# *Sepsis and Septic Shock*

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# *Sepsis and Septic Shock*
## *(point of view of infectious diseases specialist)*

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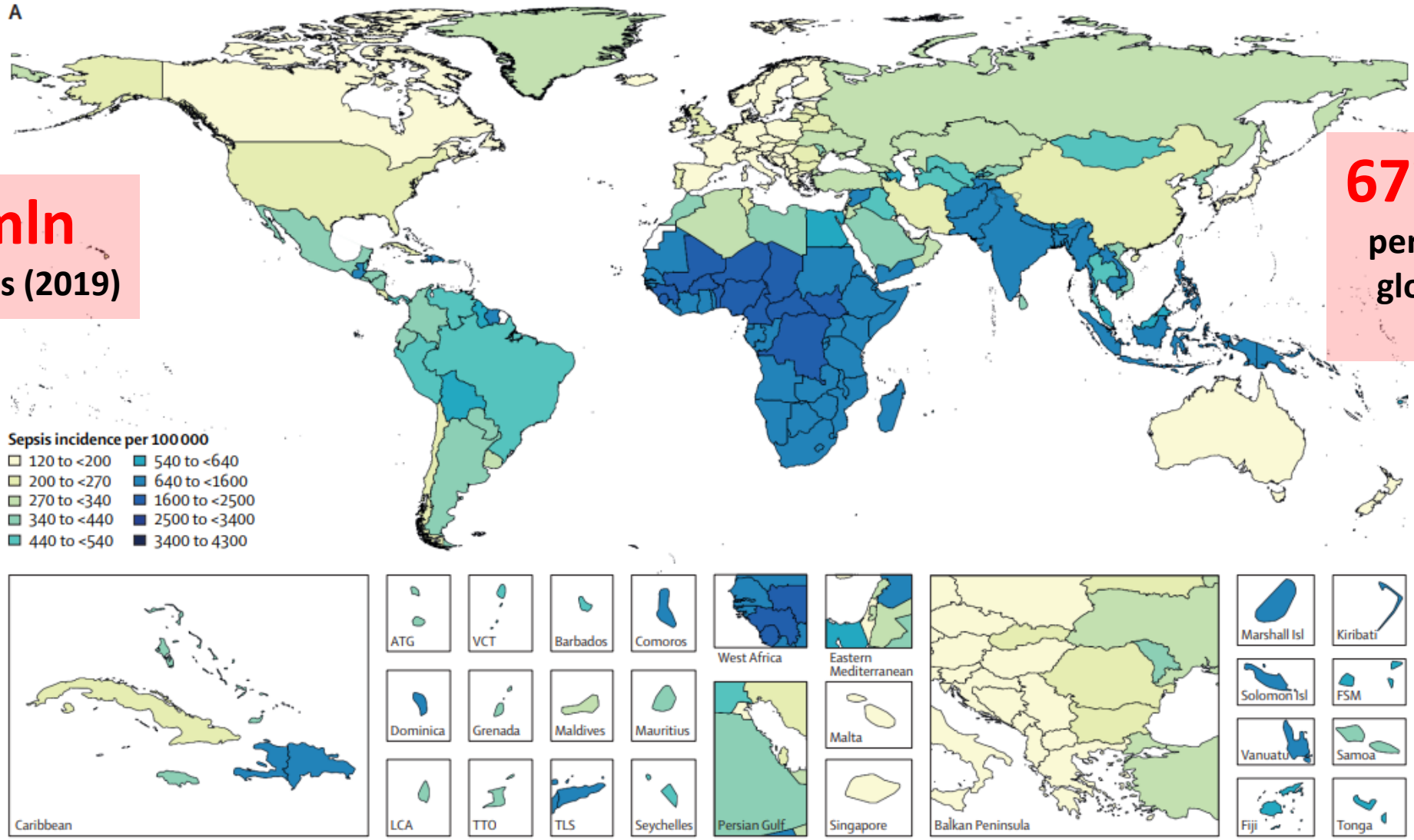
# Global sepsis incidence

**48.9 mln**
**cases of sepsis (2019)**



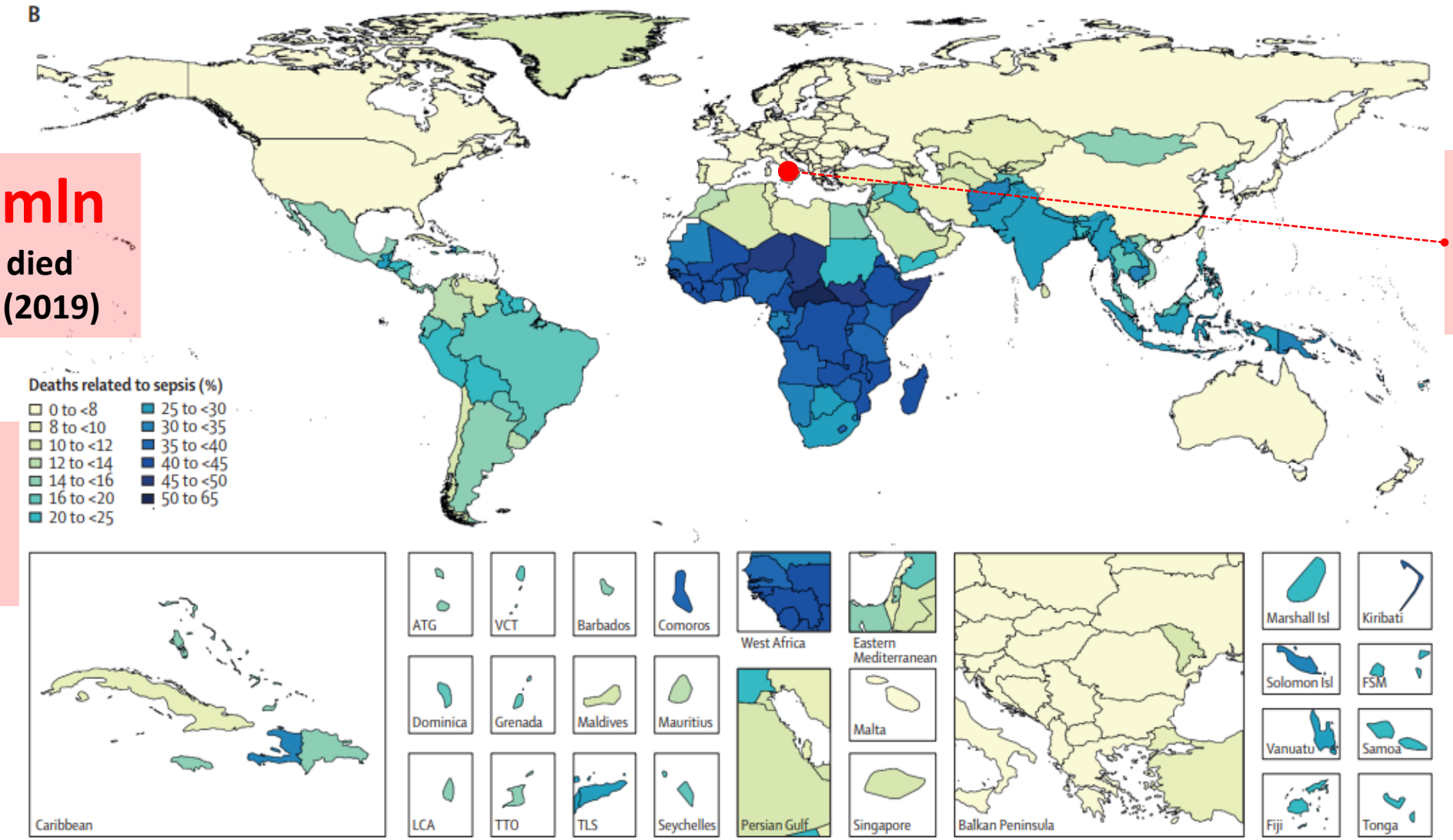

**677.5 cases**
**per 100K was the global incidence (2019)**

*https://vizhub.healthdata.org/microbe/*
*Rudd KE, Lancet. 2020 Jan 18;395(10219):200-211.*

# Global sepsis mortality

**13.6 mln**
**people died globally (2019)**

**19.7%**
**of all global deaths (2019)**




**72.3K**
**people died in Italy (2019)**

*https://vizhub.healthdata.org/microbe/*
*Rudd KE, Lancet. 2020 Jan 18;395(10219):200-211.*

# Road map

- **Time-to-antibiotics and clinical outcomes**
- **Initial treatment for MRSA infections**
- **Role of piperacillin/tazobactam in CRO-R *E. coli* infections**
- **Carbapenemase-producing *Enterobacterales* BSI in rectal carriers**
- **Impact on clinical outcome of follow-up blood cultures**
- **Early oral switch in bloodstream infections**

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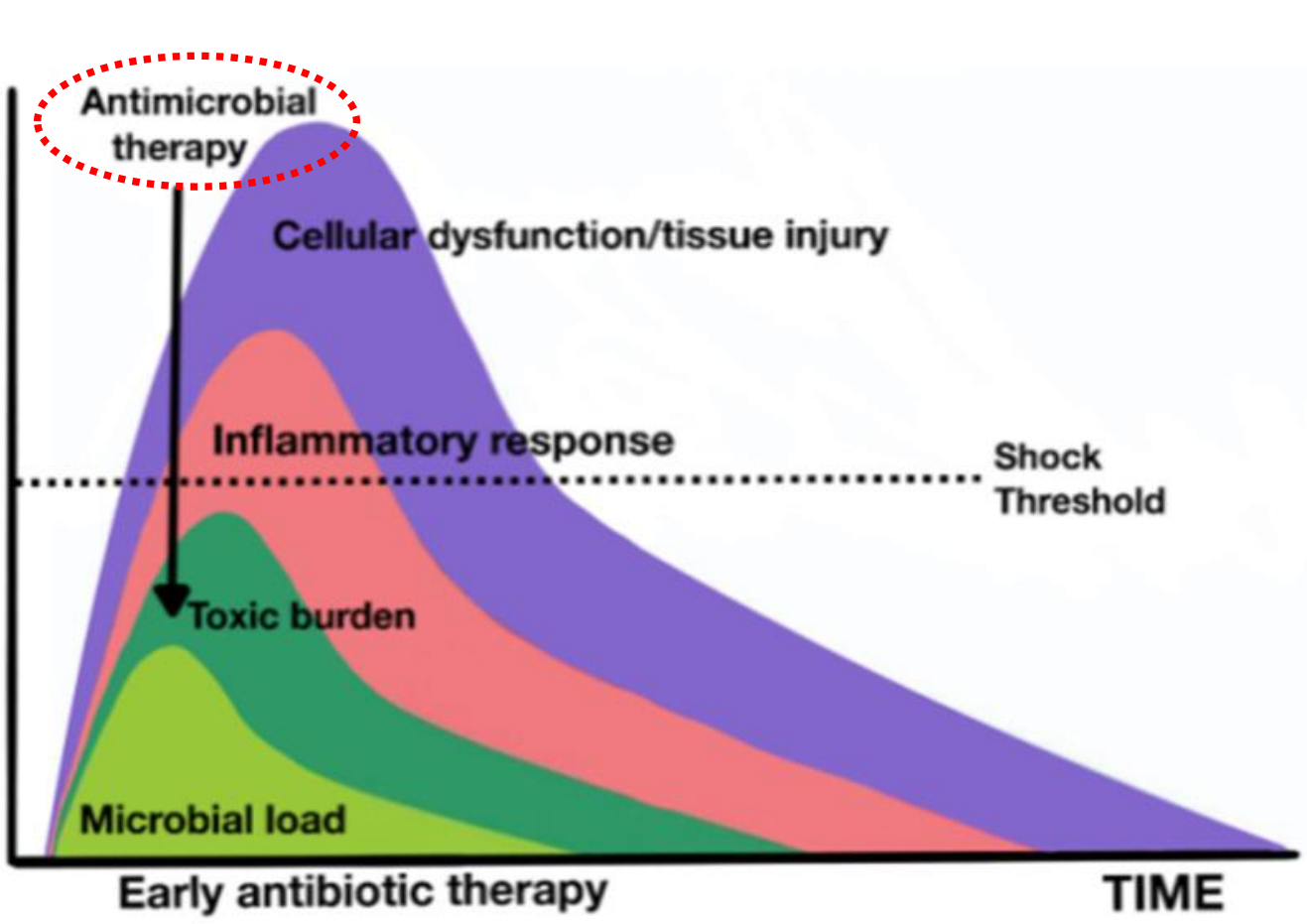
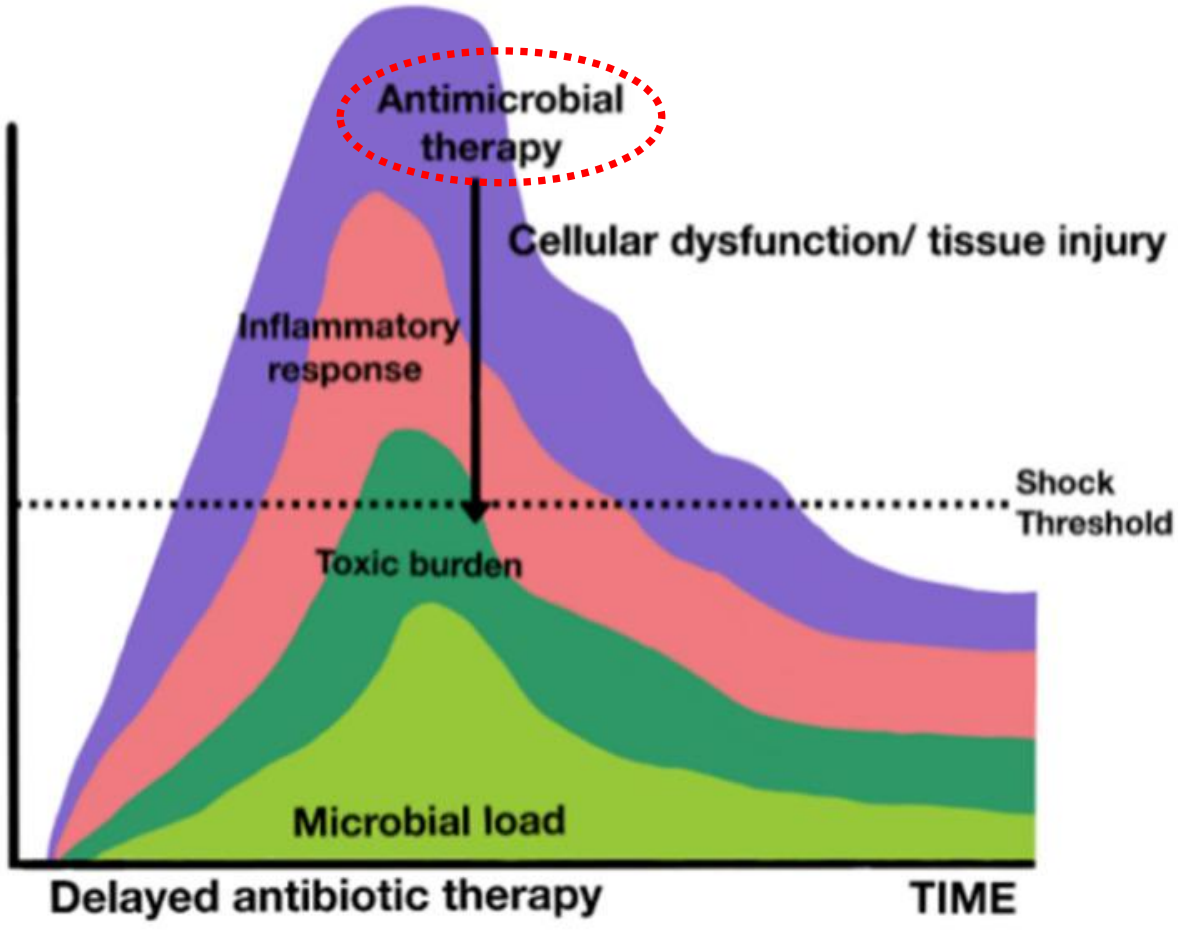
# Microbiological model of sepsis: role of antimicrobial therapy




*Ramasco F, J Pers Med. 2024 Jan 18;14(1):106*

# Hour-1 Bundle - Initial Resuscitation for Sepsis and Septic Shock Surviving Sepsis Campaign 2021

| | |
|---|---|
| **Measure lactate level** | remeasure lactate if initial lactate elevated (>2 mmol/L) |
| **Obtain blood cultures** | obtain blood cultures before administering antibiotics |
| **Antibiotic therapy** | administer broad-spectrum antibiotics |
| **Fluid resuscitation** | begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L |
| **Vasopressor therapy** | vasopressors if hypotensive after fluid resuscitation to maintain a mean arterial pressure ≥65 mm Hg |

*Evans L, Intensive Care Med. 2021 Nov;47(11):1181-1247.*

# Time-to-antibiotics and clinical outcomes in patients with sepsis and septic shock

This study analyzed prospectively collected data from an ongoing multicenter cohort of patients with sepsis identified in the emergency department. Adjusted ORs were compared for in-hospital mortality of patients who had received antibiotics within 1 h to that of those who did not.

