ΑΠΟΚΛΙΜΑΚΩΣΗ ΤΩΝ ΑΝΤΙΒΙΟΤΙΚΩΝ

ΓΝΩΣΤΕΣ ΚΑΙ ΑΝΑΔΥΟΜΕΝΕΣ ΑΝΕΠΙΘΥΜΗΤΕΣ ΕΝΕΡΓΕΙΕΣ ΤΩΝ ΑΝΤΙΜΙΚΡΟΒΙΑΚΩΝ ΠΑΡΑΓΟΝΤΩΝ

Χριστίνα Ρούτση

Α΄Κλινική Εντατικής Θεραπείας

Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

Νοσοκομείο Ευαγγελισμός, Αθήνα

de-escalation therapy
DEFINITION

No uniform definition

An antimicrobial policy consisting of

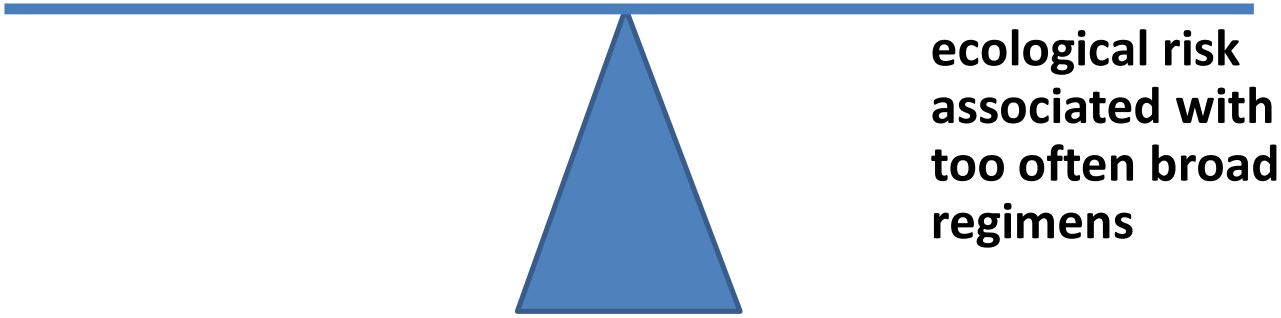
the initial use of wide-spectrum antimicrobials followed by a reassessment of treatment when culture results are available

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

2. We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (strong recommendation, moderate quality of evidence).
3. We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (BPS).

When prescribing an empirical antimicrobial therapy the clinician is facing a major dilemma

risk of inappropriate initial therapy (i.e. use of antibiotics to which the etiological microorganism is not susceptible).



ecological risk associated with using too often broad-spectrum regimens

DE-ESCALATION

De-escalation goals

- **Reduce selection of MDR bacteria**
  - Reduce colonization of MDR bacteria
  - Reduce infection with MDR bacteria
- **Reduce antibiotic use**
- **Reduce costs**
- **Reduce time to recovery, length of stay**
- **Improving or at least safe guarding the outcome**

Components of de-escalation

- ✓ 1. Reduction of the number of antibiotics
- ✓ 2. Narrowing the spectrum of the antibiotic
- ✓ 3. Reduction of the duration of antibiotic therapy
- ✓ 4. Stopping unnecessary therapy (therapy without in-vitro activity against the pathogen)
- ✓ 5. A combination of one or more of the above elements

summary

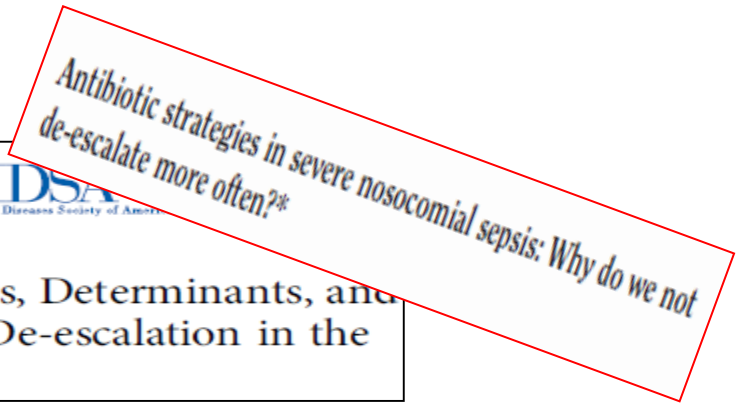
DE-ESCALATION THERAPY occurs in two stages:

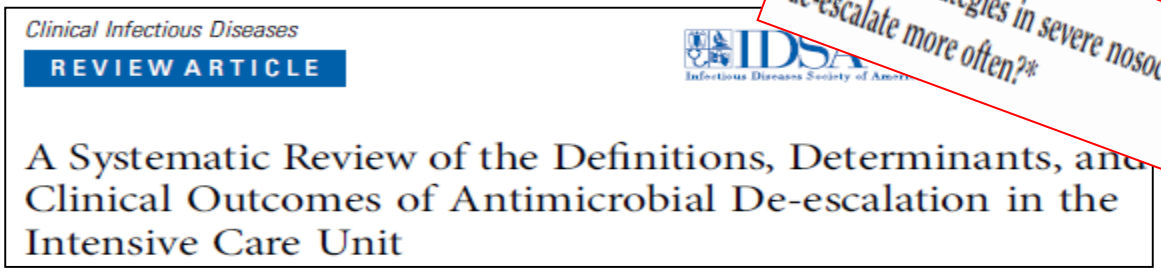
- **Stage 1 - administering the broadest-spectrum antibiotic therapy to improve outcomes (decrease mortality, prevent organ dysfunction, and decrease length of stay).**
- **Stage 2 - focusing on de-escalating as a means to minimize resistance and improve cost-effectiveness**

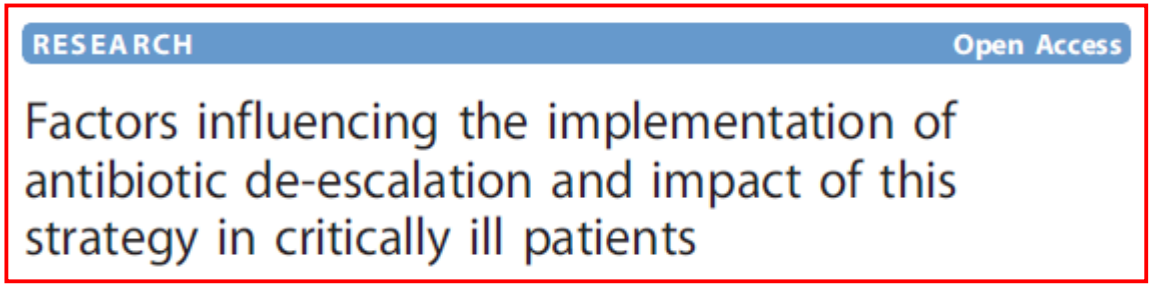
SUMMARY

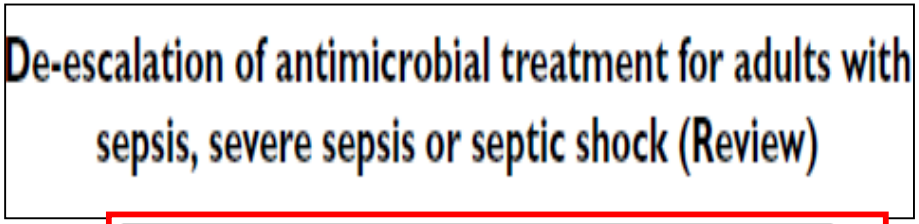
Antibiotic de-escalation is a well tolerated management strategy in critically ill patients but unfortunately is not widely adopted.

