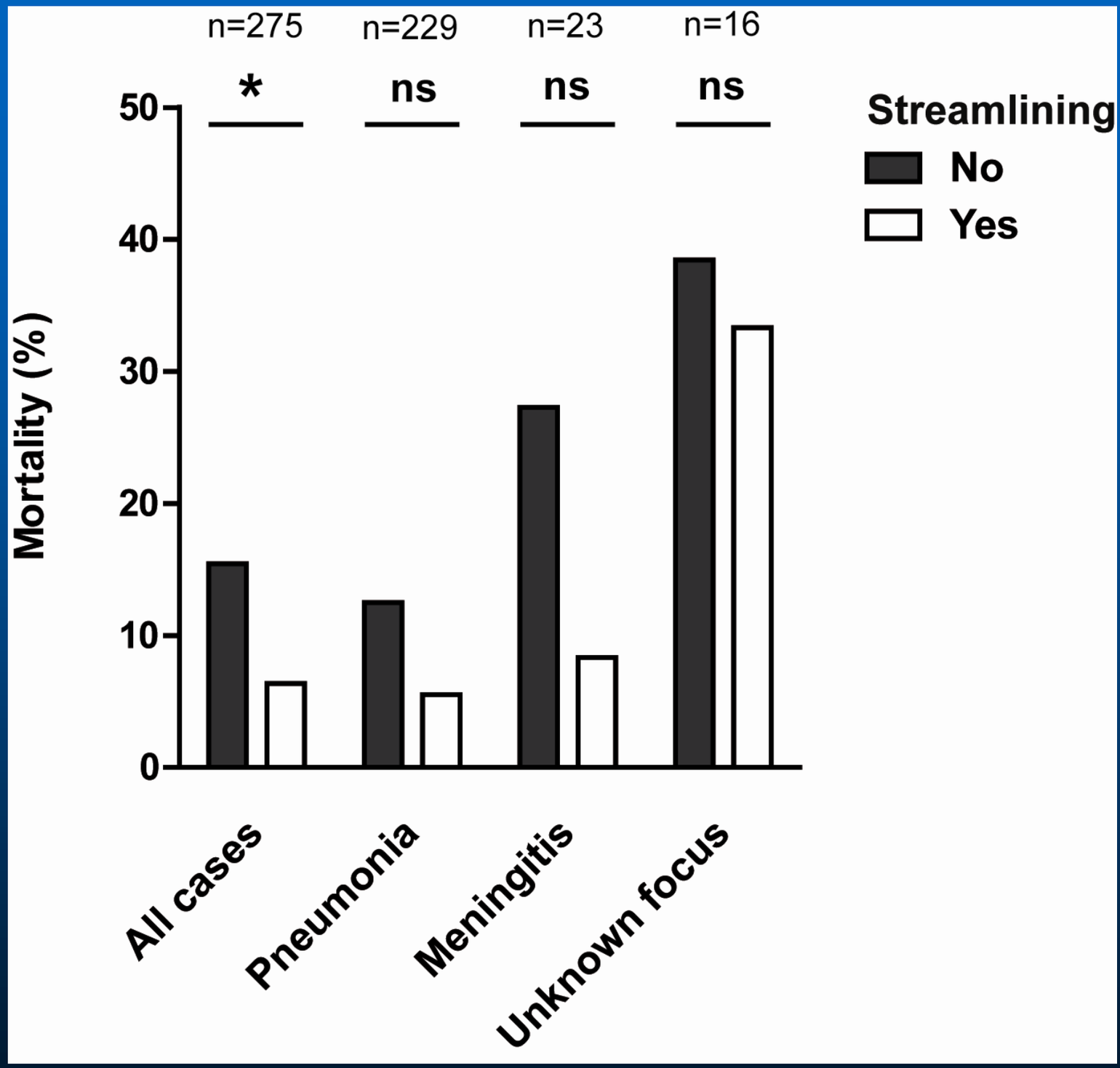
Reduce infection with MDR bacteria

Reduce Antibiotic use (DDD)

Reduce costs

Reduce time to recovery LOS, mortality

De-escalation in pneumococcal bacteremia



A.J. Cremers , T. Sprong, J. Schouten, J. Meis, G. Ferwerda, *JAC 2014*

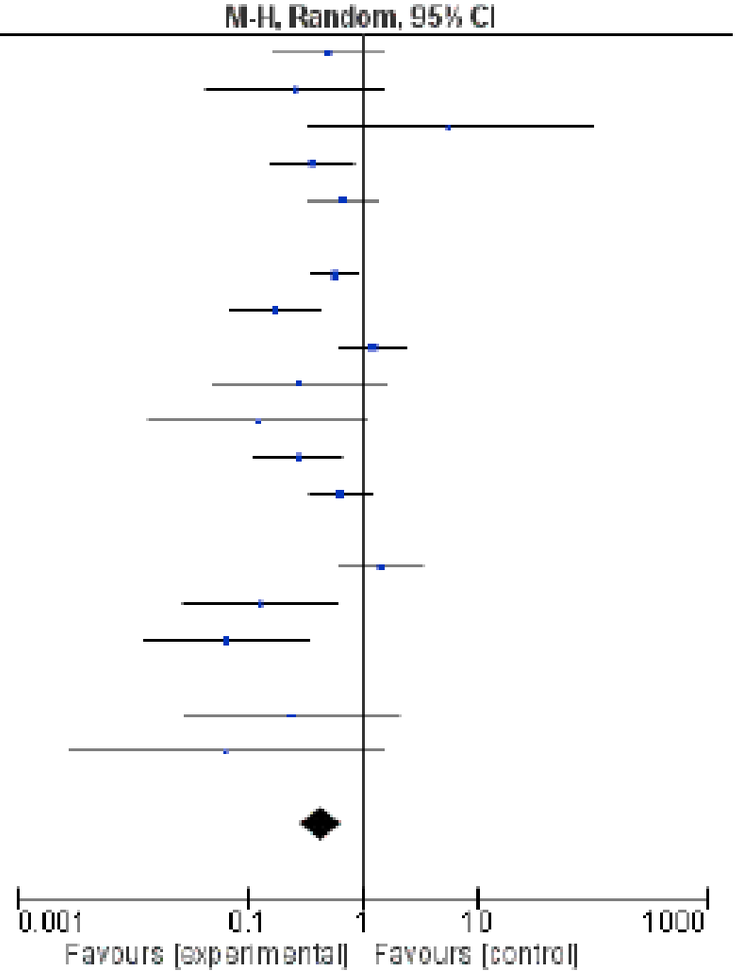
Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis

