Safety of antimicrobial stewardship in immunocompromised patients

Djamel Mokart (Marseille, France)

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Sepsis & Immuno-compromised Hosts: Challenges in 2024

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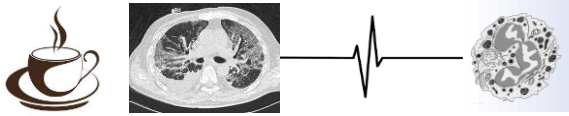


One definition …

- *Antimicrobial stewardship can been defined as selection of the best antimicrobial treatment at the optimal dose and duration, resulting in the best clinical outcome for treating and preventing infection with minimal toxicity and a minimal effect on subsequent resistance*

Antimicrobial Stewardship in Immunocompromised Hosts

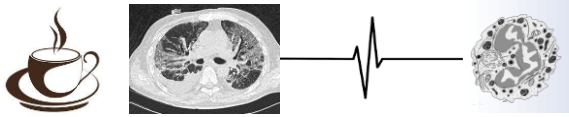
Lilian M. Abbo, MD[a,*], Ella J. Ariza-Heredia, MD[b]

Challenges to the implementation of antimicrobial stewardship in immunocompromised hosts

1. Physician perceptions and attitudes—"my patient is sicker than yours"
2. Wide range of possible infectious etiologies with diagnostic uncertainty
3. Impaired inflammatory responses
4. Difficulty in making an early diagnosis
5. Urgency for empiric effective antimicrobial therapy
6. Significant drug toxicities and potent drug interactions
7. Prolonged exposure to prophylactic antibiotics may lead to antimicrobial resistance
8. Increasing antimicrobial resistance with limited therapeutic options to appropriately treat empirically or documented infections
9. Difficulty with distinguishing rejection and graft versus host disease from infections
10. Difficulty in controlling the source of infection due to issues, such as thrombocytopenia, limiting surgical interventions
11. Prolonged duration of immunosuppressed state increases the risk for uncommon presentations of common and uncommon infections
12. Duration of antimicrobial therapy not clearly defined in many infections for these patients

Infect Dis Clin N Am 28 (2014) 263–279

Antimicrobial Stewardship in Hematological Patients at the intensive care unit: a global cross-sectional survey from the Nine-i Investigators Network



- ESBL Enterobacteriaceae, carbapenem-resistant K. pneumoniae and carbapenem-resistant P. aeruginosa were the main concerns
- In 48.8% of the ICUs, there was no antimicrobial stewardship (AMS) team focused on hematological patients.
- *Updates on local epidemiology of MDR pathogens were provided in 98% of the centers*
- Antibiotic de-escalation and/or discontinuation of therapy were considered as a promising strategy for the prevention of MDR development (32.4%)

Rello, Eur J Clin Microbiol Infect Dis. 2020 Feb;39(2):385-392

Antimicrobial stewardship in high-risk febrile neutropenia patients

Adrien Contejean[1,2,3*], Salam Abbara[4,5], Ryme Chentouh[3], Sophie Alviset[3], Eric Grignano[2], Nabil Gastli[6], Anne Casetta[7], Lise Willems[2], Etienne Canoui[3], Caroline Charlier[1,3,8], Frédéric Pène[1,9], Julien Charpentier[9], Jeanne Reboul-Marty[10], Rui Batista[11], Didier Bouscary[1,2] and Solen Kernéis[3,5,12]

ECIL4 guidelines ward

- Single-center, retrospective, observational study in FN, included hematologic malignancies and HSCT recipients.
- ECIL-4 based guideline for de-escalation and discontinuation implemented and compared preintervention ($n = 164$) vs. postintervention periods ($n = = 148$).

- After implementation of antimicrobial stewardship, glycopeptide use decreased by 85%, carbapenem use decreased by 72%.
- Risk of transfer to ICU/death decreased significantly after implementation of antimicrobial stewardship program

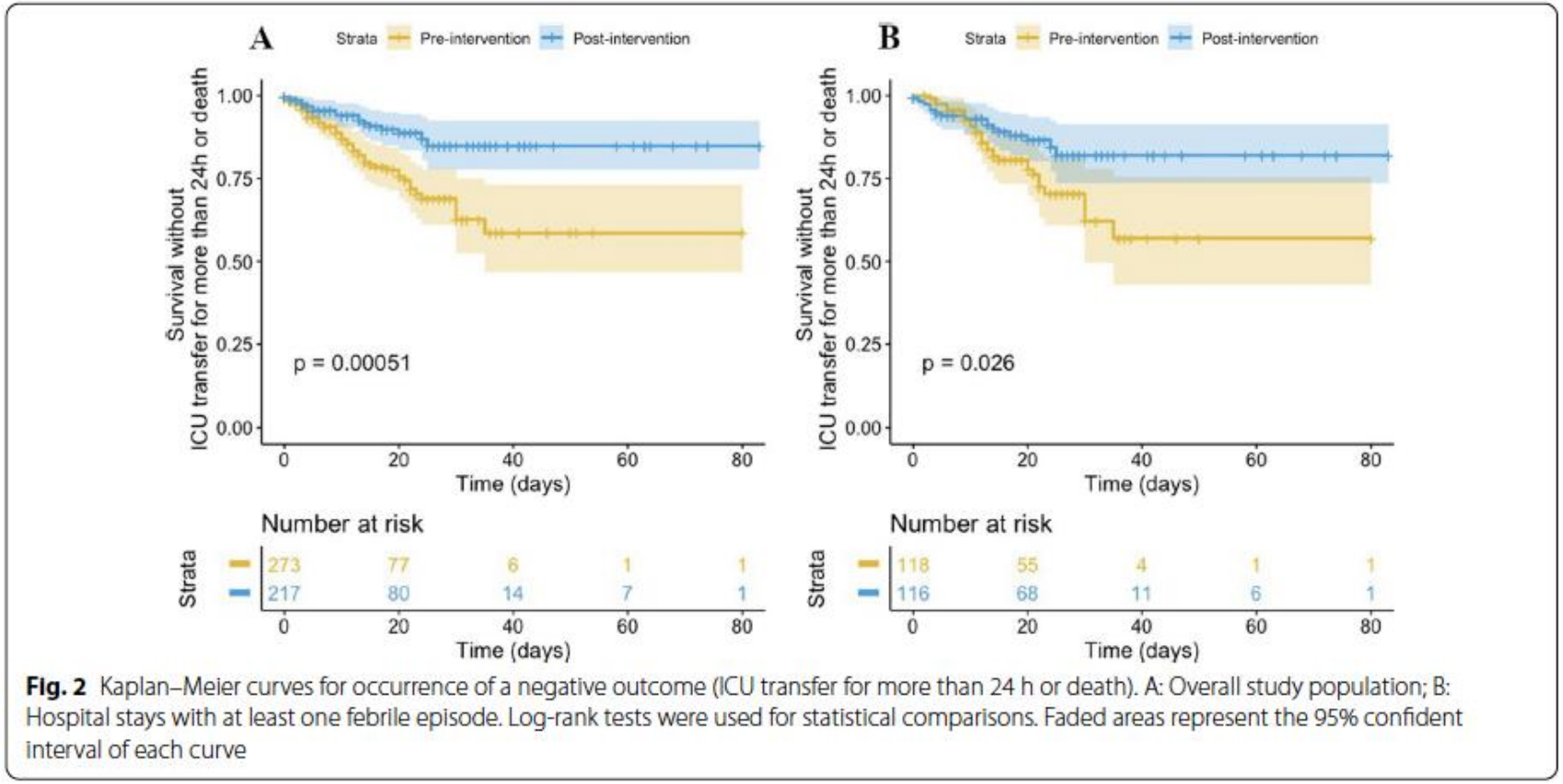


Fig. 2 Kaplan–Meier curves for occurrence of a negative outcome (ICU transfer for more than 24 h or death). A: Overall study population; B: Hospital stays with at least one febrile episode. Log-rank tests were used for statistical comparisons. Faded areas represent the 95% confident interval of each curve

Contejean *et al.*
Antimicrobial Resistance & Infection Control (2022) 11:52
https://doi.org/10.1186/s13756-022-01084-0

Advances in antibacterial treatment of adults with high-risk febrile neutropenia

Adrien Contejean [1,2,3]*, Alexis Maillard [2], Etienne Canouï [2], Solen Kernéis[3,4,5], Bruno Fantin[3,6], Didier Bouscary[3,7], Perrine Parize [8], Carolina Garcia-Vidal[9,10] and Caroline Charlier [2,3,11,12]

Table 4. Main antimicrobial stewardship interventions to consider in patients with febrile neutropenia

Clinical situation	Intervention	References
Fever of unknown origin	Consider stopping antibiotics after at least 3 days of treatment and 48 h of apyrexia	9,10,120–124
CDI or MDI with no severity criteria	Consider the same treatment duration as in non-neutropenic patients if the patient gets at least 4 days of apyrexia and clinical and microbiological resolution Consider de-escalation to targeted therapy against documented bacteria	9,10,25,120,121,123,124
Fever persistence or breakthrough under broad-spectrum antibiotics AND no new clinical sign AND no severity criteria AND no MDR bacteria colonization	Do not consider antibiotic escalation	9,10,120,121
Ongoing combination of anti-Gram-positive and anti-*P. aeruginosa* β-lactam antibiotics and no microbiological documentation at Day 3	Consider stopping anti-Gram-positive antibiotics and pursuing only anti-*P. aeruginosa* β-lactam	9,10,120,121
Ongoing carbapenem AND no microbiological documentation at Day 3 AND patient is stable	Consider de-escalation to a narrower-spectrum β-lactam covering *P. aeruginosa*	10,120,121
Ongoing aminoglycosides	Consider stopping aminoglycosides at Day 2 or 3 when patient is stable	10,120,121
Pneumonia or cutaneous cellulitis	Consider tailored-fit treatment based on bronchoscopy and broncho-alveolar lavage samples	120
Initial severity criteria or corticosteroids	Sometimes excluded from published local guidelines Consider tailored-fit treatment	120,121

CDI, clinically documented infection; MDI, microbiologically documented infection.

