UNIVERSITÀ di VERONA

SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI

PANDORA ID - 25

TIME TO WEBINAR IN INFECTIOUS DISEASES

TMT CONGRESS & EVENTS

Il paziente con infezioni del torrente circolatorio: evidenze sul passaggio per os e sull'interruzione della terapia

Dr.ssa Elena Carrara
Malattie Infettive
Università di Verona








D come ‘Decidere’ La terapia antibiotica è necessaria?

D come ‘Drug’ Quale terapia antibiotica mirata scegliere?

D come ‘De-escalation’. Terapia antibiotica mirata e ranking degli antibiotici

D come ‘Due’ è meglio di uno?

D come ‘Dose’ (e frequenza) di somministrazione degli antibiotici

D come ‘Durata’ delle terapie

D come ‘Delivery’: quale modalità di somministrazione della terapia antibiotica

D come ‘De-labeling’ delle allergie








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Osteomyelitis

Bacteremia

Endocarditis

cIAI

cUTI

CAP AND SSTI

Meta-Analysis Osteo, Bacteremia, Endocarditis

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Link to Systematic Review and Meta-Analysis (with forest plots)

Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review

Noah Wald-Dickler, MD,[a,b,c] Paul D. Holtom, MD,[a,b] Matthew C. Phillips, MD,[a] Robert M. Centor, MD,[d,e] Rachael. A. Lee, MD,[d,e] Rachel Baden, MD,[a] Brad Spellberg, MD[a]

[a]Los Angeles County + University of Southern California Medical Center, Los Angeles; [b]Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles; [c]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles; [d]Department of Medicine, University of Alabama at Birmingham School of Medicine, Birmingham; [e]Birmingham Veterans Affairs (VA) Medical Center, Birmingham, Ala.

Ts

Credit to:

Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	14
Atypical CAP	1	3	Equal	1
Possible PNA in ICU	3	14-21	Equal	1*
VAP	5-8	10-15	Equal	3
Empyema	14-21	21-42	Equal	2
Cystic Fibrosis Exacerbation	10-14	14-21	Equal	1
Bronchiectasis Exacerbation	8	14	Equal	1
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	13**
Intra-abd Infection	4	8-10	Equal	3
Complex Appendicitis	1-2	5-6	Equal	2
Bacteremia (non *S. aureus*)	7	14	Equal	4†
Cellulitis/Wound/Abscess	5-6	10	Equal	4‡
Osteomyelitis	42	84	Equal	2
Osteo Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2ᵠ
Septic Arthritis	14	28	Equal	1
Bacterial Meningitis (peds)	4-7	7-14	Equal	6
AECB & Sinusitis	≤5	≥7	Equal	>25
Variceal Bleeding	2-3	5-7	Equal	2
Neutropenic Fever	AFx72h/3 d	+ANC>500/9 d	Equal	2
Post Op Prophylaxis	0-1	1-5	Equal	57Ψ
Erythema Migrans (Lyme)	7-10	14-20	Equal	3
P. vivax Malaria	7	14	Equal	1
Early Syphilis	1 IM	3 IM in 3 wks	Equal	2

Total: 24 Conditions >150 RCTs

*Low CPIS score, CAP, HAP, VAP combined; **2 RCT included males, the smaller one found lower 10-18 d f/up cure in males with 7 days of therapy but no difference at longer follow-up, larger exclusive male study found no diff in cure, 3 Peds RCTs, 1 short course was superior on recurrence, 1 short course had more UTI failure at day 6-14 but not after day 14; 1 short course had more recurrence but still less overall abx despite retreatment with no difference in long term cure; †GNB bacteremia also in UTI/cIAI RCTs; ‡3 RCTs equal, 1 (low dose oral flucox) ↑relapses 2° endpoint; ᵠall patients debrided, in 1 study total bone resection (clean margins); ΨIncludes meta-analysis of 52 RCTs; refs at https://www.bradspellberg.com/shorter-is-better

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Shorter Is Better

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Duration of antibiotic treatment for GN-BSI: Systematic review and individual participant data (IPD) meta-analysis

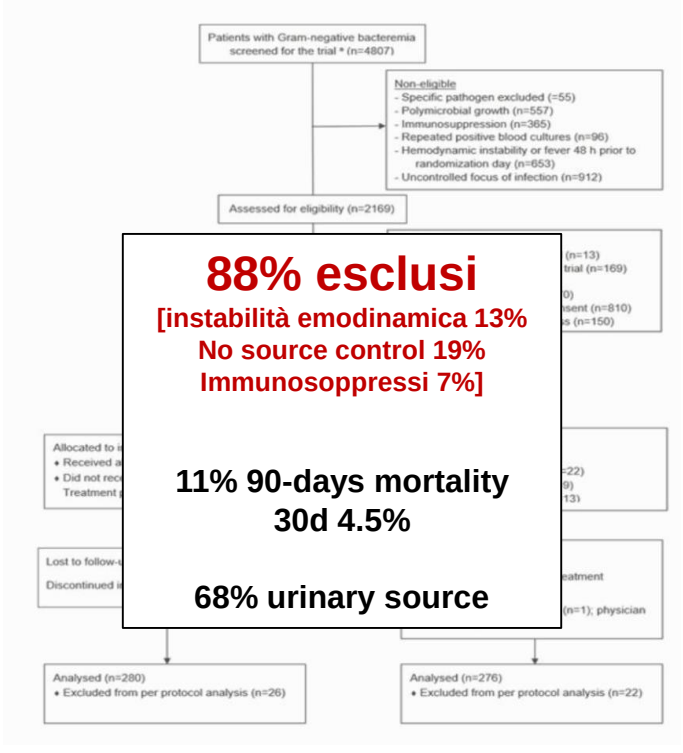
Trial characteristics	Yahav (2018) Bacteremia Duration	Von Dach (2020) PIRATE	Molina (2021) SHORTEN
Design	Investigator-initiated randomized controlled trial	Investigator-initiated randomized controlled trial	Investigator-initiated randomized controlled trial
Study period	2013–2017	2017–2019	2014–2016
Inclusion criteria	Adults with growth of Gram-negative bacteria in one or more blood cultures, hemodynamically stable and afebrile for at least 48 h.	Adults with growth of Gram-negative fermenters in at least one blood culture and treatment with a microbiologically efficacious antibiotic.	Adults with a diagnosis of *enterobacterales* bloodstream infections with appropriate source control.
Exclusion criteria	Sources of infection requiring prolonged treatment, fever or hemodynamic instability in the 48 h prior to randomization, uncontrolled focus of infection, polymicrobial growth involving Gram-positive bacteria, specific pathogens (Brucella, Salmonella), or specific immunosuppression (human immunodeficiency virus, neutropenia).	Fever or hemodynamic instability in the 24 h prior to recruitment, severe immunosuppression, bacteremia with nonfermenting bacilli or polymicrobial, gram-positive growth, recurrent bacteremia, or complicated Infections.	Pregnancy, noncontrolled source of infection and no expectation of being controlled in the subsequent 24 h, patients undergoing chemotherapy with neutropenia <500 cells/mm3 expected for more than 7 days, infections requiring prolonged antibiotic treatment, infections caused by a carbapenemase producing member of the Enterobacterales, polymicrobial bacteraemia, and expectation of survival <48 h.
Timing of randomization	At least 48 h without fever and hemodynamically stable and until day 7 from positive culture	Day 5 from first positive culture	<48 h since pathogen identification
Number randomized	604	504	248
Primary outcome of the original study	Composite at 90 days of mortality, relapse, complications, and readmission or extended hospitalization	Composite at 30 days of mortality, relapse, distal complications, and the restarting of antibiotics for suspected relapse	Number of days of antibiotic treatment required at the end of follow-up.

Variable	Yahav et al.		von Dach et al.		Molina et al.		Mantel-Haenszel OR (95% CI)	Breslow–Day P value
	7 days (n = 306)	14 days (n = 298)	7 days (n = 169)	14 days (n = 165)	7 days (n = 117)	14 days (n = 127)		
90-d mortality	36 (11.8)	32 (10.7)	14 (8.3)	9 (5.5)	10 (8.5)	15 (11.8)	1.08 (0.73–1.58)	0.41
30-d mortality	16 (5.2)	12 (4.0)	6 (3.6)	4 (2.4)	4 (3.4)	8 (6.3)	1.08 (0.62–1.91)	0.40
Relapse of bacteremia –30d	8 (2.6)	8 (2.7)	2 (1.2)	3 (1.8)	7 (5.9)	6 (4.7)	1.00 (0.50–1.97)	0.82
Readmissions - 30d	74 (24.2)	79 (26.5)	14 (8.3)	9 (5.5)	11 (9.2)	12 (9.3)	0.98 (0.73–1.33)	0.49
Hospital length of stay, Median (IQR)	1 (0–4)	1 (0–4)	4 (1.3–10)	4 (1–11)	4 (0–9)	3 (0–8)	–	0.71*

30d mortality 7 vs 14 days OR 1.08 (0.62–1.91)

Turjieman A, eClinicalMedicine 2023

Ma chi sono i pazienti arruolati in questi RCT?