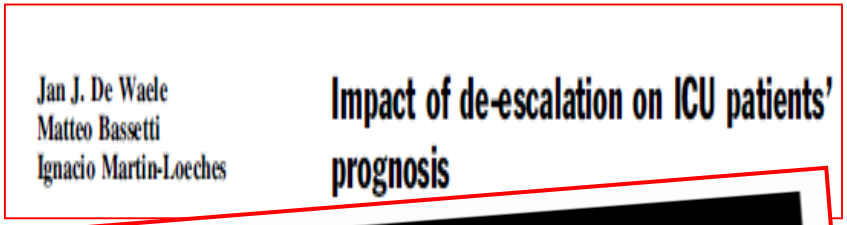

Clinical Infectious Diseases
EDITORIAL COMMENTARY
IDSA
Infectious Diseases Society of America
hivma
hiv medicine association
Antimicrobial De-escalation: What's in a Name?
Marin H. Kollef[1] and Scott T. Micek[2]

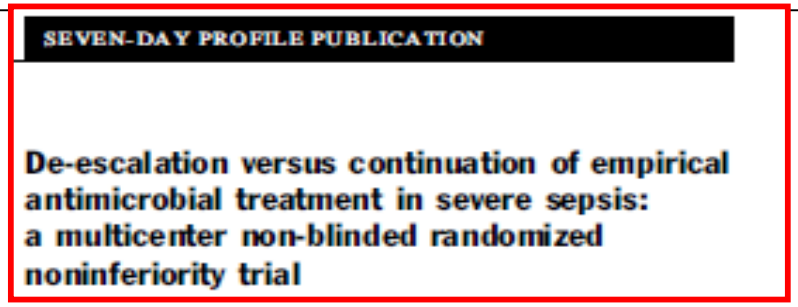

Antibiotic strategies in severe nosocomial sepsis: Why do we not de-escalate more often?*

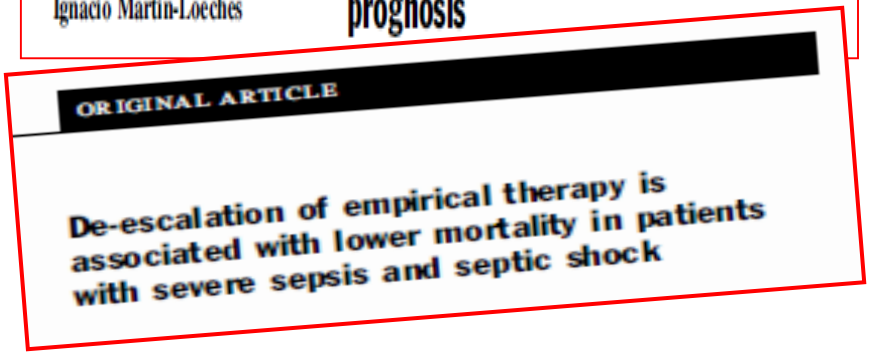

Clinical Infectious Diseases
REVIEW ARTICLE
IDSA
Infectious Diseases Society of America
A Systematic Review of the Definitions, Determinants, and Clinical Outcomes of Antimicrobial De-escalation in the Intensive Care Unit


RESEARCH
Open Access
Factors influencing the implementation of antibiotic de-escalation and impact of this strategy in critically ill patients

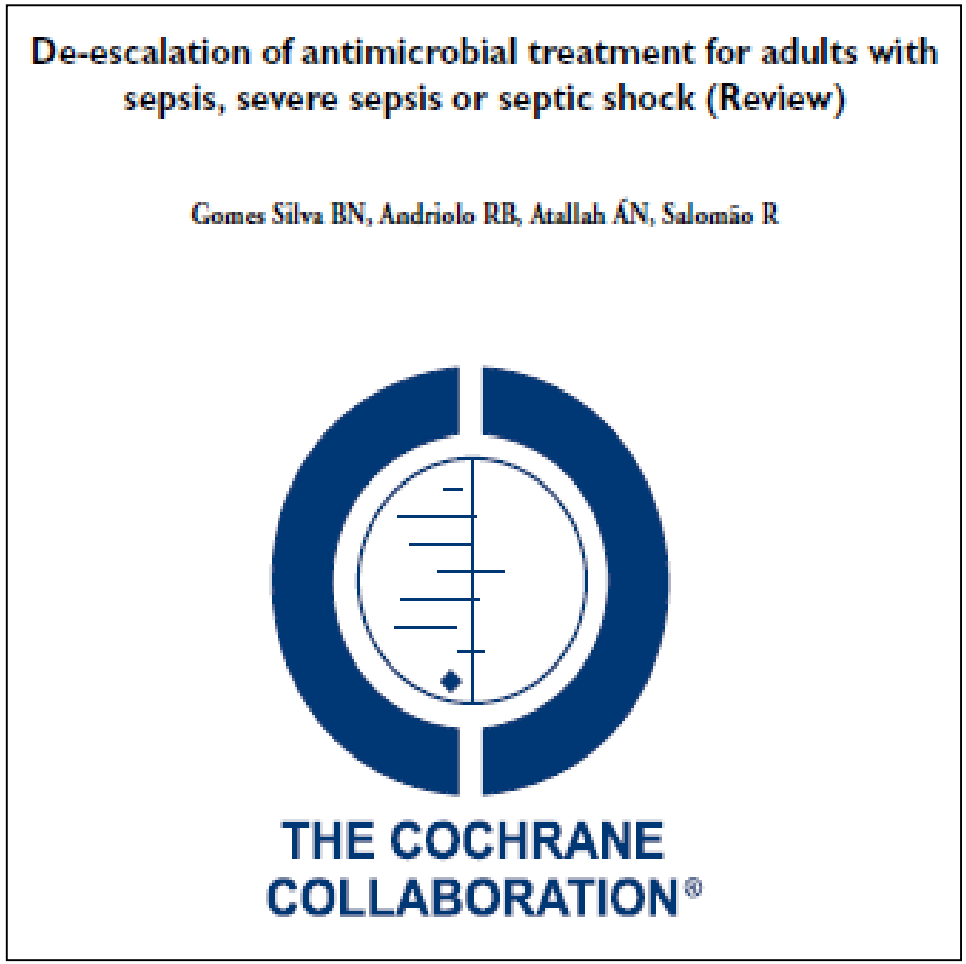

De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock (Review)


Jan J. De Waele
Matteo Bassetti
Ignacio Martin-Loeches
Impact of de-escalation on ICU patients' prognosis