Emelie C Schuts, Marlies E J L Hulscher, Johan W Mouton, Cees M Verduin, James W T Cohen Stuart, Hans W P M Overdiek, Paul D van der Linden, Stephanie Natsch, Cees M P M Hertogh, Tom F W Wolfs, Jeroen A Schouten, Bart Jan Kullberg, Jan M Prins

Fig. 2 Effect on mortality of de-escalation of therapy based on culture results

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Alvarez-Lerma et al (2006)	7	48	9	36	6.4%	0.51 [0.17, 1.54]
Bal et al (2014)	4	19	4	8	3.6%	0.27 [0.06, 1.57]
Berild et al (2006)	18	146	0	20	1.7%	5.90 [0.34, 101.78]
Cremers et al (2014)	8	126	23	149	8.0%	0.37 [0.16, 0.86]
Eachempati et al (2009)	26	77	24	57	8.9%	0.70 [0.35, 1.42]
Elhanan et al (1997)	0	0	0	0		Not estimable
Gamacho-Montero et al (2014)	45	179	65	180	10.6%	0.59 [0.38, 0.94]
Giantsou et al (2007)	7	58	37	85	7.6%	0.18 [0.07, 0.44]
Joffe et al (2008)	55	320	13	92	9.2%	1.26 [0.66, 2.43]
Khasawneh et al (2014)	2	33	5	27	3.7%	0.28 [0.05, 1.60]
Khasawneh et al (2014) - 2	1	34	6	31	2.6%	0.13 [0.01, 1.12]
Knaak et al (2013)	11	73	17	44	7.7%	0.28 [0.12, 0.68]
Kollef et al (2006)	15	88	58	245	9.4%	0.66 [0.35, 1.24]
Koupetori et al (2014)	0	36	0	93		Not estimable
Leone et al (2014)	18	59	13	57	8.0%	1.49 [0.65, 3.41]
Mokart et al (2014)	2	44	15	57	4.4%	0.13 [0.03, 0.62]
Schlueter et al (2010)	2	77	7	25	4.0%	0.07 [0.01, 0.36]
Schweizer et al (2011)	0	66	0	56		Not estimable
Shime et al (2011)	1	79	6	122	2.7%	0.25 [0.03, 2.10]
Shime et al (2013)	0	28	2	11	1.4%	0.07 [0.00, 1.52]
Total (95% CI)		**1488**		**1246**	**100.0%**	**0.44 [0.30, 0.66]**
Total events	222		304			

Heterogeneity: Tau² = 0.34; Chi² = 38.94, df = 16 (P = 0.001); I² = 59%
Test for overall effect: Z = 3.98 (P < 0.0001)

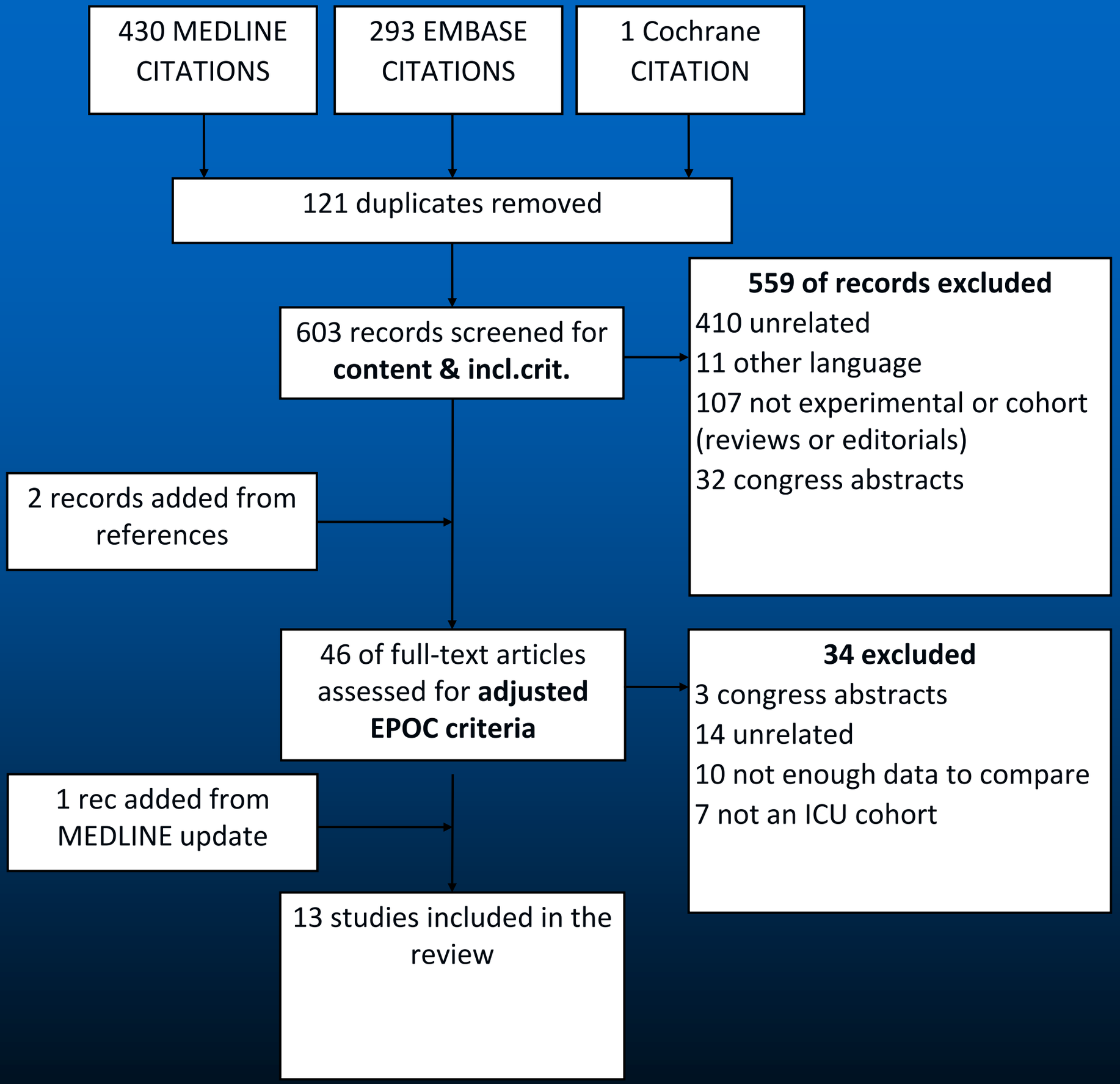


E. Schuts; M. Hulscher; BJ. Kullberg; J. Prins *Lancet Inf Dis 2016*

Goal

- Which are the definitions used for de-escalation in the literature?
- What is the effect of de-escalation on outcomes of care in ICU patients?