**Overall, 3035 patients were included in the analysis. Among them, 601 (19.8%) presented with septic shock, and 774 (25.5%) died.**

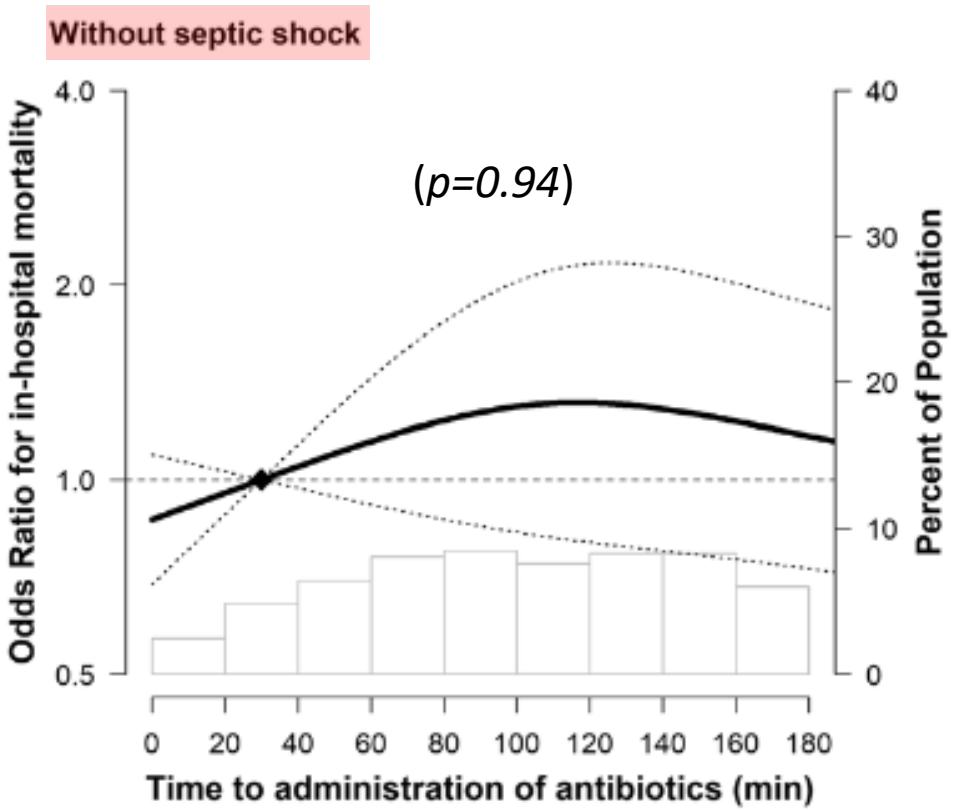
**Risk-adjusted ORs for in-hospital mortality associated with administration of broad-spectrum antibiotics in 1 h**

| In-hospital mortality | Administration of broad-spectrum antibiotics in 1 h | | *p*-value |
|---|---|---|---|
| | No | Yes OR (95% CI)* | |
| *All participants (n = 3035)* | | | |
| Overall | *Reference* | **0.78 (0.61–0.99)** | **0.046** |
| Without septic shock | *Reference* | 0.85 (0.64–1.15) | 0.300 |
| With septic shock | *Reference* | **0.66 (0.44–0.99)** | **0.049** |
| *Landmark analysis (N = 3018)* | | | |
| Overall | *Reference* | **0.78 (0.61–0.99)** | **0.046** |
| Without septic shock | *Reference* | 0.86 (0.64–1.15) | 0.310 |
| With septic shock | *Reference* | **0.65 (0.43–0.98)** | **0.042** |

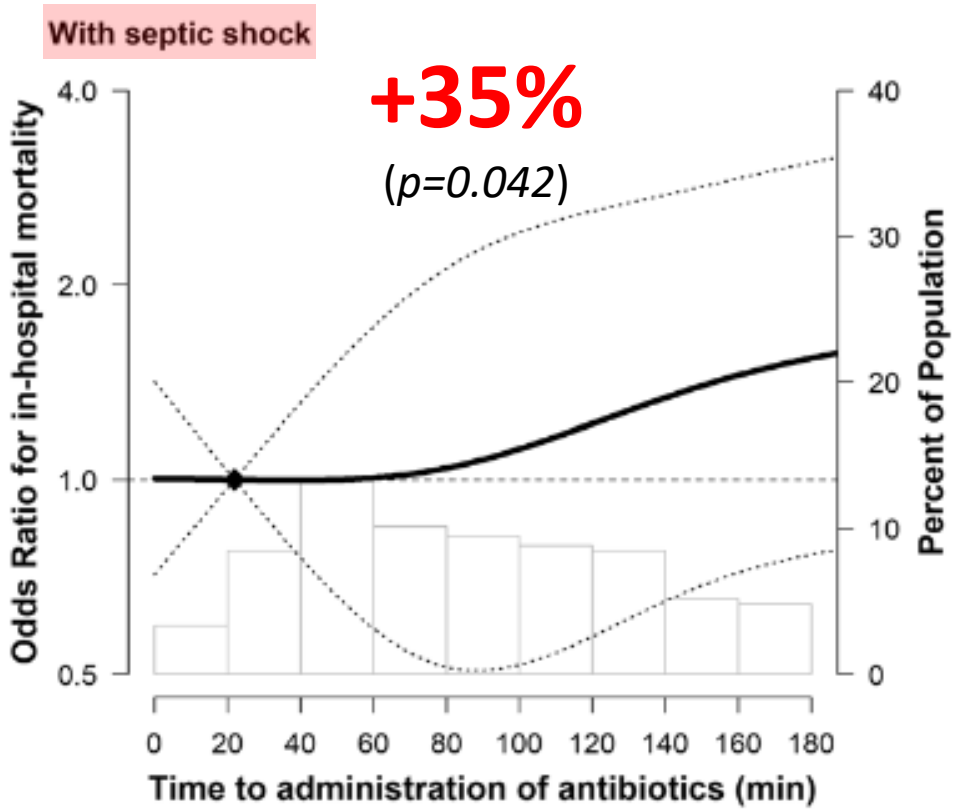
**Landmark analysis, confined to patients who survived more than 3 h*

*Im Y, Crit Care. 2022 Jan 13;26(1):19.*

# Estimated ORs for in-hospital mortality by time-to-antibiotics, confined to patients with time-to-antibiotics within 3h




Within 3 h, patients without septic shock no showed (OR 1.01; 95%CI 0.82-1.23) increased risk of mortality by every 1h delay in antibiotic administration



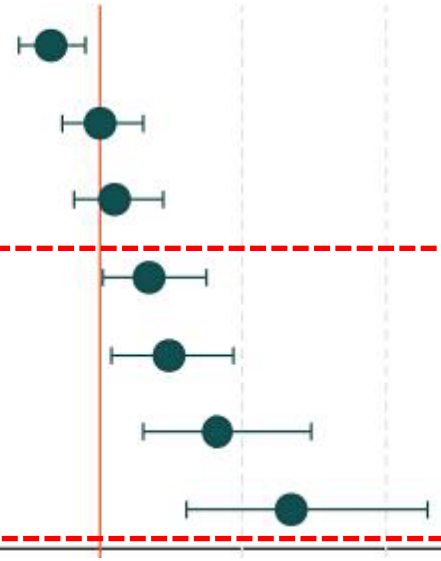

Within 3 h, patients with septic shock showed 35% (OR 1.35; 95%CI 1.01-1.812) increased risk of mortality by every 1h delay in antibiotic administration

*Im Y, Crit Care. 2022 Jan 13;26(1):19.*

# Association between time to appropriate antimicrobial treatment and 30-day mortality in patients with bloodstream infections

Retrospective cohort study (Sweden). Adult patients admitted between the years 2012 and 2019, with onset of BSI at the emergency department or general wards, were included (10628 BSI-episodes). Overall, 30-day mortality was 11.8%.

| Landmark time | Inappropriate therapy Events (Episodes) | Appropriate therapy Events (Episodes) | Risk of mortality Adjusted odds ratio (95% CI) |
|---|---|---|---|
| **Total cohort** | | | |
| 1 hour | 750 (7022) | 447 (3266) | 0.83 (.72 - .95) |
| 3 hours | 530 (4699) | 631 (5346) | 1.00 (.87 - 1.15) |
| 6 hours | 392 (3404) | 730 (6458) | 1.05 (.91 - 1.22) |
| 12 hours | 323 (2594) | 752 (7129) | 1.17 (1.01 - 1.37) |
| 24 hours | 227 (1755) | 776 (7837) | 1.24 (1.04 - 1.47) |
| 48 hours | 150 (1092) | 784 (8461) | 1.41 (1.15 - 1.74) |
| 72 hours | 99 (657) | 768 (8908) | 1.67 (1.30 - 2.15) |

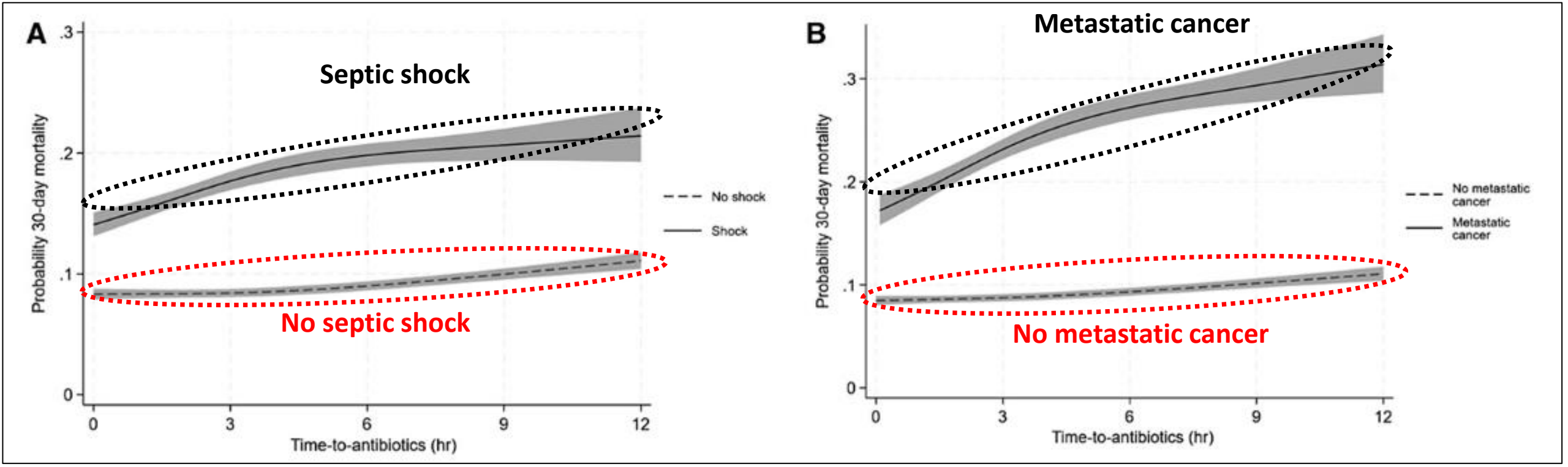


**Delays in appropriate antimicrobial treatment were associated with increased 30-day mortality after 12 hours from blood culture collection, but not at 1, 3, and 6 hours, in BSI.**

*Van Heuverswyn J, Clin Infect Dis. 2023 Feb 8;76(3):469-478.*

# Heterogeneity of benefit from earlier time-to-antibiotics for sepsis

Observational cohort study of patients hospitalized with community-onset sepsis at 173 hospitals and treated with antimicrobials within 12 hours. Among 273.255 patients with community-onset sepsis, 131.094 (48.0%) received antibiotics within 3 hours.



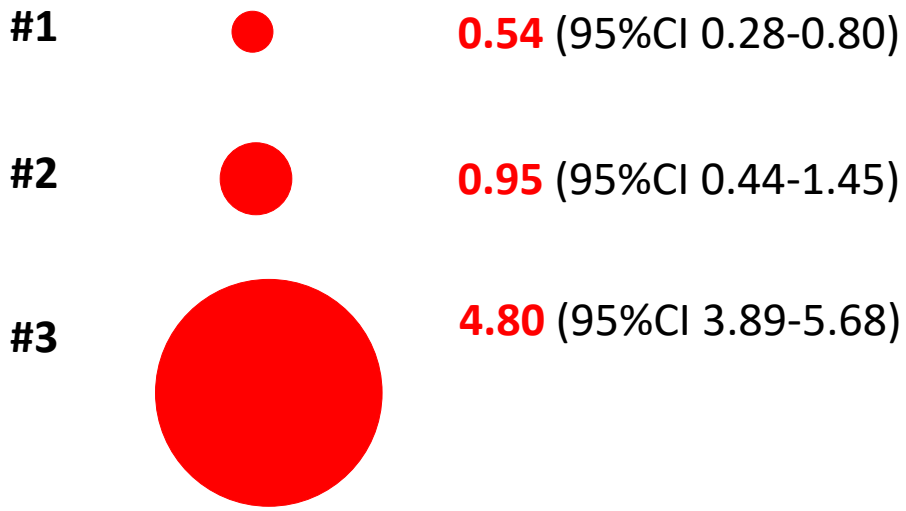

*Hechtman RK, Am J Respir Crit Care Med. 2024 Apr 1;209(7):852-860.*

# Absolute risk of 30-day mortality according to patient characteristics

Observational cohort study of patients hospitalized with community-onset sepsis at 173 hospitals and treated with antimicrobials within 12 hours. Among 273,255 patients with community-onset sepsis, 131,094 (48.0%) received antibiotics within 3 hours.

| | |
|---|---|
| **Septic shock**<br>**7.03**<br>(95%CI 5.85-8.17) | **Haematological**<br>**6.96**<br>(95%CI 5.86-8.03) |
| **Metastatic cancer**<br>**5.03**<br>(95%CI 4.28-5.76) | **Liver disorders**<br>**7.05**<br>(95%CI 5.78-8.27) |