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


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

published in *The Cochrane Library* 2010, Issue 12



Authors conclusions

- *There is <u>no adequate, direct evidence</u> that de-escalation of antimicrobial agents is effective and safe in patients with sepsis, severe sepsis and septic shock*

Intensive Care Med (2014) 40:1399–1408
DOI 10.1007/s00134-014-3411-8

SEVEN-DAY PROFILE PUBLICATION

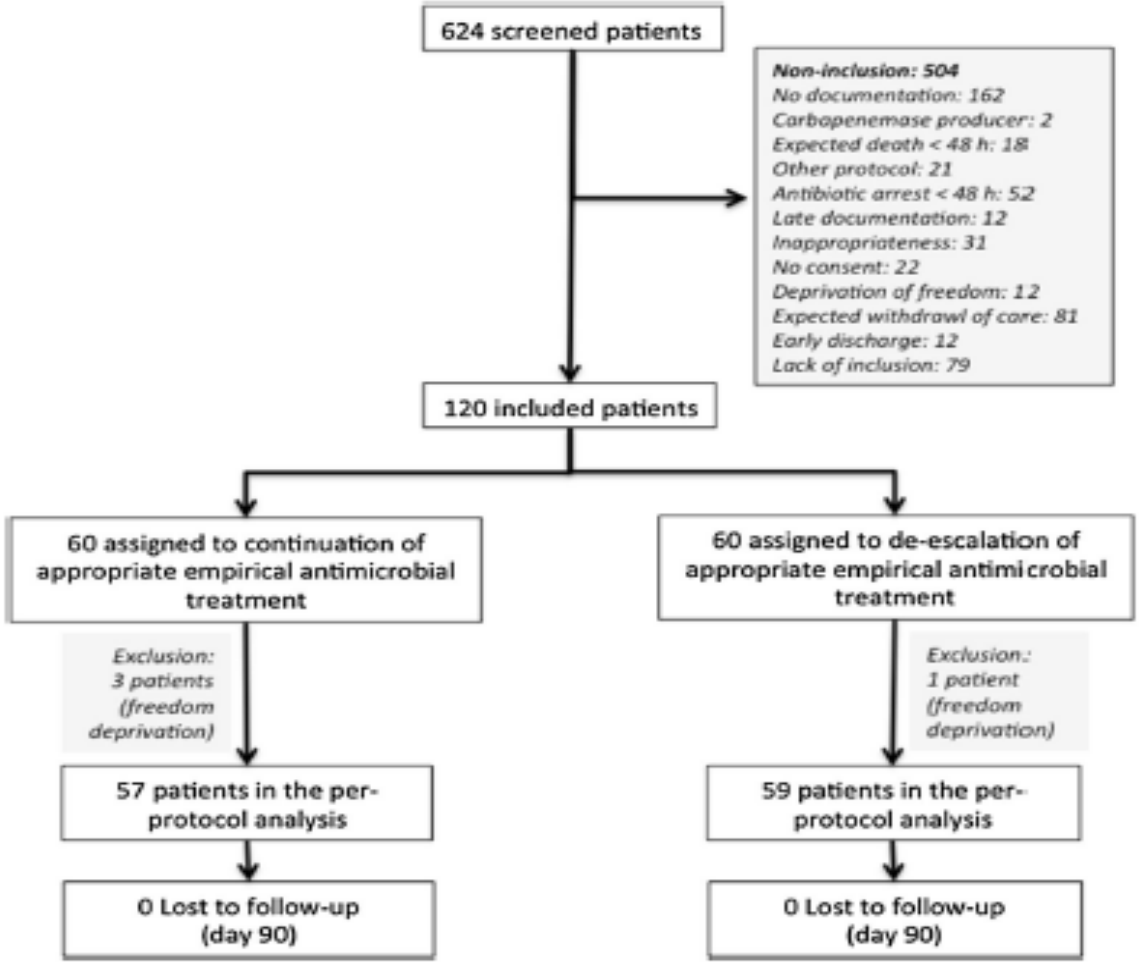
Marc Leone
Carole Bechis
Karine Baumstarck
Jean-Yves Lefrant
Jacques Albanèse
Samir Jaber
Alain Lepape
Jean-Michel Constantin
Laurent Papazian
Nicolas Bruder
Bernard Allaouchiche
Karine Bézulier
François Antonini
Julien Textoris
Claude Martin
For the AZUREA Network Investigators

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

- **Multicentre study (9 ICUs , France)**
- **Randomized (continuous vs. de-escalate)**
- **120 patients**

- **Primary outcome: Length of Stay**
- **Secondary outcomes: 90 d mortality; antibiotic free days; superinfections**

Leone et al., 2014



De-escalation: Leone et al, 2014

Conclusion:

As compared to the continuation of the empirical antimicrobial treatment, a strategy based on de-escalation of antibiotics resulted in ***prolonged duration of ICU stay***. However, **it did not affect the mortality rate.**

Limitations:

- **No consecutive patients (low inclusion rate)**
- **imbalance in baseline characteristics between the two patient groups**

Intensive Care Med (2014) 40:32–40
DOI 10.1007/s00134-013-3077-7

ORIGINAL ARTICLE

J. Garnacho-Montero
A. Gutiérrez-Pizarraya
A. Escoresca-Ortega
Y. Corcia-Palomo
Esperanza Fernández-Delgado
I. Herrera-Melero
C. Ortiz-Leyba
J. A. Márquez-Vácaro

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

- 628 patients
- De-escalation was applied in 219 patients (34.9%)

Garnacho-Montero J, et al., 2014

Table 2 Logistic regression analyses adjusted by the propensity score

	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

Clinical Infectious Diseases

REVIEW ARTICLE

A Systematic Review of the Definitions, Determinants, and Clinical Outcomes of Antimicrobial De-escalation in the Intensive Care Unit

Alexis Tabah,[1,2,a] Menino Osbert Cotta,[1,2,3,a] Jose Garnacho-Montero,[6] Jeroen Schouten,[7] Jason A. Roberts,[1,2,3] Jeffrey Lipman,[1,2,4] Mark Tacey,[5] Jean-François Timsit,[8,9] Marc Leone,[10] Jean Ralph Zahar,[11] and Jan J. De Waele[12]; for the Working Group for Antimicrobial Use in the ICU

- **14 studies**
- **2 randomized clinical trials (unblinded)**
- **12 cohort studies**

- **Limited quality of cohort studies**
- **No uniform definition of de-escalation**
- **the effects of de-escalation on bacterial resistance not adequately investigated**

Factors associated with antimicrobial de-escalation

Tabah A, et al. Clin Infect Dis 2016; 62:1009-1017

Positively associated

- Initially appropriate empiric antimicrobial treatment
- Broad spectrum empiric therapy
- Compliance with national prescribing guidelines
- Positive microbiological cultures
- Lower severity of illness at
  - baseline
  - time of de-escalation

Negatively associated

- Isolation of a MDR pathogen
- Polymicrobial infections
- Intraabdominal infections