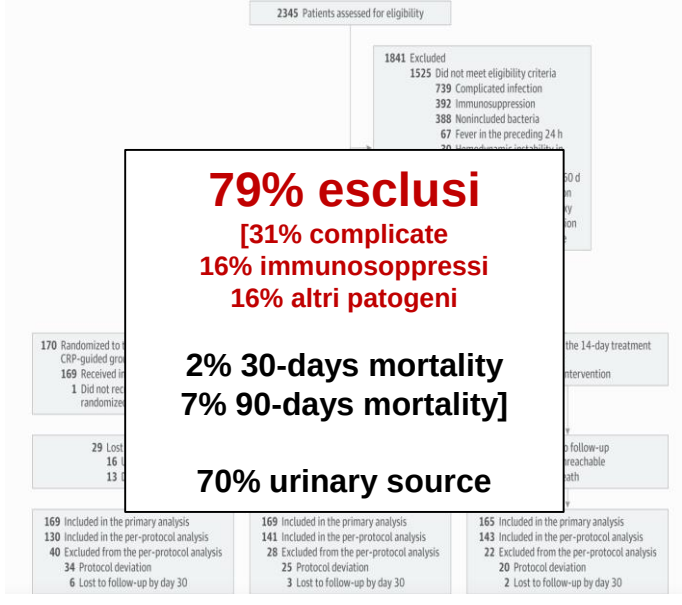


88% esclusi
[instabilità emodinamica 13%
No source control 19%
Immunosoppressi 7%]

11% 90-days mortality
30d 4.5%

68% urinary source

Yahav (2018)
Bacteremia Duration

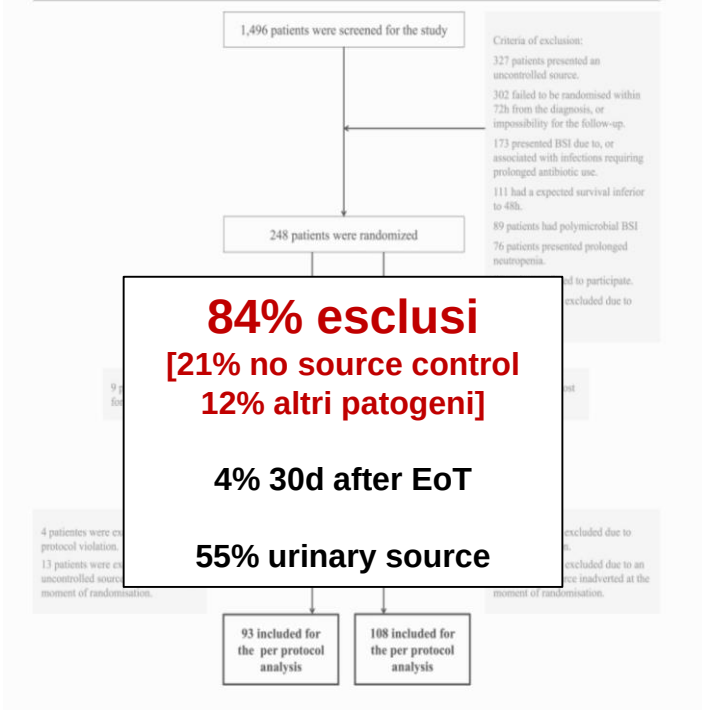


79% esclusi
[31% complicate
16% immunosoppressi
16% altri patogeni

2% 30-days mortality
7% 90-days mortality]

70% urinary source

Von Dach (2020)
PIRATE



84% esclusi
[21% no source control
12% altri patogeni]

4% 30d after EoT

55% urinary source

Molina
(2021)SHORTEN

Duration of antibiotic treatment for Gram-negative bacteremia - Systematic review and individual participant data (IPD) meta-analysis

	Yahav et al. (2018)	von Dach et al. (2020)	Molina et al. (2021)
Trial characteristics			
Design	Investigator-initiated randomized controlled trial	Investigator-initiated randomized controlled trial	Investigator-initiated randomized controlled trial
Study period	2013–20		
Inclusion criteria	Adults w more bl afebrile f		*nterobacterales* bloodstream ource control.
Exclusion criteria	Sources fever or randomi polymicr specific immuno neutrope		urce of infection and no ed in the subsequent 24 h, nerapy with neutropenia more than 7 days, d antibiotic treatment, benemase producing ales, polymicrobial of survival <48 h.
Timing of randomization	At least and unti		fication
Number randomized	604		
Primary outcome of the original study	Composi complica hospitali		treatment required at the

Uncontrolled source;

Hemodynamically instable /

febrile after 48hrs;

Severely immunocompromised;

Polymicrobial

Non-fermenters, CRE

Variable								ow–Day ue
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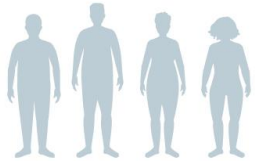
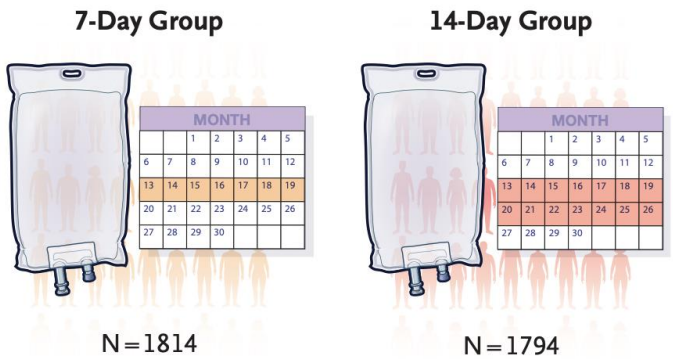
Turjieman A, eClinicalMedicine

Antibiotic Treatment for 7 or 14 Days for Bloodstream Infection (BALANCE Trial)

Patients

- 3608 patients
- Median age, [illegible] years
- Male 53%; Female 47%





Daneman N, N Engl J Med 2025

Table S2. Full BALANCE Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1) Patient is in an intensive care unit or non-	1) Patient already enrolled in the trial 2) Patient has severe immune system compromise, as defined by: absolute neutrophil count <0.5x10^9/L; or is receiving immunosuppressive treatment for solid organ or bone marrow or stem cell transplant 3) Patient has a prosthetic heart valve or synthetic endovascular graft (post major vessel repair with synthetic material) (note: coronary artery stents are not an exclusion) 4) Patient has documented or suspicion of
	for
	i) infective endocarditis; ii) osteomyelitis/septic arthritis;
	c.) ing
	not
	ith ng
	(CLSI) Guidelines: coagulase negative staphylococci; or *Bacillus spp.;* or *Corynebacterium spp.;* or *Propionibacterium spp.*; or *Aerococcus spp.;* or *Micrococcus spp.*
	lugdunensis
	7) Patient has a positive blood culture with Candida spp. or other fungal species.

✓ ***Ospedalizzati ICU/non-ICU***

✓ ***Batteriemie clinicamente significative***

✗ Neutropenici/SOT/HSCT

✗ Portatori di: protesi valvolari/ device endovascolari

✗ Sospetta endocardite/osteomielite

✗ Inadeguato source control (ascessi non drenati, protesi ritenute)

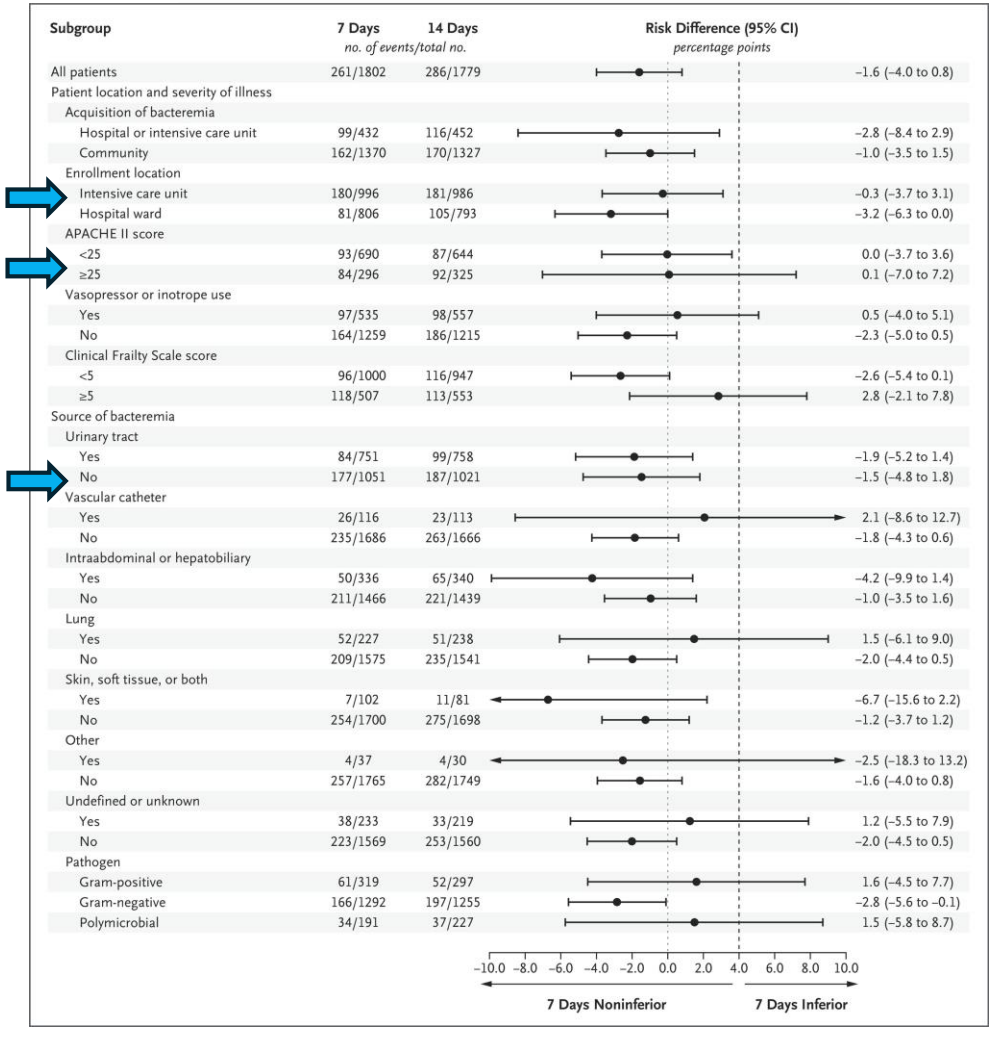
✗ Staph aureus e Candida

LO STUDIO ‘BALANCE’ RIESCE A DIRCI QUALCOSA IN PIU’?

