

**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

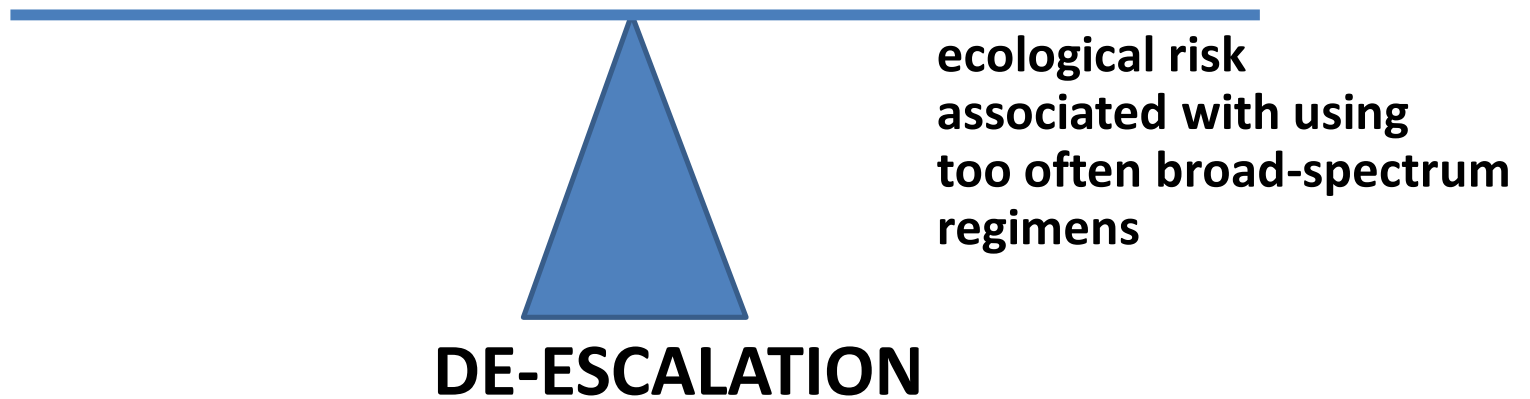
An antimicrobial policy consisting of the initial use of wide-spectrum antimicrobials followed by a reassessment of treatment when culture results are available

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).



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.

Antimicrobial De-escalation: What's in a Name?

Marin H. Kollef¹ and Scott T. Micek²

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

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

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

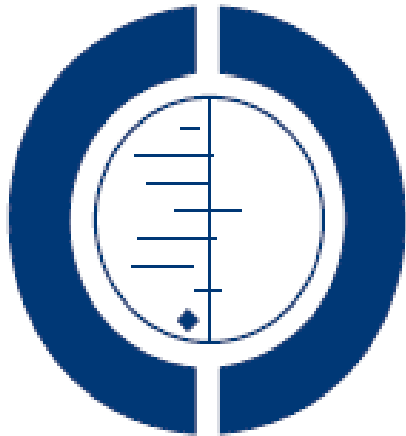
De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial

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

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

Gomes Silva BN, Andriolo RB, Atallah ÁN, Salomão R



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COLLABORATION®

Authors conclusions

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

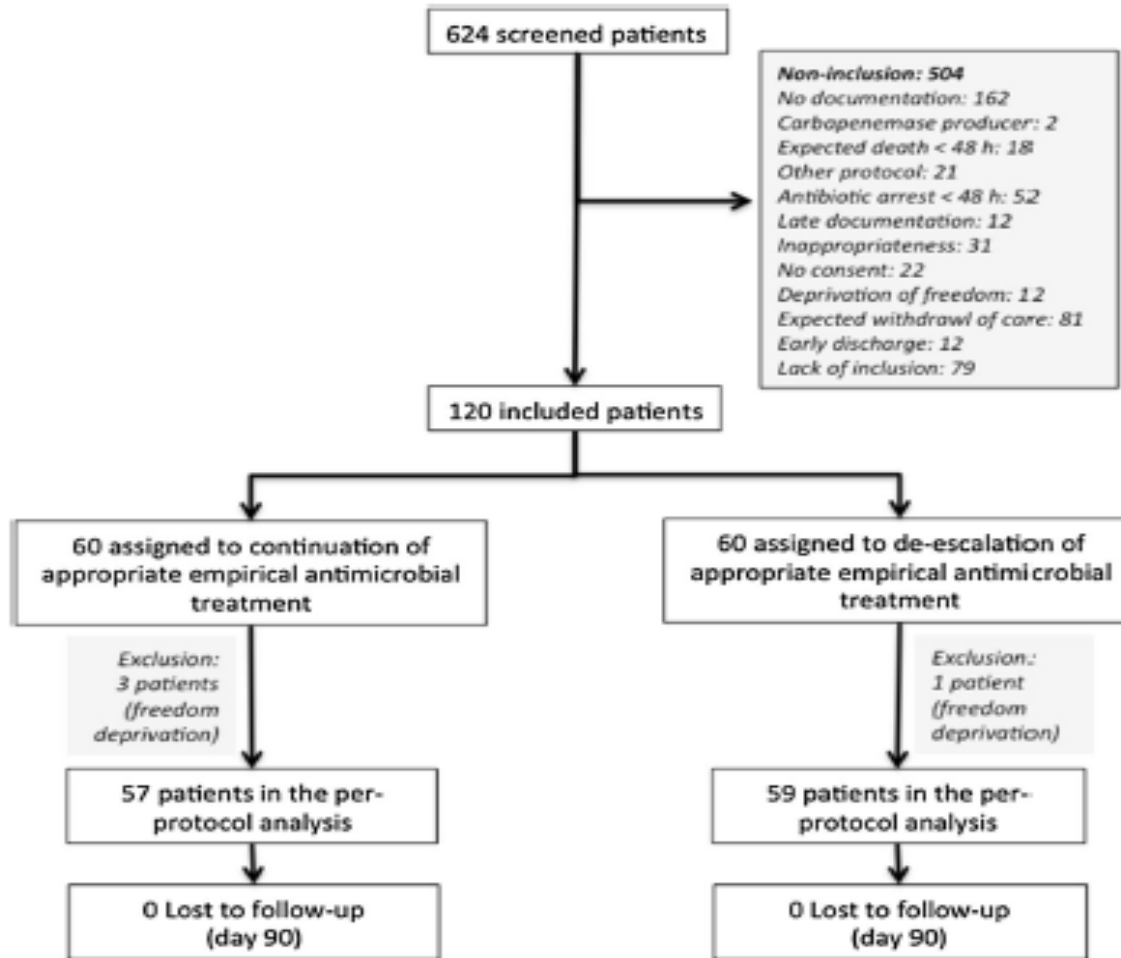
Marc Leone
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François Antonini
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For the AZUREA Network Investigators

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

J. Garnacho-Montero
A. Gutiérrez-Pizarra
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Y. Corcia-Palomo
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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 (<i>n</i> = 628)		Cohort with adequate empirical antimicrobial therapy (<i>n</i> = 403)	
	Adjusted by PS OR (95 % CI)	<i>p</i>	Adjusted by PS OR (95 % CI)	<i>p</i>
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

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

Alexis Tabah,^{1,2*} Menino Osbert Cotta,^{1,2,3*} Jose Garnacho-Montero,⁶ Jeroen Schouten,⁷ Jason A. Roberts,^{1,2,3} Jeffrey Lipman,^{1,2,4} Mark Tacey,⁵ Jean-François Timsit,^{4,5} Marc Leone,¹⁰ Jean Ralph Zahar,¹¹ and Jan J. De Waele¹²; 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