A. Tabah, J.F. Timsit, J. Schouten, J. Dewaele, *CID 2016*



A. Tabah, J.F. Timsit, J. Schouten, J. Dewaele *CID 2016*

What evidence exists to support antimicrobial de-escalation in the intensive care unit?
A systematic review

Results: 14 studies

- two randomised clinical trials (unblinded) Cochrane Risk of Bias tool
- 12 cohort studies Newcastle–Ottawa Quality Assessment Scale

A. Tabah, J.F. Timsit, J. Schouten, J. Dewaele *CID 2016*

What evidence exists to support antimicrobial de-escalation in the intensive care unit?
A systematic review

Which definitions are used for de-escalation in the literature?

- Always described as “narrowing” or “streamlining” therapy, considerable variability
- Ranking “broadness of spectrum” in 4/14 studies
- Concept of the “pivotal” antibiotic (Leone)

What evidence exists to support antimicrobial de-escalation in the intensive care unit?
A systematic review

Outcomes after de-escalation:

- Lower or improving severity scores associated with DE (p=0.04 to <0.001)
- Pooled effect of DE on mortality protective (RR 0.68, 95% CI 0.52-0.88)
- Limited quality of cohort studies
  - Adjustment and multivariable analysis on the effect of DE on outcome only in 4 /12 cohort studies
  - Two studies accounted for severity of illness <u>at the moment</u> where DE was considered

What evidence exists to support antimicrobial de-escalation in the intensive care unit?
A systematic review

Secondary outcomes after de-escalation:

- Non-inferiority length of stay in DE group
- More superinfections and longer AB use in DE
- No (measurable) effect on ecology

RCT de-escalation in ICU

Intensive Care Med
DOI 10.1007/s00134-014-3411-8

SEVEN-DAY PROFILE PUBLICATION

Marc Leone
Carole Bechis
Karine Baumstarck
Jean-Yves Lefrant
Jacques Albanèse
Samir Jaber
Alain Lepape
Jean-Michel Constantin
Laurent Papazian
Nicolas Bruder
Bernard Allaouchiche
Karine Bézulier
François Antonini
Julien Textoris
Claude Martin
For the AZUREA Network Investigators

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

De-escalation: Leone et al. 2014

- Multicenter (9) ICU study in France
- Radomised: continue vs. de-escalate
- Unblinded
- 120 patients
- Primary outcome: LOS (non-inferiority de-escalation)
- Secundary outcomes: 90 day M; AB free days; superinfections; *Clostridium difficile* infections

De-escalation: Leone et al. 2014

- *Inclusion* severe sepis / septic shock
- Randomisation as soon as positive cultures available
- Adequate empirical therapy acc. guidelines
- *Definition* de-escalation:
  - *Change”Pivotal antibiotic” to AB with narrowest possible spectrum*
  - *Stop combination therapy (quinolone, amino-glycoside or macrolide) at day 3*
  - *Stop Vancomycin if no rationale for MRSA*

De-escalation: Leone et al. 2014

- *Definition* continue:
  - *Continue”Pivotal antibiotic”*
  - *Stop combination therapy (quinolone, amino-glycoside or macrolide) between day 3 and 5*
  - *Stop Vancomycin if no rationale for MRSA*
  - *Therapy duration acc. to international guidelines*

624 screened patients

Non-inclusion: 504
No documentation: 162
Carbapenemase producer: 2
Expected death < 48 h: 18
Other protocol: 21
Antibiotic arrest < 48 h: 52
Late documentation: 12
Inappropriateness: 31
No consent: 22
Deprivation of freedom: 12
Expected withdrowl of care: 81
Early discharge: 12
Lack of inclusion: 79

120 included patients

60 assigned to continuation of appropriate empirical antimicrobial treatment

60 assigned to de-escalation of appropriate empirical antimicrobial treatment

Exclusion: 3 patients (freedom deprivation)

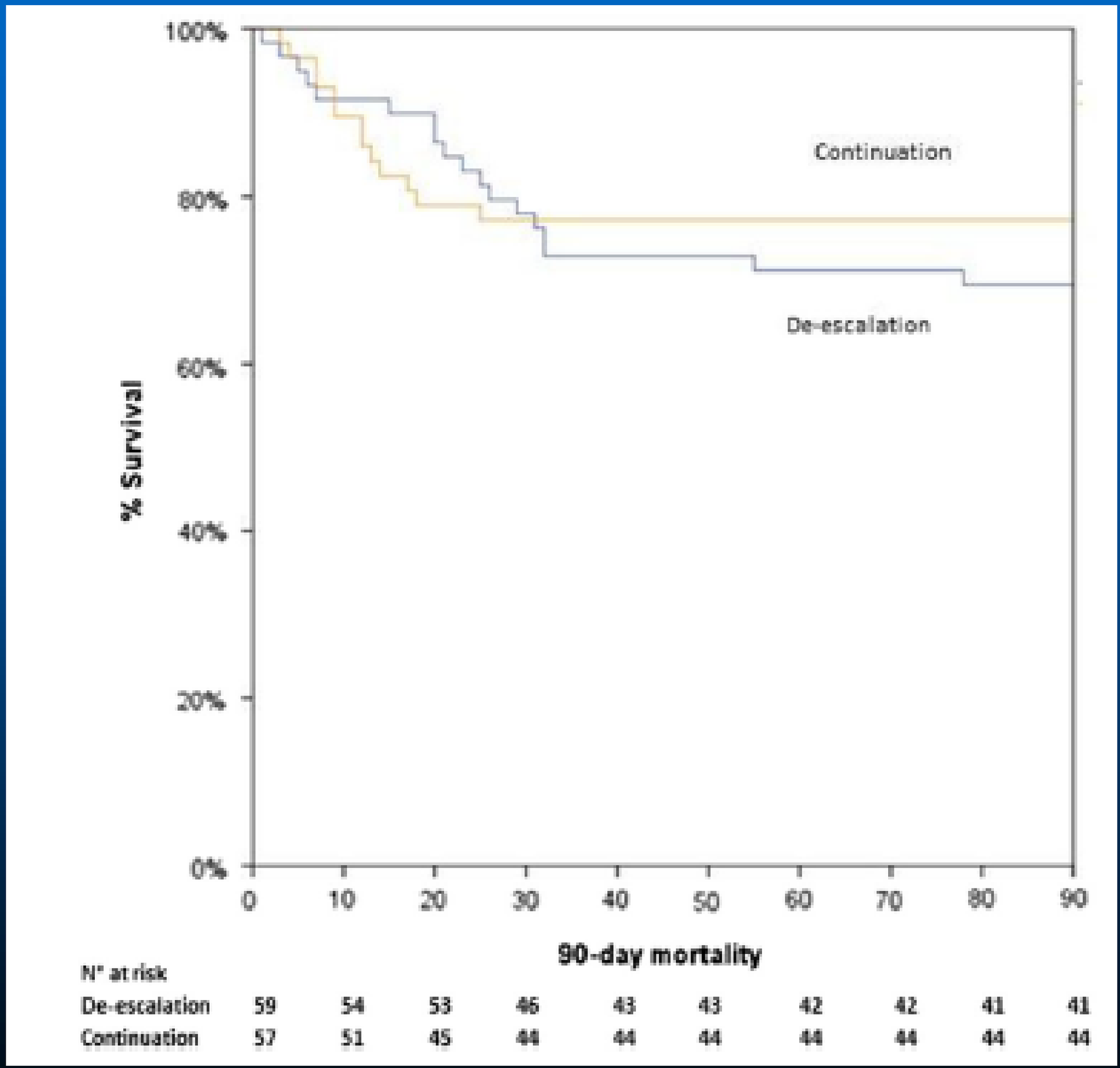
Exclusion: 1 patient (freedom deprivation)