Advances in antibacterial treatment of adults with high-risk febrile neutropenia

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Table 1. Main pharmacological modifications of antibiotics in febrile neutropenia

Pharmacological modifications	Involved antibiotics	References
Increase in volume of distribution	β-Lactams[a] Glycopeptides Daptomycin Aminoglycosides	57–65
Increase in drug clearance and decrease in elimination half-life	β-Lactams[a] Glycopeptides Daptomycin Aminoglycosides	57–65
Decrease in peak concentration (C_{max})	Daptomycin Aminoglycosides	63–65
Decrease in AUC	Glycopeptides Daptomycin	61–63
Decrease in post-antibiotics effect	Carbapenems Aminoglycosides	66,67

[a]Ceftolozane/tazobactam and ceftazidime/avibactam have not been specifically studied in patients with febrile neutropenia.

J Antimicrob Chemother 2023; **78**: 2109–2120

Advances in antibacterial treatment of adults with high-risk febrile neutropenia

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J Antimicrob Chemother 2023; **78**: 2109–2120

Table 2. Proposed dosage and infusion modalities of parenteral antibiotics in patients with high-risk febrile neutropenia and no otherwise specified condition

Antibiotics	Infusion modalities	Administration rules	Stability	Therapeutic drug monitoring	References
Piperacillin/ tazobactam	4 g loading dose over 30 min 12 g/day CI	Dilution in saline serum C_{max} 80 mg/mL + 10 mg/mL	24 h at 25°C	Piperacillin concentration at steady state (≥24 h)	76,78–80
Cefepime	2 g loading dose over 30 min 6 g/day CI	Dilution in saline serum C_{max} 50 mg/mL Administration in three separate infusions over 8 h	8 h at 25°C	Cefepime concentration at steady state (≥24 h)	78–83
Ceftazidime	2 g loading dose over 30 min 6 g/day CI	Dilution in saline serum C_{max} 80 mg/mL Administration in three separate infusions over 8 h	8 h at 25°C	Ceftazidime concentration at steady state (≥24 h)	78–80,84
Meropenem	2 g loading dose over 30 min 6 g/day CI	Dilution in saline serum C_{max} 50 mg/mL Administration in three separate infusions over 8 h	8 h at 25°C	Meropenem concentration at steady state (≥24 h)	80,85,86
Vancomycin	25 mg/kg loading dose over 2 h (max. 2 g) 40 mg/kg/day CI	Dilution in saline serum or G5% C_{max} 40 mg/mL	48 h at 25°C	Vancomycin concentration at steady state (24 h after loading dose)	78,79,87–91
Daptomycin	10 mg/kg/day over 30 min	Dilution in saline serum C_{max} 500 mg/50 mL	12 h at 25°C	Efficacy: 24 h AUC/MIC or daptomycin concentration at peak (30 min after the end of infusion) Toxicity: daptomycin trough concentration, before subsequent infusion	63,79,92–95
Amikacin	30 to 35 mg/kg/day over 30 min	Dilution in saline serum or G5% C_{max} 20 mg/mL	24 h at 25°C	Efficacy: amikacin concentration at peak (30 min after the end of infusion) Toxicity: amikacin trough concentration, before subsequent infusion	64,65
Gentamicin	6 to 7 mg/kg/day over 30 min	Dilution in saline serum or G5% C_{max} 10 mg/mL	24 h at 25°C	Efficacy: gentamicin concentration at peak (30 min after the end of infusion) Toxicity: gentamicin trough concentration, before subsequent infusion	64,65,79

G5%, Glucose 5%.

Existing scientific data…

- Antibiotics allergy
- Neutropenia
  - Prophylaxis
  - Duration
  - De-escalation
- Pneumonia
- UTI and bacteruria
- Clostridium difficile colitis
- Antiviral stewardhip
- Antifungal stewardship
- Rapid diagnostic methods

Infect Dis Clin N Am 37 (2023) 823–851

The Impact of Reported Beta-Lactam Allergy in Hospitalized Patients With Hematologic Malignancies Requiring Antibiotics

Kuan-Hsiang Gary Huang,[1,2] Valerie Cluzet,[3] Keith Hamilton,[3] and Olajumoke Fadugba[1]

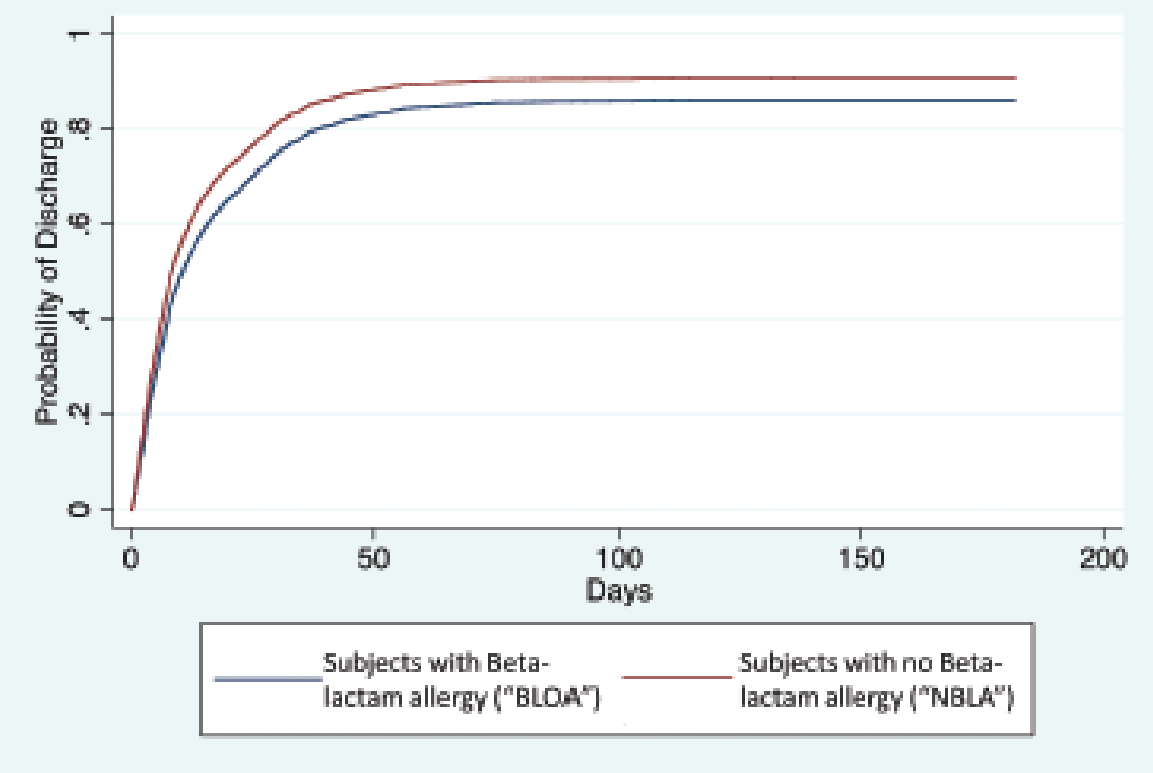


Figure 1. Cumulative probability of discharge, according to study group. Abbreviations: BLOA, BL-only allergy; NBLA, no BL allergy.

Table 4. Multivariable Logistic Regression Model of Association Between Beta-Lactam Only Allergy and 30-Day Mortality

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Beta-lactam allergy	1.41 (1.00, 2.00)	.050
Leukemia	1.22 (0.92, 1.63)	.164
Neutropenia	0.41 (0.26, 0.64)	<.001
Severity of illness index on admission	3.66 (2.83, 4.72)	<.001

CID 2018:67 (1 July)

What should I do if my patient is allergic to β-lactam?

- Systematic screening
- Not prohibit the use of all β-lactams given the low 2% rate of crossed-allergy
- In case of non-severe skin rashes to amoxicillin
  - cefepime or meropenem
- Aztreonam
  - Except in cases of allergy to ceftazidime ?

JAMA | Original Investigation

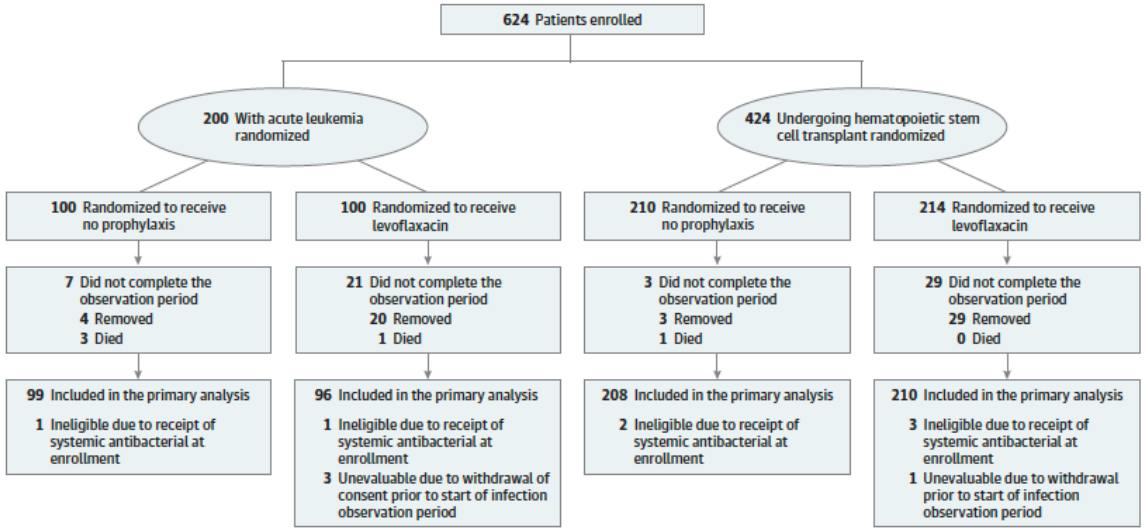
Effect of Levofloxacin Prophylaxis on Bacteremia in Children With Acute Leukemia or Undergoing Hematopoietic Stem Cell Transplantation