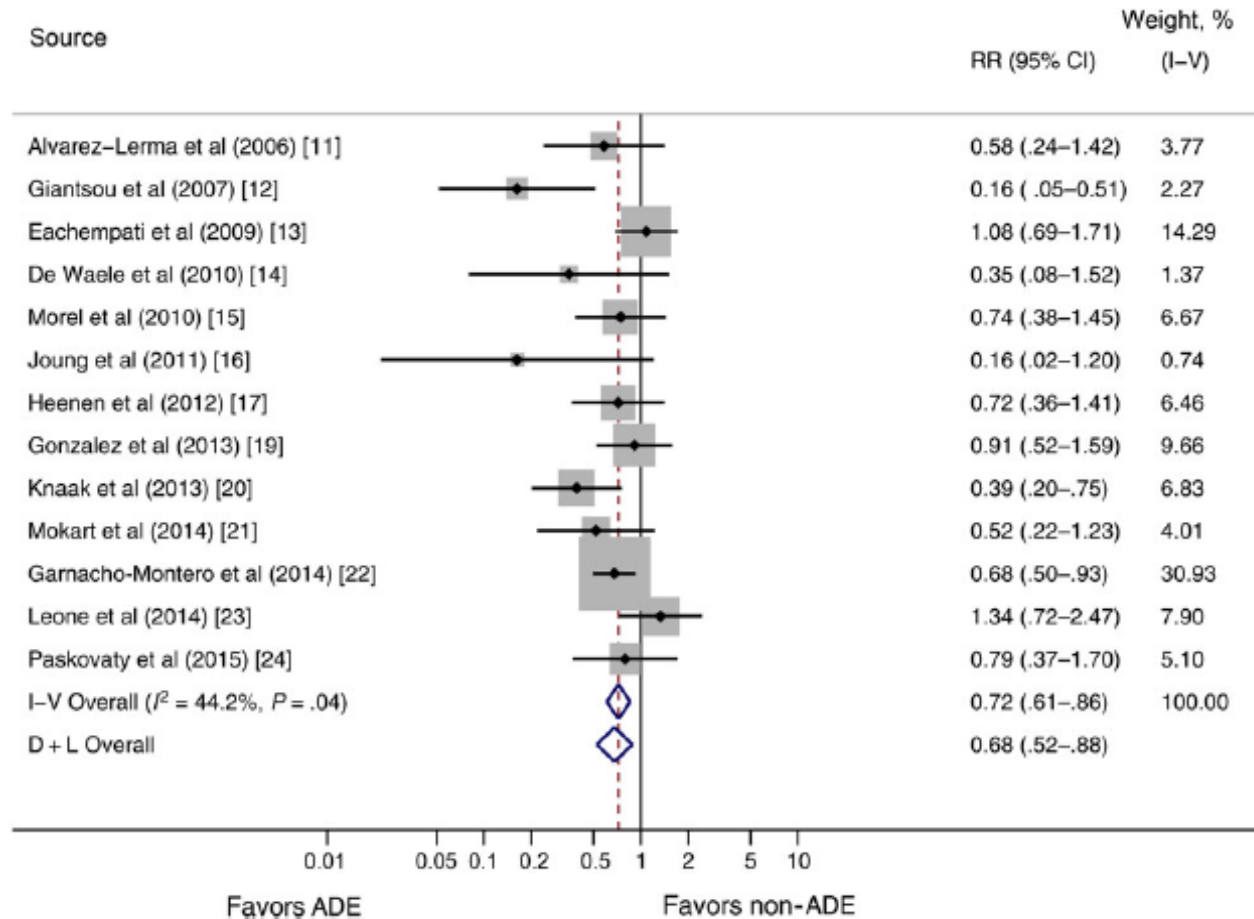
- Isolation of a MDR pathogen
- Polymicrobial infections
- Intraabdominal infections

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>



RESEARCH ARTICLE

Open Access

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

Marina Koupetori¹, Theodoros Retsas², Nikolaos Antonakos³, Glykeria Vlachogiannis⁴, Ioannis Perdios⁵, Christos Nathanail⁶, Konstantinos Makaritsis⁷, Antonios Papadopoulos³, Dimitrios Sinapidis², Evangelos J Giamarellos-Bourboulis^{3*}, Ioannis Pneumatikos⁸, Charalambos Gogos⁹, Apostolos Armaganidis¹⁰, Elisabeth Paramythiotou¹⁰ on behalf of the Hellenic Sepsis Study Group

Ελληνική Εταιρεία Αντιμικροβιακής 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