57 patients in the per-protocol analysis

59 patients in the per-protocol analysis

0 Lost to follow-up (day 90)

0 Lost to follow-up (day 90)

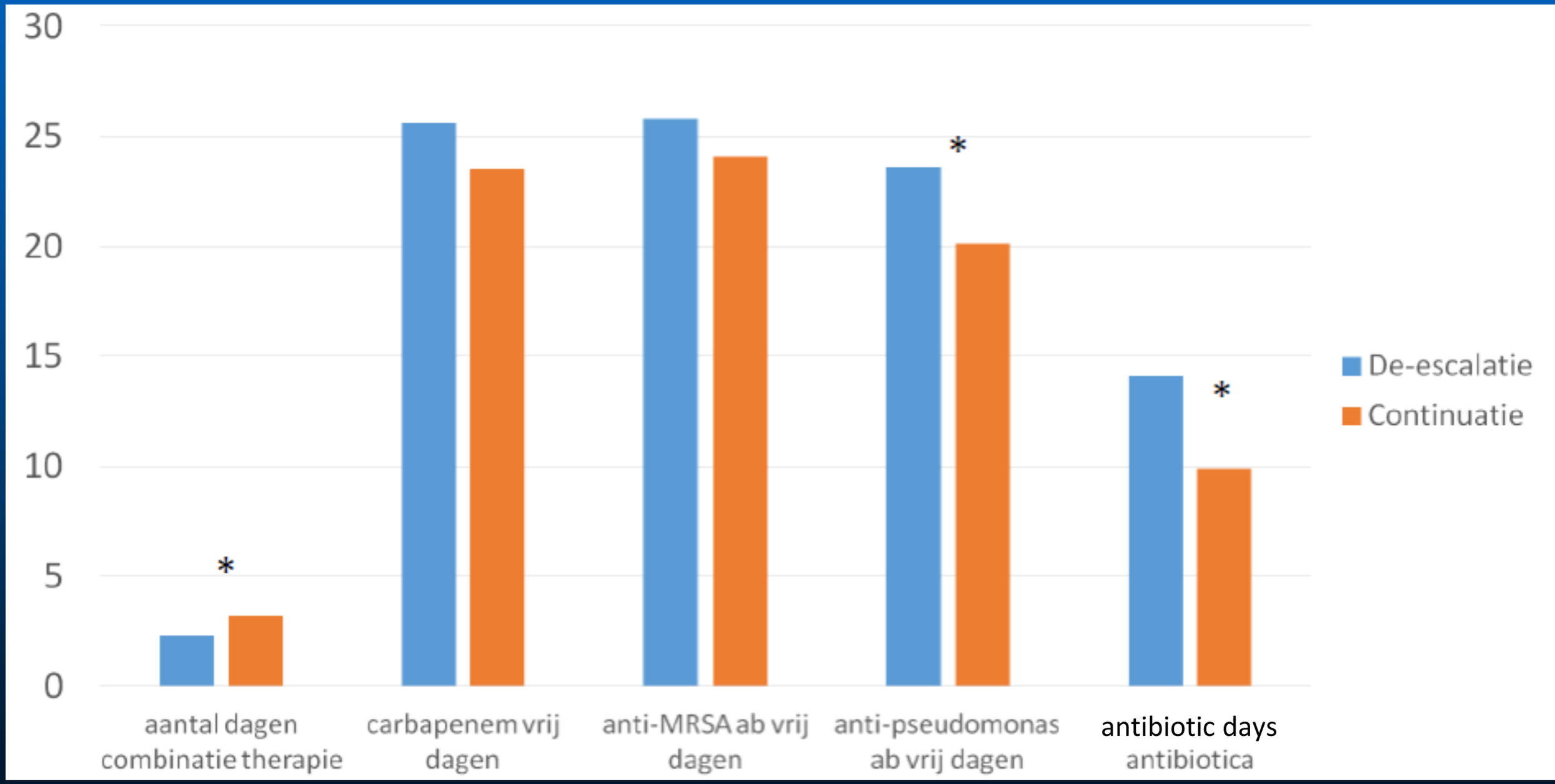

100%
80%
60%
40%
20%
0%
% Survival
Continuation
De-escalation
0
10
20
30
40
50
60
70
80
90
90-day mortality
N° at risk
De-escalation 59 54 53 46 43 43 42 42 41 41
Continuation 57 51 45 44 44 44 44 44 44 44