A Randomized Clinical Trial

Sarah Alexander, MD; Brian T. Fisher, DO, MSCE; Aditya H. Gaur, MD; Christopher C. Dvorak, MD; Doojduen Villa Luna, MS; Ha Dang, PhD; Lu Chen, PhD; Michael Green, MD, MPH; Michael L. Nieder, MD; Beth Fisher, MSN; L. Charles Bailey, MD, PhD; John Wiernikowski, Pharm D; Lillian Sung, MD, PhD; for the Children's Oncology Group

Table 2. Comparison of Bacteremia Incidence per Patient During the Infection Observation Period and Bacteremia Rate per 1000 Patient-Days Between Randomized Groups for Acute Leukemia and HSCT Groups (N = 613)

	Bacteremia Incidence, No./Total (%)		Risk Difference, % (95% CI)	Risk Ratio (95% CI)	*P* Value
	Levofloxacin	No Prophylaxis			
Primary Analysis[a]					
Total acute leukemia	21/96 (21.9)	43/99 (43.4)	21.6 (8.8-34.4)	0.50 (0.32-0.78)	.001
AML	15/64 (23.4)	25/63 (39.7)	16.3 (0.3-32.2)	0.59 (0.35-1.01)	.05
Relapsed ALL	6/32 (18.8)	18/36 (50.0)	31.2 (10.1-52.5)	0.38 (0.17-0.83)	.007
Total HSCT	23/210 (11.0)	36/208 (17.3)	6.3 (0.3-13.0)	0.63 (0.39-1.03)	.06
Autologous	3/79 (3.8)	9/78 (11.5)	7.7 (5.1-16.0)	0.33 (0.09-1.17)	.07
Allogeneic	20/131 (15.3)	27/130 (20.8)	5.5 (3.8-14.8)	0.74 (0.43-1.24)	.25
Post hoc Analysis[b]					
	Bacteremia Rate/1000 Patient-Days (95% CI)			Adjusted Rate Ratio (95% CI)[c]	
Total acute leukemia	4.9 (3.3-7.3)[c]	9.4 (7.1-12.3)[c]	4.3 (1.3-7.4)	0.52 (0.32-0.85)	.008
Person-days of observation, No.	5327	5973			
Total HSCT	5.3 (3.5-8.0)[c]	10.0 (6.6-14.8)[c]	5.2 (1.1-9.3)	0.53 (0.32-0.88)	.02
Person-days of observation, No.	4042	3766			



Fluoroquinolone Prophylaxis Selects for Meropenem-nonsusceptible *Pseudomonas aeruginosa* in Patients With Hematologic Malignancies and Hematopoietic Cell Transplant Recipients

Clinical Infectious Diseases® 2019;68(12):2045–52

Morgan Hakki,[1] Romney M. Humphries,[2] Peera Hemarajata,[3] Gregory B. Tallman,[4] Ryan K. Shields,[5] Roberta T. Mettus,[5] Yohei Doi,[5,6] and James S. Lewis II[7]

Fluoroquinolone breakthroughs (P = .001; OR11.3, 95% CI 3.1–50.6) were independently predictive of meropenem-nonsusceptibility.

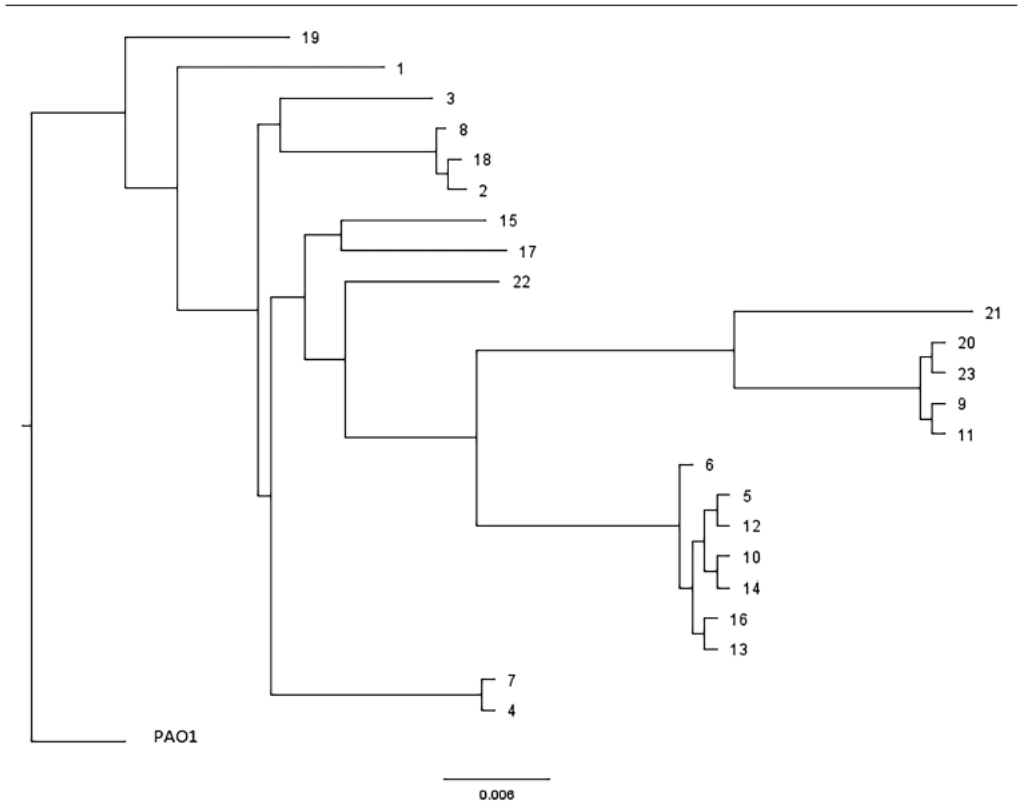


Figure 1. Single-nucleotide variation analysis of *Pseudomonas aeruginosa* bloodstream clinical isolates selected for whole-genome sequencing using *P. aeruginosa* PAO1 strain (GenBank sequence AE004091.2) as the reference. Isolates 4 and 7 were obtained from the same patient, and isolates 10 and 14 were obtained from another patient.

Table 2. Susceptibility of *Pseudomonas aeruginosa* Isolates According to Antibiotic Use at Time of Bacteremia

	Antibiotic		
	FQ (n = 26)	Non-FQ or None (n = 29)	
Antibiotic	Susceptible isolates, n (%)	Susceptible isolates, n (%)	*P* Value
Ciprofloxacin	0	21 (72.4)	<.0001
Meropenem	4 (15.4)	21 (72.4)	<.0001
Cefepime	21 (80.8)	26 (89.6)	.4
Ceftazidime	19 (73.1)	25 (86.2)	.3
Gentamicin	21 (80.8)	28 (96.5)	.1
P/T	19 (73.1)	25 (86.2)	.3
Tobramycin	25 (96.1)	29 (100)	.5

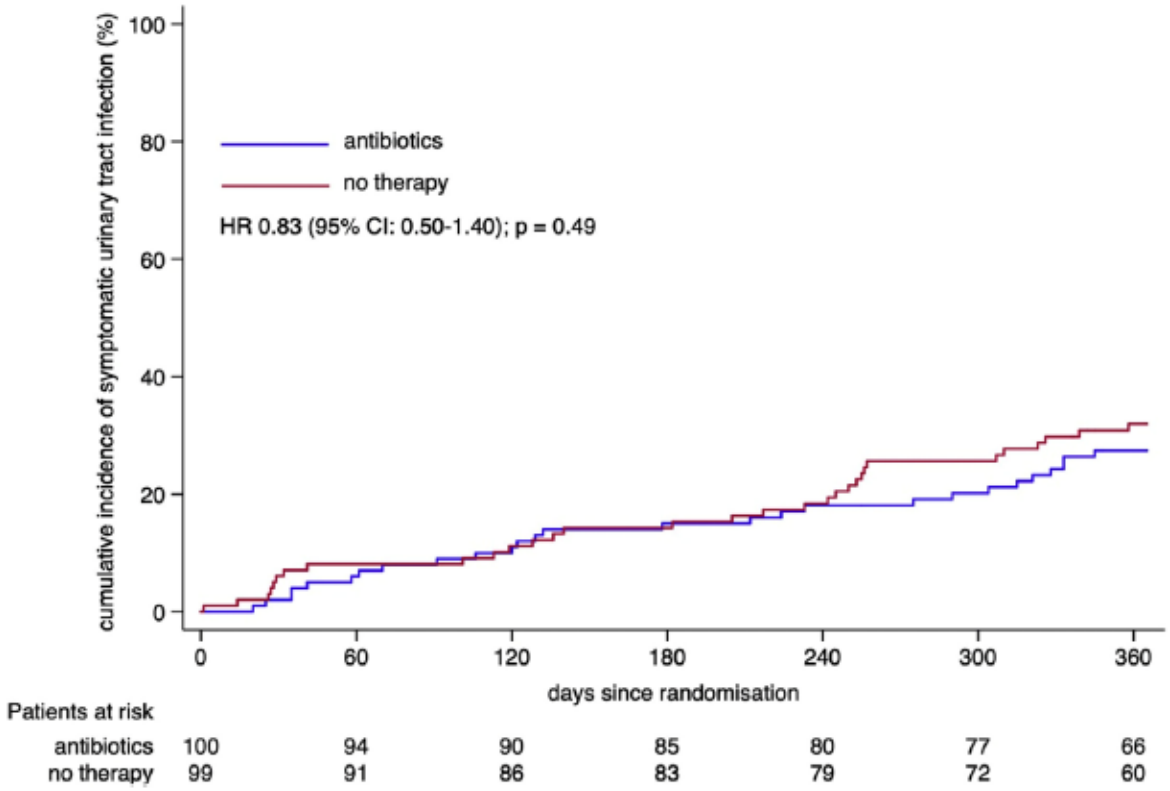
Abbreviations: FQ, fluoroquinolone; P/T, piperacillin-tazobactam.