Table S3. Full List of Pathogens Causing Bloodstream Infections (for Primary Intention-to-Treat Analysis)

	Overall	7-Day Arm	14-Day Arm
	N=3608	N=1814	N=1794
Escherichia coli	1582 (43.8)	805 (44.4)	777 (43.3)
Klebsiella pneumoniae	552 (15.3)	273 (15)	279 (15.6)
Enterococcus species	250 (6.9)	119 (6.6)	131 (7.3)
Coagulase-negative staphylococci	174 (4.8)	81 (4.5)	93 (5.2)
Pseudomonas species	170 (4.7)	80 (4.4)	90 (5)
Streptococcus pneumoniae	164 (4.5)	86 (4.7)	78 (4.3)
Enterobacter species	157 (4.4)	80 (4.4)	77 (4.3)
Proteus species	133 (3.7)	58 (3.2)	75 (4.2)
Serratia species	86 (2.4)	38 (2.1)	48 (2.7)
Streptococcus agalactiae	75 (2.1)	40 (2.2)	35 (2)
Streptococcus pyogenes	74 (2.1)	39 (2.1)	35 (2)
Bacteroides species	57 (1.6)	28 (1.5)	29 (1.6)
Citrobacter species	45 (1.2)	19 (1)	26 (1.4)
Streptococcus anginosus	43 (1.2)	18 (1)	25 (1.4)
Acinetobacter species	40 (1.1)	24 (1.3)	16 (0.9)
Viridans streptococci	40 (1.1)	22 (1.2)	18 (1)
Hemophilus influenzae	37 (1)	16 (0.9)	21 (1.2)
Group G streptococci	37 (1)	25 (1.4)	12 (0.7)
Streptococcus species	31 (0.9)	14 (0.8)	17 (0.9)
Klebsiella aerogenes	29 (0.8)	17 (0.9)	12 (0.7)
Morganella morganii	25 (0.7)	12 (0.7)	13 (0.7)
Group C streptococci	23 (0.6)	10 (0.6)	13 (0.7)
Streptococcus bovis/ Streptococcus gallolyticus	22 (0.6)	15 (0.8)	7 (0.4)

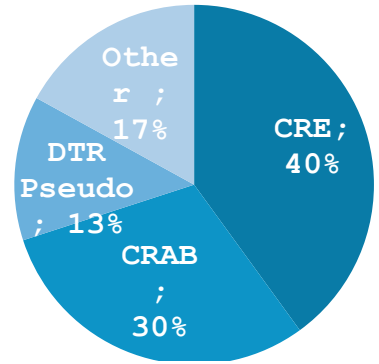
Monomicrobial Gram-Neg 71%
Monomicrobial Gram-Pos 17%
Polymicrobial 11%



Daneman N, N Engl J Med 2025

E I PAZIENTI CON INFEZIONI DA MDR?

Seven versus 14 days of antimicrobial therapy for severe multidrug-resistant Gram-negative bacterial infections in intensive care unit patients (OPTIMISE): a randomised, open-label, non-inferiority clinical trial.

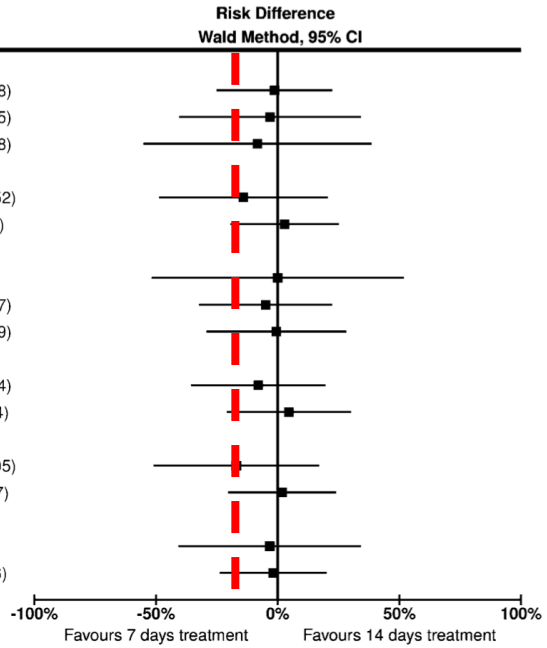


- ✓ Adults hospitalized in the ICU (> 48 hours) with a severe infection caused by a MDR-GNB;
- ✓ **hemodynamically stable and afebrile for at least 48 h on day 7±1 of appropriate antimicrobial therapy**

- ✗ Required longer therapy *(endo, osteo, IAI with no appropriate source control, SNC, empyema)*
- ✗ immunosuppression *(neutropenia, AIDS, SOT, HSCT)*;
- ✗ Persistent BSI
- ✗ concomitant uncontrolled infection by another GNB
- ✗ DNR order

A

Subgroup (ITT)	7 days Event	7 days Total	14 days Event	14 days Total	RD (95% CI)
1. Microorganisms					
Enterobacterales	15	34	15	33	-1.34 (-25.16; 22.48)
Acinetobacter baumannii	7	19	4	10	-3.16 (-40.47; 34.15)
Pseudomonas aeruginosa	7	12	4	6	-8.33 (-55.24; 38.58)
2. Carbapenem susceptibility profile					
Susceptible	5	13	10	19	-14.17 (-48.86; 20.52)
Resistant	24	52	13	30	2.82 (-19.5; 25.14)
3. Infection severity criteria					
Bloodstream infection	1	4	1	4	0 (-60.01; 60.01)
Pneumonia	12	28	11	23	-4.97 (-32.41; 22.47)
Sepsis or Septic Shock	12	27	9	20	-0.56 (-29.31; 28.19)
4. Appropriate empirical therapy					
Yes	12	26	13	24	-8.01 (-35.66; 19.64)
No	13	33	8	23	4.61 (-21.02; 30.24)
5. Combination therapy					
Yes	3	14	5	13	-17.03 (-51.11; 17.05)
No	22	45	16	34	1.83 (-20.41; 24.07)
6. Site of infection					
Low risk	6	14	6	13	-3.3 (-40.8; 34.2)
High risk	19	45	15	34	-1.9 (-23.96; 20.16)



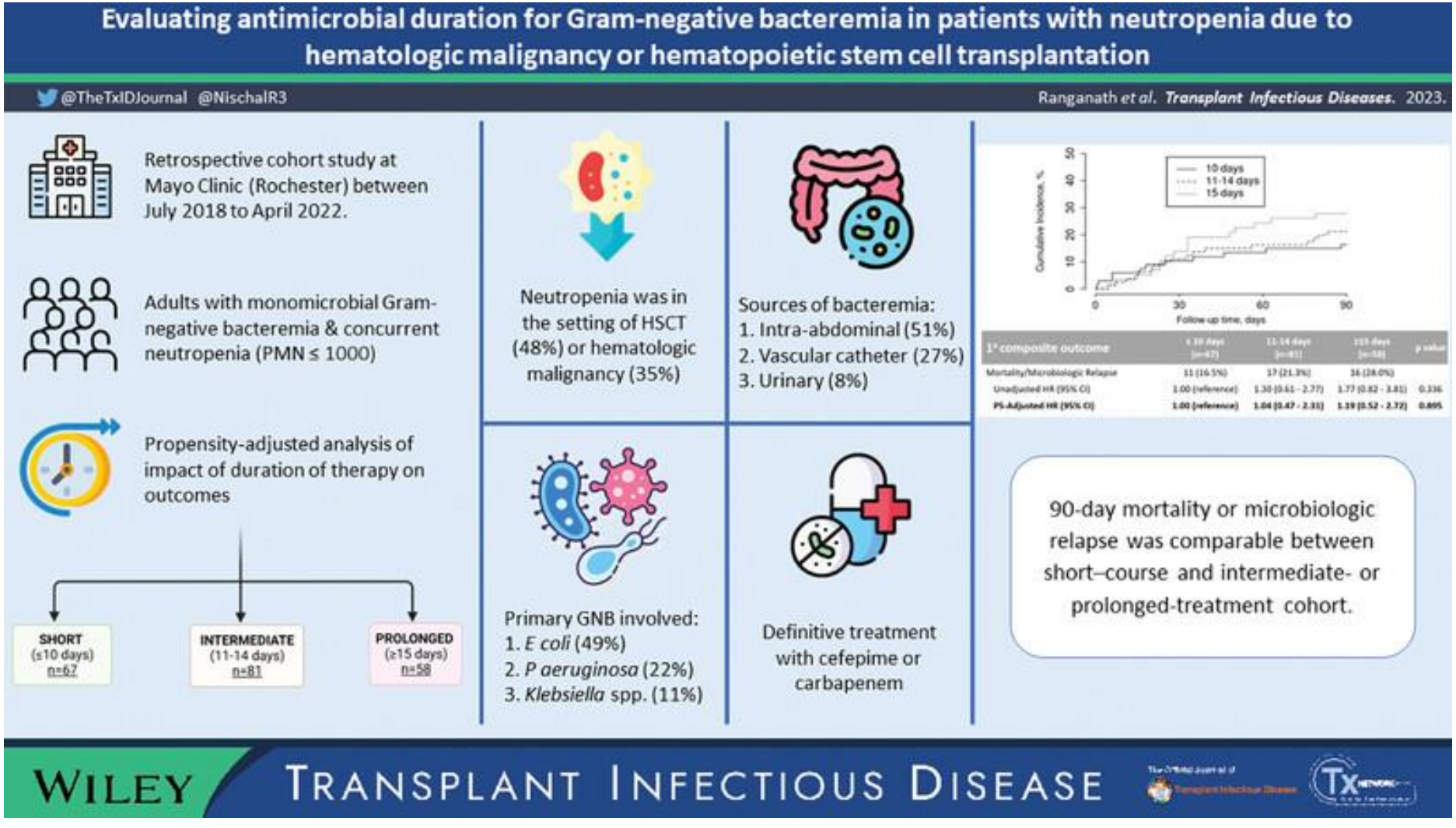
106 patients [520]
- **CRE 40%**
- **CRAB 30%**
- **DTR Pseudo 13%**