p = 0.35

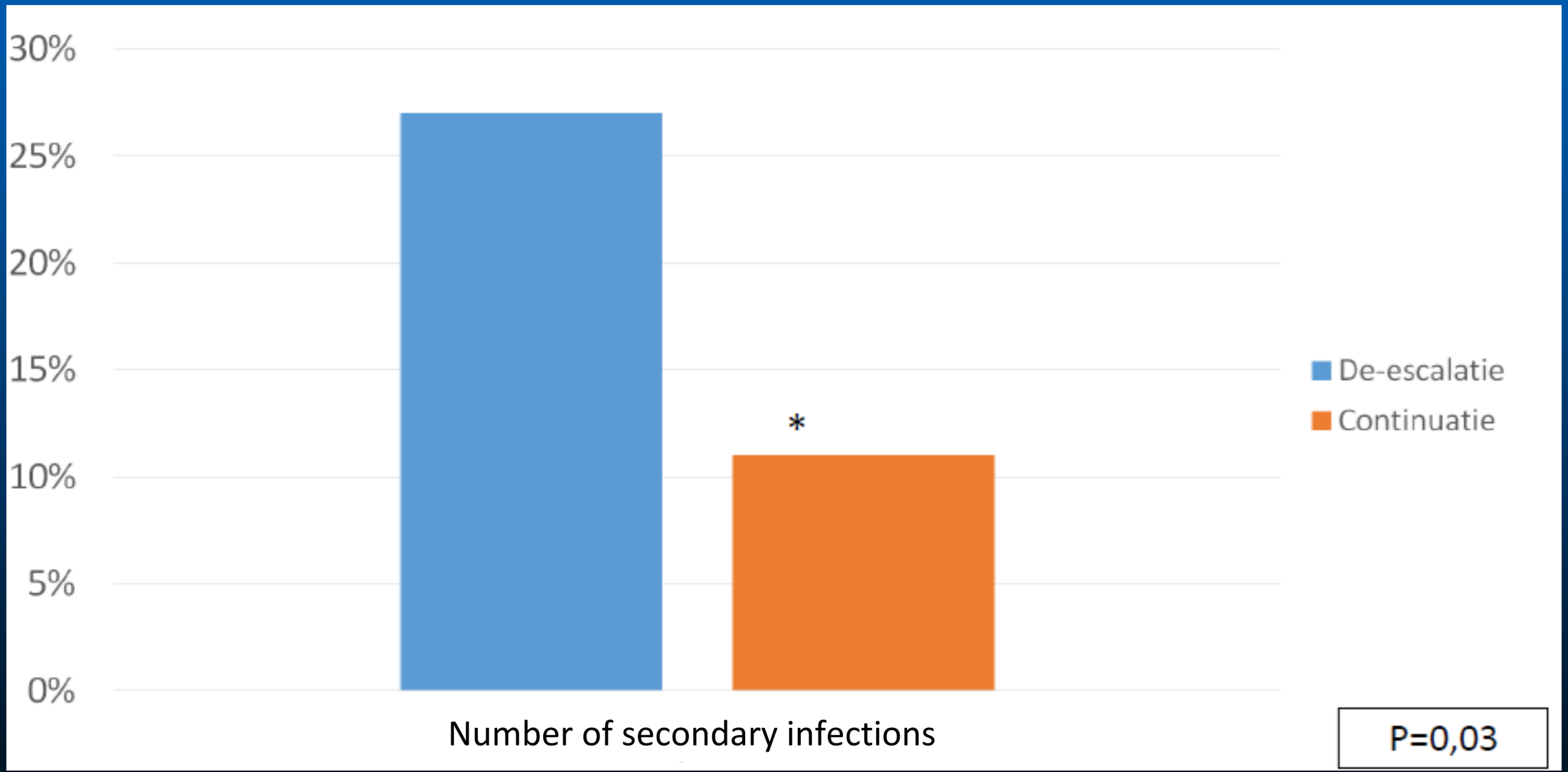
De-escalation: Leone et al. 2014

Duration	De-escalation group ($n = 59$)	Continuation group ($n = 57$)	P
Duration of ICU stay (days)			
From inclusion to discharge	15.2 ± 15.0	11.8 ± 12.6	0.71
	9 [1–79]	8 [1–60]	
From admission to discharge	29.1 ± 50.0	18.1 ± 15.7	0.11
	13 [1–375]	12 [3–67]	

De-escalation: Leone et al. 2014



De-escalation: Leone et al. 2014



De-escalation: goals?

Reduce selection of MDR bacteria

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Reduce infection with MDR bacteria

Reduce Antibiotic use (DDD)

Reduce costs

Reduce time to recovery LOS, mortality ?

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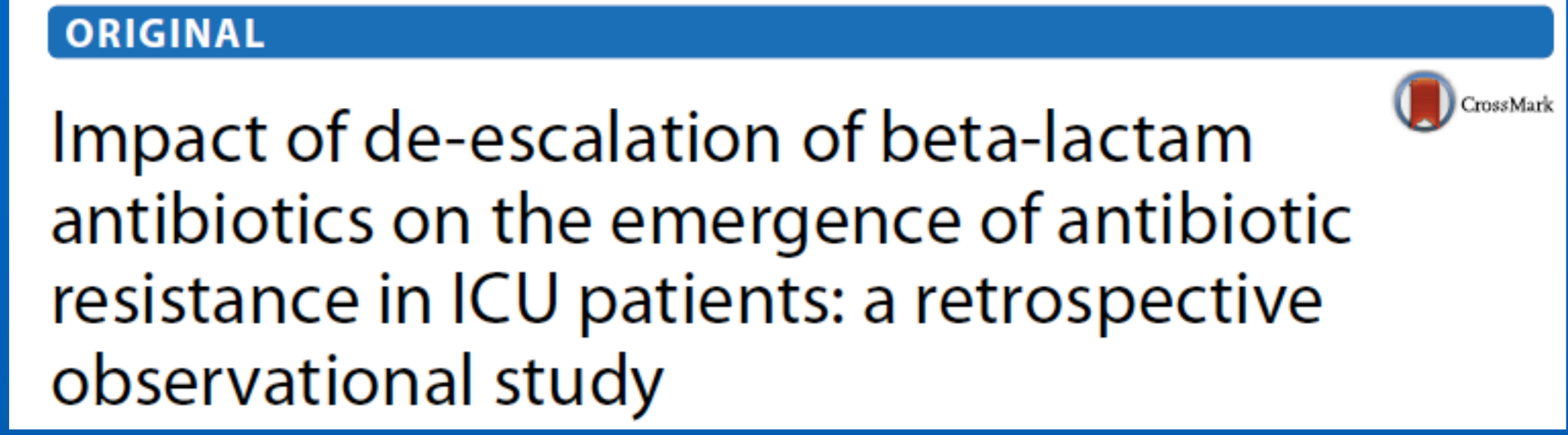

- Retrospective study comparing de-escalation vs. escalation vs. continuation for betalactam use
- Outcomes:
  - ✴ Duration of antibiotic course, Antibiotic consumption
  - ✴ Cumulative incidence of MDR resistant pathogens to the initial betalactam antibiotic using systematically collected surveillance cultures (!)