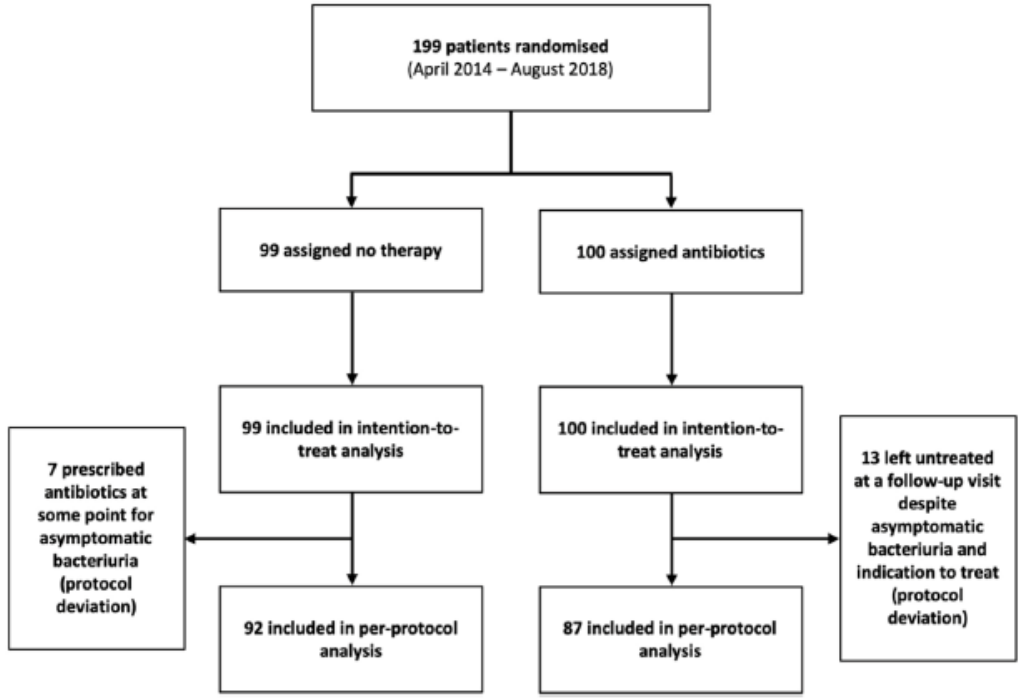
Table 5. Effect of Efflux Pump Inhibition on Meropenem Minimum Inhibitory Concentrations for Select *Pseudomonas aeruginosa* Isolates

	MIC (mg/L)	
Isolate	PAβN-	PAβN+
ATCC	0.5	1
1	1	2
2	0.25	2
3	32	8
5	8	4
9	4	2
10	4	2
11	32	4
12	4	2
13	32	16
16	32	4

Abbreviations: ATCC, American Type Culture Collection; MIC, minimum inhibitory concentration; PAβN, phenyl-arginine-β-naphthylamide.

Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): a pragmatic, multicentre, randomized, controlled trial





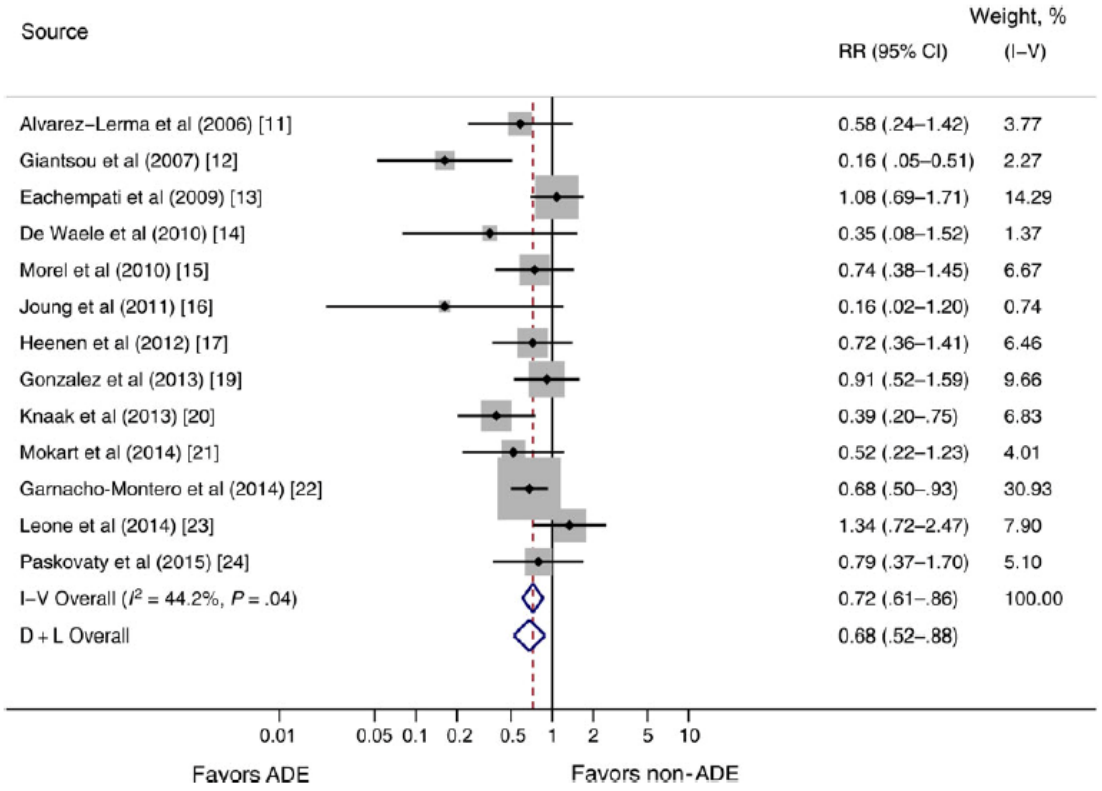
Characteristics of first episode of symptomatic urinary tract infection (UTI) (primary endpoint; intention-to-treat analysis)

	No therapy (31 episodes)	Antibiotics (27 episodes)	p
Same species present without symptoms at study visit immediately preceding the symptomatic UTI, *n* (%)	18 (58)	6 (22)	**0.006**

J. Coussement et al. / Clinical Microbiology and Infection 27 (2021) 398–405

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

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

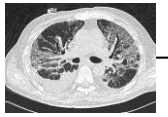
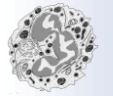


ADE rates = 34%-62%

Table 3. Factors Associated With Antimicrobial De-escalation

Factors Associated With ADE
Positively associated
Initially appropriate empiric antimicrobial therapy
Broad-spectrum empiric therapy
Compliance with national prescribing guidelines
Treatment with multiple and "companion" antimicrobials
Positive microbiological cultures
Lower severity of illness scores at
Baseline
Time of ADE
Day 5 of therapy
Negatively associated
Isolation of a multiresistant pathogen
Polymicrobial infections
Intra-abdominal infections

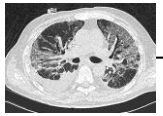
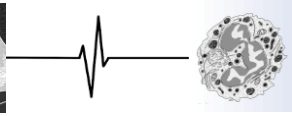
Antimicrobial de-escalation in the critically ill patient and assessment of clinical cure: the DIANA study

	Total $n=1495$	No change $n=934$; 62.5%	ADE $n=240$; 16.1%	Other change $n=321$; 21.5%	ADE vs no change p value	Other change vs no change p value	% of available data
Δ SOFA[a,b]	1 [0–3]	1 [0–3]	2 [0–4]	0 [-1; 2]	<0.001	<0.001	90
Number of days in the ICU[c]							
On vasoactive drugs	2 [0–5]	2 [0–5]	2 [0–4]	3 [0–5]	0.32	0.003	98.3
On invasive mechanical ventilation	3 [0–9]	3 [0–9]	2 [0–8]	4 [0–9]	0.05	0.31	98.4
Receiving renal replacement therapy	0 [0–0]	0 [0–0]	0 [0–0]	0 [0–0]	0.48	0.002	98.5
Antimicrobial-free days (28 days after onset of infection)[d] (n=1166)	13 [4–19]	13 [4–20]	14 [5–20]	9.5 [2–16]	0.29	<0.001	85.5
Number of days in ICU following onset of infection under study[c,e] (n=1219)	8 [5–18]	9 [5–19]	7 [4–12]	10 [5–24]	<0.001	0.09	99.9
Number of days in hospital following onset of infection under study[c,f] ($n=1166$)	26 [13–28]	27 [14–28]	19 [10–28]	28 [16–28]	<0.001	0.26	99.9

	Total $n=1495$	No change $n=934$; 62.5%	ADE $n=240$; 16.1%	Other change $n=321$; 21.5%	p value	Relative risk (95% CI)	p value	Relative risk (95% CI)	
Clinical cure on day 7[g]	650 (43.5%)	399 (42.7%)	139 (57.9%)	112 (34.9%)	<0.001	1.34 (1.18–1.52)	0.03	0.83 (0.71–0.98)	95.9
Infection relapse[c]	103 (6.9%)	61 (6.5%)	22 (9.2%)	20 (6.2%)	0.24	1.37 (0.86–2.18)	0.96	0.96 (0.59–1.56)	96.5
Infections other than the infection under study or a relapse infection[c]	184 (12.3%)	109 (11.7%)	38 (15.8%)	37 (11.5%)	0.12	1.34 (0.95–1.89)	1	0.99 (0.69–1.40)	95.5
Emergence of MDR pathogens between day 2 and day 28[h]	192 (12.8%)	111 (11.9%)	18 (7.5%)	63 (19.6%)	0.06	0.63 (0.39–1.01)	0.001	1.63 (1.23–2.16)	98.7
28-day mortality	296 (19.8%)	181 (19.4%)	38 (15.8%)	77 (24%)	0.27	0.83 (0.60–1.14)	0.07	1.26 (0.99–1.59)	97.8
ICU mortality	243 (16.3%)	145 (15.5%)	28 (11.7%)	70 (21.8%)	0.18	0.76 (0.52–1.11)	0.009	1.42 (1.10–1.84)	97.8

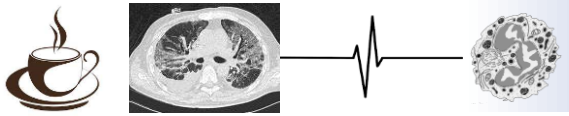
Intensive Care Med (2020) 46:1404–1417

Main outcomes for ADE

- Mortality
- Failure/relapse/escalation/superinfection
- Emergence of MDR bacteria

Clinical context



- Microbiological documentation vs no documentation vs FUO
- MDR bacteria
- Polymicrobial sepsis
  - Translocation of enteric bacteria
- ICU vs ward
- Neutropenia
  - Neutropenia recovery

Neutropenia and antibiotics: when, what, how and why?