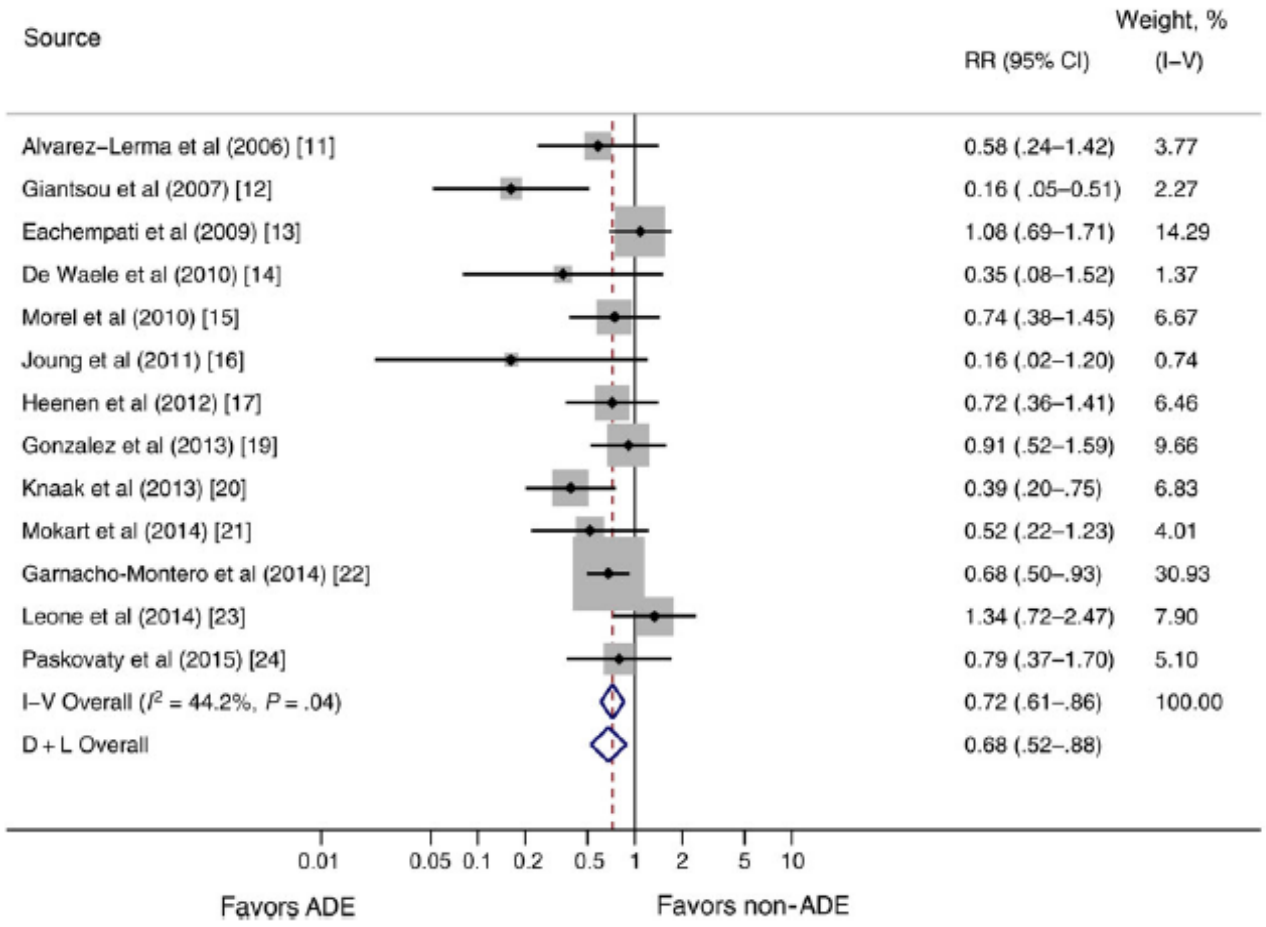
The NEW ENGLAND JOURNAL of MEDICINE

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, 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, for the STOP-IT Trial Investigators†

Tabah A, et al., Clin Infect Dis 2016; 62:1009



De-escalation strategies for life-threatening infections appear to offer a survival advantage over sustained antibiotic treatment

Fewer antibiotics and shorter treatment courses lessen adverse side effects and might even improve survival

Lancet Infect Dis 2016; 216:16:819

1575 patients

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

De-escalation of empirical antimicrobial therapy in ICUs *with highly resistant bacteria:* a prospective observational study

Magiorakos AP, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance.
Clin Microbiol Infect 2011;18:268-81.

Antibiotic-resistant pathogens classification

- multi-drug resistant (MDR) if non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories;
- extensively drug resistant (XDR) if non-susceptible to ≥ 1 agent in all but ≤ 2 categories and as
- pan-drug resistant (PDR) if non-susceptible to all available antimicrobial agents

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΝΤΙΜΙΚΡΟΒΙΑΚΗΣ ΧΗΜΕΙΟΘΕΡΑΠΕΙΑΣ

Η αποκλιμάκωση της αντιμικροβιακής αγωγής σε ασθενείς ΜΕΘ με σήψη ή σηπτική καταπληξία: προοπτική πολυκεντρική μελέτη παρατήρησης

objectives

To describe :

- ✓ **the empirical antibiotic therapy for infections in the ICU**
- ✓ **The rate of antibiotic de-escalation as well as the associated outcome (length of stay on ICU, infection relapse, subsequent infection)**
- ✓ **Factors associated with no de-escalation therapy**
- ✓ **The feasibility of de-escalation in the era of multi-drug resistance**

De-escalation in BSIs by fully susceptible Gram-negatives did not affect final outcome.

Koupetori et al. BMC Infectious Diseases 2014, 14:272
http://www.biomedcentral.com/1471-2334/14/272

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Bloodstream infections and sepsis in Greece: over-time change of epidemiology and impact of de-escalation on final outcome

Marina Koupetori[1], Theodoros Retsas[2], Nikolaos Antonakos[3], Glykeria Vlachogiannis[4], Ioannis Perdios[5], Christos Nathanail[6], Konstantinos Makaritsis[7], Antonios Papadopoulos[3], Dimitrios Sinapidis[2], Evangelos J Giamarellos-Bourboulis[3*], Ioannis Pneumatikos[8], Charalambos Gogos[9], Apostolos Armaganidis[10], Elisabeth Paramythiotou[10] on behalf of the Hellenic Sepsis Study Group

Ελληνική Εταιρεία Αντιμικροβιακης Χημειοθεραπείας

ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΣΤΡΑΤΗΓΙΚΗΣ ΑΠΟΚΛΙΜΑΚΩΣΗΣ ΤΗΣ ΕΜΠΕΙΡΙΚΗΣ ΑΝΤΙΜΙΚΡΟΒΙΑΚΗΣ ΑΓΩΓΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΕΛΛΗΝΙΚΩΝ ΜΕΘ: ΠΡΟΟΠΤΙΚΗ, ΠΟΛΥΚΕΝΤΡΙΚΗ ΜΕΛΕΤΗ