**Number of acute organ dysfunctions**




*Hechtman RK, Am J Respir Crit Care Med. 2024 Apr 1;209(7):852-860.*

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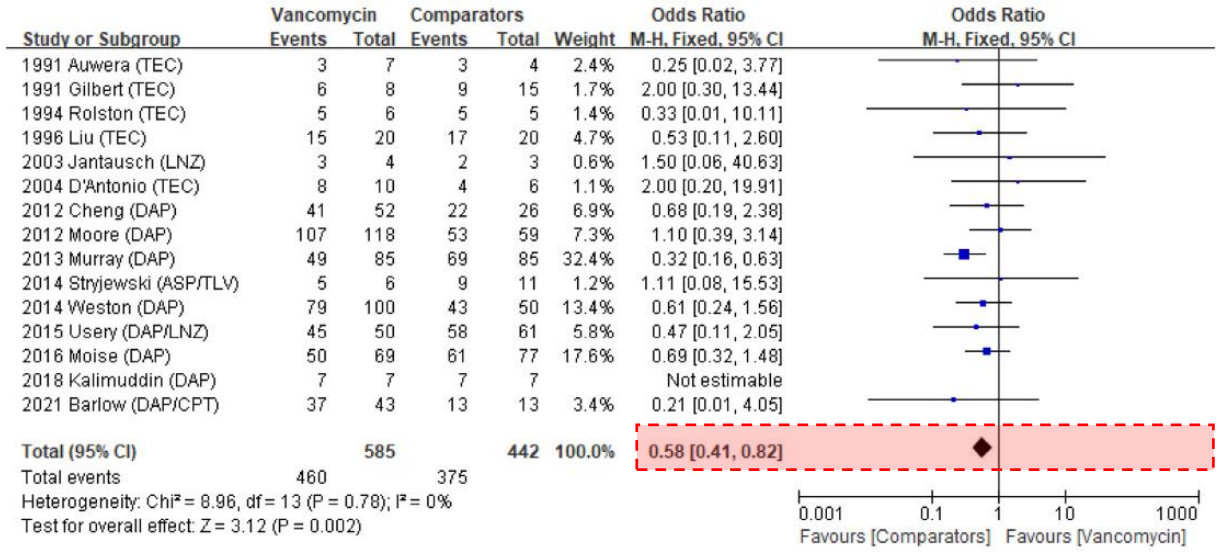
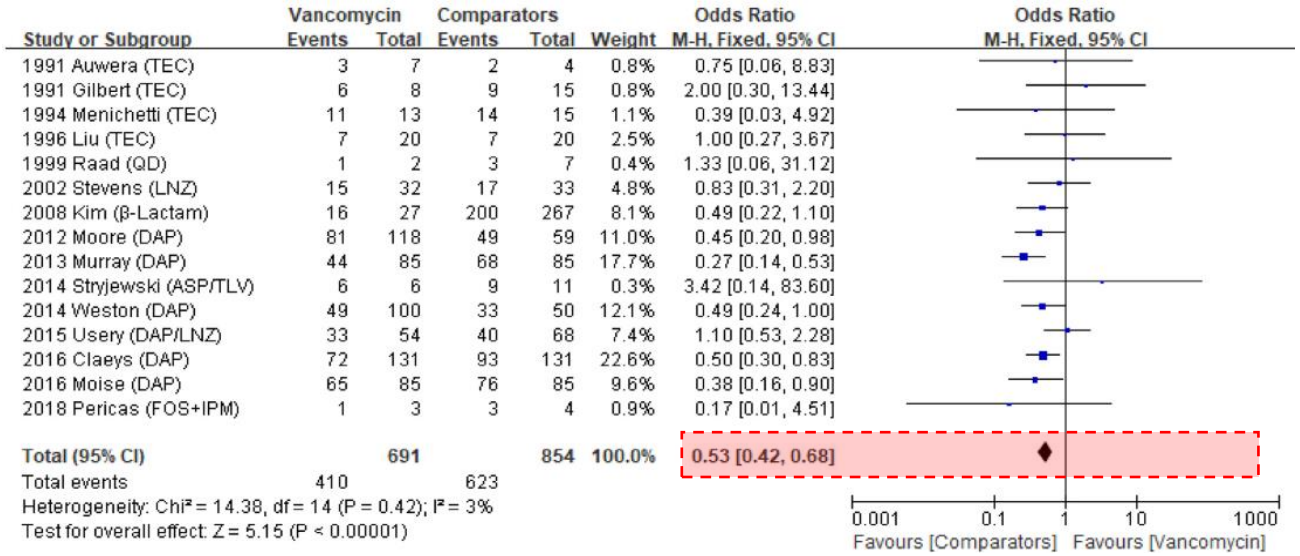
# Efficacy and safety of vancomycin for the treatment of *S. aureus* bacteraemia: a systematic review and meta-analysis

## Microbiological response
## 15 controlled studies, including 1027 patients




The subgroup analysis of TEC and LNZ showed no differences. The difference was concentrated in the subgroup of DAP (888 cases, **OR=0.55, 95%CI 0.38-0.80, p=0.002**), in which VAN had a significantly lower microbiological eradication rate.

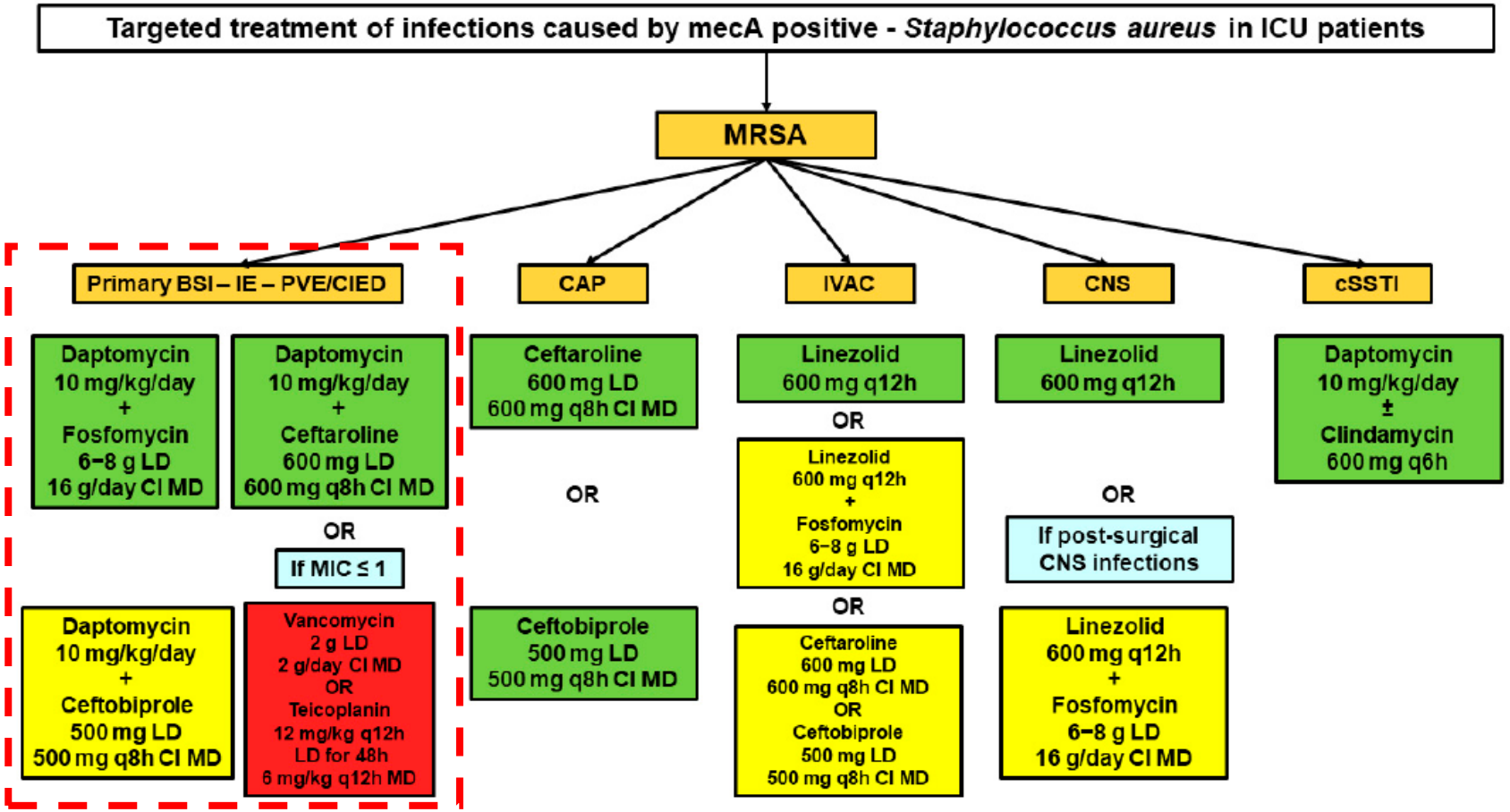
## Clinical response
## 15 controlled studies, including 1545 patients




The subgroup analysis of TEC and LNZ showed no differences. The difference was concentrated in the subgroup of DAP (1036 cases, **OR=0.48, 95%CI 0.36-0.63, p<0.00001**), in which VAN had a significantly lower clinical cure rate.

*Zhang G, Int J Antimicrob Agents. 2023 Oct;62(4):106946.*

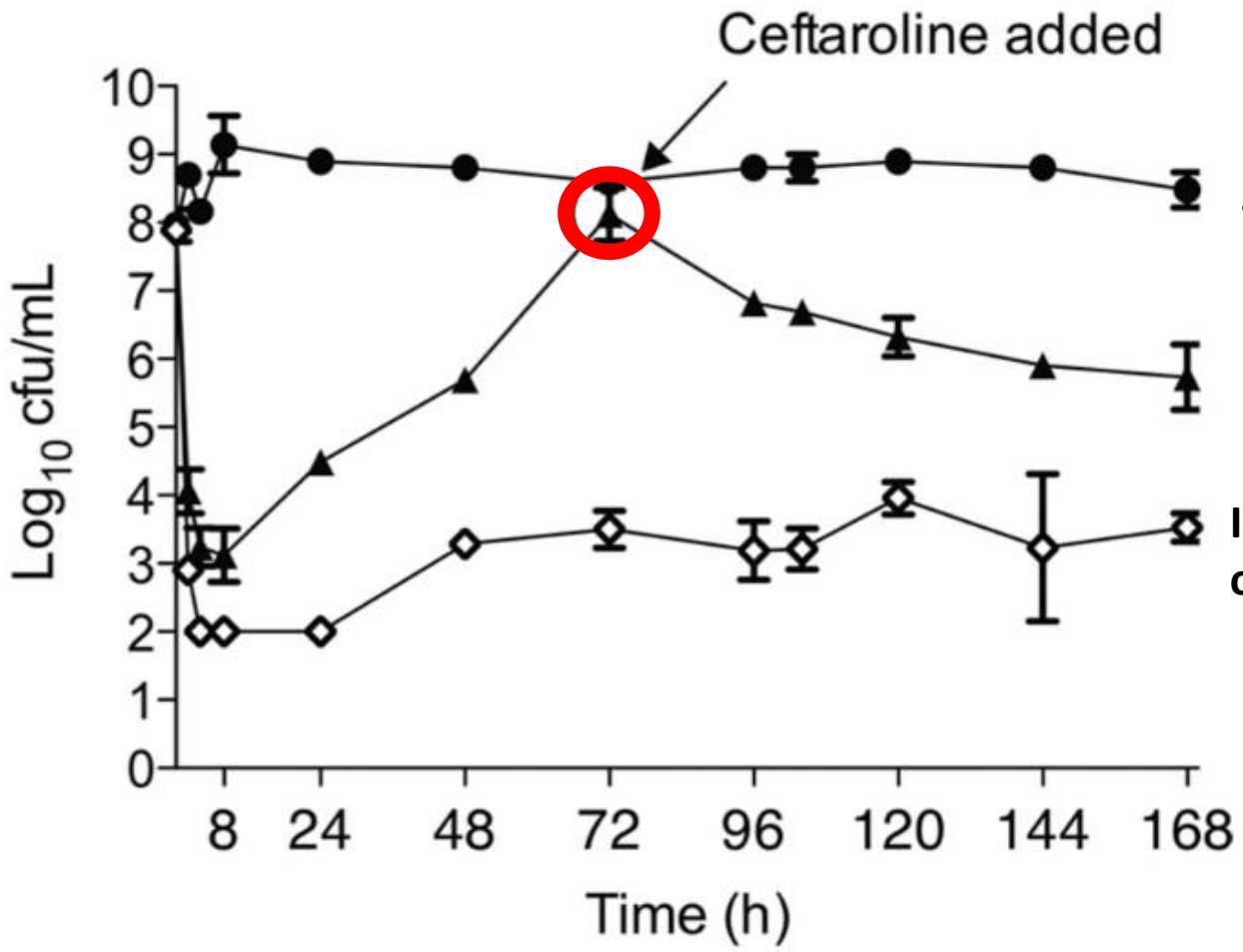
# Targeted therapy of severe infections caused by *S. aureus* in critically ill adult patients




Green box: best therapeutic regimen according to current evidence; yellow box: alternative therapeutic regimen according to current evidence; red box: therapeutic regimen recommended only in specific situations.

*Gatti M, Microorganisms. 2023 Feb 3;11(2):394.*

# Addition of ceftaroline to daptomycin after emergence of daptomycin-nonsusceptible *S. aureus* during therapy improves antibacterial activity




**growth control**

**DAP with CPT added on day 3**

**Initial Tx with DAP combined with CPT on day 1**

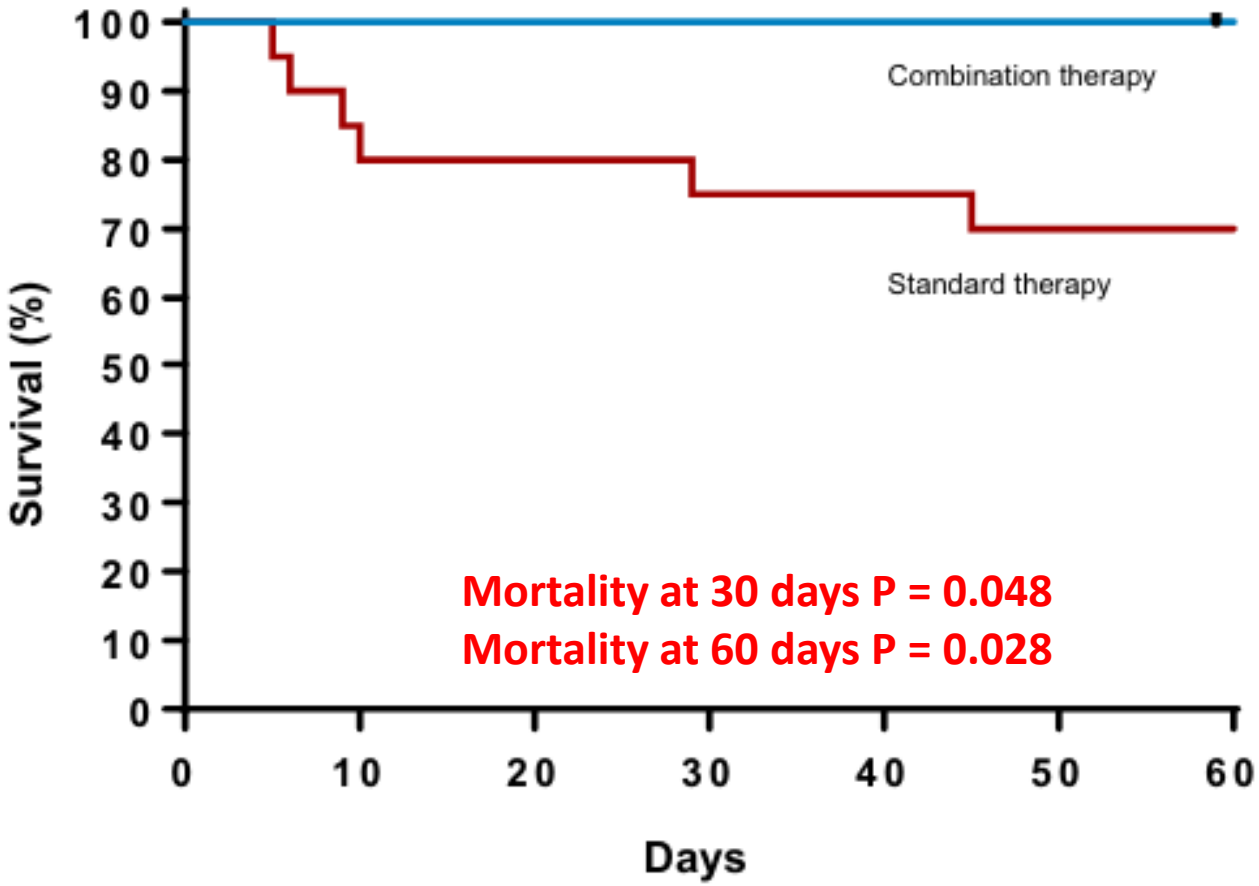
*Rose WE, Antimicrob Agents Chemother. 2012 Oct;56(10):5296-302.*

# Clinical data on daptomycin plus ceftaroline versus standard of care monotherapy in the treatment of MRSA bacteremia

Pilot study, 40 adult patients who were randomized to receive 6-8 mg/kg of body weight per day of DAP and 600 mg CPT every 8 h (q8h) (*n*=17) or standard monotherapy (*n*=23) with vancomycin (VAN; dosed to achieve serum trough concentrations of 15 to 20 mg/liter; *n*=21) or 6-8 mg/kg/day DAP (*n*=2) were evaluated.