Jana Dickter[a], *Cathy Logan*[b] *and Randy Taplitz*[a]

WHEN CAN WE DE-ESCALATE OR STOP ANTIBIOTICS?

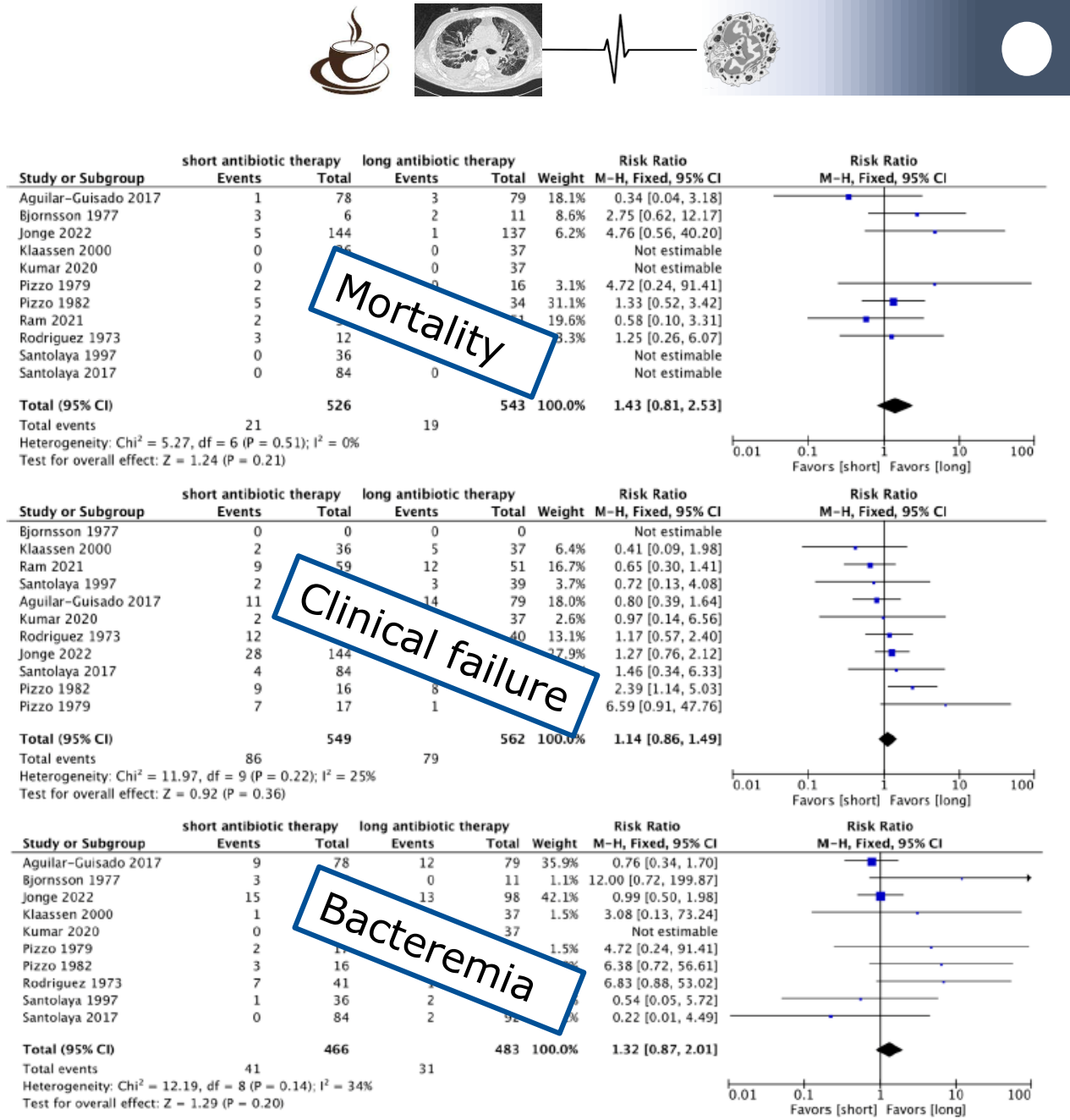
- IDSA guidance recommend to continue BSA until neutrophil recovery
- ECIL guidelines recommend modification of the initial regimen at 72 to 96h based on the patient's clinical course and microbiological results
- ECIL guidelines recommend discontinuation of antibiotics after 72 h or later may be considered in neutropenic patients with fever of unknown origin FUO) who are hemodynamically stable and afebrile for 48 h, irrespective of neutrophil count and expected duration of neutropenia

Systematic Review of the Short-Term versus Long-Term Duration of Antibiotic Management for Neutropenic Fever in Patients with Cancer

Kazuhiro Ishikawa [1,*], Tetsuhiro Masaki [1], Fujimi Kawai [2], Erika Ota [3,4] and Nobuyoshi Mori [1]

- Meta-analysis of 11 RCTs.
- 1128 patients with FN (1977–2022).
- Compared short- and long-term antibiotics for FN and cancer.
- 8/11 of these articles were also included in meta-analysis by Stern 2019.

- No significant differences in mortality, bacteremia, or clinical failure.
- A low certainty of evidence was observed.



Cancers 2023, 15, 1611.

Is Short-Course Antibiotic Therapy Suitable for *Pseudomonas aeruginosa* Bloodstream Infections in Onco-hematology Patients With Febrile Neutropenia? Results of a Multi-institutional Analysis

Xiaomeng Feng,[1,2] Chenjing Qian,[3] Yuping Fan,[1,2] Jia Li,[1,2] Jieru Wang,[1,2] Qingsong Lin,[1,2] Erlie Jiang,[1,2] Yingchang Mi,[1,2] Lugui Qiu,[1,2] Zhijian Xiao,[1,2] Jianxiang Wang,[1,2] Mei Hong,[3] and Sizhou Feng[1,2]

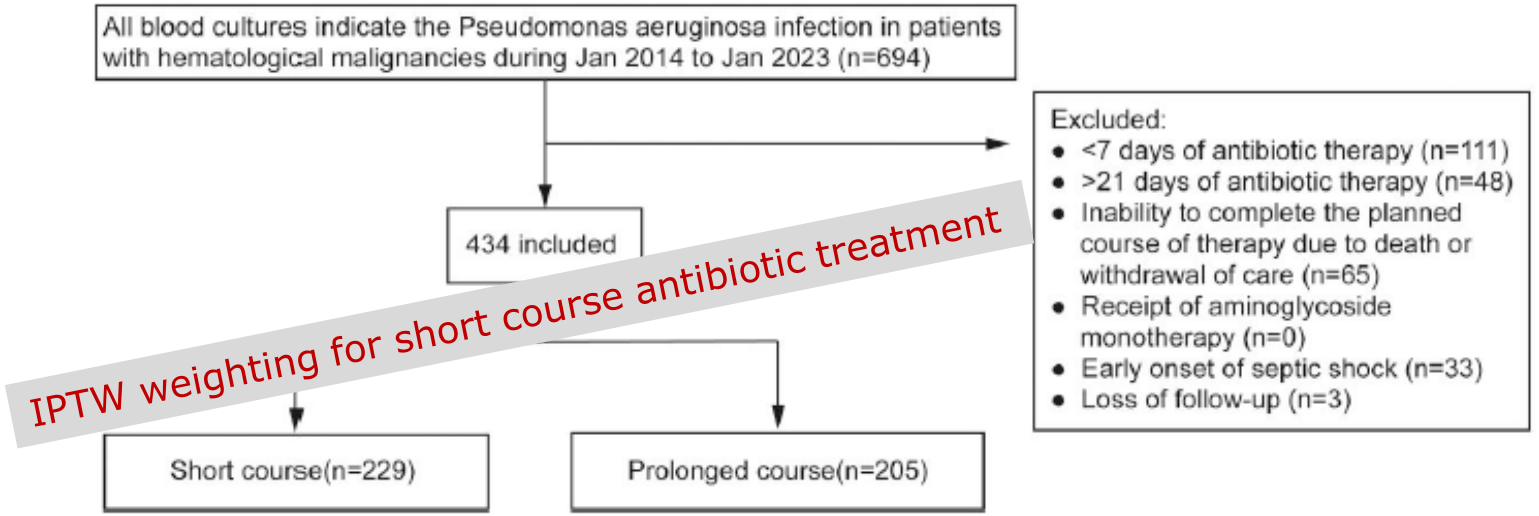


Figure 1. Study population.