Ρούτση Χ, Πουλάκου Γ, Αρβανίτη Κ. Γκούφα Α, Θεοδώρου Β, Βεμβέτσου Α, Παραμυθιώτου Ε, Κασιανίδης Α, Αμερικάνου Α, Τουρτόγλου Α, , Αναγνωστούλης Κ, Κονογλου Μ, Ποντίκης Κ, Κόκκορης Σ, Κουτσούκου Α, Μανδραγός Κ, Πρεκατές Α, Πνευματικός Ι, Αρμαγανίδης Α, Ζακυνθινός Σ, Γιαμαρέλλου Ε

ΠΑΡΑΓΟΝΤΕΣ ΠΟΥ ΣΥΝΔΕΟΝΤΑΙ ΜΕ ΜΗ-ΕΦΑΡΜΟΓΗ ΑΠΟΚΛΙΜΑΚΩΣΗΣ ΤΗΣ ΕΜΠΕΙΡΙΚΗΣ ΑΝΤΙΜΙΚΡΟΒΙΑΚΗΣ ΑΓΩΓΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕΘ

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Ρούτση Χ, Αρβανίτη Κ, Πουλάκου Γ, Θεοδώρου Β, Τουρτόγλου Α, Γκούφα Α, Βεμβέτσου Α, Καναβού Α, Χάσου Ε, Νικολάου Χ, Ντορλής Κ, Βασιλιάγκου Σ, Κόκκορης Σ, Μιχαλιά Μ, Αντωνιάδου Ε, Μαθάς Χ, Ματάμης Δ, Πνευματικός Ι, Ζακυνθινός Σ, Γιαμαρέλλου Ε

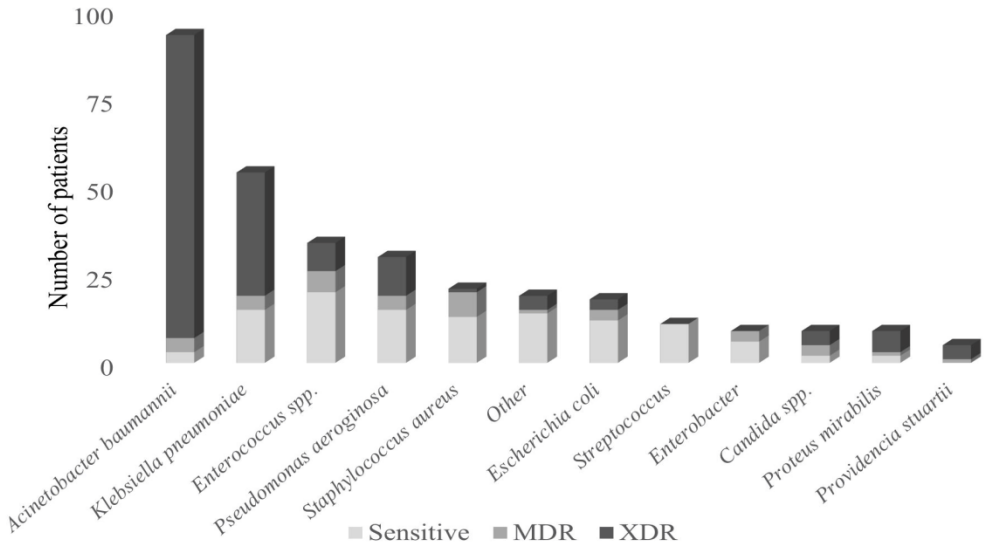
Crit Care , under review

De-escalation of antimicrobial therapy in ICU settings with high prevalence of multidrug resistant bacteria: a multicenter prospective observational cohort study in patients with sepsis or septic shock

Christina Routsi[1,2], Aikaterini Gkoufa[2], Kostoula Arvaniti[3], Stelios Kokkoris[1], Alexandros Tourtoglou[4], Vassiliki Theothorou[5], Anna Vemvetsou[3], Georgios Kassianidis[6], Athena Amerikanou[6], Elisabeth Paramythiotou[7], Efstathia Potamianou[8], Kyriakos Ntorlis[9], Angeliki Kanavou[10], Georgios Nakos[11], Eleftheria Hassou[12], Helen Antoniadou[12], Ilias Karaiskos[2,13], Athanasios Prekates[4], Apostolos Armaganidis[7], Ioannis Pnevmatikos[5], Miltiades Kyprianou[15], Spyros Zakynthinos[1], Garyfallia Poulakou[2,14], Helen Giamarellou[2,13]

- 262 PATIENTS

Supplemental Digital Content-Figure 1.



Characteristics	All patients N=211	De-escalation N= 44 (21%)	No de-escalation N= 175 (83%)	p
Age, years	62 ± 15	65±15	61±14	0.24
Male gender, %	67%	57%	69%	0.14
APACHE II score on admission	20± 8	20±9	20±8	0.62
SOFA score on admission	9 ± 3	9±3	10±3	0.30
Diagnosis				
Medical, n (%)	45%	57%	42%	0.17
Surgical, (%)	45%	34%	50%	
trauma non- surgical, n(%)	9%	9%	8%	
Septic shock, on septic episode (%)	76	66%	79%	0.06
Empiric antibiotic therapy appropriate, n (%)	70%	84%	67%	0.02
Possibility for de-escalation according to antibiogram, n (%)	64%	98%	56%	0.001
ICU-acquired infection, n (%)	43 %	45%	42%	
Infection on ICU admission, n (%)	57%	54%	58%	0.70
Renal dysfunction after septic episode, n (%)	24%	2%	30%	0.001
Noradrenaline, days	8±7	4±5	9±7	0.001
ICU length of stay, days	30± 19	31±23	30±18	0.80
ICU mortality, %	40%	15.4 %	46.4 %	0.001

characteristics	All patients N=116	De-escalation N= 19 (17%)	No de-escalation N= 93 (83%)	p
Age, years	62 ± 16	63±18	62±15	0.9
male/female	73 / 43	33%	58%	0.07
APACHE II on admission	21 ± 9	18±10	21±8	0.15
SOFA on admission	10 ± 3.4	9±3	10±3	0.38
SOFA on septic episode	9.5 ± 3.4	8±3	10±3	0.12
Diagnosis Medical, n (%) Surgical, (%) trauma non- surgical, n(%)	 53 44 17	 52.6% 26% 21%	 45.3% 41% 14%	0.43
Septic shock, n (%)	88 (79 %)	63%	82%	0.31
Empiric antibiotic therapy appropriate, n (%)	79 (69 %)	90%	65%	0.05
Possibility for de-escalation, n (%)	65 (58%)	100%	49%	**0.001**

Multivariate analysis

variables associated with no de-escalation

- a deteriorating clinical course as indicated by an increasing SOFA score

  (OR 14.7, p< 0.001)

- a lack of de-escalation possibility due to recovery of MDR pathogens

  (OR 27.3, p=0.008)

- We have to choose only those patients that had a de-escalation possibility.