**The findings led the investigators to stop early the study due to an unacceptable higher risk of mortality in the monotherapy arm (0% [0/17] for combination therapy and 26% [6/23] for monotherapy).**

**Survival analysis of patients receiving DAP/CPT compared with those receiving SOC**




*Geriak M, Antimicrob Agents Chemother. 2019 Apr 25;63(5):e02483-18.*

# Vancomycin or daptomycin plus a β-Lactam versus vancomycin or daptomycin alone for MRSA bloodstream infections: a meta-Analysis

Literature search identified 3 randomized clinical trials and 10 observational studies involving at least 1796 patients

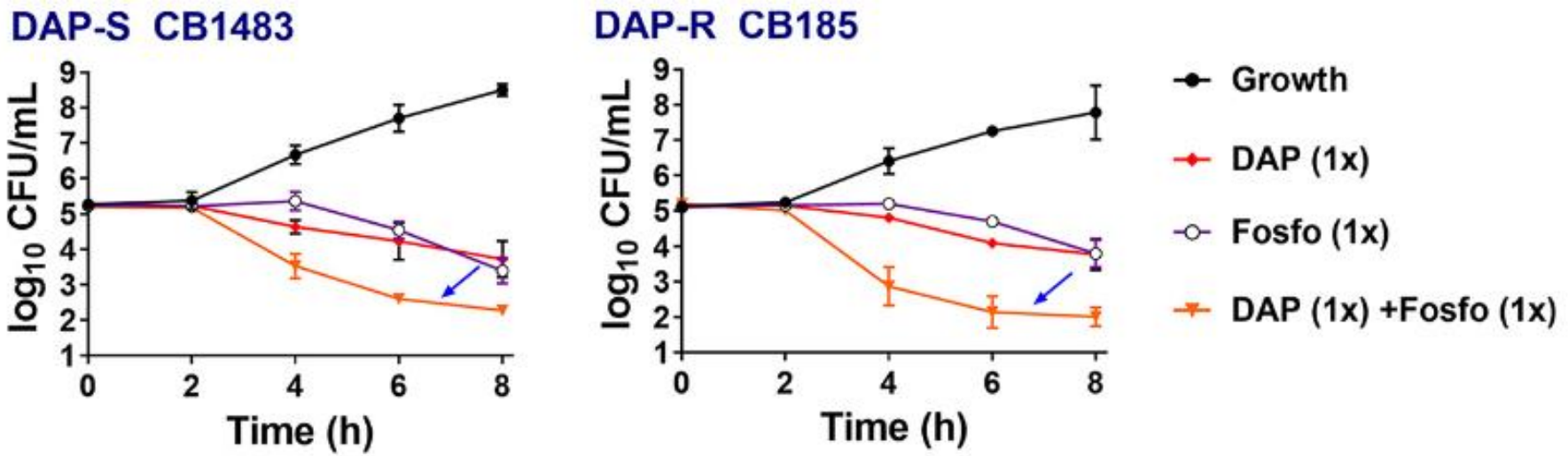
| | | |
|---|---|---|
| **in-hospital mortality**<br>RR 0.59<br>95%CI 0.31-1.13 | **risk of 30-day mortality**<br>RR 1.10<br>95%CI 0.82-1.46 | **risk of 60-90-day mortality**<br>RR 0.91<br>95%CI 0.64-1.29 |
| **shorter duration of bacteremia**<br>mean difference -1.06 days<br>95%CI -1.53 to -0.60 | **risk of persistent bacteremia**<br>RR 0.63<br>95%CI 0.51-0.79 | **risk of bacteremia 60-90-day recurrence**<br>RR 0.61<br>95%CI 0.40-0.92 |

In subgroup analysis, **when the analysis was limited to the studies comparing using DAP plus ceftaroline with monotherapy, the former had a lower risk of mortality within 30 days**. In addition, a subgroup analysis limited to RCTs showed that the combination therapy was associated with a higher risk of AKI compared with using VAN or DAP alone.

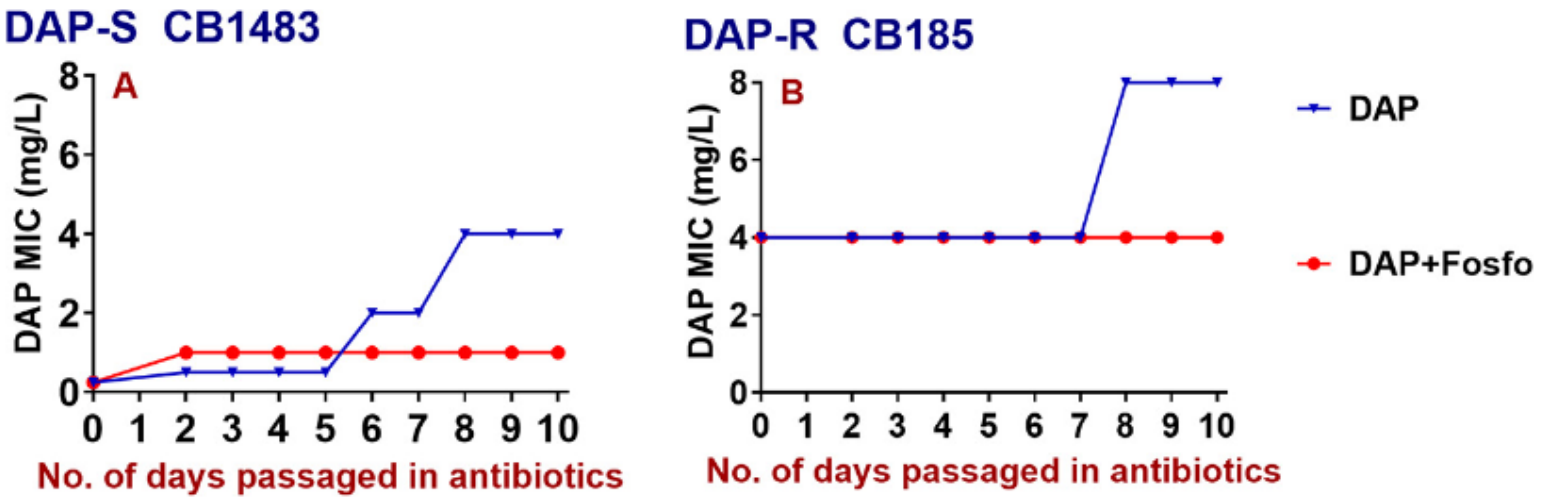
*Yi YH, Microb Drug Resist. 2021 Aug;27(8):1044-1056*

# Synergy mechanisms of daptomycin-fosfomycin combinations in daptomycin-susceptible and -resistant MRSA

**In vitro time-kill curve analysis**




**Resistance prevention and resensitization during in vitro serial passaging**

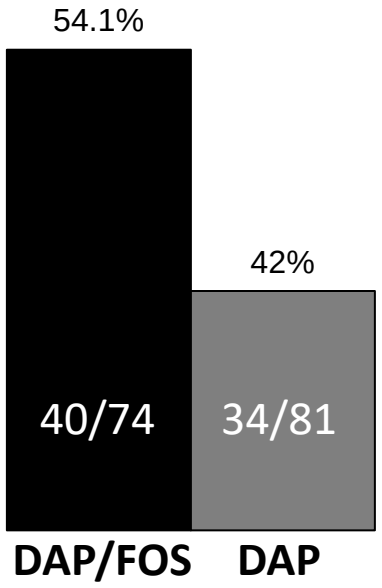



*Mishra NN, Antimicrob Agents Chemother. 2022 Jan 18;66(1):e0164921.*

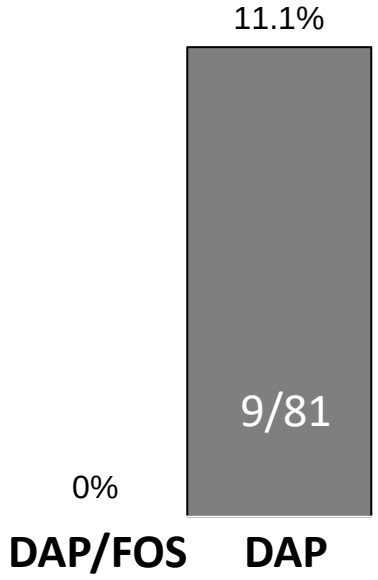
# Daptomycin plus fosfomycin vs daptomycin alone for MRSA bacteremia and endocarditis: a randomized clinical trial (BACSARM study)

A randomized phase 3 superiority, open-label, and parallel group clinical trial of adult inpatients with MRSA bacteremia was conducted in Spain (18 hospitals). Patients were randomly assigned to receive either daptomycin plus fosfomycin, or daptomycin alone. Primary endpoint was treatment success 6 weeks after the end of therapy.

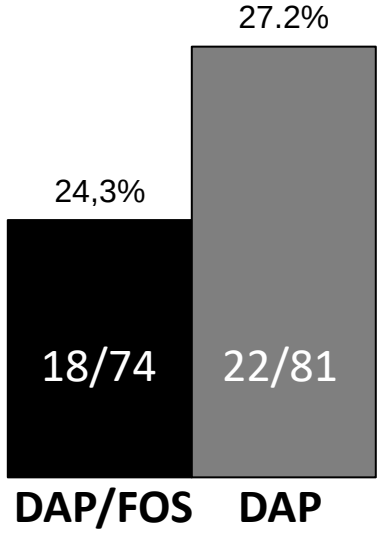
**Treatment success at TOC**




**Microbiological failure at TOC**




**Overall mortality at TOC**




*Pujol M,Clin Infect Dis. 2021 May 4;72(9):1517-1525.*

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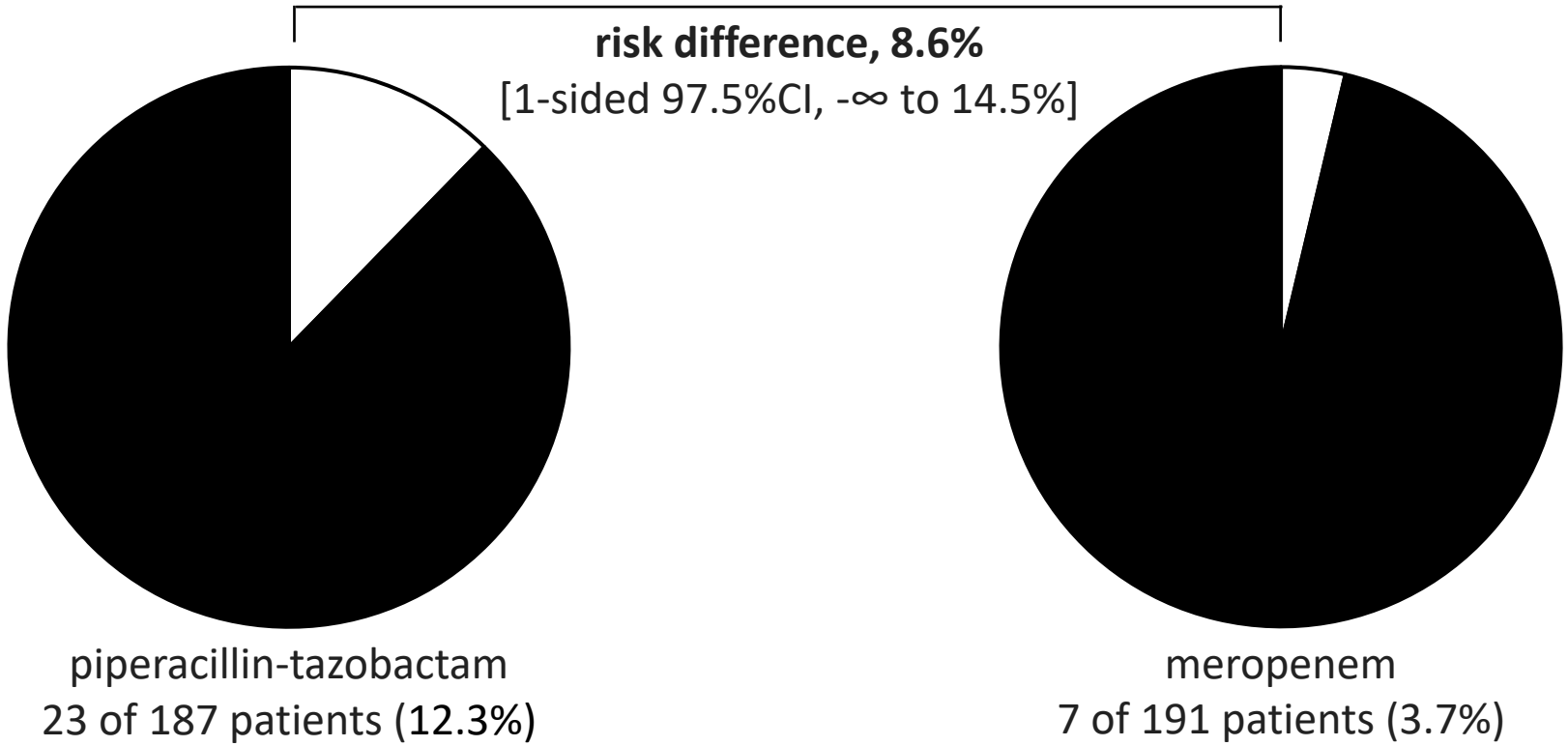
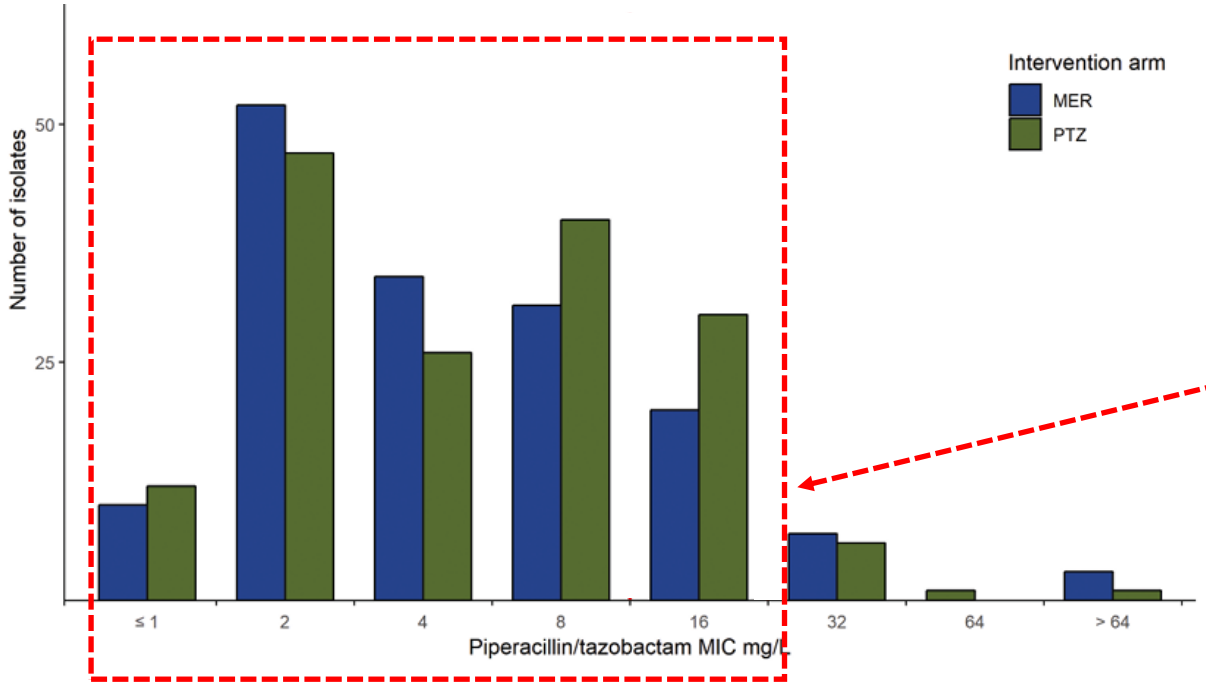
# Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for E. coli or K. pneumoniae BSI and CRO-R (MERINO)

Noninferiority, RCT included hospitalized patients enrolled from 26 sites in 9 countries (2014 to 2017) to determine whether definitive therapy with TZP is noninferior to meropenem in patients with BSI caused by CRO-R *E. coli* or *K. pneumoniae*. The primary outcome was all-cause mortality at 30 days after randomization.




*Harris PNA, JAMA. 2018 Sep 11;320(10):984-994.*

# Association between MIC and mortality for patients treated with piperacillin/tazobactam or meropenem from the MERINO study




TZP nonsusceptible breakpoint (MIC >16 mg/L) best predicted 30-day mortality after accounting for confounders (OR 14.9, 95%CI 2.8-87.2).