28-day mortality
37% short vs 40% long

Arns *et al. Critical Care (2024) 28:412*

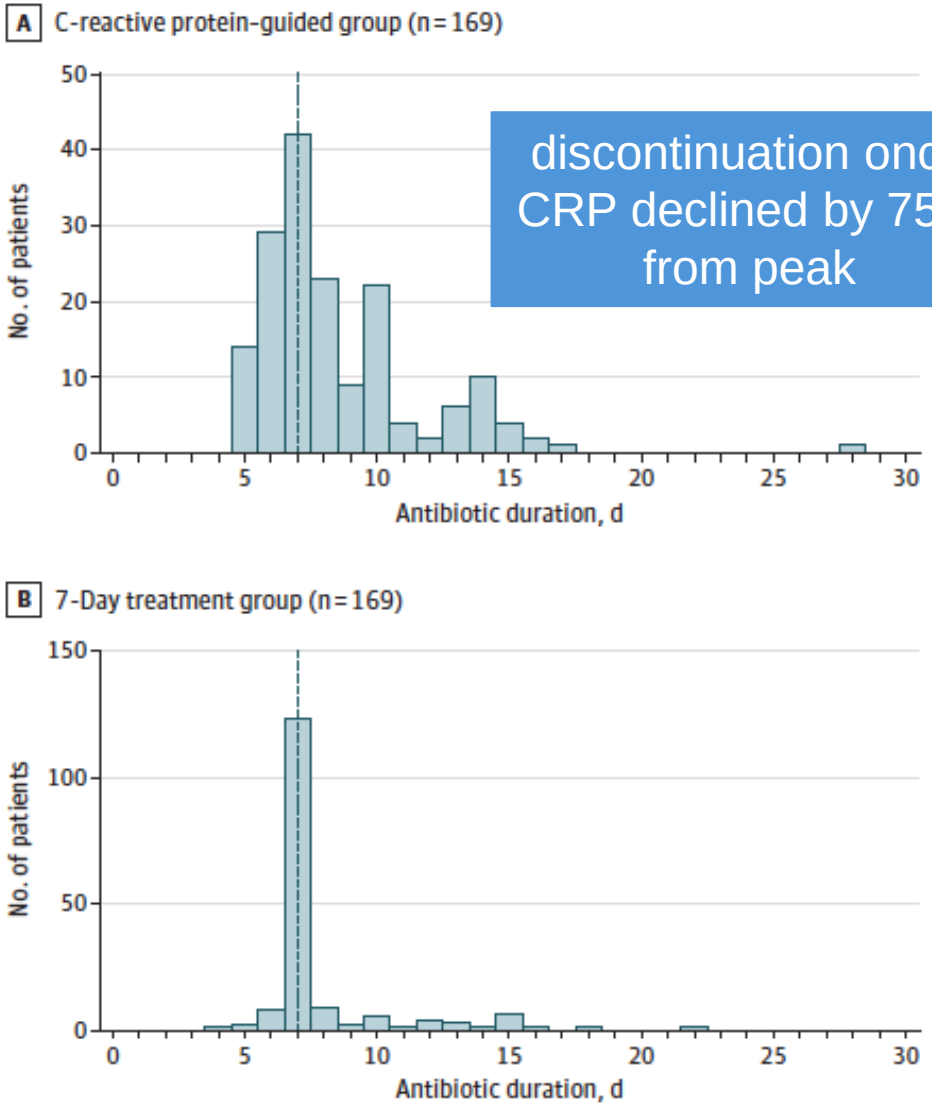
E I NEUTROPENICI?

Treatment duration in FN patients with GN-BSI



C’è qualcosa che mi aiuta a decidere caso per caso??

Figure 2. Durations of Antibiotic Therapy in the Primary Analysis Set in a Study of the Effect of C-Reactive Protein (CRP)–Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on Clinical Failure in Patients With Uncomplicated Gram-Negative Bacteremia



discontinuation once CRP declined by 75% from peak

The dotted vertical line indicates the median antibiotic duration for that group. The patient in the CRP group who received 28 days of antibiotics was diagnosed with multiple kidney abscesses the day after randomization, so CRP was not used to guide therapy.

The median N of antibiotic days:

- 9 (8-14) in the CRP guided group,
- 9 (7-14) in the 7-day group,
- and 16 (14-18) in the 14-day group

Von Dach, JAMA 2020

Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis: The ADAPT-Sepsis Randomized Clinical Trial

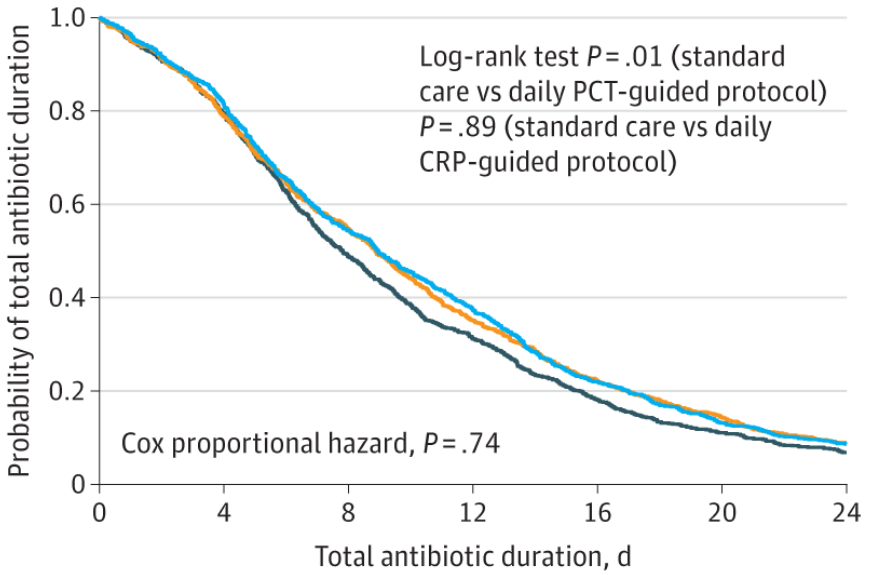
'no test' (control group). The antibiotic discontinuation protocols are as follows, described alongside identical standardised advice for each group:

PCT protocol	CRP protocol	Advice for PCT and CRP protocols	Advice for control group
Standard care + daily serum PCT measurement until antibiotic discontinuation	Standard care + daily serum CRP measurement until antibiotic discontinuation	Written advice delivered daily by local research team to treating clinician until antibiotic discontinuation	Written advice delivered daily by local research team to treating clinician until antibiotic discontinuation
PCT < 0.25µg/l	CRP < 25mg/l	*"Protocol **STRONGLY** supports stopping antibiotics"*	*"Protocol supports usual care"*
PCT fall by ≥80% from baseline or PCT ≥ 0.25 & ≤ 0.50 µg/l	CRP fall by 50% from baseline	*"Protocol **suggests** stopping antibiotics"*	*"Protocol supports usual care"*

- 41 hospitals in UK
- 2760 patients
- mean age 60
- 67%Community-acquired
- Source:
  - 40% pneumonia
  - 13% UTI
  - 25% IAI
- 50% septic shock

From: **Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis: The ADAPT-Sepsis Randomized Clinical Trial**

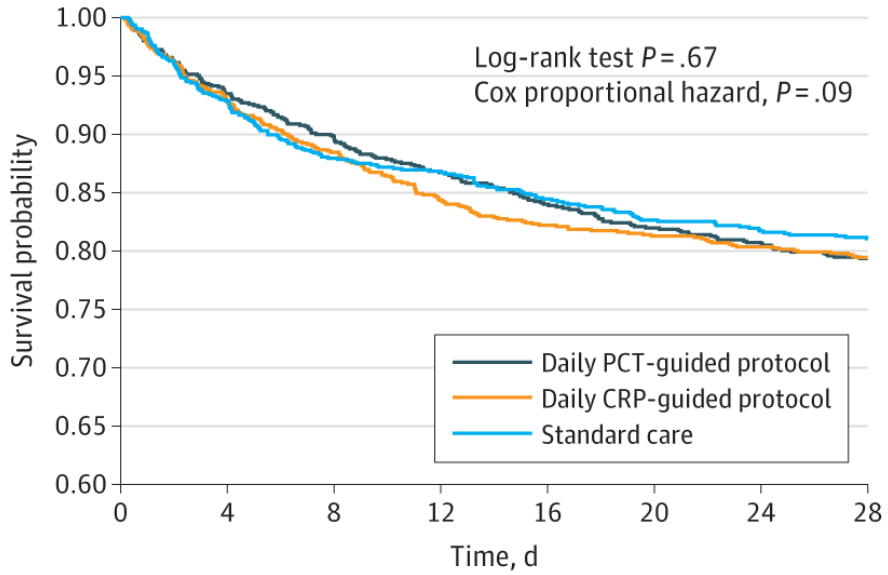
A Probability of total antibiotic duration (primary effectiveness outcome)



No. at risk

Guided protocol							
Daily PCT	897	713	438	280	163	99	61
Daily CRP	891	703	488	313	197	128	80
Standard care	904	737	491	339	199	119	78

B All-cause mortality up to 28 days (safety outcome)



No. at risk

Guided protocol							
Daily PCT	917	837	797	768	742	722	709	695
Daily CRP	923	831	783	742	720	710	701	691
Standard care	918	838	784	769	744	728	715	708

Kaplan-Meier Curves for Probability of Antibiotic Duration and Mortality to 28 DaysThe medians of the total antibiotic treatment duration up to 28 days for each of the 3 groups are 7.8 (IQR, 4.5-13.6) days for the daily procalcitonin (PCT)–guided protocol, 8.9 (IQR, 4.5-14.9) days for the daily C-reactive protein (CRP)–guided protocol, and 9.0 (IQR, 4.7-14.6) days for standard care.

‘Test of cure’ microbiologico

19. For adults with uncomplicated bacteremia (defined as patients with positive blood culture results and the following: exclusion of endocarditis; no implanted prostheses; follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow MRSA; defervescence within 72 h of initiating effective therapy; and no evidence of metastatic sites of infection), vancomycin **(A-II)** or daptomycin 6 mg/kg/dose IV once daily **(AI)** for at least 2 weeks. For complicated bacteremia (defined as patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia), 4–6 weeks of therapy is recommended, depending on the extent of infection. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily **(B-III)**.

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children, 2011

11. Follow-up blood cultures should be performed every day or every other day to establish the time point at which candidemia has been cleared *(strong recommendation; low-quality evidence)*.
12. Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia *(strong recommendation; moderate-quality evidence)*.

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by IDSA

Drug treatment of PVE should last longer (≥6 weeks) than that of NVE (2–6 weeks) but is otherwise similar. In staphylococcal PVE, the regimen should include rifampin whenever the strain is susceptible, even if some recent data have shown no differences in outcomes between patients with PVE treated with rifampin vs. those treated without.[260,261]

In NVE needing valve replacement by a prosthesis during antibiotic therapy, the post-operative antibiotic regimen should be that recommended for NVE, not for PVE. In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy (negative blood culture in the case of initial positive blood culture), not on the day of surgery. A new full course of treatment should only start if valve cultures are positive.