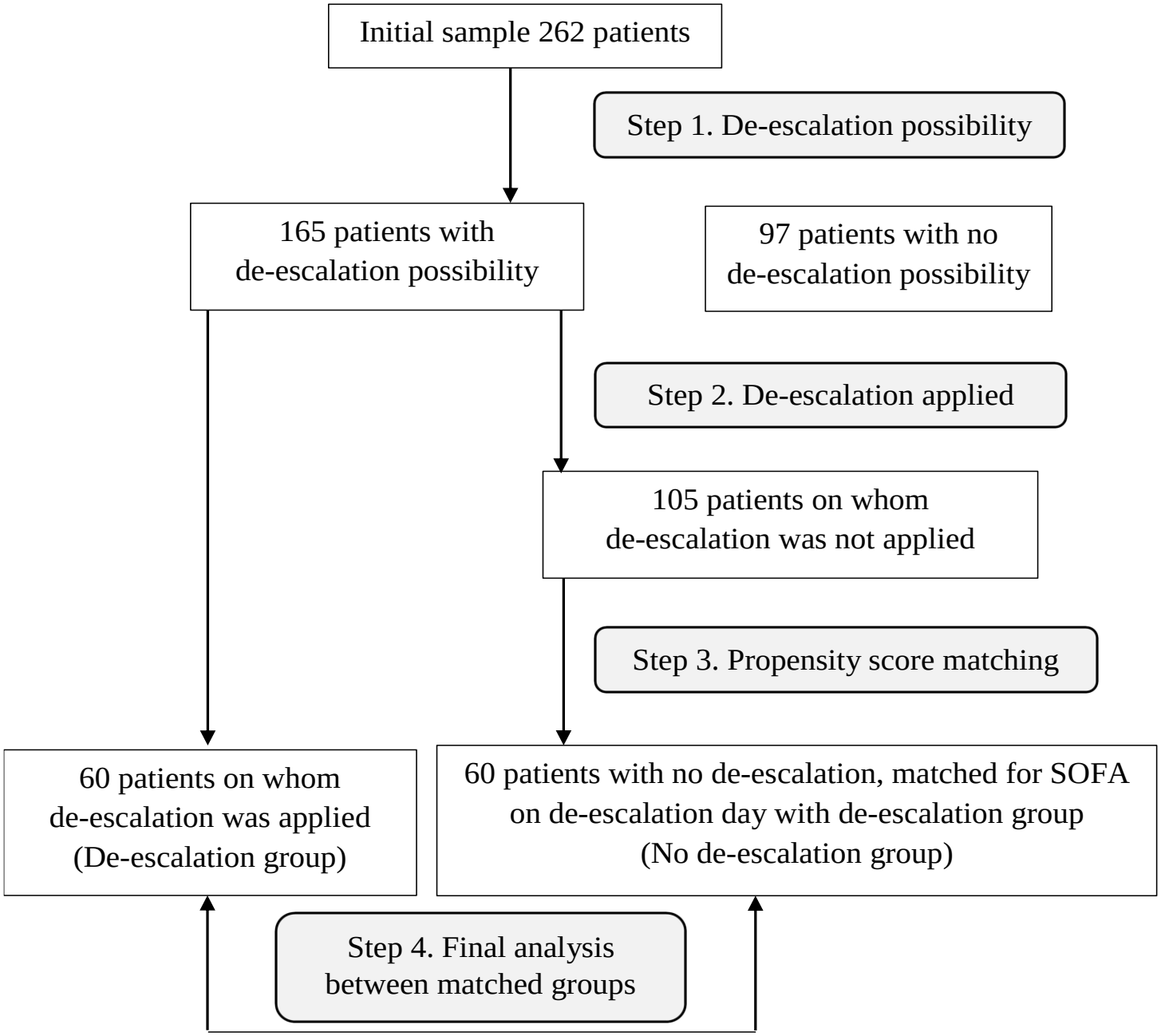
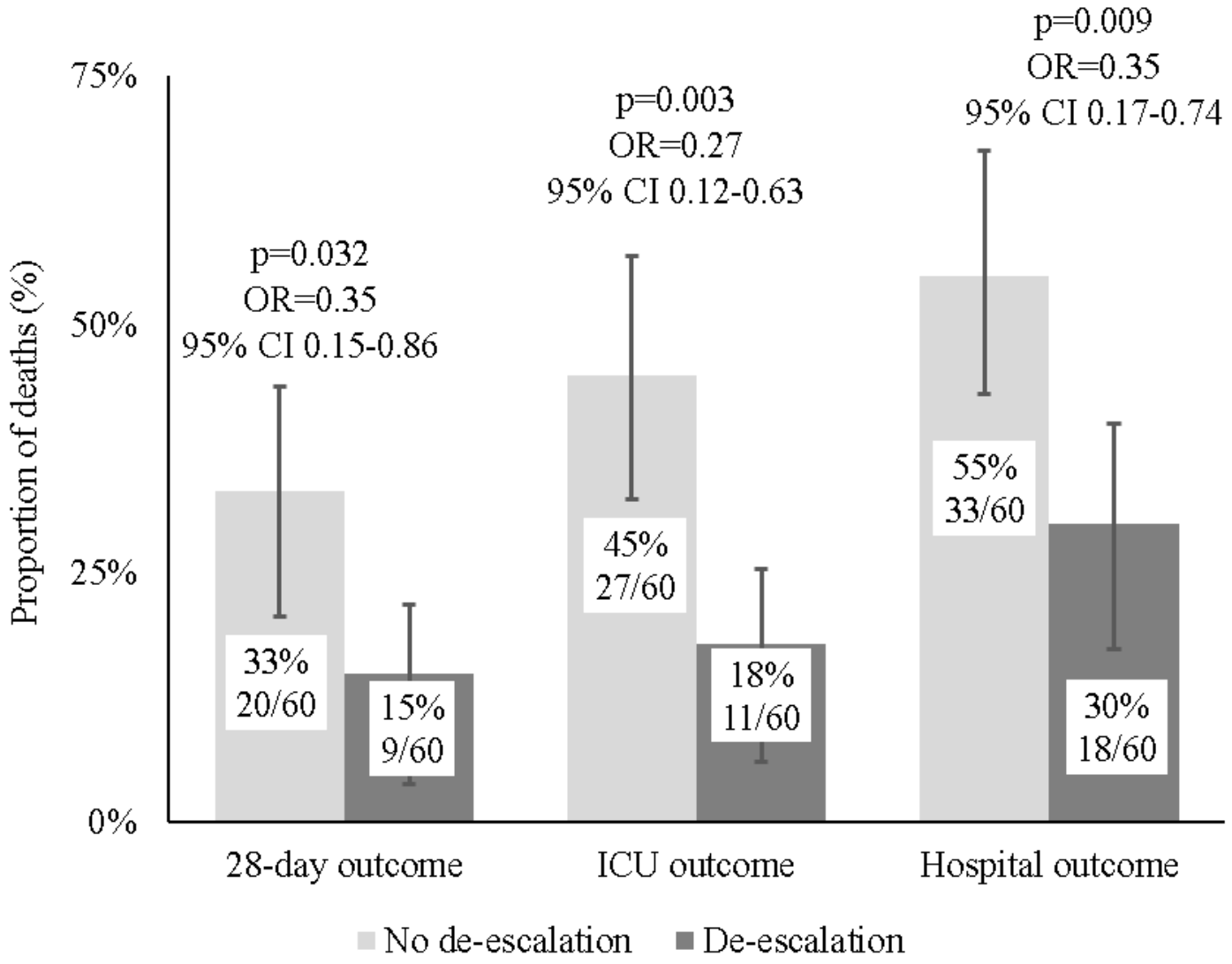
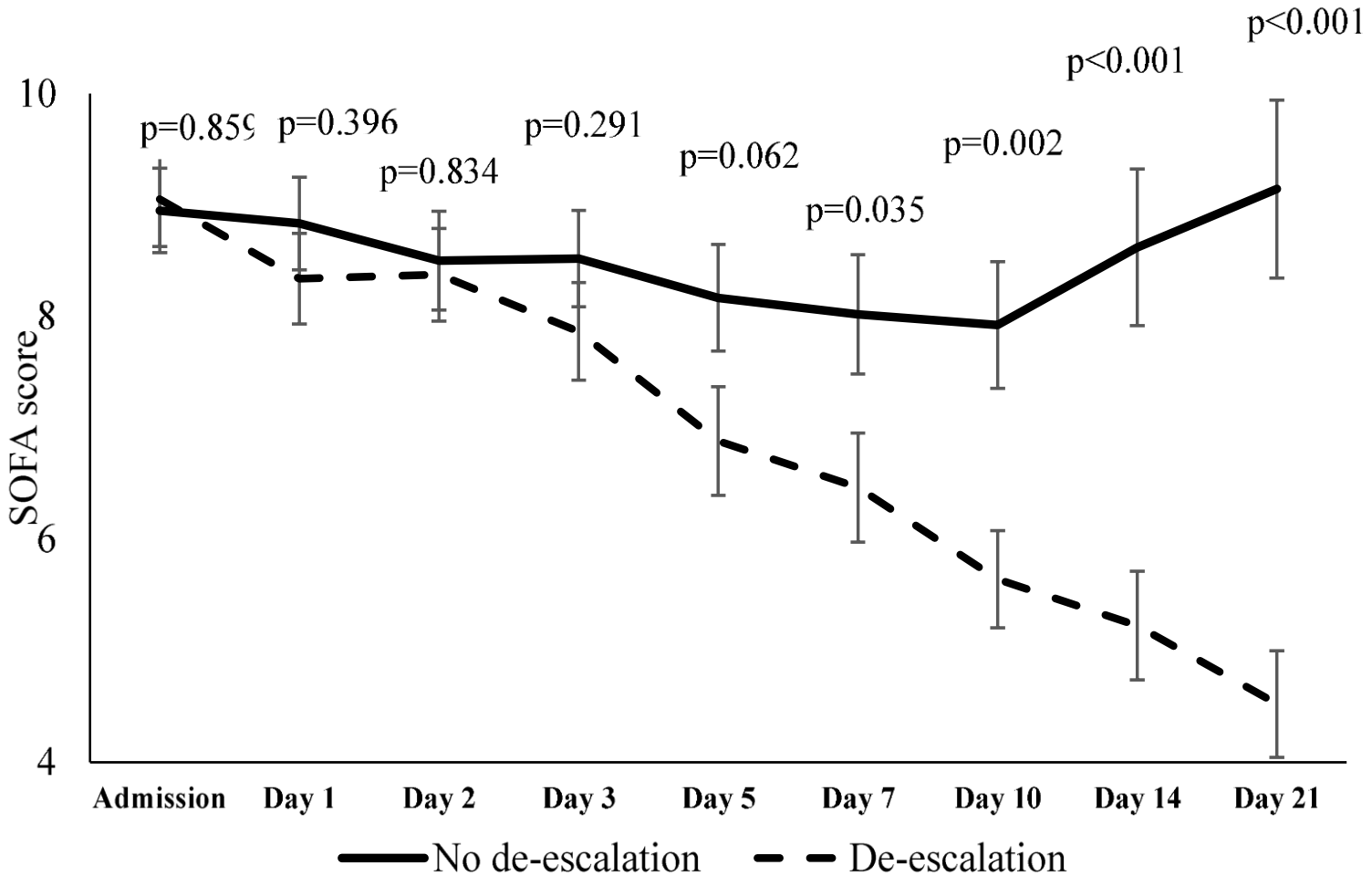