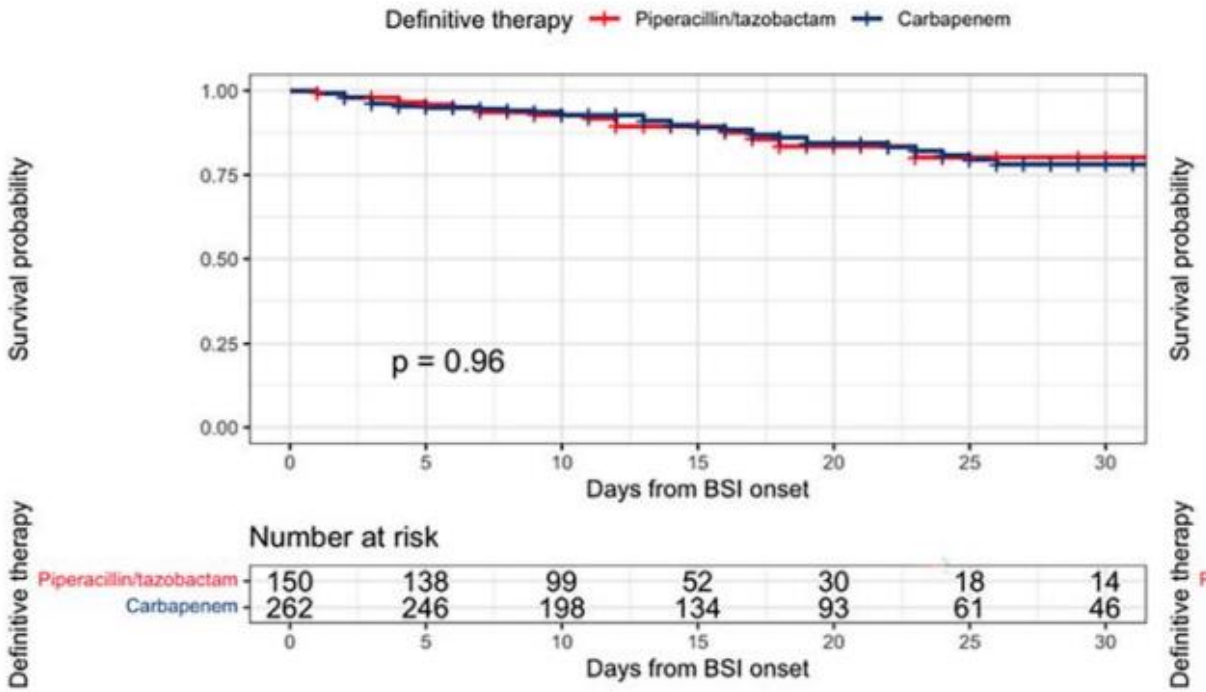
Absolute risk increase for 30-day mortality for patients treated with TZP compared with meropenem reduced to 5% (95%CI -1% to 10%) after excluding strains with TZP MIC values >16 mg/L.

*Henderson A, Clin Infect Dis. 2021 Dec 6;73(11):e3842-e3850.*

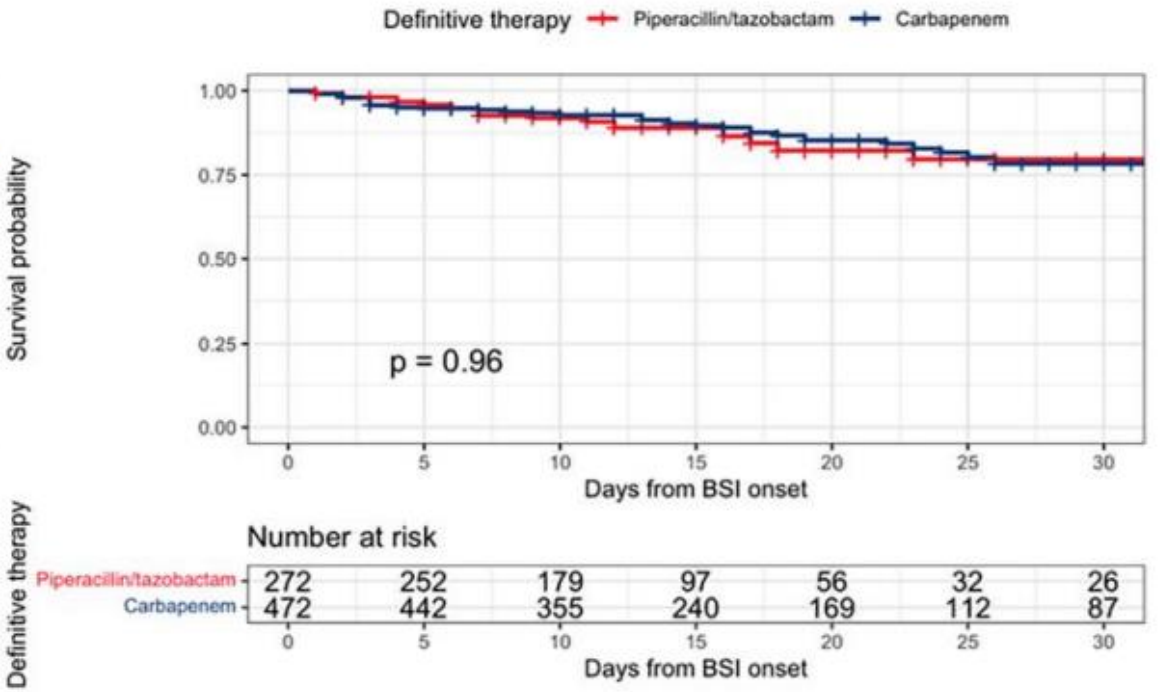
# Association of piperacillin/tazobactam MIC and mortality in a cohort of CRO-R *E. coli* BSIs treated with TZP and carbapenems

A multicentre retrospective cohort study was conducted in 3 hospitals in Italy between 2018 and 2022. The study population comprised patients with monomicrobial 3GC-R *E. coli* BSI, who received either empirical Tx with TZP or carbapenem therapy within 48h of blood culture collection. The primary outcome was in-hospital 30-day all-cause mortality. Of the 412 consecutive patients, 51% received TZP, while 49% received carbapenems.

**Crude KM curves of definitive Tx cohorts**




**Adjusted KM curves of definitive Tx cohorts**




*Rando E, .J Antimicrob Chemother. 2024 Feb 1;79(2):453-461.*

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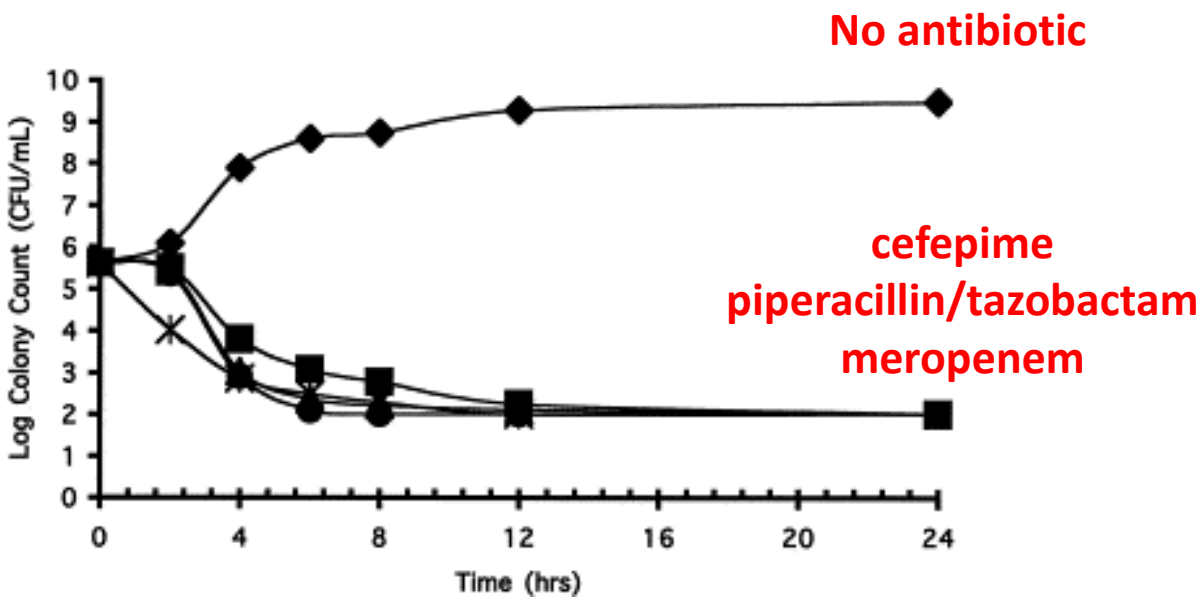
**Multiple Cox regression models for in-hospital 30-day mortality**

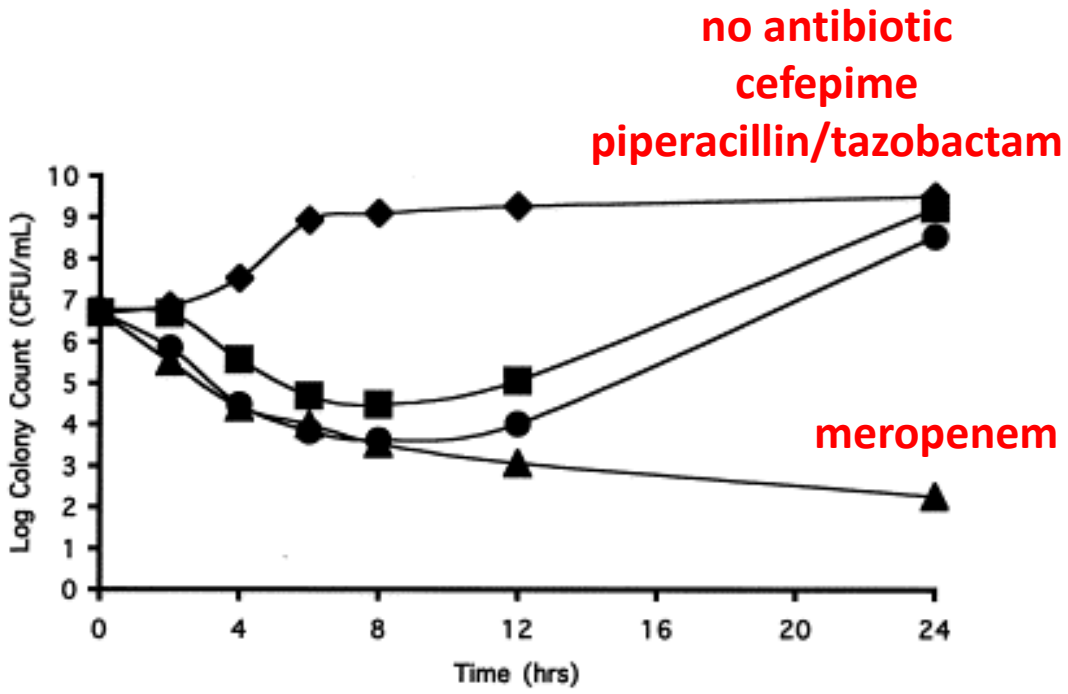
| | Crude model | | Propensity-adjusted | |
|---|---|---|---|---|
| Characteristic | HR | 95% CI | HR | 95% CI |
| Empirical TZP | 1.34 | 0.78–2.32 | 1.38 | 0.85–2.16 |
| Immunocompromised | 0.88 | 0.47–1.66 | 0.79 | 0.43–1.41 |
| CCI | 1.07 | 0.96–1.19 | 1.08 | 0.98–1.17 |
| Pitt bacteraemia score | 1.23 | 1.10–1.38 | 1.26 | 1.13–1.40 |
| TZP MIC (mg/L) | | | | |
| 8 | 2.29 | 1.25–4.21 | 2.35 | 1.35–3.95 |
| ≥16 | 3.04 | 1.49–6.19 | 3.69 | 1.86–6.91 |

*Rando E, .J Antimicrob Chemother. 2024 Feb 1;79(2):453-461.*

# In vitro killing of parenteral beta-lactams against standard and high inocula of ESBL producing K. pneumoniae




Low inoculum ESBL growth curve




High inoculum ESBL growth curve

*Burgess DS, Diagn Microbiol Infect Dis. 2004 May;49(1):41-6.*

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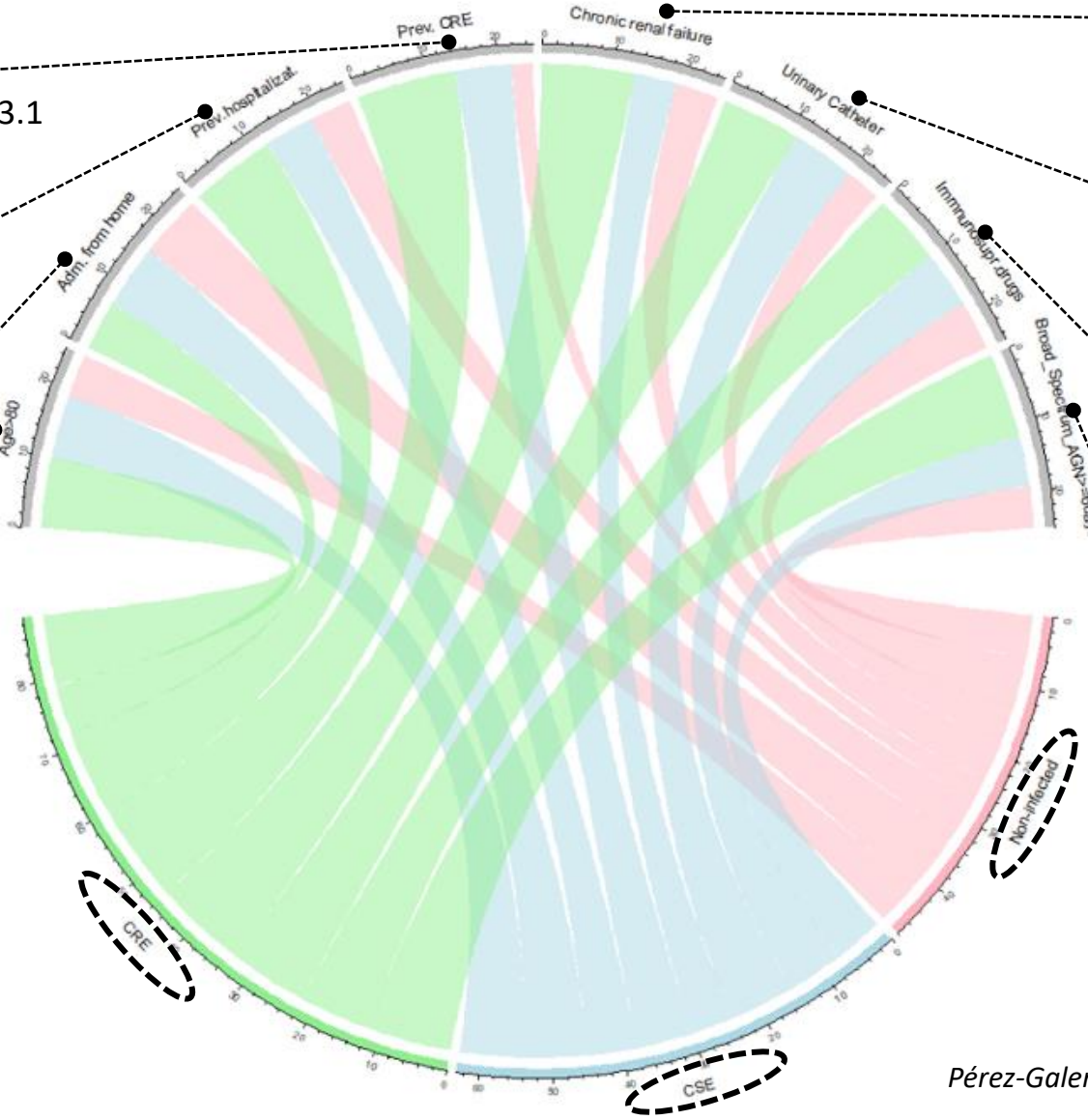
# Risk factors for infections caused by CRE: EURECA study