2023 ESC Guidelines for the management of endocarditis

ESC European Society of Cardiology

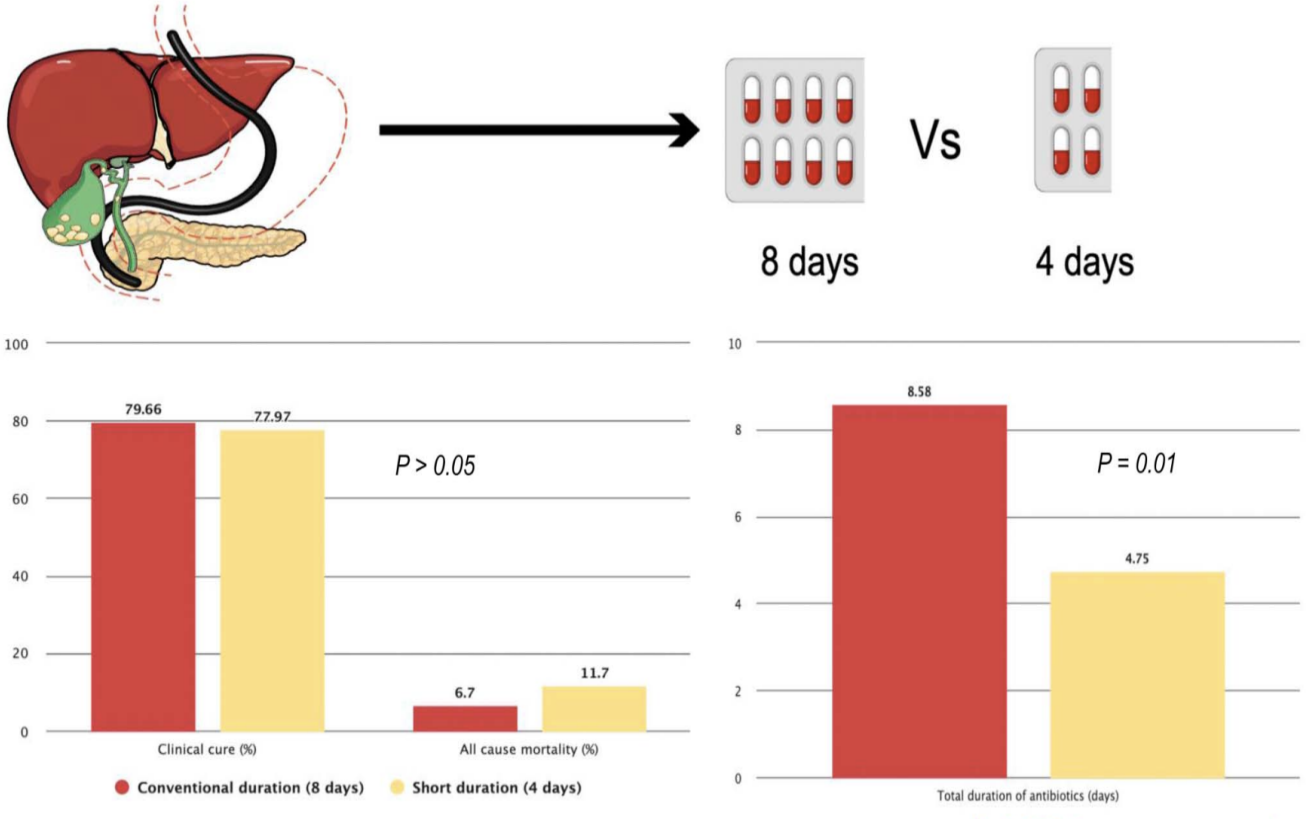
Source control chirurgico:
Shorter is better (or not worse) - Cholangitis

Single-center, randomized, open-label, non-inferiority trial in North India

Included adult patients (N120) with moderate or severe **cholangitis AFTER SOURCE CONTROL!!**

Randomized to receive 4 days (SD, n=60) vs. 8 days (CD, n=60) of antibiotics post-drainage

Conventional vs short duration of antibiotics in moderate/severe cholangitis



Deshidi S et al. *Am J Gastroenterol.* 2024. doi:10.14309/ajg.0000000000002499

AJG The American Journal of GASTROENTEROLOGY

Source control: device removal

Guidelines for the Management of Intravascular Catheter–Related Infections

Leonard A. Mermel,[1] Barry M. Farr,[2] Robert J. Sherertz,[3] Issam I. Raad,[4] Naomi O'Grady,[5] JoAnn S. Harris,[6] and Donald E. Craven[7]

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EXECUTIVE SUMMARY

These guidelines from the Infectious Diseases Society of America (IDSA), the American College of Critical Care Medicine (for the Society of Critical Care Medicine), and the Society for Healthcare Epidemiology of America contain recommendations for the management of adults and children with, and diagnosis of infections related to, peripheral and nontunneled central venous catheters (CVCs), pulmonary artery catheters, tunneled central catheters, and implantable devices. The guidelines, written for clinicians, contain IDSA evidence-based recommendations for assessment of the quality and strength of the data. Recommendations are presented according to the type of catheter, the infecting organism, and the associated complications.

Intravascular catheter–related infections are a major cause of morbidity and mortality in the United States. Coagulase-negative staphylococci, *Staphylococcus aureus*, aerobic gram-negative bacilli, and *Candida albicans* most commonly cause catheter-related bloodstream infection. Management of catheter-related infection varies according to the type of catheter involved. After appropriate cultures of blood and catheter samples are done, empirical iv antimicrobial therapy should be initiated on the basis of clinical clues, the severity of the patient's acute illness, underlying disease, and the potential pathogen(s) involved. In most cases of nontunneled CVC–related bacteremia and fungemia, the CVC should be removed. For management of bacteremia and fungemia from a tunneled catheter or implantable device, such as a port, the decision to remove the catheter or device should be based on the severity of the patient's illness, documentation that the vascular-access device is infected, assessment of the specific pathogen involved, and presence of complications, such as endocarditis, septic thrombosis, tunnel infection, or metastatic seeding. When a catheter-related infection is documented and a specific pathogen is identified, systemic antimicrobial therapy should be narrowed and consideration given for antibiotic lock therapy, if the CVC or implantable device is not removed.

These guidelines address the issues related to the management of catheter-related bacteremia and associated complications. Separate guidelines will address specific issues related to the prevention of catheter-related infections. Performance indicators for the management of catheter-related infection are included at the end of the document. Because the pathogenesis of catheter-related infections is complicated, the virulence of the pathogens is variable, and the host factors have

Received 14 December 2000; electronically published 3 April 2001.

This guideline was prepared jointly by the Intravenous Guideline Subcommittee of the Infectious Diseases Society of America, the American College of Critical Care Medicine (for the Society of Critical Care Medicine), and the Society for Healthcare Epidemiology of America. The guideline is published concurrently in *Infection Control and Hospital Epidemiology* (2001, vol. 22, no. 4) and will be published in the *Journal of Intravenous Nursing* (2001, vol. 24, no. 3).

Reprints or correspondence: Dr. Donald E. Craven, Lahey Clinic Medical Center, Burlington, MA 01806 (Donald.E.Craven@Lahey.org).

Clinical Infectious Diseases 2001;32:1249–72

1058-4838/2001/3209-0001$03.00

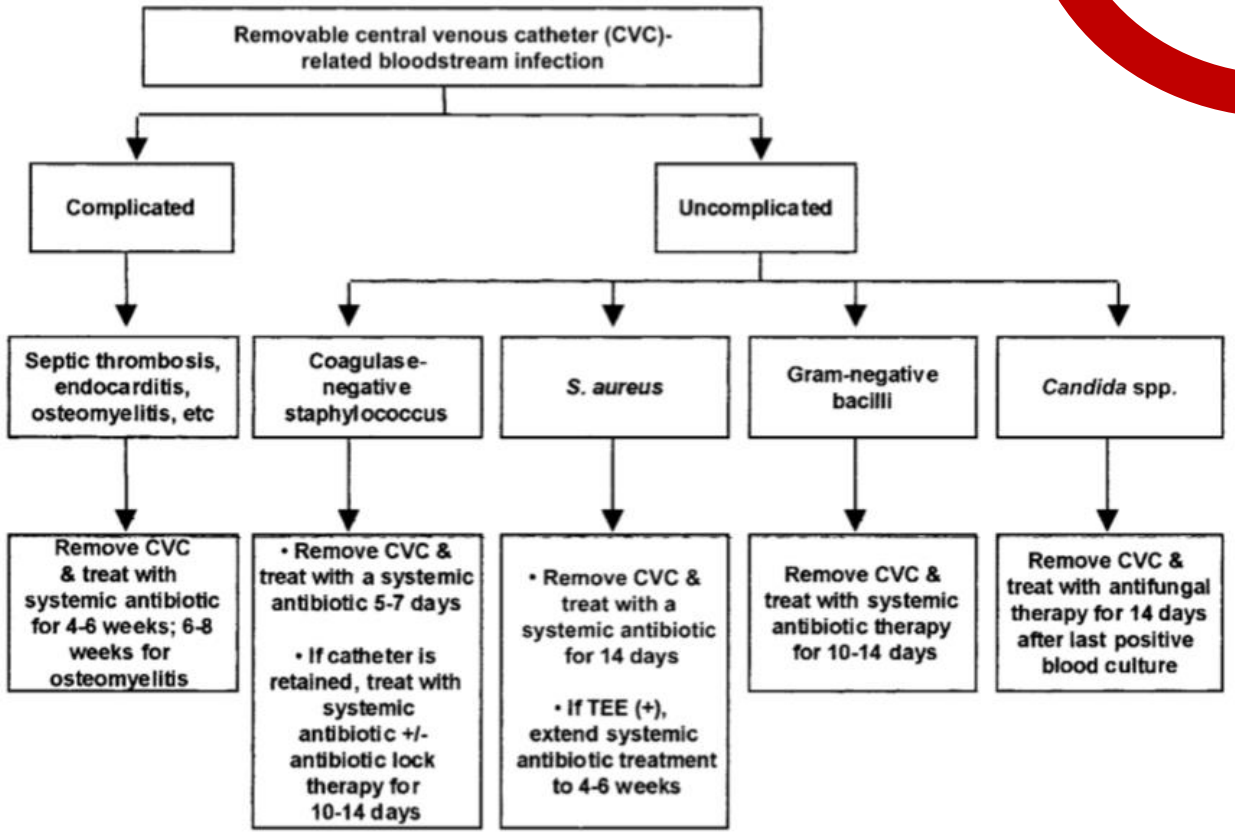


Figure 2. Approach to the management of patients with nontunneled central venous catheter (CVC)–related bloodstream infection. Duration of treatment will depend on whether the infection is complicated or uncomplicated. The catheter should be removed and systemic antimicrobial therapy should be initiated, except in some cases of uncomplicated catheter-related infection due to coagulase-negative staphylococci. For infections due to *Staphylococcus aureus,* transesophageal echocardiography (TEE) may reveal the presence of endocarditis and help to determine the duration of treatment. +, positive; −, negative.