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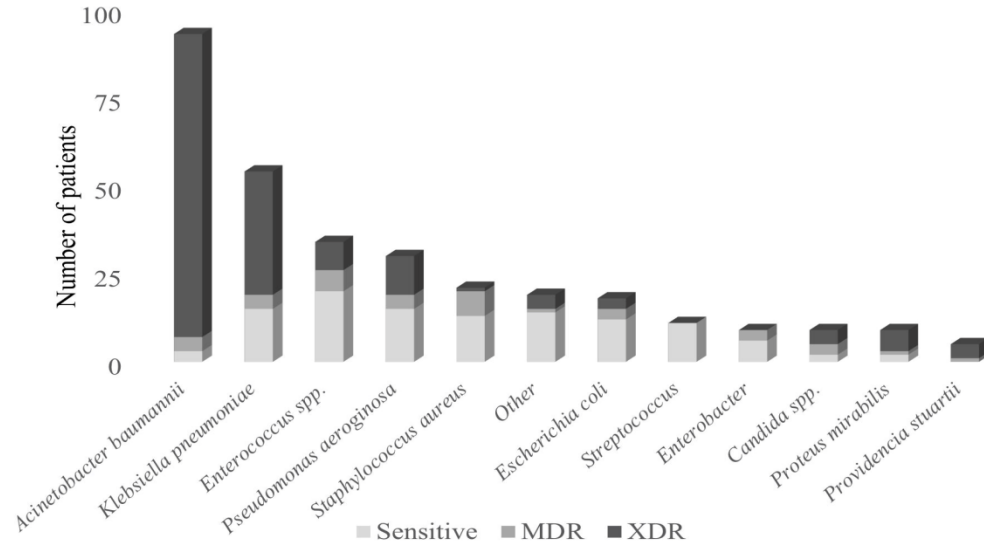
1 **De-escalation of antimicrobial therapy in ICU settings with high prevalence of**
2 **multidrug resistant bacteria: a multicenter prospective observational cohort study in**
3 **patients with sepsis or septic shock**

4
5 Christina Routsis^{1,2}, Aikaterini Gkoufa², Kostoula Arvaniti³, Stelios Kokkoris¹, Alexandros
6 Tourtoglou⁴, Vassiliki Theothorou⁵, Anna Vemvetsou³, Georgios Kassianidis⁶, Athena
7 Amerikanou⁶, Elisabeth Paramythiotou⁷, Efstathia Potamianou⁸, Kyriakos Ntorlis⁹, Angeliki
8 Kanavou¹⁰, Georgios Nakos¹¹, Eleftheria Hassou¹², Helen Antoniadou¹², Ilias Karaiskos^{2,13},
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11

- 262 PATIENTS

Supplemental Digital Content-Figure 1.



Characteristics	All patients	De-escalation	No de-escalation	p
	N=211	N= 44 (21%)	N= 175 (83%)	
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 (%)	53	52.6%	45.3%	0.43
Surgical, (%)	44	26%	41%	
trauma non- surgical, n(%)	17	21%	14%	
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.**