**previous CRE**
CRE vs CSE: aOR 6.94
CRE vs non-infect: aOR 13.1

**previous hospitalization**
CRE vs non-infect: aOR 1.84

**admission from home**
CRE vs CSE: aOR 0.44

**age**
CRE vs non-infect: aOR 1.03




**chronic renal failure**
CRE vs CSE : aOR 2.81

**urinary catheter**
CRE vs CSE : aOR 1.78
CRE vs non-infect: aOR 3.68

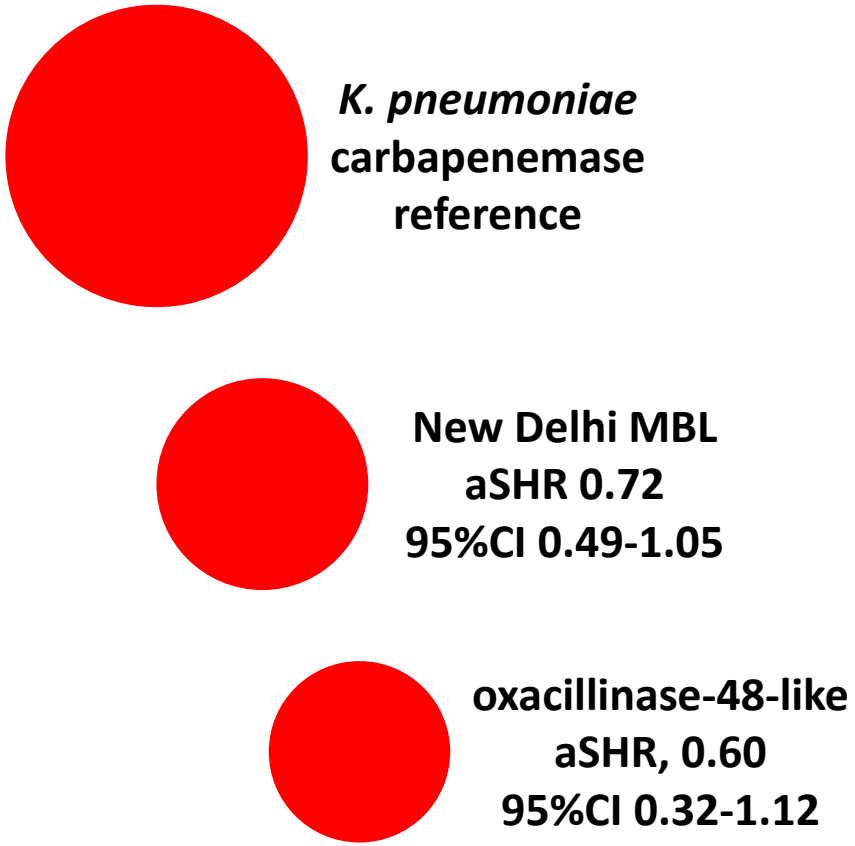
**immunosuppression**
CRE vs non-infect: aOR 3.38

**broad spectrum antibiotics**
CRE vs CSE: aOR 2.20
CRE vs non-infect: aOR 2.89

*Pérez-Galera S, EClinicalMedicine. 2023 Feb 27;57:101871*

# Progression from carriage of various carbapenemases to BSI

A nationwide population-based retrospective cohort study using national databases was conducted. The cohort consisted of all patients in Israel with CPE detected by screening from 1/1/2020 to 10/10/2022. The study included 6828 CPE carriers.




**intensive care units**

**x2**

aSHR 2.10
95%CI 1.27-3.49

**onco-hematology units**

**x4**

aSHR 3.95
95%CI 2.51-6.22

*Temkin E, Clin Infect Dis. 2024 Mar 6:ciae110.*

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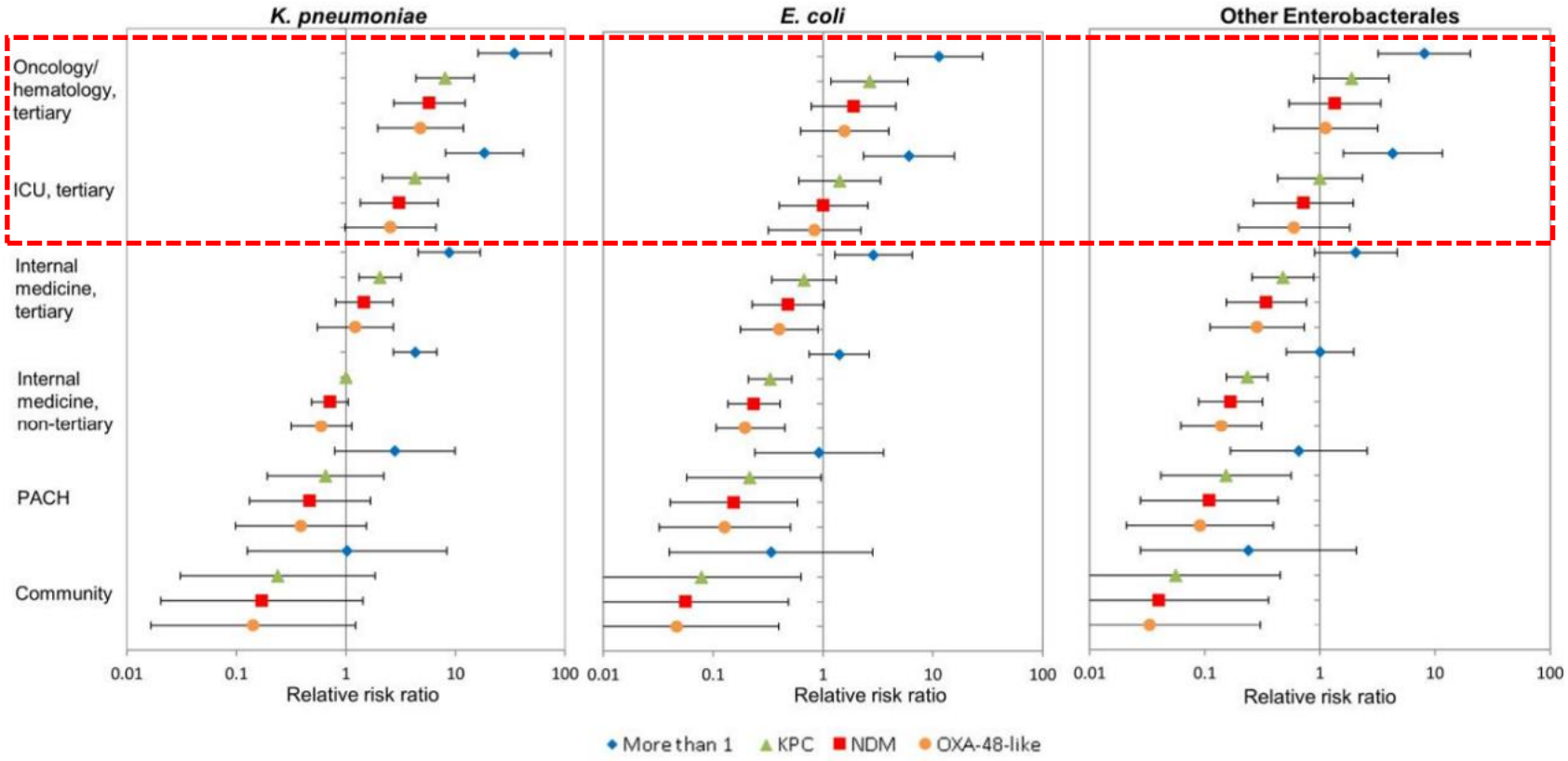


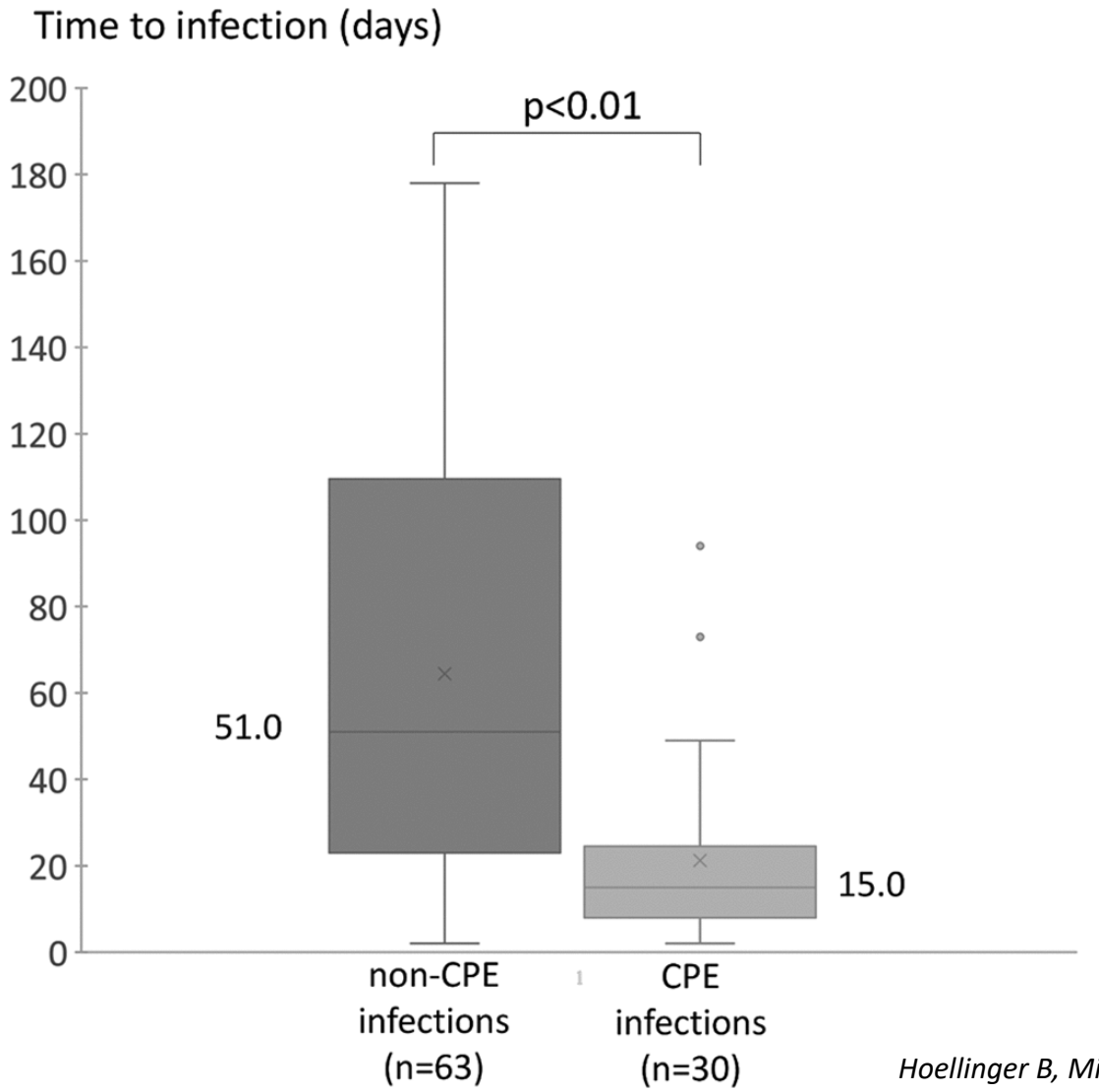

More than 1: more than 1 carbapenemase; Tertiary/nontertiary refers to acute care hospital type; PACH: post-acute care hospital; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase

*Temkin E, Clin Infect Dis. 2024 Mar 6:ciae110.*

# Time-to-onset of carbapenemase-producing *Enterobacterales* infections in CPE carriers

A retrospective cohort study was performed over a 10-year period in a University Hospital in France.

All infectious episodes within the first 6 months following the diagnosis of CPE rectal carriage were considered

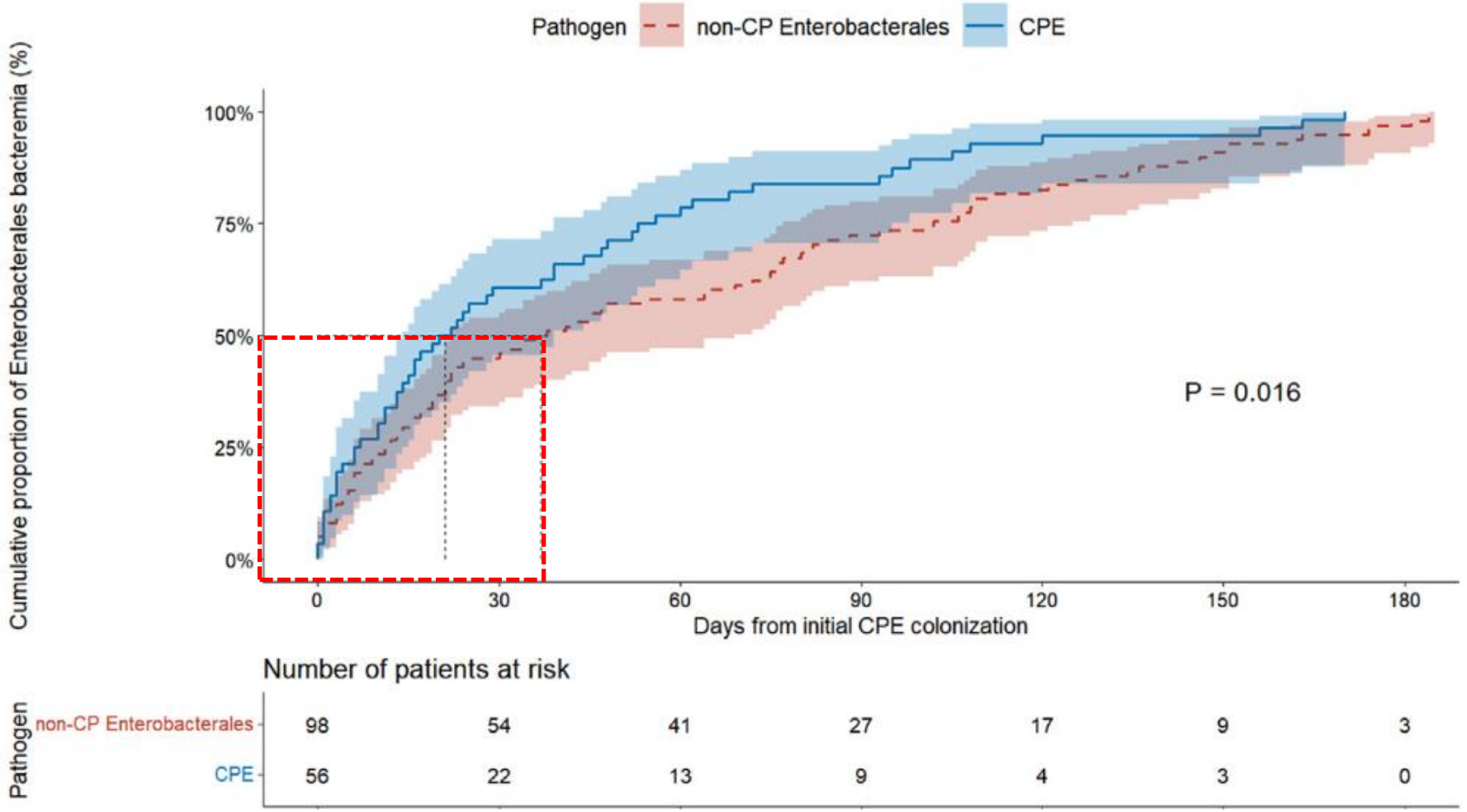



93 infectious episodes were identified in the first 6 months following its diagnosis.