INDICAZIONI PER L'INTERRUZIONE PRECOCE DELLA TERAPIA NELLE INFEZIONI DEL TORRENTE CIRCOLATORIO

- Interruzione precoce a 7 giorni (o anche meno?) in pazienti con batteriemie in cui viene fatto un **adeguato source control**, indipendentemente dal tipo di patogeno (tranne Candida e SA) e dalla severità della presentazione clinica;
- Probabilmente posso generalizzare anche a pazienti immunocompromessi e a patogeni MDR;

Cosa mi aiuta a decidere un trattamento più individualizzato (utile soprattutto per le infezioni complicate in cui il controllo della fonte non è immediato):

- Biomarcatori (protocolli per guidare durata e non inizio!)
- Colture di follow-up
- Rimozione del device
- Source control chirurgico

THE BUG DOESN'T CARE HOW THE DRUG GETS THERE!!!

D come 'Decidere' La terapia antibiotica è necessaria?

D come 'Drug' Quale terapia antibiotica empirica scegliere?

D come 'De-escalation'. Terapia antibiotica mirata e ranking degli antibiotici

D come 'Due' è meglio di uno?

D come 'Dose' (e frequenza) di somministrazione degli antibiotici

D come 'Durata' delle terapie

D come 'Delivery': quale modalità di somministrazione della terapia antibiotica

D come 'De-labeling' delle allergie

D COME ‘DELIVERY’: THE BUG DOESN’T CARE HOW THE DRUG GETS THERE (BUT IT NEEDS TO GET THERE!!)

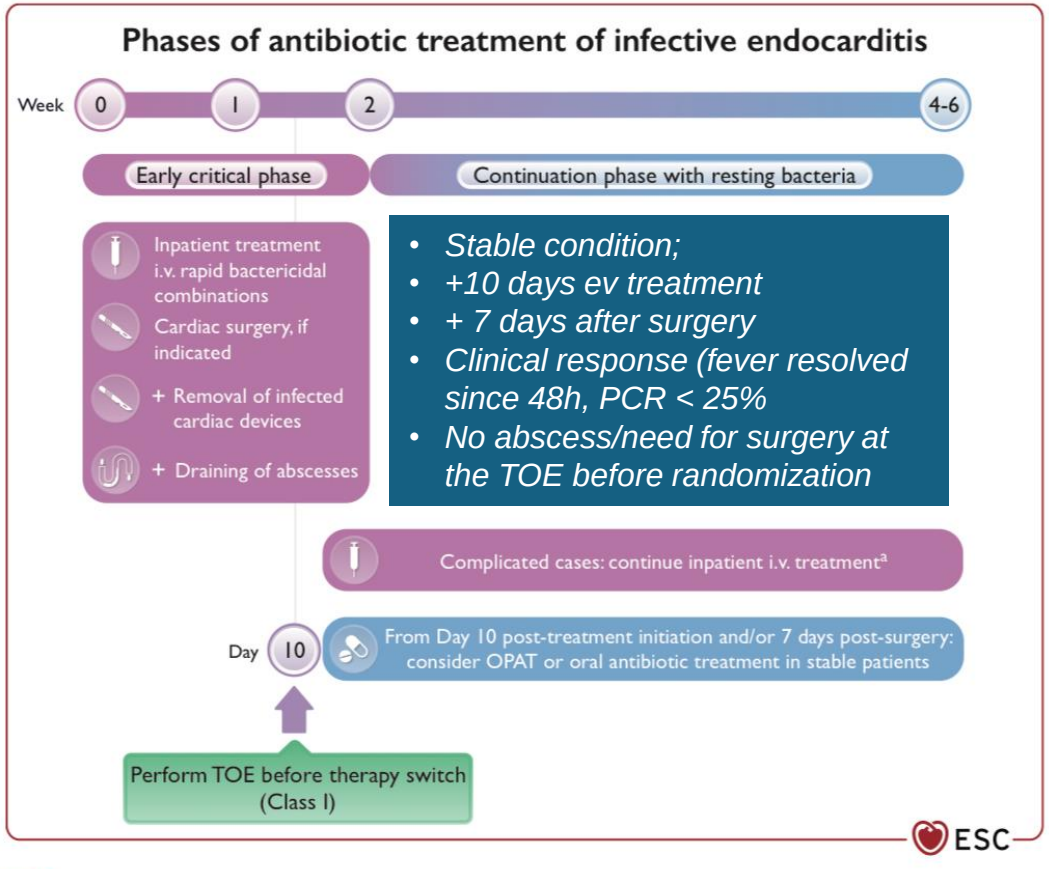
Oral Antibiotics and Their Coverage and Bioavailability (%)

Staphylococcus	*Enterococcus*	*Streptococcus*	*Enterobacteriaceae*	*Pseudomonas*
MRSA	Linezolid[a] (100%)	**GAS/GBS**	Ciprofloxacin[c] (70%)	Ciprofloxacin[c] (70%)
Linezolid[a] (100%)	Ampicillin[d] (50%)	Penicillin VK (50%)	Levofloxacin[c] (99%)	Levofloxacin[c] (99%)
TMP/SMX	Nitrofurantoin	Amoxicillin (85%)	Moxifloxacin (90%)	Delafloxacin (60%)
(90%-100%)	(80%)	Cephalexin (90%)	Amox/Clav (85%)	
Clindamycin[b] (90%)	Amox/Clav (85%)	Levofloxacin[c] (99%)	Amoxicillin (85%)	
Doxycycline[c] (95%)		Clindamycin[b] (90%)	Cefixime (40%-50%)	
		Linezolida (100%)	Cefuroxime[b] (70%)	
MSSA			Cephalexin (90%)	
Cephalexin (90%)		***S Pneumoniae***	TMP/SMX (90%-100%)	
Dicloxacillin[d]		Amoxicillin (85%)		
(50%-75%)		Doxycycline[c] (95%)		
		Azithromycin (30%-50%)		
		Levofloxacin[c] (99%)		

[a] *Concurrent ingestion of foods rich in tyramine or tyrosine could lead to hypertensive crisis or serotonin syndrome.*
[b] *Take with food.*
[c] *Oral absorption is decreased with concurrent calcium/magnesium-containing foods and products. Avoid taking with antacids and separate 2 h before or 6 h after calcium foods.*
[d] *Take on empty stomach.*
Amox/Clav: amoxicillin/clavulanate; GAS/GBS: group A Streptococcus/*group B* Streptococcus; *MRSA: methicillin-resistant* S aureus; *MSSA: methicillin-resistant susceptible* S aureus; *TMP/SMX: trimethoprim/sulfamethoxazole.*
Source: Reference 18.

Gilbert DN, Chambers HF, Eliopoulos GM, et al. *Sanford Guide To Antimicrobial Therapy*. 50th ed. Dallas, TX: Antimicrobial Therapy, Inc. 2020.

D COME ‘DELIVERY’: THE BUG DOESN’T CARE HOW THE DRUG GETS THERE (ENDOCARDITIS)



- *Stable condition;*
- *+10 days ev treatment*
- *+ 7 days after surgery*
- *Clinical response (fever resolved since 48h, PCR < 25%*
- *No abscess/need for surgery at the TOE before randomization*

Figure 8 Phases of antibiotic treatment for infective endocarditis in relation to outpatient parenteral antibiotic therapy and partial oral endocarditis treatment. i.v., intravenous: OPAT, outpatient parenteral antibiotic treatment; TOE, transoesophageal echocardiography. [a]Criteria for switching to OPAT or partial oral treatment of endocarditis are given in the Supplementary data online, Table S8.

Table S2
Oral regimens recommended in the POET trial

Penicillin and methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci:

1) Amoxicillin 1 g x 4 and fusidic acid 0.75 g x 2
2) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
3) Linezolid 0.6 g x 2 and fusidic acid 0.75 g x 2
4) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

Methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

1) Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2
2) Dicloxacillin 1 g x 4 and rifampicin 0.6 g x 2
3) Linezolid 0.6 g x 2 and fucidic acid 0.75g x 2
4) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

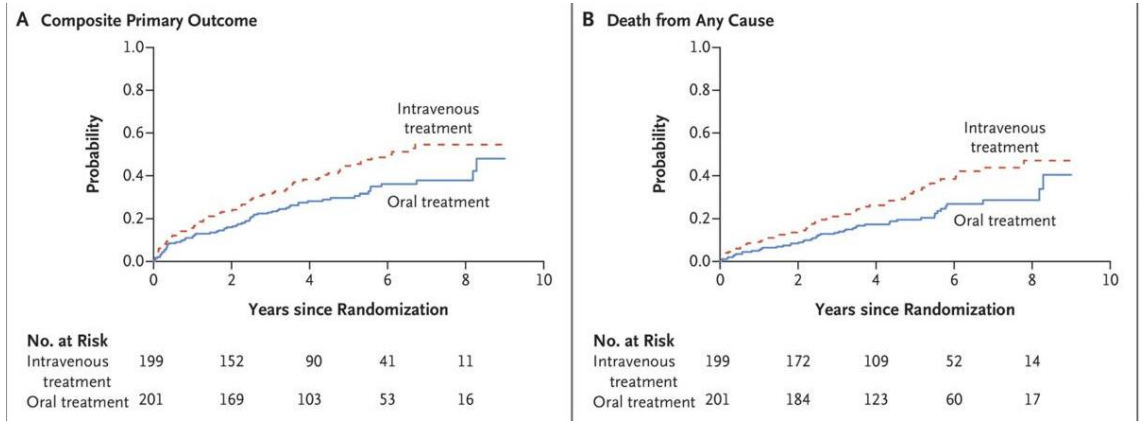
Methicillin resistant coagulase-negative staphylococci