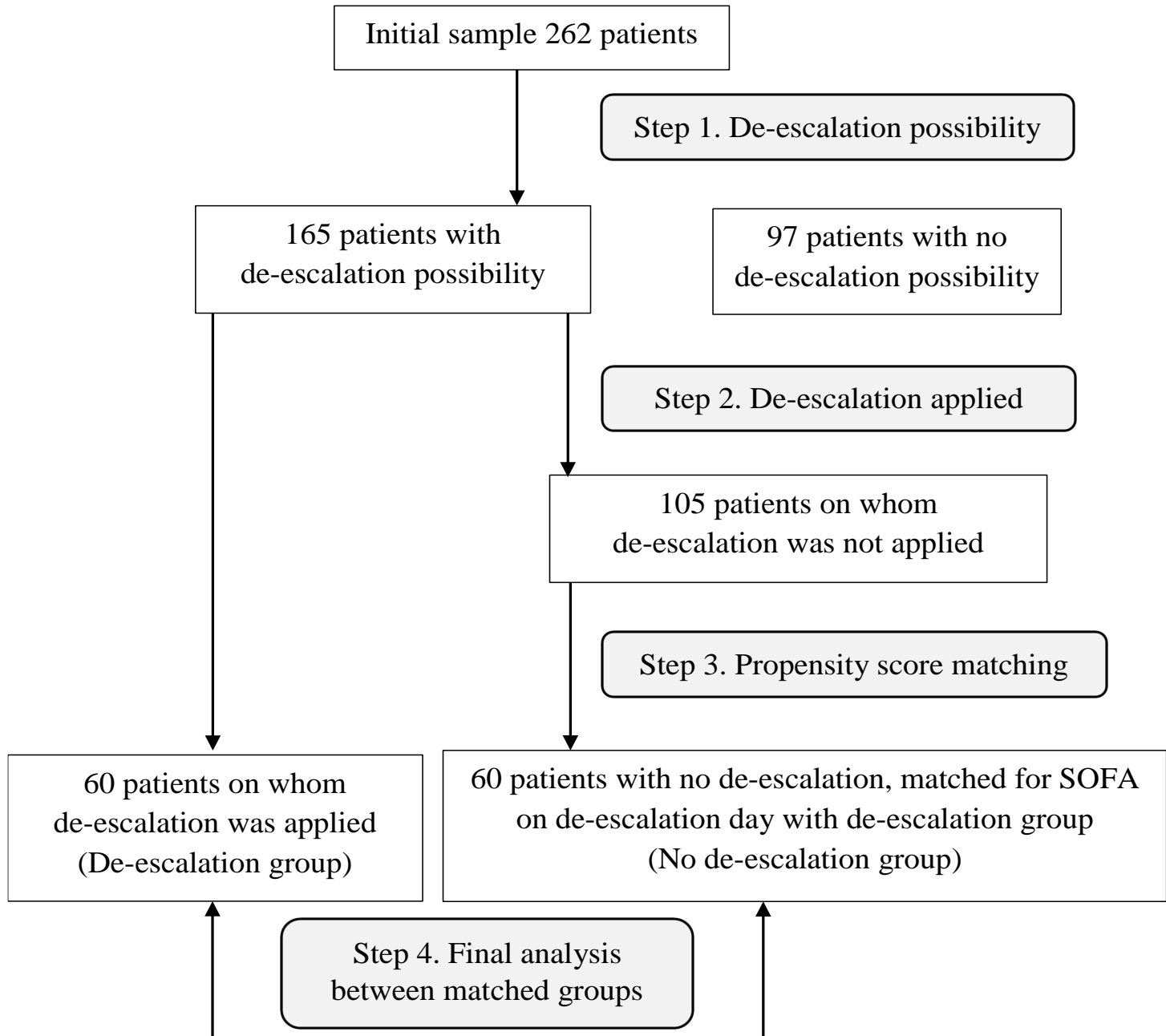