L.De Bus, W. Denys, J. Decruyenaere, P. Depuydt *Intensive Care Medicine 2016*

Table 3 Patient outcome after de-escalation and escalation of anti-pseudomonal beta-lactam therapy

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
Antibiotic-free days (14 days after onset of infection)[a] ($n = 116$)	1 (0–4)	2 (0–6)	1 (0–3)	0 (0–1)	0.04	<0.001

L.De Bus, W. Denys, J. Decruyenaere, P. Depuydt *Intensive Care Medicine 2016*

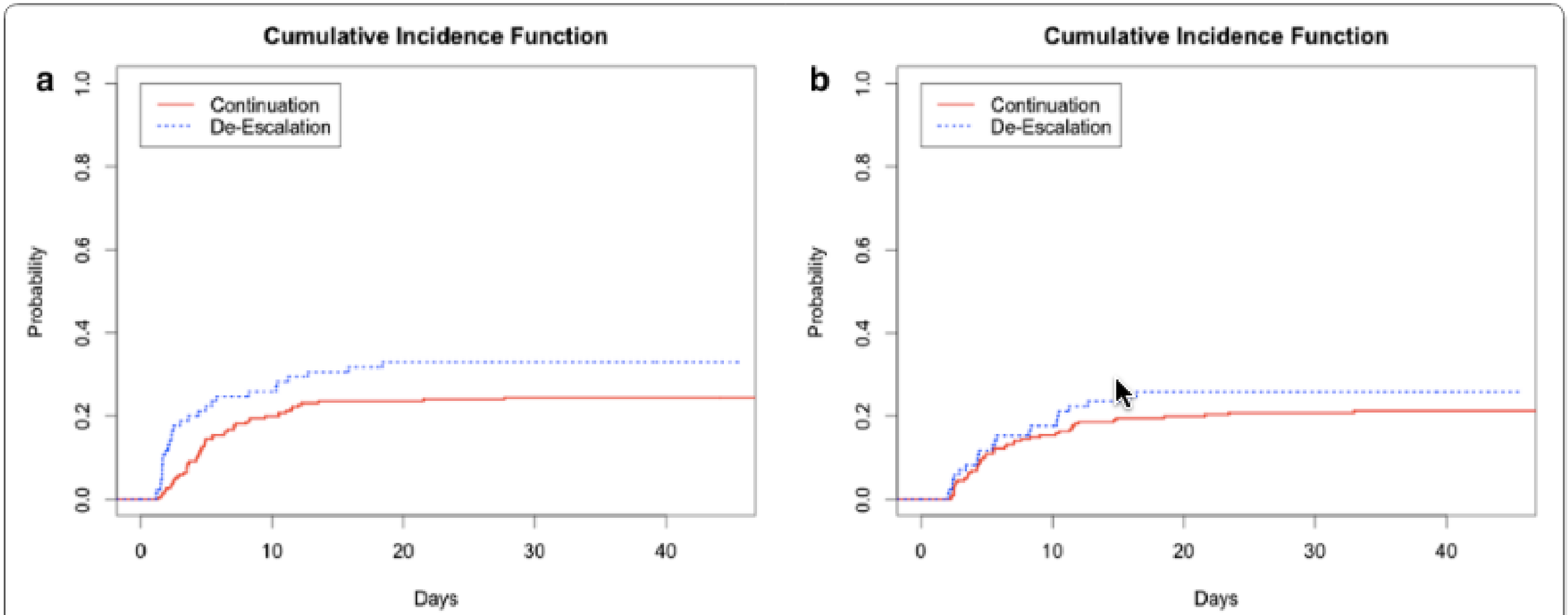

Fig. 2 **a** Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of pathogens resistant to the initial anti-pseudomonal betalactam antibiotic. **b** Cumulative incidence function (after adjustment for ICU discharge and death as competing risk events) of emergence of MDR pathogens

ation of expected favorable effect of de-escalation on selection of antimicrobia

L.De Bus, W. Denys, J. Decruyenaere, P. Depuydt *Intensive Care Medicine 2016*

Table 2 Multivariate analysis on determinants of de-escalation and escalation of anti-pseudomonal beta-lactam antibiotic therapy

Factors associated with de-escalation or escalation	De-escalation versus continuation		Escalation versus continuation	
	Adjusted OR (95% CI)[a]	*p* value	Adjusted OR (95% CI)[b]	*p* value
ICU department (medical/surgical ICU)	0.81 (0.5–1.3)	0.39	0.24 (0.1–0.61)	0.003
Hospitalization duration prior to initiation of BL therapy (days)	0.99 (0.98–1)	0.11	0.96 (0.92–0.99)	0.04
Antibiotic exposure during ICU stay prior to initiation of BL therapy	0.68 (0.41–1.15)	0.15	0.52 (0.2–1.34)	0.17
Type of initial BL therapy	0.98 (0.75–1.28)	0.88	1.17 (0.67–2.1)	0.59
Focus of infection	0.98 (0.86–1.12)	0.76	0.92 (0.73–1.17)	0.5
Severe sepsis/septic shock	1.1 (0.65–1.85)	0.72	0.38 (0.15–0.9)	0.03
ΔSOFA[c]	1.01 (0.94–1.08)	0.83	0.87 (0.79–0.97)	0.008
Microbiologically documented infection	3.96 (2.4–6.55)	<0.001	1.4 (0.62–3.15)	0.42
Presence of (non-etiologic) isolates resistant to the initial BL therapy	1.46 (0.87–2.48)	0.16	3 (1.26–7.11)	0.01

L.De Bus, W. Denys, J. Decruyenaere, P. Depuydt *Intensive Care Medicine 2016*

De-escalation: goals?

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De-escalation: future ?

Increase MDR

Broad Spectrum empirical R/

Link antibiotic use and development of resistance

Rapid, adequate therapy

Narrow spectrum, reduced AB

Severely ill patient in ICU

Narrow Spectrum

Cost reduction

De-escalation: future

De-escalation?

-no uniform definition

-no reduction of AB duration, costs or length of stay

-no effects on AMR

-protective of mortality? bias!

large cluster-RCT required

De-escalation: future

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tion

De-escalation?

rather focus on early stop!