1) Linezolid 0.6 g x 2 and fusidic acid
2) Linezolid 0.6 g x 2 and rifampicin 0.6 g x2

Enterococcus faecalis:

1) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
2) Amoxicillin 1 g x 4 and moxifloxacin 0.4 g x 1
3) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
4) Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x 1

Iversen, NEJM 2019



Pries-Heje, NEJM 2022

ORAL VERSUS IV FOR BACTEREMIA

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review

Noah Wald-Dickler, MD,[a,b,c] Paul D. Holtom, MD,[a,b] Matthew C. Phillips, MD,[a] Robert M. Centor, MD,[d,e] Rachael. A. Lee, MD,[d,e] Rachel Baden, MD,[a] Brad Spellberg, MD[a]

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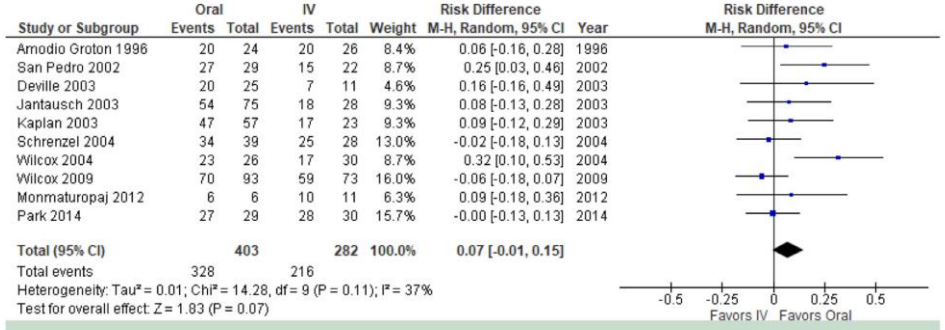


Figure 3 Meta-analysis forest plot of bacteremia treatment success. Overall treatment success was not significantly different, although the confidence interval favored oral therapy.

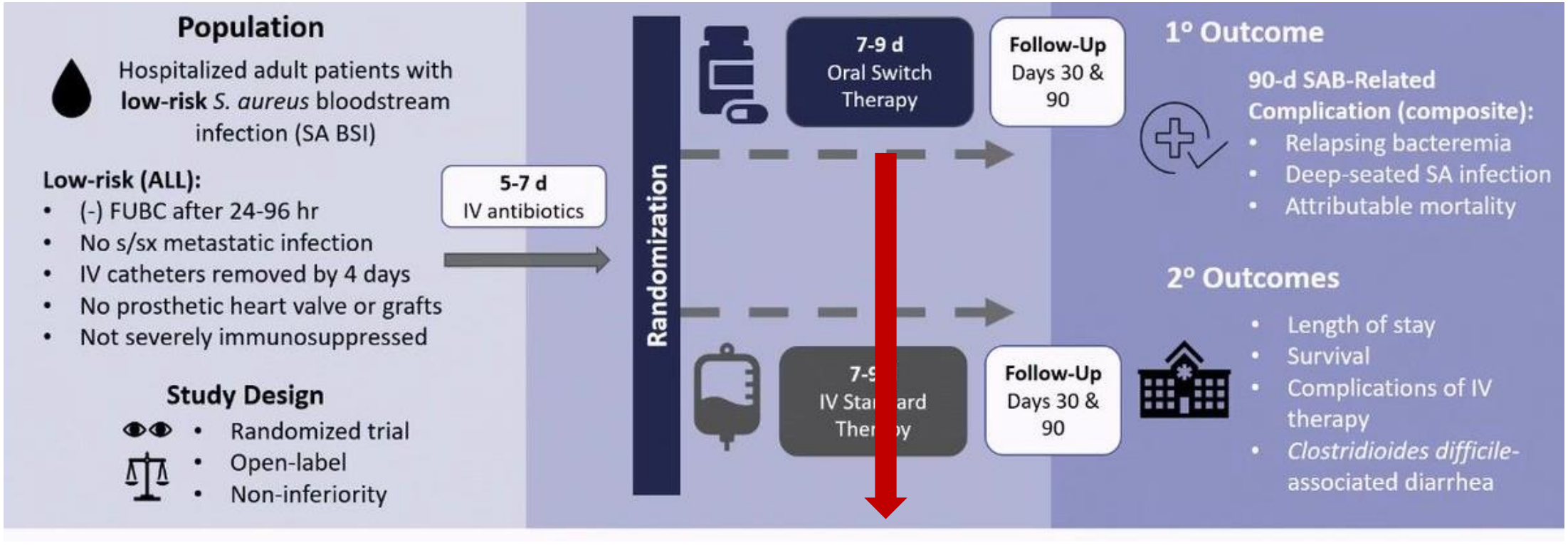
Author	Yr	N	Regimen (Oral vs. IV)	Success
Amodio-Groton	'96	50	Ciprofloxacin oral vs. IV—GNB	83% (20/24) v 77% (20/26)
Deville	'03	36	Linezolid vs. vanco—GPC (peds)	80% (20/25) v 64% (7/11)
Jantausch	'03	103	Linezolid vs. vanco—GPC (peds)	72% (54/75) v 64% (18/28)
Kaplan	'03	80	Linezolid vs. vanco—GPC (peds)	82% (47/57) v 74% (17/23)
Schrenzel	'04	67	FQ + rif vs. βL/vanco—*Staph* (<24 h IV lead in)	87% (34/39) v 89% (25/28)
Wilcox	'04	56	Linezolid vs. teicoplanin—GPC	89% (23/26) v 57% (17/30)
Wilcox	'09	166	Linezolid vs. vancomycin—GPC	75% (70/93) v 81% (59/73)
Monmaturopaj*	'12	17	Cefditoren vs. ceftriaxone—GNB	100% (6/6) v 91% (10/11)
Park	'14	59	Ciprofloxacin vs. std IV—GNB	93% (27/29) v 93% (28/30)
Omrani	'23	165	FQ/TMPSMX/BL vs. std IV—GNB	78% (65/83) v 74% (61/82)
Kaasch	'24	213	Various Abx IV/Oral—*S. aureus*	87% (94/108) v 88% (92/105)
Total (N=11 RCTs)		1,012		81% (460/565) v 79% (354/447)

*N = 82 pts with pyelonephritis of whom 17 were bacteremic with *E. coli*, patients were randomized to continue ceftriaxone or switch to oral ceftditoren at day 3. Refs at https://www.bradspellberg.com/oral-antibiotics

https://www.bradspellberg.com/oral-antibiotics

31 tertiary care hospitals in Germany, France, the Netherlands, and Spain

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



- cotrimoxazole every 12 h for MSSA and MRSA,
- clindamycin 600 mg every 8 h for MSSA
- or linezolid 600 mg every 12 h for MRSA

Kaash, Lancet ID 2024

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

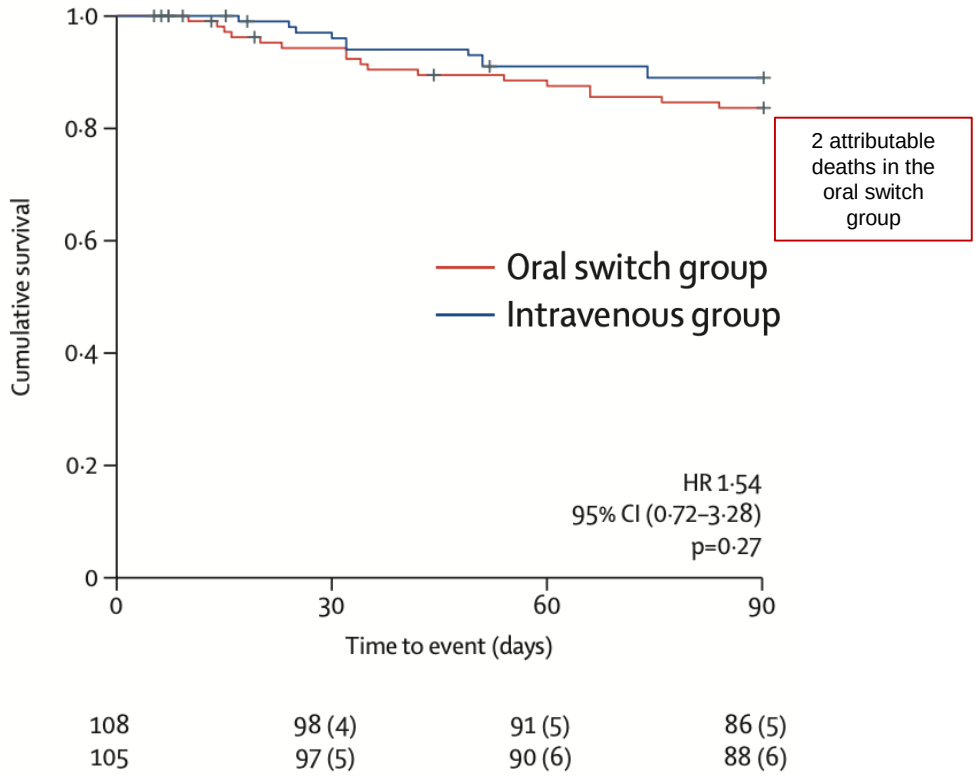
Due to slow recruitment, the trial was stopped in Jan 2018 (start in 2013)
[215 out of the planned 430 were randomized: 108 oral 105 IV]

- ✓ 16% MRSA
- ✓ 66% catheter-related
- ✓ 24% SSTI
- ✓ 6 days EV before randomization
- ✓ ABT median duration 14 days

Primary Outcome

13	Occurrence of any complication related to S. Aureus bloodstream infection within 90 days %	12

Difference: 0.7, CI: −7•8 to 9•1 (P = 0.013)



(D) Cumulative survival (all-cause mortality, Kaplan-Meier method) with HRs estimated from Cox regression.