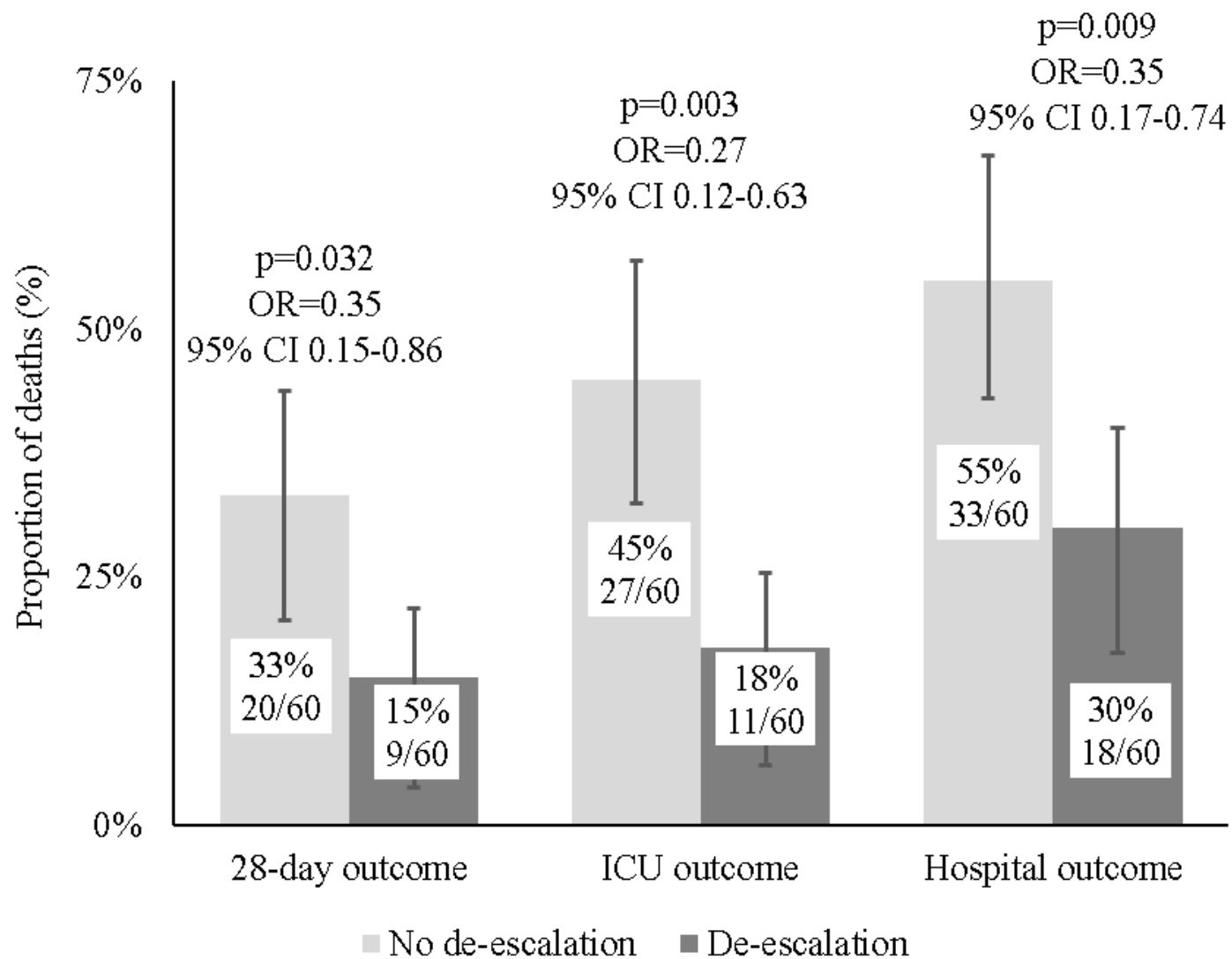