Even short courses of antibiotics cause selection of resistant bacteria

Harbarth Circulation 2000

Taconelli AAC 2010

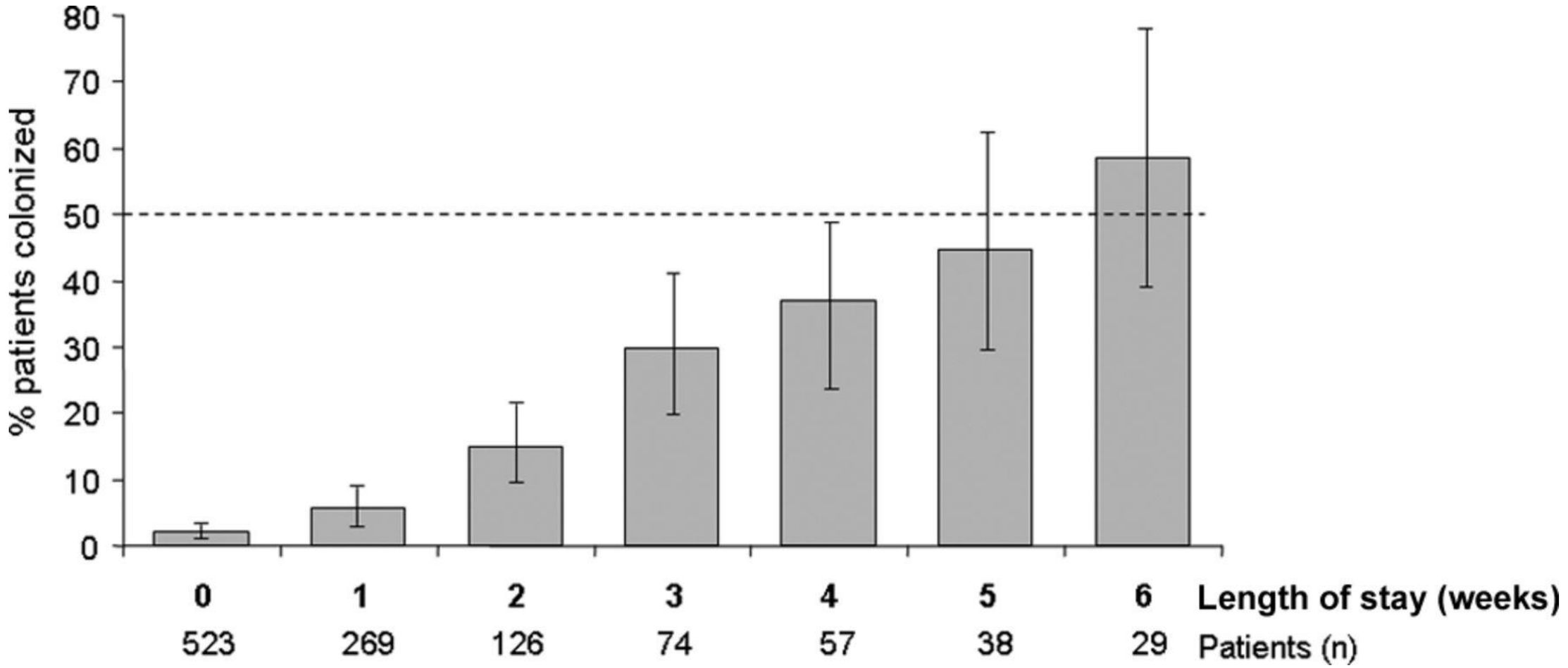
Lefevre AAC 2013

- we need to move to more rapid culture-independent micro identification methods
- we need swift communication between micro lab and ICU:

-leading to faster achievement of appropriate therapy

-duration of empirical therapy may be limited

Rates of intestinal colonization by imipenem-resistant gram-negative bacilli in intensive care patients.



Laurence Armand-Lefèvre et al. Antimicrob. Agents Chemother. 2013;57:1488-1495

Antimicrobial Agents and Chemotherapy

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

Evelien de Jong, Jos A van Oers, Albertus Beishuizen, Piet Vos, Wytze J Vermeijden, Lenneke E Haas, Bert G Loef, Tom Dormans, Gertrude C van Melsen, Yvette C Kluiters, Hans Kemperman, Maarten J van den Elsen, Jeroen A Schouten, Jörn O Streefkerk, Hans G Krabbe, Hans Kieft, Georg H Kluge, Veerle C van Dam, Joost van Pelt, Laura Bormans, Martine Bokelman Otten, Auke C Reidinga, Henrik Endeman, Jos W Twisk, Ewoudt M W van de Garde, Anne Marie G A de Smet, Jozef Kesecioglu, Armand R Girbes, Maarten W Nijsten, Dylan W de Lange

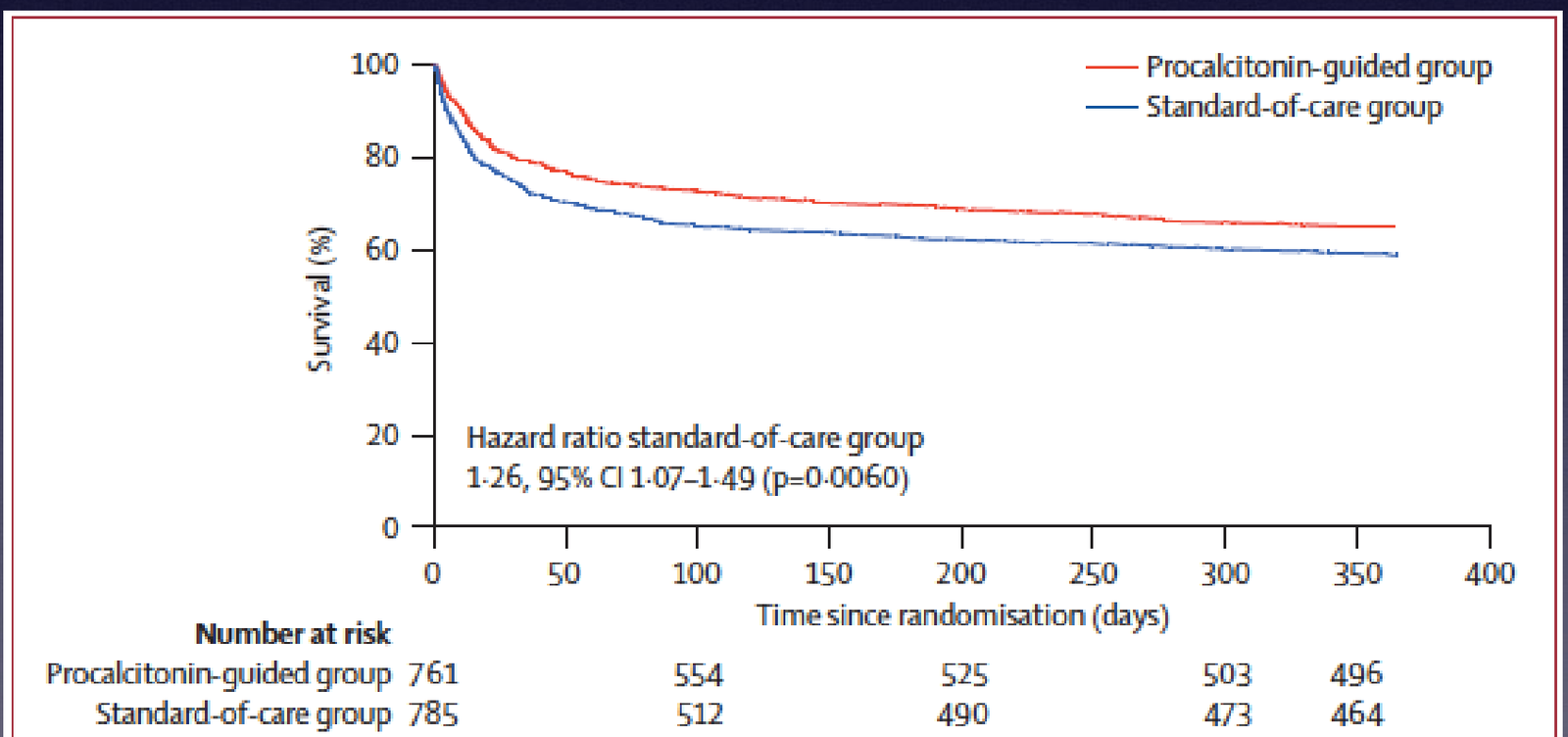


Figure 2: **Kaplan-Meier plot for probability of survival from random assignment to day 365, in the modified intention-to-treat population**