Initial sample 262 patients
Step 1. De-escalation possibility
165 patients with de-escalation possibility
97 patients with no de-escalation possibility
Step 2. De-escalation applied
105 patients on whom de-escalation was not applied
Step 3. Propensity score matching
60 patients on whom de-escalation was applied (De-escalation group)
60 patients with no de-escalation, matched for SOFA on de-escalation day with de-escalation group (No de-escalation group)
Step 4. Final analysis between matched groups

Table 2. Comparison of baseline characteristics between patients with or without de-escalation in the propensity score-matched sample

Parameter	No de-escalation (N=60)	De-escalation (N=60)	p-value
APACHE II score on admission, mean ± SD	19.4±8.5	19.8±8.7	0.810
SOFA score on admission, mean ± SD	9.0±2.9	9.1±3.2	0.859
SOFA score on de-escalation day, mean ± SD	8.1±3.5	7.9±3.5	0.855
Age (years), mean ± SD	60.9±16.0	63.6±16.1	0.371
Gender (Males/Females), n	43/17	37/23	0.333
Appropriate antimicrobial therapy, n	56	50	0.153
Proportion of antibiotic-resistant* pathogens	43.4%	45.8%	0.843

*both multidrug-resistant and extensively-drug-resistant


p=0.009
OR=0.35
95% CI 0.17-0.74
p=0.003
OR=0.27
95% CI 0.12-0.63
p=0.032
OR=0.35
95% CI 0.15-0.86
75%
50%
25%
0%
Proportion of deaths (%)
55%
33/60
45%
27/60
33%
20/60
30%
18/60
18%
11/60
15%
9/60
28-day outcome
ICU outcome
Hospital outcome
No de-escalation
De-escalation


p=0.859
p=0.396
p=0.834
p=0.291
p=0.062
p=0.035
p=0.002
p<0.001
p<0.001
10
8
6
4
SOFA score
Admission
Day 1
Day 2
Day 3
Day 5
Day 7
Day 10
Day 14
Day 21
No de-escalation
De-escalation