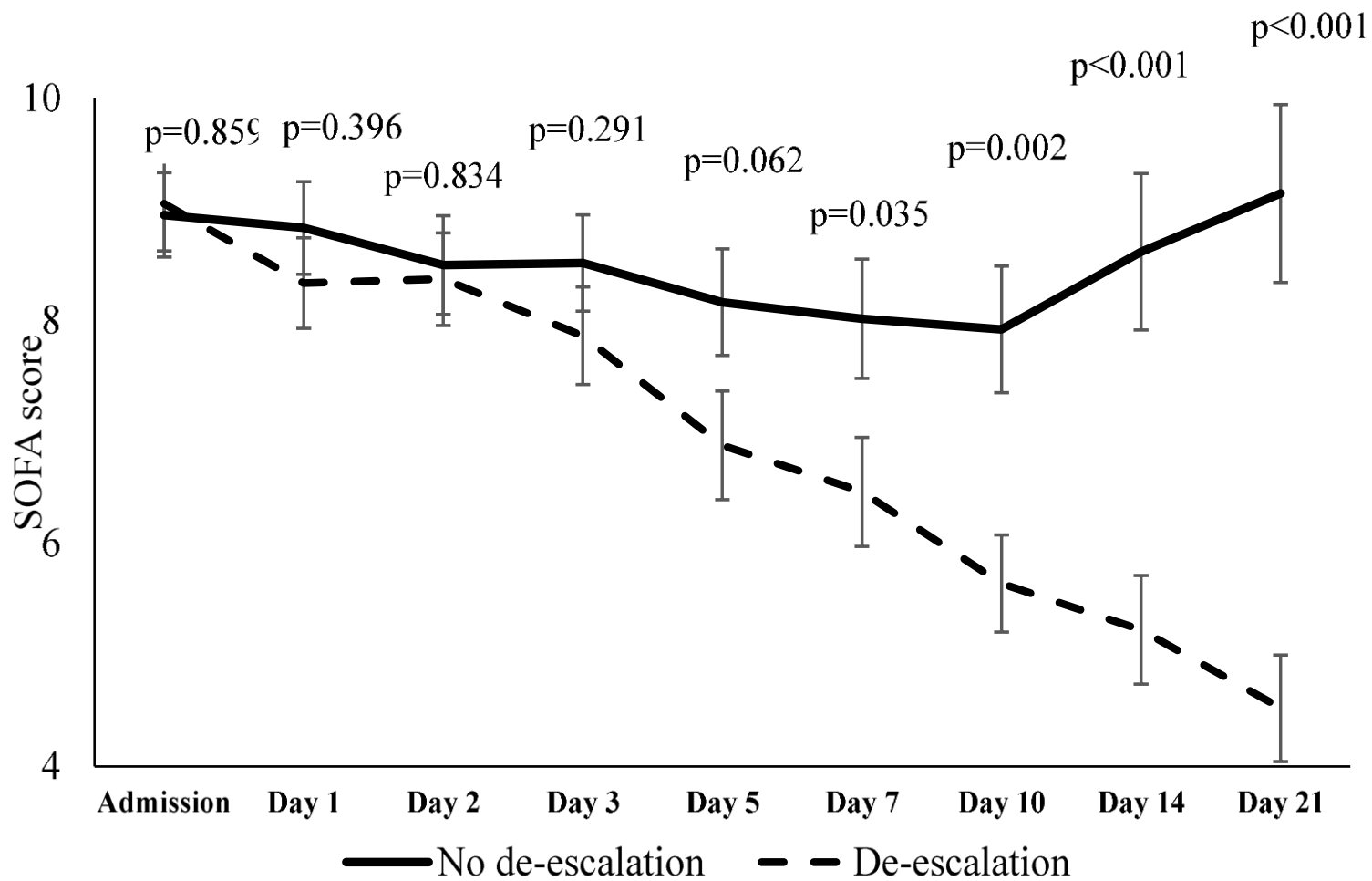