E de Jong, *Lancet Infect Dis March 2016*

	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)	Between-group absolute difference in means (95% CI)	p value
Antibiotic consumption (days)				
Daily defined doses in first 28 days	7·5 (4·0 to 12·8)	9·3 (5·0 to 16·5)	2·69 (1·26 to 4·12)	<0·0001
Duration of treatment	5·0 (3·0 to 9·0)	7·0 (4·0 to 11·0)	1·22 (0·65 to 1·78)	<0·0001
Antibiotic-free days in first 28 days	7·0 (0·0 to 14·5)	5·0 (0 to 13·0)	1·31 (0·52 to 2·09)	0·0016
Mortality (%)				
28-day mortality	149 (19·6%)	196 (25·0%)	5·4% (1·2 to 9·5)	0·0122
1-year mortality	265 (34·8%)	321 (40·9%)	6·1% (1·2 to 10·9)	0·0158
Adverse events				
Reinfection	38 (5·0)	23 (2·9)	−2·1% (−4·1 to -0·1)	0·0492
Repeated course of antibiotics	175 (23·0)	173 (22·0)	−1·0% (−5·1 to 3·2)	0·67
Time (days) between stop and reinstitution of antibiotics	4·0 (2·0 to 8·0)	4·0 (2·0 to 8·0)	−0·22 (−1·31 to 0·88)	0·96
Costs				
Total cumulative costs of antibiotics	€150 082	€181 263	NA	NA
Median cumulative costs antibiotics per patient	€107 (51 to 229)	€129 (66 to 273)	€33·6 (2·5 to 64·8)	0·0006
Length of stay (days)				
On the intensive care unit	8·5 (5·0 to 17·0)	9·0 (4·0 to 17·0)	−0·21 (−0·92 to 1·60)	0·56
In hospital	22·0 (13·0 to 39·3)	22·0 (12·0 to 40·0)	0·39 (−2·69 to 3·46)	0·77

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs.
NA=not applicable.

Table 2: **Primary and secondary outcome measures**

E de Jong, *Lancet Infect Dis march 2016*

De-escalation needs a more solid evidence base

- How quickly is the damage to the microbiota done and how long does it last?
- Does sequential therapy with two different antimicrobials increase damage or is it beneficial? What about combination therapy?
- What is the impact of dosing and duration of therapy on AMR selection?

De-escalation: a revised view

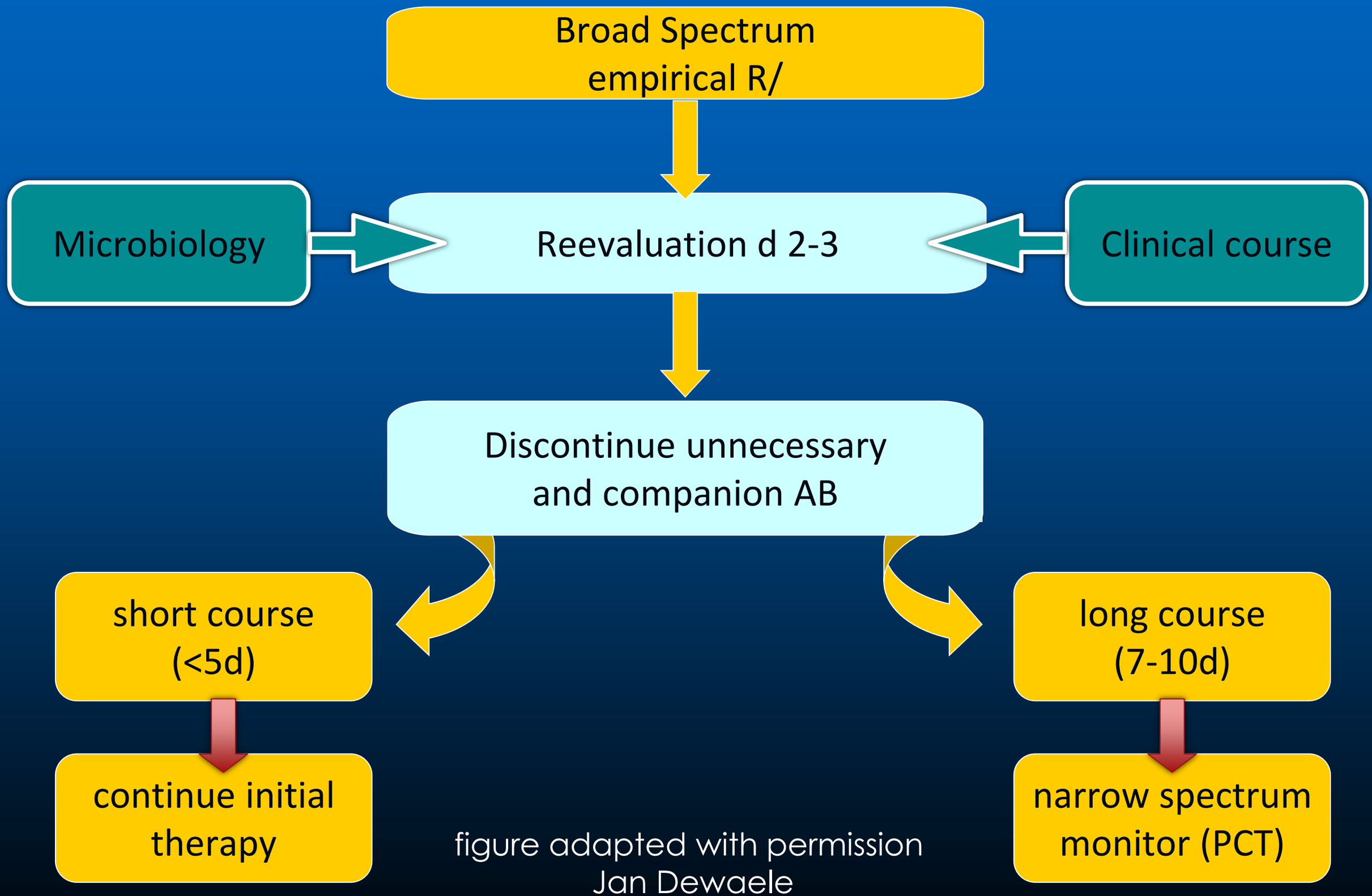


figure adapted with permission
Jan Dewaele