Table 2. Univariate Analysis on the Clinical Outcomes of the Weighted Cohort

	Mortality or Recurrent Infection Within 30 D			Fever Relapse Within 7 D			Recurrent Infection Within 90 D		
Characteristic	No	Yes	*P* Value	No	Yes	*P* Value	No	Yes	*P* Value
Day 1 ANC 0–100 cells/mL	208 (53.1)	13 (72.2)	.111	202 (53.6)	19 (57.6)	.659	202 (53.3)	19 (61.3)	.391
Duration of neutropenia, median (IQR)	10.0 (4.0–15.0)	10.5 (6.0–22.5)	.391	10.0 (4.0–15.0)	10.0 (5.0–20.0)	.531	10.0 (4.0–15.0)	11.0 (8.0–20.0)	.095
IET48h	34 (8.7)	3 (16.7)	.247	33 (8.7)	4 (12.5)	.694	31 (8.2)	6 (18.2)	.110
ANC 0–500 cells/mL at the day of discontinuation of antibiotics	39 (9.9)	8 (44.4)	**<.001**	36 (9.5)	11 (34.4)	**<.001**	38 (10.1)	9 (27.3)	**.007**
Monotherapy	209 (53.3)	6 (33.3)	.156	199 (52.6)	16 (50.0)	.918	200 (53.1)	15 (45.5)	.512
MDR-PA	42 (10.7)	7 (38.9)	**<.001**	41 (10.8)	8 (25.0)	**.037**	39 (10.3)	10 (30.3)	**.002**
CRPA	76 (19.4)	7 (38.9)	**.044**	74 (19.6)	9 (28.1)	.354	73 (19.4)	10 (30.3)	.203
Short course antibiotic therapy	197 (50.3)	8 (44.4)	.630	190 (50.3)	15 (46.9)	.854	186 (49.3)	19 (57.6)	.468

Abbreviations: ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematologic stem-cell transplantation; AML, acute myeloid leukemia; ANC, absolute neutrophil counts; BSI, bloodstream infection; CRPA, carbapenems-resistant *Pseudomonas aeruginosa*; CZA, Ceftazidime-Avibactam; Day 1 ANC 0–500 cells/mL, day at the onset of BSI; IET48h, inadequate empirical therapy within 48 h of the onset of PA BSI; IQR, interquartile range; MDR-PA, multidrug resistant *Pseudomonas aeruginosa*; Others, containing myelodysplastic syndrome (MDS) and lymphoma; PA, *Pseudomonas aeruginosa*; SMD, standardized mean difference. Values in bold means $P < .05$.

Safety and risk of febrile recurrence after early antibiotic discontinuation in high-risk neutropenic patients with haematological malignancies: a multicentre observational study

Raphael Paret[1], Amandine Le Bourgeois[2], Gaëlle Guillerm[3], Benoit Tessoulin[2], Schéhérazade Rezig[1], Thomas Gastinne[2], Marie-Anne Couturier[3], David Boutoille[4,5], Raphael Lecomte[4], Florence Ader[6], Steven Le Gouill[2], Séverine Ansart[1], Jean-Philippe Talarmin[7] and Benjamin Gaborit[4,5]*

- Retrospective, multicenter observational study, in FN after induction chemotherapy or HSCT, compared to a historical cohort, $n = 325$.
- Patients included if empiric BSA were discontinued early during FUO according to ECIL-4 recommendations: at least 72 h of BSA if patient had been afebrile for $\geq$ 48 h and stable. Excluded patients with infectious source of fever.

- No significant differences in febrile recurrences, ICU admissions, septic shock, and 30-day mortality.
- In ECIL-4 cohort group bacteremia rate was higher and antibiotic consumption was significantly lower. No sepsis-related mortality.
- After early antibiotic discontinuation in ECIL-4 cohort, febrile recurrence was higher among patients with enterocolitis and mucositis; additionally, the only factor associated with bacteremia was presence of stage III-IV oral mucositis.

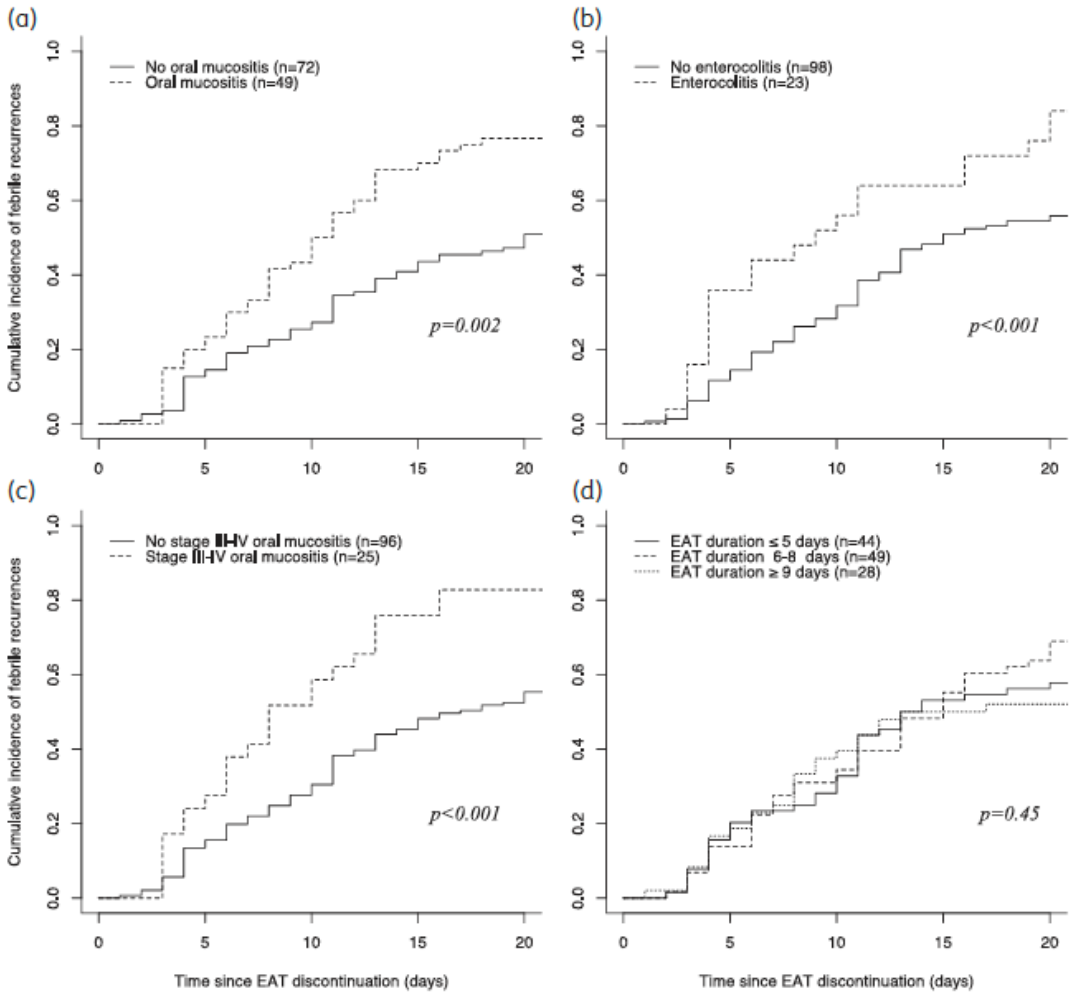


Figure 2. Cumulative incidence of febrile recurrences after EAT discontinuation according to the presence of oral mucositis (a), enterocolitis (b), stage III–IV oral mucositis (c) and EAT duration (d).

J Antimicrob Chemother 2022; 77: 2546–2556

Efficacy and safety of withholding antimicrobial treatment in children with cancer, fever and neutropenia, with a demonstrated viral respiratory infection: a randomized clinical trial

M.E. Santolaya [1, 7], A.M. Alvarez [3, 7], M. Acuña [4, 7], C.L. Avilés [5, 7], C. Salgado [6, 7], J. Tordecilla [4, 7], M. Varas [3, 7], M. Venegas [3], M. Villarroel [1, 7], M. Zubieta [6, 7], A. Toso [1], A. Bataszew [1], M.J. Farfán [1], V. de la Maza [1], A. Vergara [2], R. Valenzuela [1], J.P. Torres [1, *]

- Randomized, prospective, multicenter trial, 176 children with FN with clinical improvement after 48 h of antibiotics.
- De-escalation group (84): BSA discontinued.
- Comparator group (92): continued BSA until ANC recovery.

- Fewer antibiotic days in de-escalation group vs. standard group.
- No significant difference in frequency of uneventful resolution, similar number of days of fever, LOS, and bacterial infections.
- No deaths.

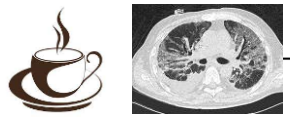
Table 2
Outcome of 176 children with fever, neutropenia and a demonstrated respiratory viral infection, according to intervention

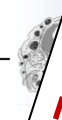
Characteristics	Type of intervention		Total	p
	Maintain antimicrobial	Antimicrobial withholding		
	$n = 92$	$n = 84$		
Days of antimicrobial therapy, median (IQR)	7 (7–9)	3 (3–4)	6 (3–7)	< 0.0001
Days of fever after admission, median (IQR)	2 (1–3)	1 (1–2)	1 (1–2)	0.44
Days of hospitalization, median (IQR)	6 (4–8)	6 (4–7)	6 (4–7)	0.65
Days of ANC <500/mm^3, median (IQR)	5 (3–8)	4 (3–8)	5 (3–8)	0.23
Days of AMC <100/mm^3, median (IQR)	3 (0–6)	2 (0–5)	3 (0–5)	0.46
Resolving uneventfully, *n* (%)	89 (97)	80 (95)	169 (96)	0.61
Demonstrated/probable invasive bacterial infection, *n* (%)	2 (2)	1 (1)	3 (2)	0.93
Re-instalment of antimicrobials, *n* (%)		4 (5)	4 (2)	
Development of sepsis, *n* (%)	1 (1)	0	1 (1)	
Admission to PICU, *n* (%)	1 (1)	0	1 (1)	
Death, *n* (%)	0	0	0	

Abbreviations: AMC, absolute monocyte count; ANC, absolute neutrophil count; IQR: Interquartile range; PICU, paediatric intensive care unit.

Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial

Manuela Aguilar-Guisado, Ildefonso Espigado, Almudena Martín-Peña, Carlota Gudiol, Cristina Royo-Cebrecos, José Falantes, Lourdes Vázquez-López, María Isabel Montero, Clara Rosso-Fernández, María de la Luz Martino, Rocío Parody, José González-Campos, Sebastián Garzón-López, Cristina Calderón-Cabrera, Pere Barba, Nancy Rodríguez, Montserrat Rovira, Enrique Montero-Mateos, Jordi Carratalá, José Antonio Pérez-Simón, José Miguel Cisneros





Neutropenia recovery
Non documented

- Superiority, open-label, randomized, controlled phase 4 clinical trial in 157 adults.
- Experimental group: empiric BSA withdrawn after 72 h or more of apyrexia plus clinical recovery.

Control group: extended BSA until ANC recovery.

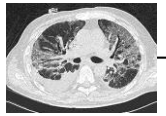
- Decreased BSA in experimental group vs. control group.
- No difference in fever, bacteremia, or mortality.
- No deaths due to bacterial infection.
- More adverse events (mostly mild) in the experimental group (341 vs. 295 in control group).

	Experimental group (n=78)	Control group (n=79)	Between-group absolute difference (95% CI)	p value
Intention-to-treat population				
Number of patients (%)	78 (100%)	79 (100%)	--	--
Efficacy variable				
EAT-free days	16·1 (6·3)	13·6 (7·2)	−2·4 (−4·6 to −0·3)	0·026
Safety variables				
Crude mortality	1 (1·3)	3 (3·8)	NA	0·62
Days of fever	5·7 (5·0)	6·3 (5·9)	0·5 (−1·2 to 2·3)	0·53
Per-protocol population				
Number of patients (%)	66 (85%)	66 (84%)	--	--
Efficacy variable				
EAT-free days	16·9 (5·8)	13·0 (7·2)	−3·8 (−6·1 to −1·6)	0·0010
Safety variables				
Crude mortality	0 (0)	2 (3)	NA	0·49
Days of fever	5·9 (5·1)	6·7 (6·1)	0·86 (−1·1 to 2·8)	0·38
Modified per-protocol population				
Number of patients (%)	36 (46%)	30 (38%)	--	--
Efficacy variable				
EAT-free days	17·5 (6·4)	11·3 (7·0)	−6·4 (−9·7 to −3·0)	0·0003
Safety variables				
Crude mortality	0 (0)	0 (0)	NA	1·00
Days of fever	4·9 (5·4)	5·4 (6·3)	0·5 (−2·4 to 3·4)	0·72

Data are n (%) or mean (SD), unless otherwise stated. EAT=empirical antimicrobial therapy. NA=not applicable.

Table 3: **Efficacy and safety endpoints**

www.thelancet.com/haematology **Published online November 15, 2017** http://dx.doi.org/10.1016/S2352-3026(17)30211-9


Early Antibiotic Discontinuation or De-escalation in High-Risk Patients With AML With Febrile Neutropenia and Prolonged Neutropenia

William Alegria, PharmD[1,2]; Bernard L. Marini, PharmD, BCOP[3,4]; Kevin Sellery Gregg, MD[3,5]; Dale Lee Bixby, MD, PhD[3,6]; Anthony Perissinotti, PharmD[3,4]; and Jerod Nagel, PharmD, BCIDP[3,4]

- Single-center, pre-post quasiexperimental study; adult patients with AML and FN. $N = 93$.
- De-escalation guideline: Afebrile 48 h, clinically stable, then categorized into 3 groups: 1-low suspicion bacterial infection (de-escalate to fluroquinolone prophylaxis); 2-suspected bacterial infection (tailor therapy to targeted suspicious infection then de-escalate to fluoroquinolone prophylaxis); 3-documented bacterial infection (tailor antibiotics based on susceptibilities, then de-escalate to fluoroquinolone prophylaxis).

Table 3. Infection- and Treatment-Related Endpoints After De-escalation Intervention

Endpoint	Historical Group n (%)	Intervention Group n (%)	*P* Value
Development of suspected or documented infection after antibiotic de-escalation[a]	18 (45.0)	18 (34.0)	.29
All-cause mortality at 30 d	6 (15.0)	6 (11.3)	.76
Hospital LoS, median (IQR), d	29 (24–37)	27 (24–39)	.47
Incidence of CDI	11 (27.5%)	3 (5.7%)	.007
De-escalation of IV antipseudomonal therapy	3 (7.5%)	38 (71.7%)	<.001
IV antipseudomonal DoT, median	25	14	<.001

Abbreviations: CDI, *Clostridioides difficile* infection; DoT, days of therapy; IQR, interquartile range; IV, intravenous; LoS, length of stay.
[a]Patients in both groups were counted as having developed infection after meeting criteria for de-escalation (clinical stability between days 5 and 7), regardless of whether IV antipseudomonal antibiotics were continued or de-escalated.

De-escalation of antimicrobial therapy in critically ill hematology patients: a prospective cohort study

David Schnell[1], Claire Montlahuc[2], Fabrice Bruneel[3], Matthieu Resche-Rigon[2], Achille Kouatchet[4], Jean-Ralph Zahar[5], Michael Darmon[1], Frédéric Pene[6], Virginie Lemiale[1], Antoine Rabbat[7], François Vincent[8], Elie Azoulay[1] and Djamel Mokart[9*]

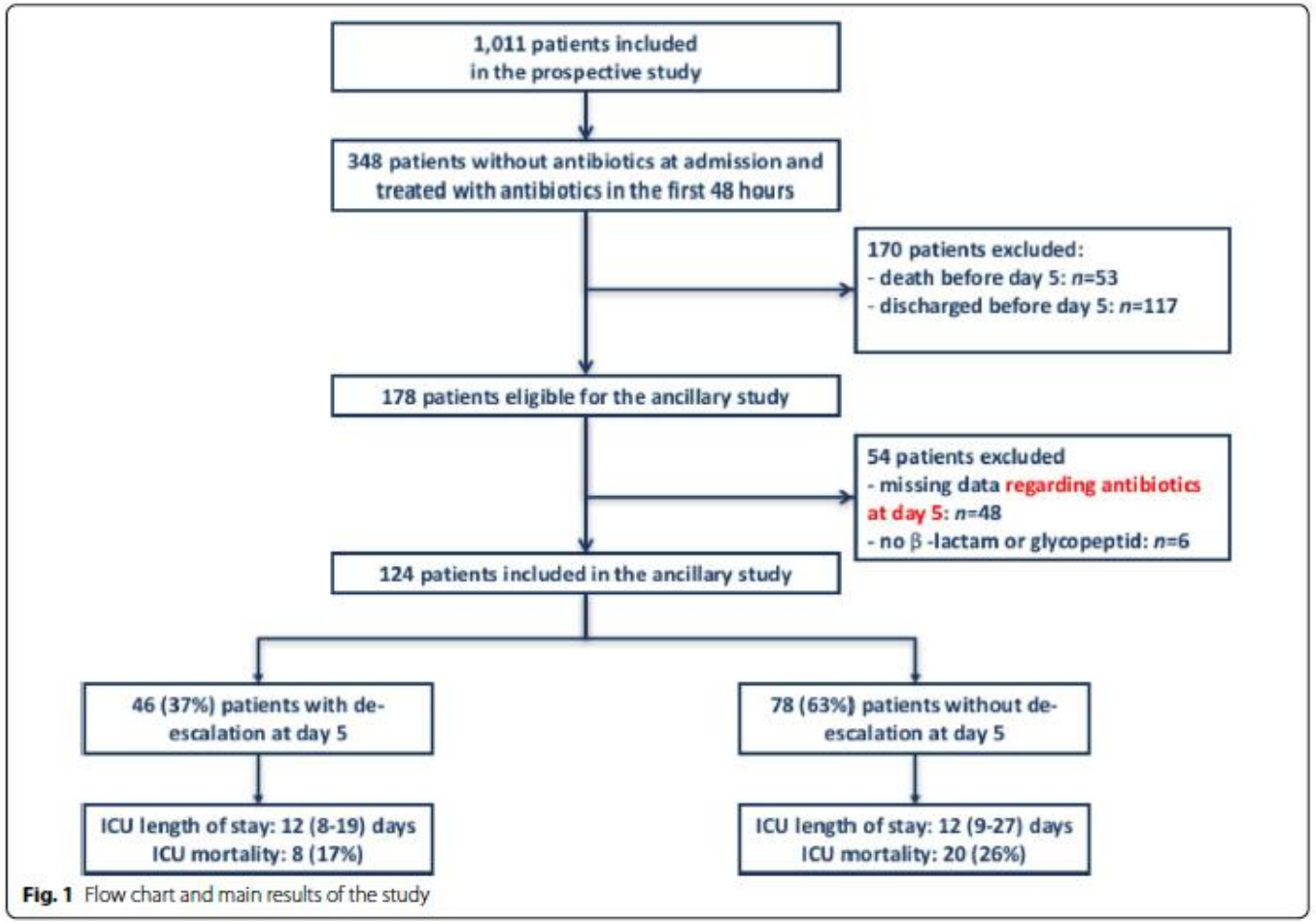
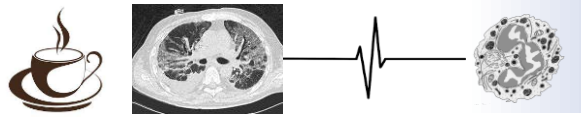


Fig. 1 Flow chart and main results of the study

Intensive Care Med . 2019 May;45(5):743-745.