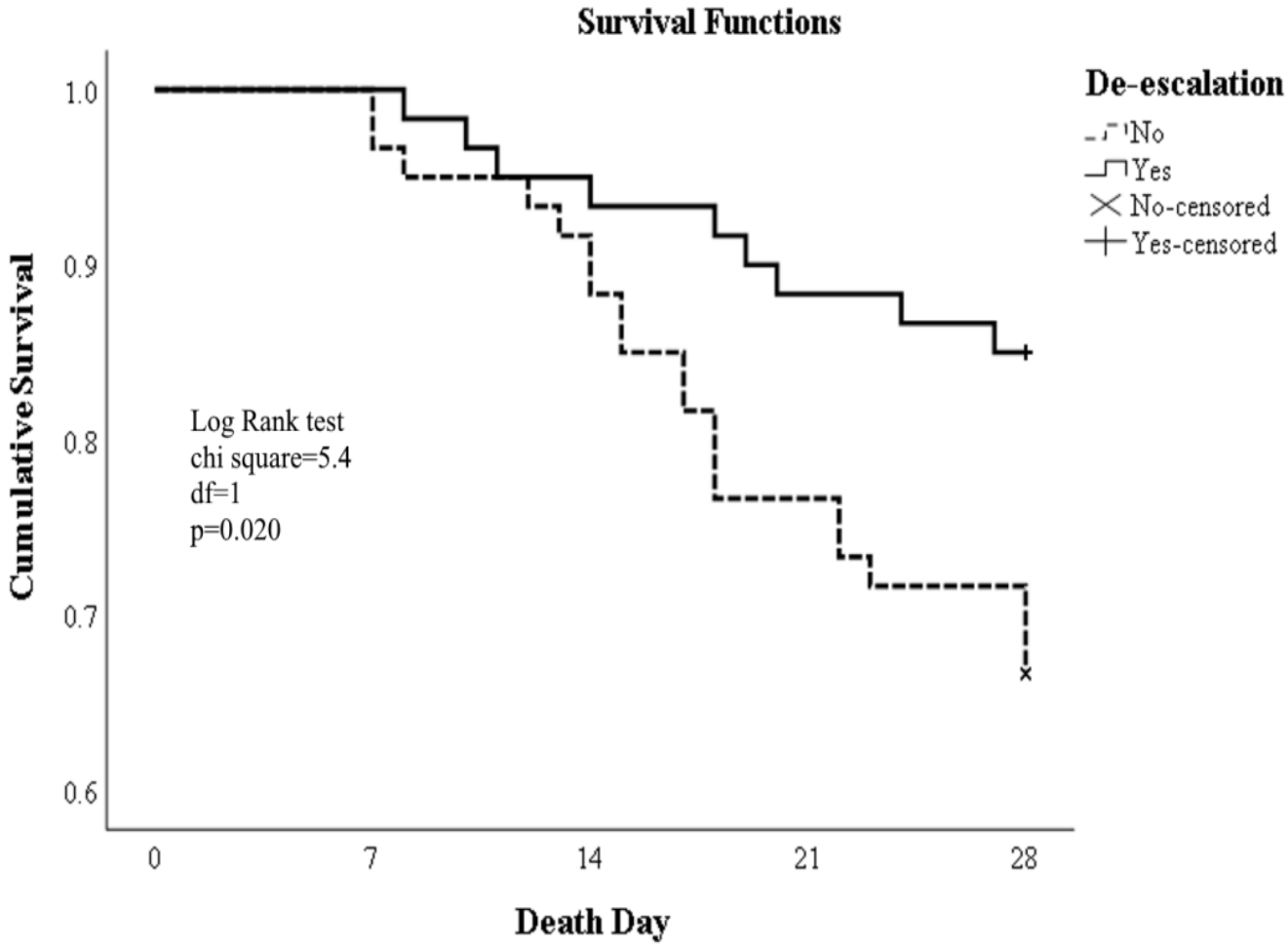

Survival Functions
De-escalation
No
Yes
No-censored
Yes-censored
Cumulative Survival
1.0
0.9
0.8
0.7
0.6
Log Rank test
chi square=5.4
df=1
p=0.020
0
7
14
21
28
Death Day

Table 3. Cox proportional hazards multivariate regression of the 28-day outcome

Predictor	p-value	HR	95% CI
APACHE II score on admission	0.042	1.06	1.00-1.11
SOFA score on admission	0.549	1.04	0.91-1.20
Gender	0.045	2.16	1.02-4.59
Age	0.070	1.03	0.10-1.06
De-escalation	0.007	0.33	0.15-0.74

Mervyn Singer: restricted and abbreviated use of antimicrobials for infection

Marini et al. Critical Care 2019, 23(Suppl 1):197

Antibiotics are effective *not only against the offending organism* but also the *host tissues*, as well. Apart from their widely acknowledged potential for side effects, renal and hepatic dysfunction, *the ability of certain agents to impair mitochondrial function* (e.g., linezolid) and to *adversely alter both immunity and the microbiome* is extensively documented.

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The Good and the Bad of Antibiotics

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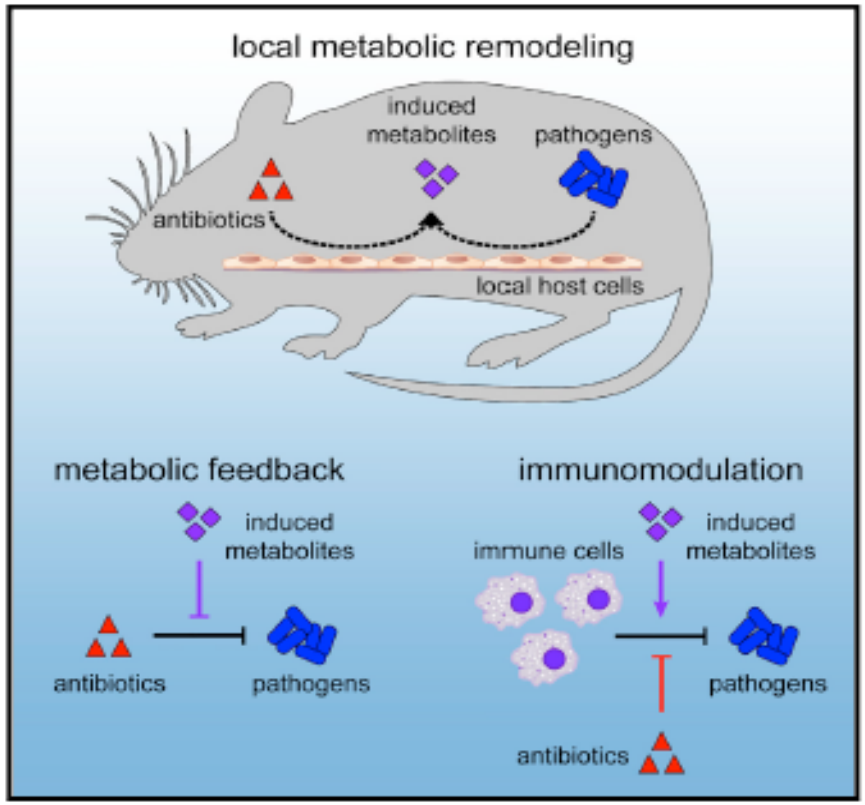
Abstract

Bactericidal antibiotics with diverse mechanisms of action induce generation of mitochondrial reactive oxygen species in mammalian cells (Kalghatgi *et al*., this issue).

Cell Host & Microbe

Antibiotic-Induced Changes to the Host Metabolic Environment Inhibit Drug Efficacy and Alter Immune Function

Graphical Abstract



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In Brief

Antibiotic susceptibility is sensitive to metabolites, but how this affects *in vivo* treatment efficacy remains unexplored. Yang, Bhargava et al. characterize antibiotic-induced changes to the metabolic environment during infection and find that direct actions of antibiotics on host cells induce metabolites that impair drug efficacy and enhance phagocytic activity.

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