CPE infection occurred earlier than any other infections (P < 0.01), with a median of 15 days (Q1 to Q3 = 8 to 24) compared with 51 days (Q1 to Q3 = 25 to 109)

*Hoellinger B, Microbiol Spectr. 2022 Dec 21;10(6):e0186822.*

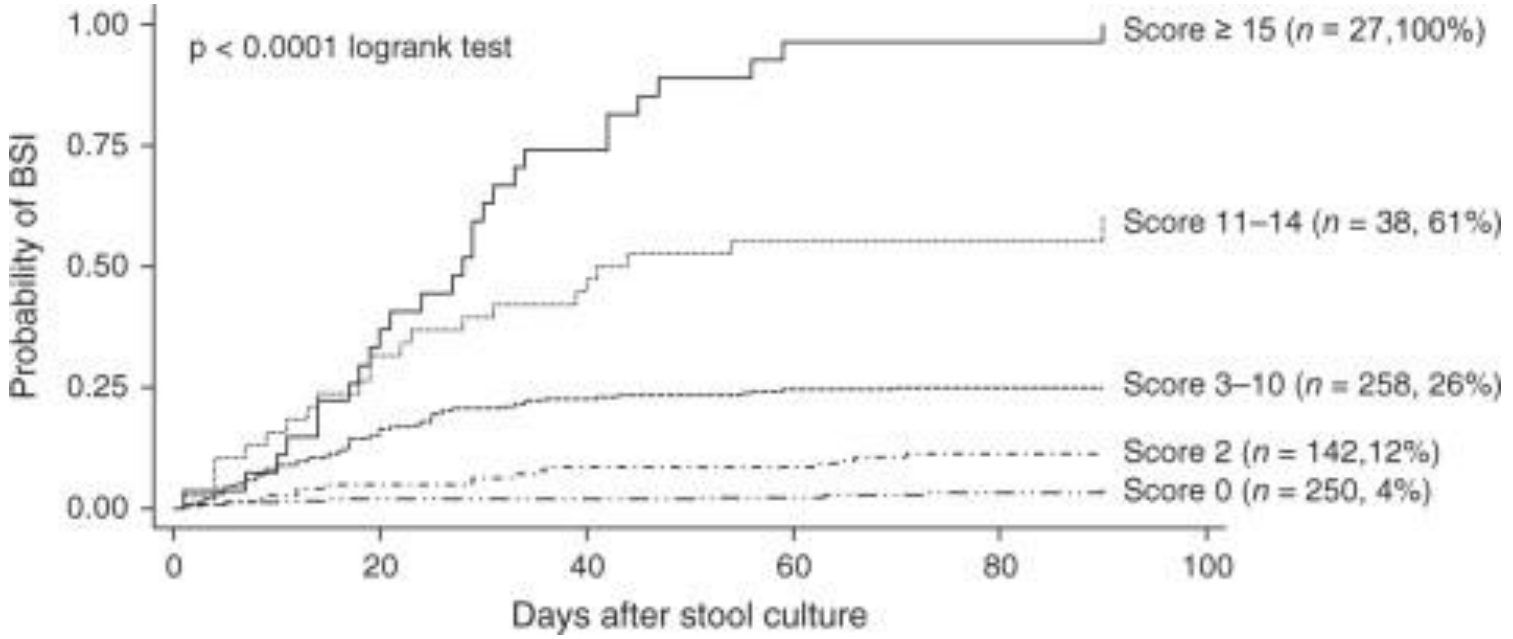
# Proportion of carbapenemase-producing *Enterobacterales*-colonised patients developing bacteraemia caused by non-CPE vs. CPE




*Kang SW, Int J Antimicrob Agents. 2023 Nov;62(5):106959.*

# Risk factors for carbapenem-resistant *K. pneumoniae* bloodstream infection among rectal carriers

**KM analysis of CR-KP of BSI probability at five risk score levels**



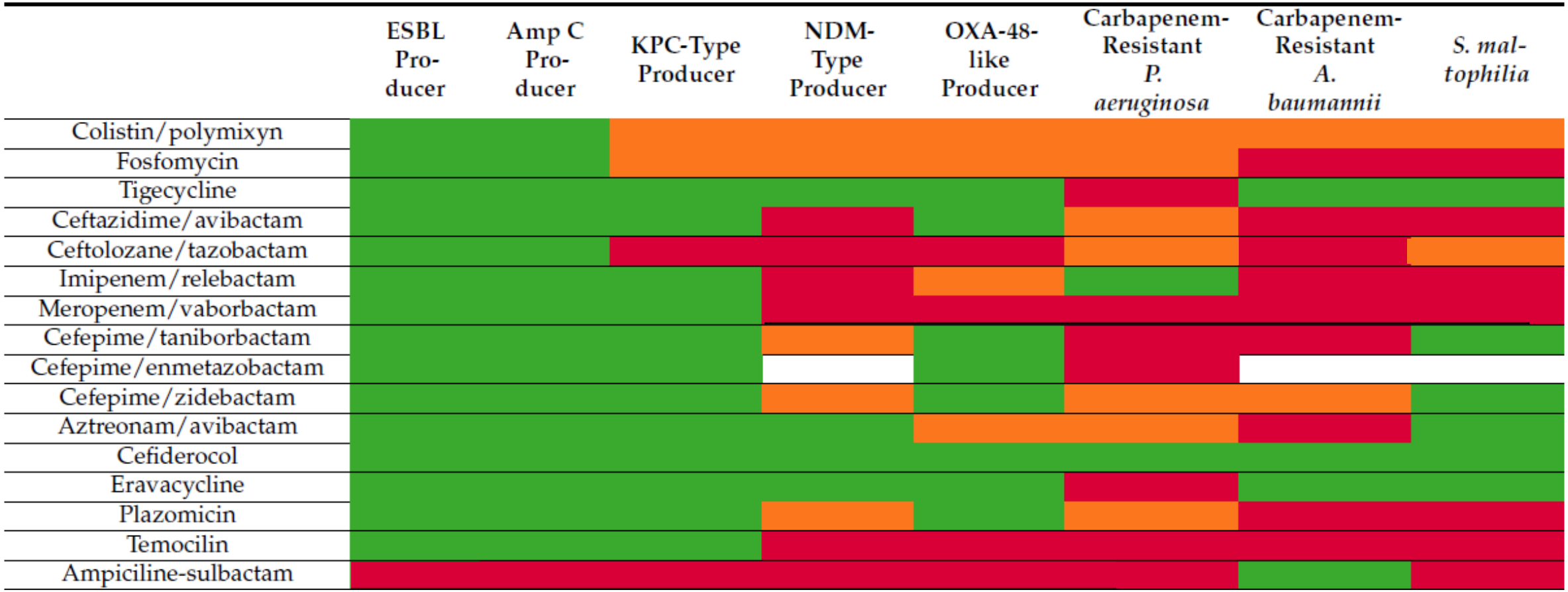

| Score | 30-day | 90-day |
|---|---|---|
| 0 | 2% | 4% |
| 2 | 7% | 12% |
| 3-10 | 22% | 26% |
| 11-14 | 38% | 61% |
| ≥15 | 63% | 100% |

**KM analysis of CR-KP of BSI probability at five risk score levels**

| | | |
|---|---|---|
| ICU | OR 1.65; p = 0.03 | 2 points |
| abdominal invasive procedure | OR 1.87; p = 0.01 | 3 points |
| chemotherapy/radiation therapy | OR 3.07; p<0.0001 | 4 points |
| number of additional colonization sites | OR 3.37 per site; p<0.0001 | 5 points per site |

*Giannella M, Clin Microbiol Infect. 2014 Dec;20(12):1357-62.*

# Antimicrobial activity spectrum chart



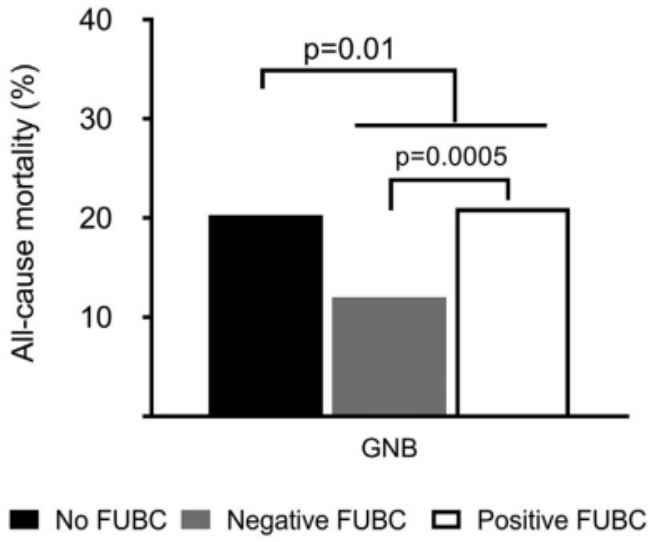

*Ramasco F, J Pers Med. 2024 Jan 18;14(1):106*

# Road map

- Time-to-antibiotics and clinical outcomes
- Initial treatment for MRSA infections
- Role of piperacillin/tazobactam in CRO-R *E. coli* infections
- Carbapenemase-producing *Enterobacterales* BSI in rectal carriers
- **Impact on clinical outcome of follow-up blood cultures**
- Early oral switch in bloodstream infections

# Positive follow-up blood cultures identify high mortality risk among patients with Gram-negative bacteraemia

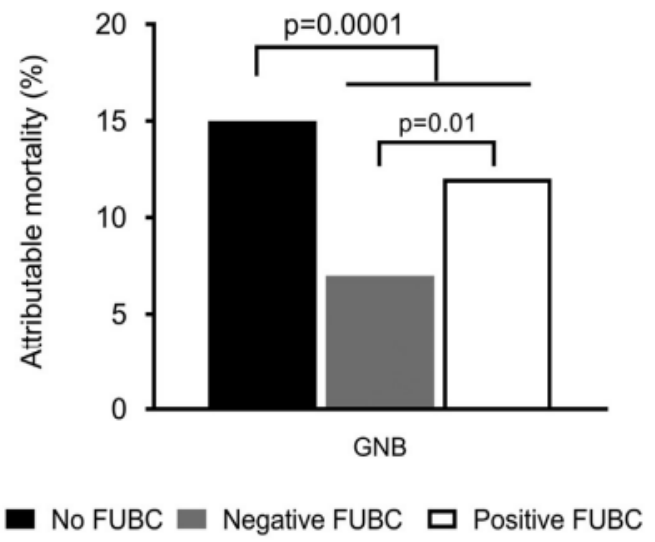
**all-cause mortality**




Propensity score-weighted Cox model revealed that:
-obtaining FUBCs was associated with reductions in all-cause mortality (**HR 0.63; 95%CI 0.51-0.77**)

-positive FUBCs were associated with increased all-cause mortality (**HR 2.10; 95%CI 1.57-2.81**)

**attributable mortality**



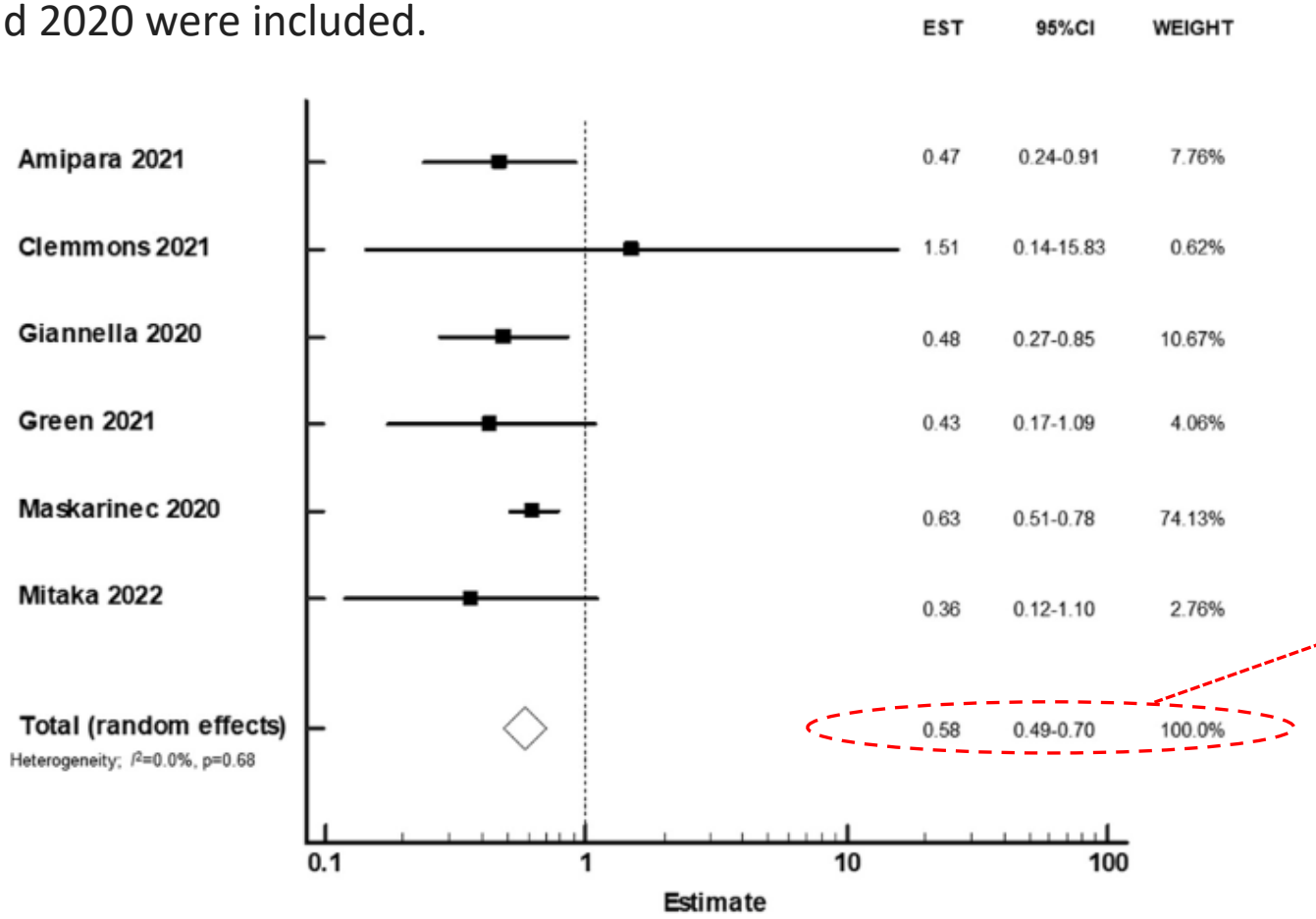

Propensity score-weighted Cox model revealed that:
-obtaining FUBCs was associated with reduction in attributable mortality (**HR 0.63; 95%CI 0.48-0.82**)

-positive FUBCs were associated with increased attributable mortality (**HR 1.80; 95%CI 1.24-2.60**)

*Maskarinec SA, Clin Microbiol Infect. 2020 Jul;26(7):904-910.*

# Impact on clinical outcome of follow-up blood cultures and risk factors for persistent bacteraemia in patients with gram-negative bloodstream infections: a systematic review with meta-analysis

A Meta-analysis was performed. A total of 3747 articles were screened, and 11 observational studies (6 assessing impact on outcome (N = 4631), and 5 investigating risk factors for persistent GN-BSI (N = 2566), conducted between 2002 and 2020 were included.




The execution of follow-up blood cultures was associated with a significantly lower risk of mortality (**OR, 0.58; 95% CI, 0.49-0.70**).