Table 2. Comparison of baseline characteristics between patients with or without de-escalation in the propensity score-matched sample

Parameter	No de-escalation (N=60)	De-escalation (N=60)	p-value
APACHE II score on admission, mean \pm SD	19.4 \pm 8.5	19.8 \pm 8.7	0.810
SOFA score on admission, mean \pm SD	9.0 \pm 2.9	9.1 \pm 3.2	0.859
SOFA score on de-escalation day, mean \pm SD	8.1 \pm 3.5	7.9 \pm 3.5	0.855
Age (years), mean \pm SD	60.9 \pm 16.0	63.6 \pm 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





Survival Functions

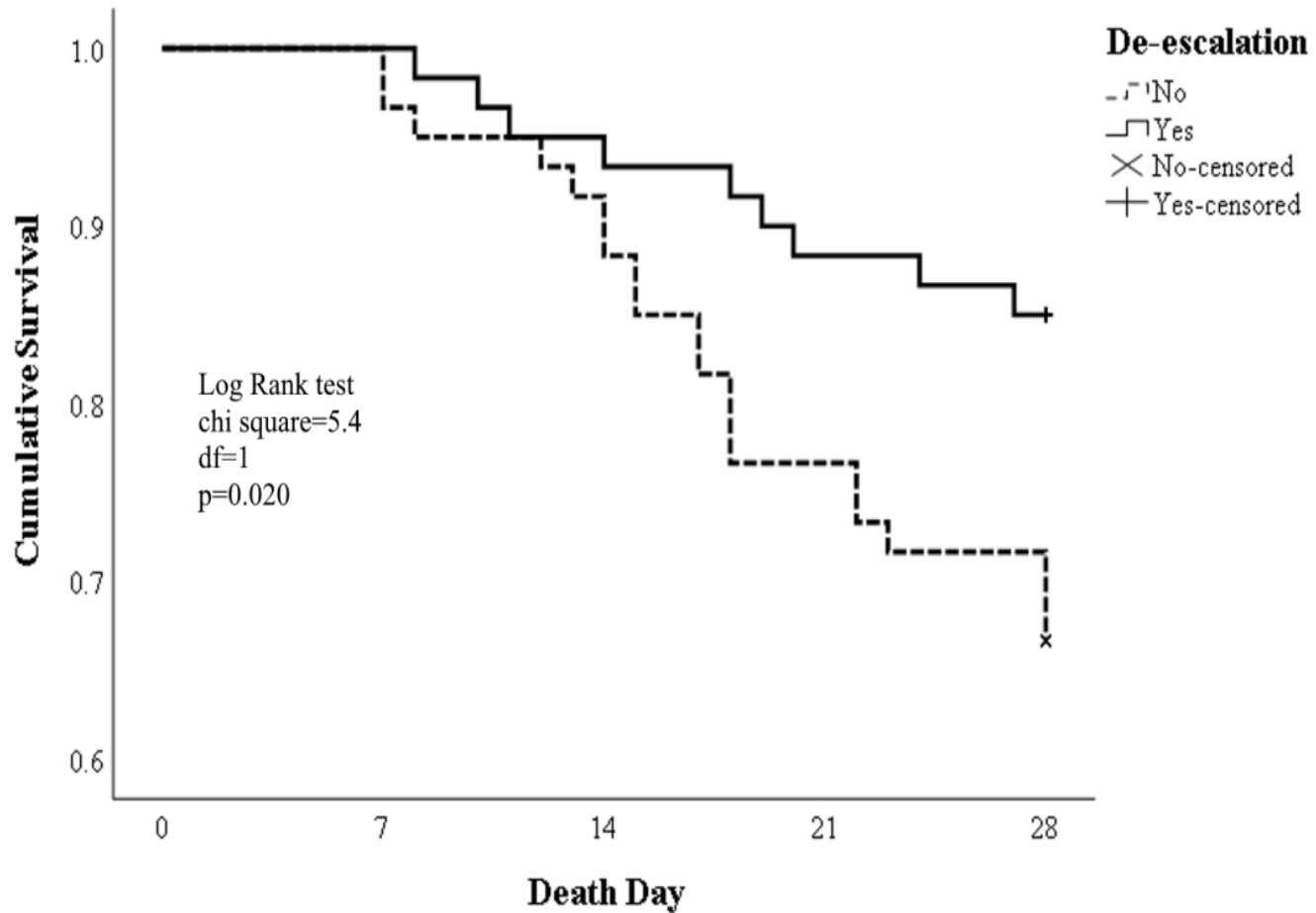


Table 3. Cox proportional hazards multivariate regression of the 28-day outcome

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.



NIH Public Access

Author Manuscript

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The Good and the Bad of Antibiotics

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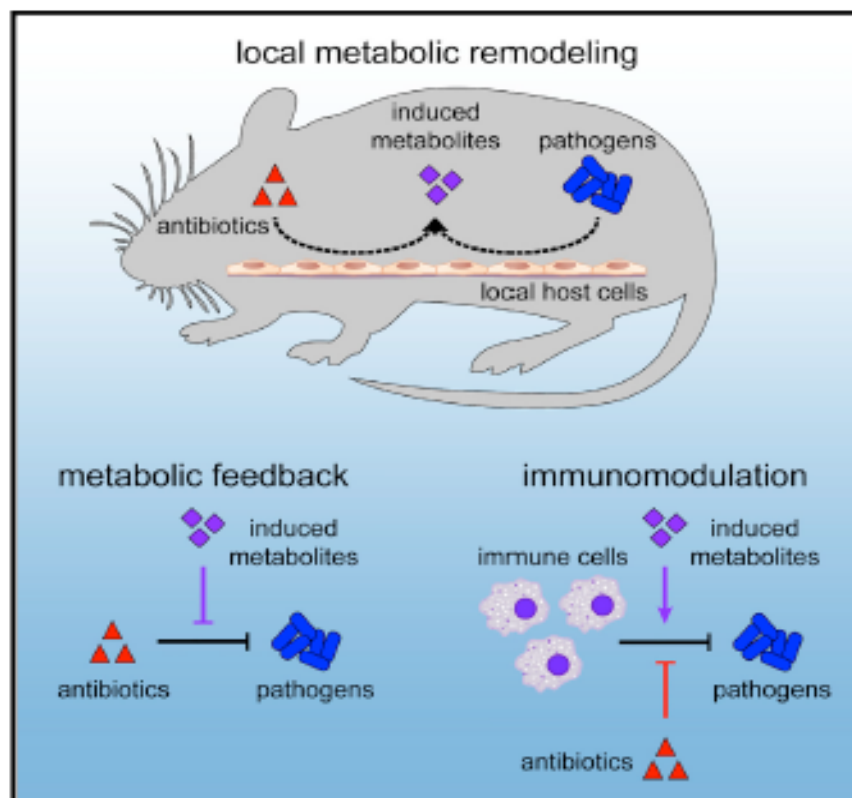
Abstract

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



Authors

Jason H. Yang, Prerna Bhargava,
Douglas McCloskey, Ning Mao,
Bernhard O. Palsson, James J. Collins

Correspondence

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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.

List of co-investigators

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