Kaash, Lancet ID 2024

Switch to oral antibiotics in Gram-negative bacteraemia: a randomized, open-label, clinical trial (SOAB)

- Monomicrobial Ent-BSI susceptible to ≥1 oral beta-lactam, FQ, or TMP-SMX;
- 3-5 days of active IV therapy,
- afebrile and haemodynamically stable for ≥48 hours,
- absence of an uncontrolled source of infection

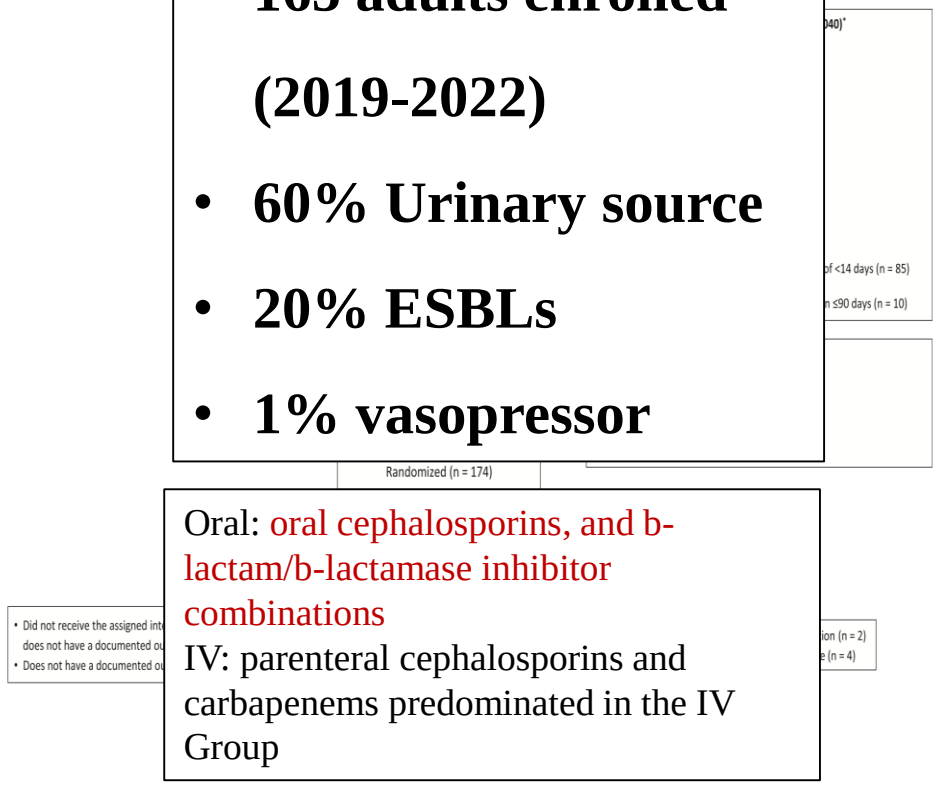
Switch to oral (molecule or duration decided by the treating physician)

Continue IV

Treatment failure

[90D mortality, need for additional ABTs, readmission, relapse]

- **165 adults enrolled (2019-2022)**
- **60% Urinary source**
- **20% ESBLs**
- **1% vasopressor**



Oral: oral cephalosporins, and b-lactam/b-lactamase inhibitor combinations
IV: parenteral cephalosporins and carbapenems predominated in the IV Group

Omrani, CMI 2024

Switch to oral antibiotics in Gram-negative bacteraemia: a randomized, open-label, clinical trial (SOAB)

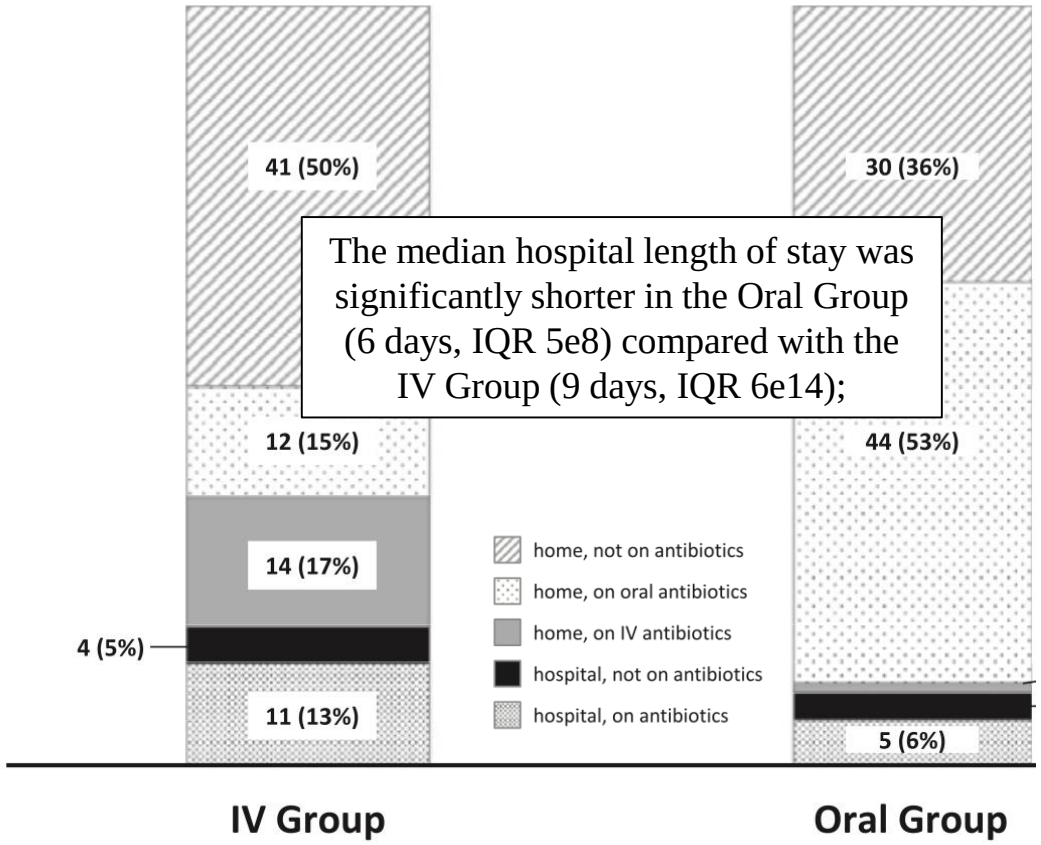
Treatment failure
21 of 82 (25.6%) IV vs 18 of 83 (21.7%) ORAL

[Mortality: 6 events IV vs 7 events oral]

Primary and secondary outcomes

Outcome	Difference (95% CI)[a]
Treatment failure within 90 d	−3.7% (−16.6% to 9.3%)
	−3.7% (−16.6% to 9.2%)
90-d all-cause mortality	0.8% (−7.0% to 8.6%)
	−0.04% (−5.8% to 5.7%)
Additional antimicrobial therapy	−6.8% (−16.1% to 2.6%)
	−7.1% (−15.5% to 1.3%)
Microbiological relapse	−4.1% (−14.1% to 5.9%)
	−4.8% (−14.0% to 4.3%)
Infection-related re-admission	7.2% (−4.0% to 18.3%)
	7.5% (−3.1% to 18.1%)

The median hospital length of stay was significantly shorter in the Oral Group (6 days, IQR 5e8) compared with the IV Group (9 days, IQR 6e14);



Omrani, CMI 2024

D COME 'DELIVERY': QUALCHE EVIDENZA SULLE BATTERIEMIE, QUANDO POSSIAMO FARE LO SWITCH?

Study Design & Setting

- Observational study of patients with **uncomplicated GN BSI** at 4 hospitals in Denmark
- Patients had to be **clinically stable within 4 days of initial blood culture, AST by day 4 and initiation of appropriate empiric IV treatment within 24h of blood cultures**
- Primary outcome: Association of switching to PO abx within 4d after initial cx on 90d mortality

Results

- 914 patients included: 433 (47.4%) transitioned to early PO
- Early PO patients were younger with fewer comorbidities and more likely to have a urinary source
- PO Beta-lactams were the most common PO agent (63.1%), then FQs (16.6%), <1% SMX-TMP
- ITT analysis, 90-d mortality risk was 9.1% for early PO vs 11.7% vs prolonged IV (RR 0.78, 95% CI 0.60-1.10).

Considerations

- Inverse probability of treatment weighting balanced groups but still potential for residual confounding
- Very few drug-resistant infections, and **a substantial number of patients with severe or complicated GN BSI were excluded** → limits population of applicability
- Limited secondary outcomes assessed beyond mortality alone

Tingsgard S, et al. JAMA Netw Open 2024;7(1):e2352314.

PO from the get-go?

Retrospective observational cohort study of patients with occult bloodstream infections (oBSIs) diagnosed *after* discharge from the ED.

Clinical Criterial for Low-Risk oBSI Eligible for Outpatient Management
Patient asymptomatic or paucisymptomatic at first telephonic contact when oBSI is informed
Active PO option available
No clinical suspicion of complicated BSI
No severe immunosuppression
Accessibility to close ambulatory follow-up

- 123 patients diagnosed with oBSI, outpatient management recommended in 83.7%
- Majority of patients (73%) received no parenteral antibiotics in the ED prior to discharge; 92% prescribed empiric PO abx at discharge
- Most common antibiotics given were beta- lactams (83%); followed by ciprofloxacin (14%)
- 96.1% finished their follow-up without hospitalization
- 14d mortality rate 0%, 90-day mortality rate 1.9%

Casado A, et al. Antimicrob Agent Chemother 2023;67(11):e00780-23.

INDICAZIONI PER IL PASSAGGIO ALLA TERAPIA ORALE NELLE INFEZIONI DEL TORRENTE CIRCOLATORIO

- Pazienti con infezioni NON COMPLICATE che hanno raggiunto una buona stabilità clinica (apiressia, PCR, fonte di infezione risolta/rimossa);
- Ho a disposizione un antibiotico efficace in vitro
- Il paziente ha una buona compliance e NON ha problemi di assorbimento

- RICORDIAMOCI PERO' CHE PER QUESTA TIPOLOGIA DI PAZIENTI SPESSO POTREBBE ESSERCI GIA' INDICAZIONE ALLA SOSPENSIONE PRECOCE!!

Grazie per l'attenzione!!!

elena.carrara@univr.it

IT www.save.veneto.it

GB www.id-care.net

UNIVERSITÀ di VERONA

SAVE Stewardship Antibiotici VERONA

ID-CARE