*Gatti M, Clin Microbiol Infect. 2023 Sep;29(9):1150-1158.*

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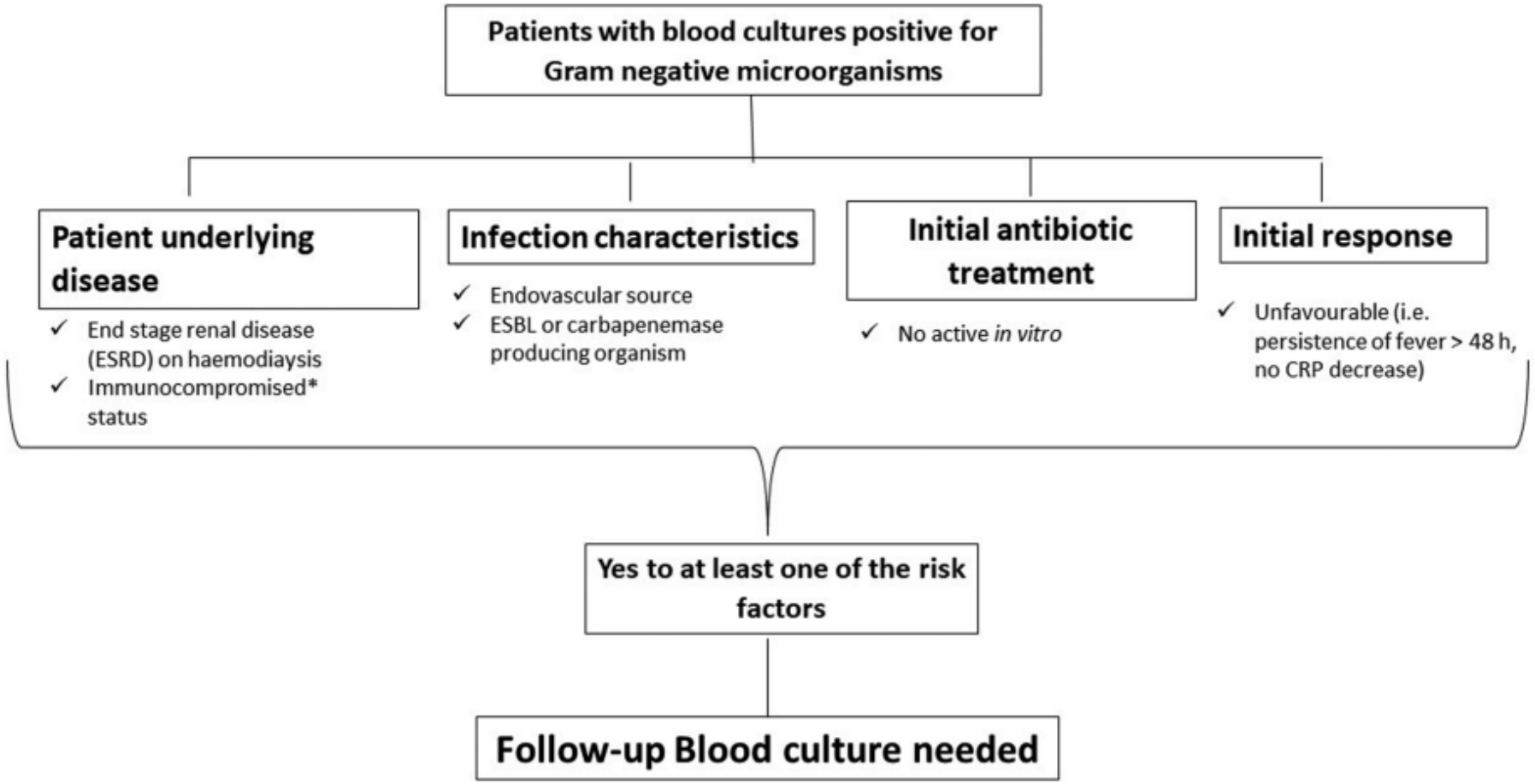
**Independent risk factors for persistent bacteraemia**

| | |
|---|---|
| end-stage renal disease | OR 2.99; 95%CI 1.77-5.05 |
| central venous catheter | OR 3.30; 95%CI 1.82-5.95 |
| infections due to ESβL-producing strains | OR 2.25; 95%CI 1.18-4.28 |
| resistance to empirical treatment | OR 2.70; 95%CI 1.65-4.41 |
| unfavourable response at 48 hours | OR 2.99; 95%CI 1.44-6.24 |

*Gatti M, Clin Microbiol Infect. 2023 Sep;29(9):1150-1158.*

# Follow-up blood culture in Gram-negative bacilli bacteraemia: for whom is follow-up blood culture useful?




*Giannella M, Curr Opin Infect Dis. 2022 Dec 1;35(6):552-560.*

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- Impact on clinical outcome of follow-up blood cultures
- **Early oral switch in bloodstream infections**

# Efficacy and safety of an early oral switch in low-risk *S. aureus* bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial

An international RCT done in 31 tertiary care hospitals in Europe, patients with low-risk *S. aureus* BSI were randomly assigned after 5-7 days of IV therapy to oral therapy or to continue IV therapy.

Adult patients with *S aureus* isolated from at least 1 blood culture were eligible if they had received 5-7 days of appropriate IV therapy, initiated within 72 h after the first positive blood culture was drawn, and at least 1 follow-up blood culture obtained within 24-96h after the start of appropriate therapy. Blood cultures taken in this period had to be negative for *S aureus* for the patient to be included.

Oral antimicrobials were selected by the study physician (according to susceptibility and suspected allergy or intolerance): co-trimoxazole for MSSA and MRSA, clindamycin for MSSA or linezolid for MRSA in the oral switch group; and IV flucloxacillin or cloxacillin, cefazolin, or vancomycin for MSSA or vancomycin or daptomycin for MRSA in the IV group.

**The clinically evaluable population consisted of 165 participants, with 86 participants in the oral switch group and 79 participants in the intravenous standard therapy group.**

*Kaasch AJ, Lancet Infect Dis. 2024 May;24(5):523-534.*

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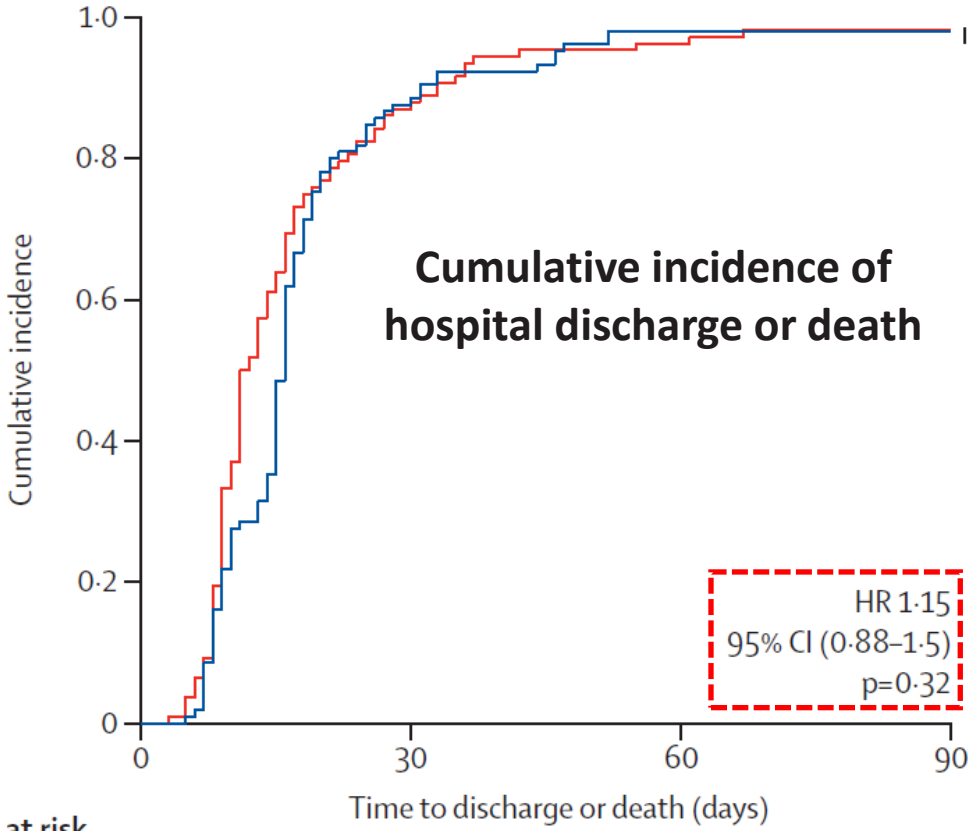


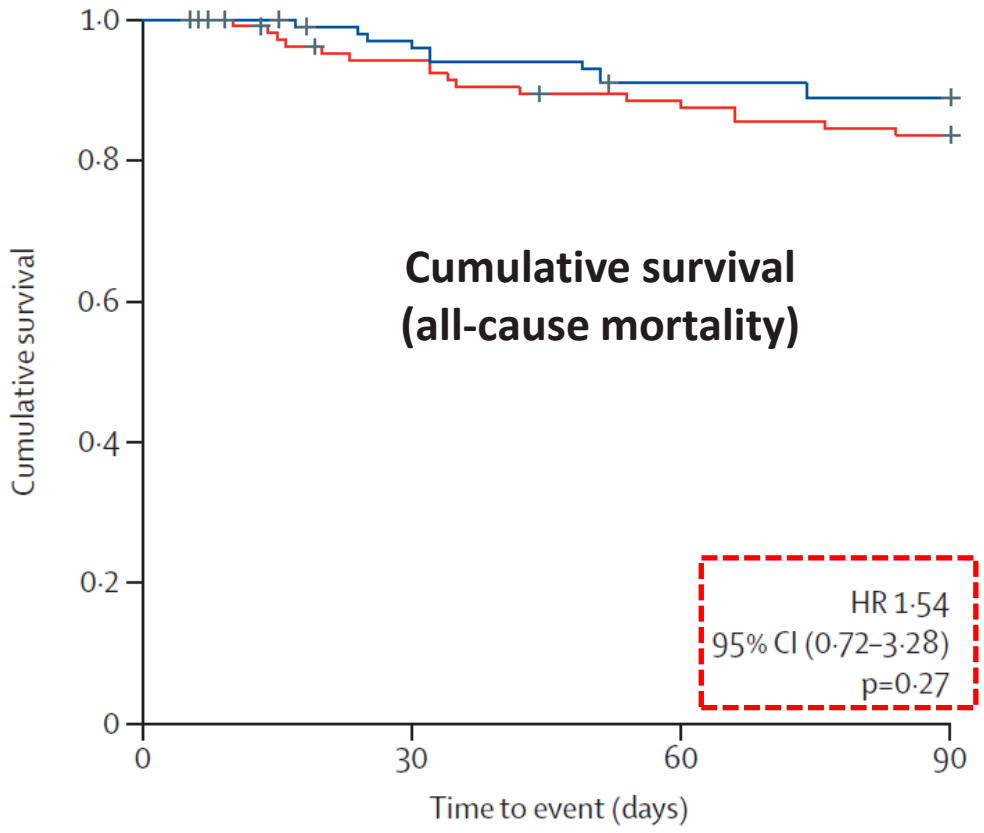


*Kaasch AJ, Lancet Infect Dis. 2024 May;24(5):523-534.*

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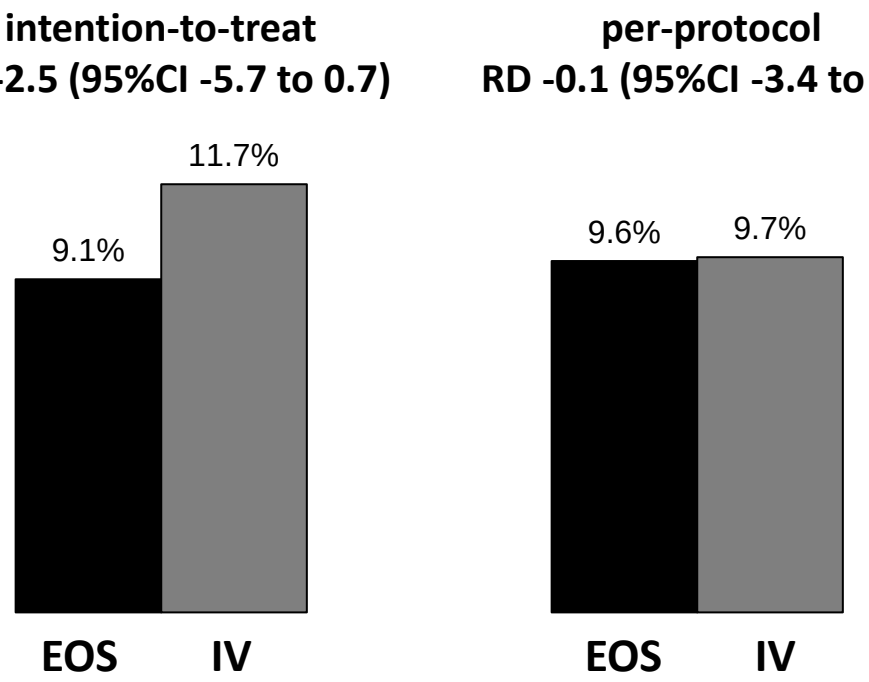
| | Intention-to-treat population | | | Clinically evaluable population | | |
|---|---|---|---|---|---|---|
| | Oral switch group (n=108) | Intravenous group (n=105) | Percentage-point difference (95% CI) | Oral switch group (n=86) | Intravenous group (n=79) | Percentage-point difference (95% CI) |
| **Primary endpoint** | | | | | | |
| SAB-related complication within 90 days | 14 (13%) | 13 (12%) | 0·7 (–7·8 to 9·1) | 3 (4%) | 4 (5%) | –2·9 (–9·6 to 3·9) |
| Reason primary outcome was met | | | | | | |
| SAB-related complication | 6 (6%) | 8 (8%) | –2·1 (–9·7 to 5·5) | 3 (4%) | 4 (5%) | –1·6 (–9·0 to 5·8) |
| Relapsing SAB | 3 (3%) | 4 (4%) | –1·0 (–6·8 to 4·7) | 2 (2%) | 2 (3%) | –0·2 (–5·1 to 4·7) |
| Deep-seated infection with *S aureus* | 5 (5%) | 8 (8%) | –3·0 (–10·4 to 4·4) | 3 (4%) | 4 (5%) | –1·6 (–9·0 to 5·8) |
| Death attributable to SAB | 2 (2%) | 0 | 1·9 (–1·6 to 5·3) | 1 (1%) | 0 | 1·2 (–2·3 to 4·6) |

*Kaasch AJ, Lancet Infect Dis. 2024 May;24(5):523-534.*

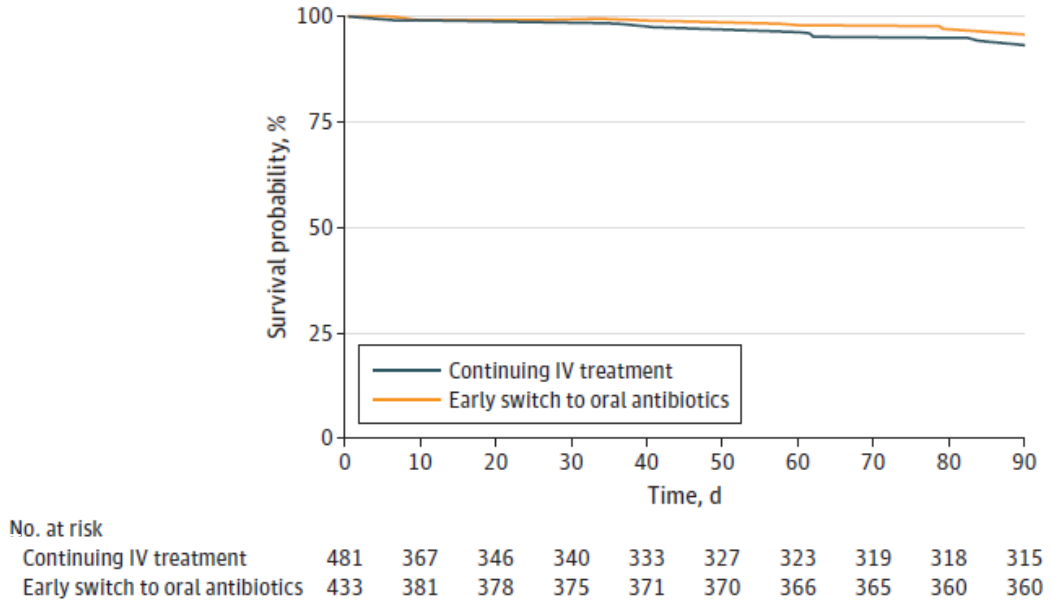
# Early switch from intravenous to oral antibiotics for patients with uncomplicated Gram-Negative bacteremia

Cohort study conducted in adults with uncomplicated GNB bacteremia in 4 hospitals in Denmark. The duration of follow-up was 90 days. Eligibility criteria included a blood culture positive for growth of GNB, clinical stability within 4 days of initial blood culture, an available susceptibility report on day 4, and initiation of appropriate IV antibiotic Tx within 24 hours of blood culture. Of 914 eligible individuals, 433 (47.4%) switched early to oral antibiotics while 481 (52.6%) received prolonged IV antibiotics (minimum of 5 days).

**IPW 90-day risk of all-cause mortality among individuals continuing IV therapy vs early switch to oral antibiotic**




**Survival curves for individuals who continued or switched to early oral antibiotics**




*Tingsgård S, .JAMA Netw Open. 2024 Jan 2;7(1):e2352314.*

# Ongoing RCTs on early oral stepdown

**INVEST trial**

**Early oral stepdown antibiotic therapy for uncomplicated Gram-negative bacteraemia - NCT05199324.**

*Recruiting*

INVEST trial randomizes patients to either early oral stepdown within 3 days or continuation of IV antibiotic therapy for at least 24 hours after randomization before clinical reassessment.

**SOAB trial**

**Switch to Oral Antibiotics in Gram-Negative Bacteremia - NCT04146922.**

*Completed*

SOAB trial randomized patients to either early oral stepdown between days 3 to 5 or continuation of IV treatment for the entire treatment duration.

In both trials, clinical stability, defined as being afebrile and hemodynamically stable, was required for eligibility.

*https://classic.clinicaltrials.gov/ct2/show/NCT05199324*
*https://classic.clinicaltrials.gov/ct2/show/ NCT04146922*