Antimicrobial de-escalation in septic cancer patients: is it safe to back down?



Alla Paskovaty
Stephen M. Pastores
Zivile Gedrimaite
Natalie Kostelecky
Elyn R. Riedel
Susan K. Seo

Table 1 Baseline characteristics and outcomes of de-escalation and non de-escalation groups

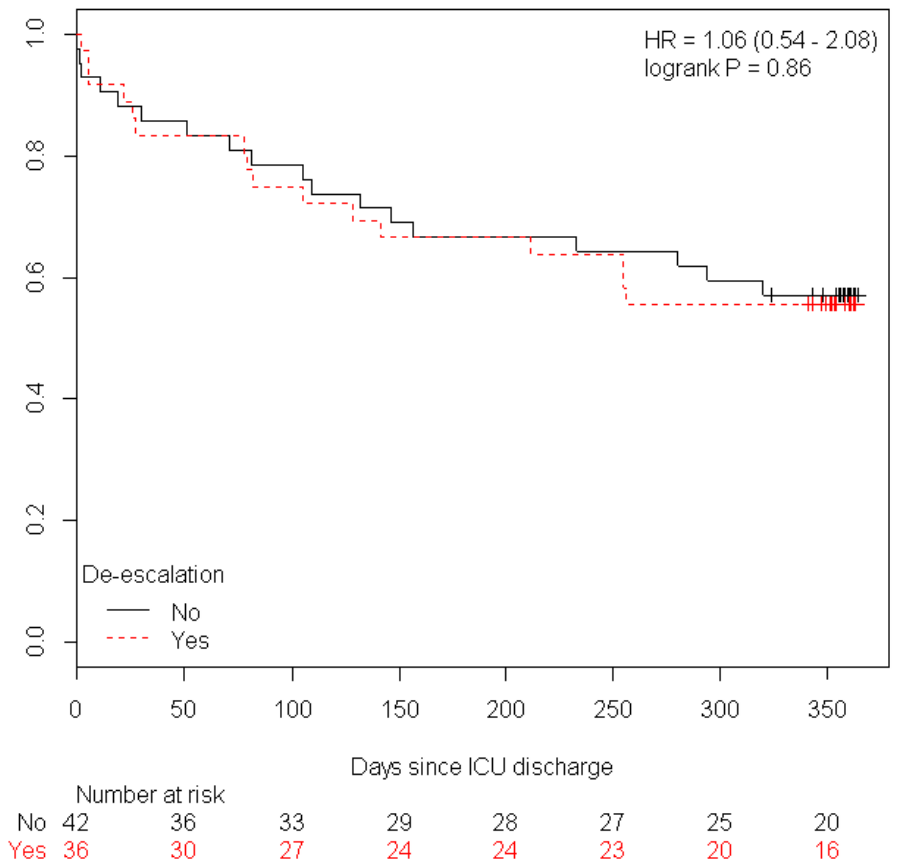
Variable	De-escalation ($N = 61$)	Non de-escalation ($N = 44$)	P value
Age (years)	62.5 (±13.2)	61.7 (±12.8)	0.7
Gender (male)	39 (64 %)	28 (64 %)	1
Cancer type			
Hematologic	24 (39 %)	17 (39 %)	1
Solid	37 (61 %)	27 (61 %)	
Neutropenia on ICU admission	13 (21 %)	11 (26 %)	0.64
History of antibiotic allergy	15 (25 %)	8 (18 %)	0.48
Prior history of resistant organism	2 (3 %)	7 (16 %)	0.03
Lactate level (mmol/L) on ICU admission	2.4 (±2.1)	3.2 (±2.3)	0.03
Blood culture on ICU admission that turned positive	15 (25 %)	7 (16 %)	0.34
Time to first antibiotic administration from initial blood culture collection (hours)	1.1 (±3)	1 (±3)	0.86
Concomitant multiple infections	10 (16 %)	16 (36 %)	0.02
Use of MV during ICU stay	29 (48 %)	22 (50 %)	0.84
Use of MV on day 5	20 (33 %)	18 (41 %)	0.42
Total MV duration (days) (for those on MV)	7.1 (±3.4)	10.1 (±6.6)	0.18
Use of VP during ICU stay	42 (69 %)	35 (80 %)	0.27
MPM II score on ICU admission	0.5 (±0.2)	0.5 (±0.3)	0.96
SOFA score on ICU admission	7.2 (±3.3)	8 (±3.4)	0.18
SOFA score on ICU day 5	5.1 (±3.9)	7 (±3.5)	0.002
Difference between SOFA on day 5 and SOFA on ICU admission	−2.1 (±3.5)	−1 (±3.5)	0.05
Duration of therapy	13.3 (±7.2)	15.5 (±11.1)	0.6
ICU mortality	11 (18 %)	10 (23 %)	0.62
Hospital mortality	21 (34 %)	15 (34 %)	1
28-day mortality	24 (39 %)	15 (34 %)	0.68
ICU LOS	8.1 (±4.6)	11.2 (±7.4)	0.001
Hospital LOS	17.1 (±22.9)	23.4 (±17.6)	0.005

Intensive Care Med (2015) 41:2022–2023

De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study

Djamel Mokart
Géraldine Slehofer
Jérôme Lambert
Antoine Sannini
Laurent Chow-Chine
Jean-Paul Brun
Pierre Berger
Ségolène Duran
Marion Faucher
Jean-Louis Blache
Colombe Saillard
Norbert Vey
Marc Leone

- **De-escalation rate = 40%**
- **Associated factors**
  - Adequation of the empirical antimicrobial treatment used in ICU [OR = 10.8 (95 % CI 1.20–96)] for adequate documented treatment versus appropriate empirical treatment
  - Compliance with guidelines regarding the empirical anti-pseudomonal betalactam used in ICU [OR = 10.8 (95 % CI 1.3–89.5)]



Intensive Care Med. 2014 Jan;40(1):41-9.

ORIGINAL ARTICLE

Septic shock and biliary sepsis: 90-day mortality and associated risk factors

Pierre Thibaud[1], Laurent Chow-Chine[1], Frédéric Gonzalez[1], Magali Bisbal[1], Luca Servan[1], Antoine Sannini[1], Marie Tezier[1], Maxime Tourret[1], Sylvie Cambon[1], Camille Pouliquen[1], Florence Ettori[1], Jean Manuel de Guibert[1], Marion Faucher[1], Fabrice Caillol[2] & Djamel Mokart[1]

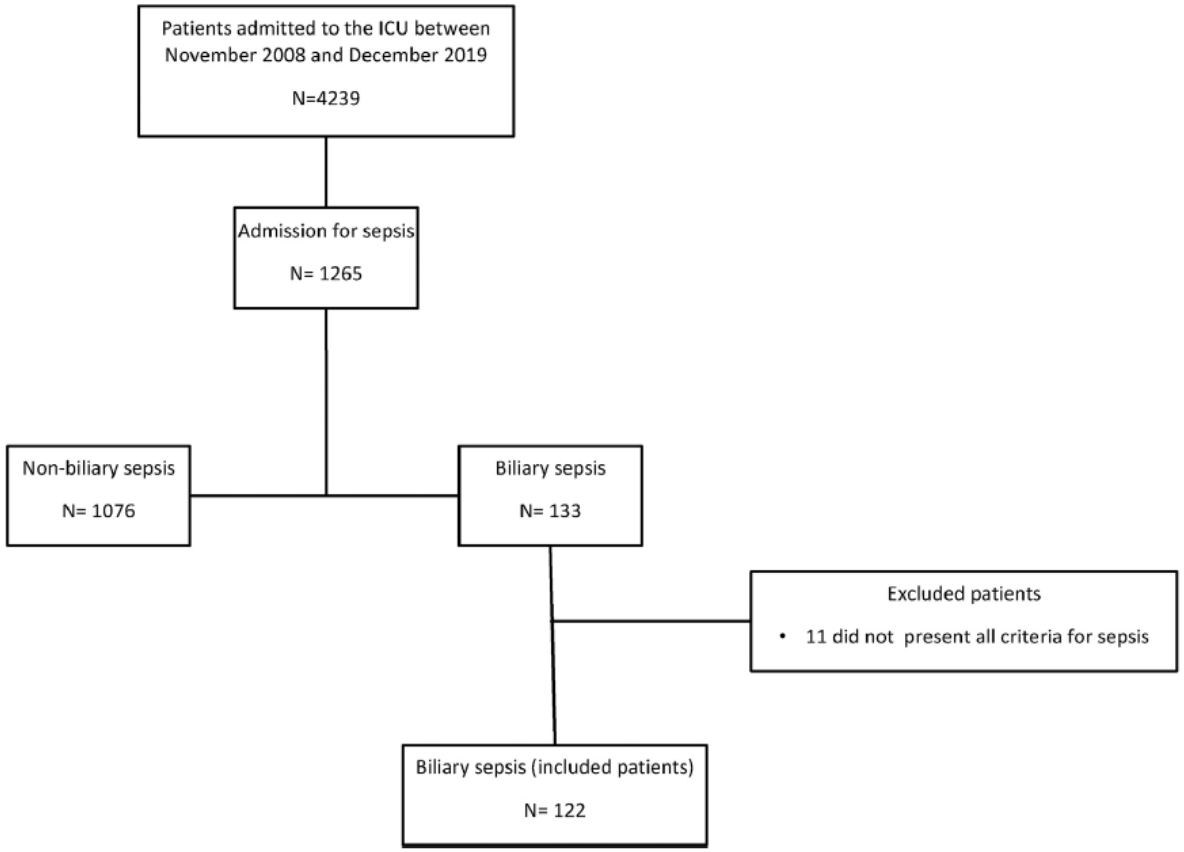
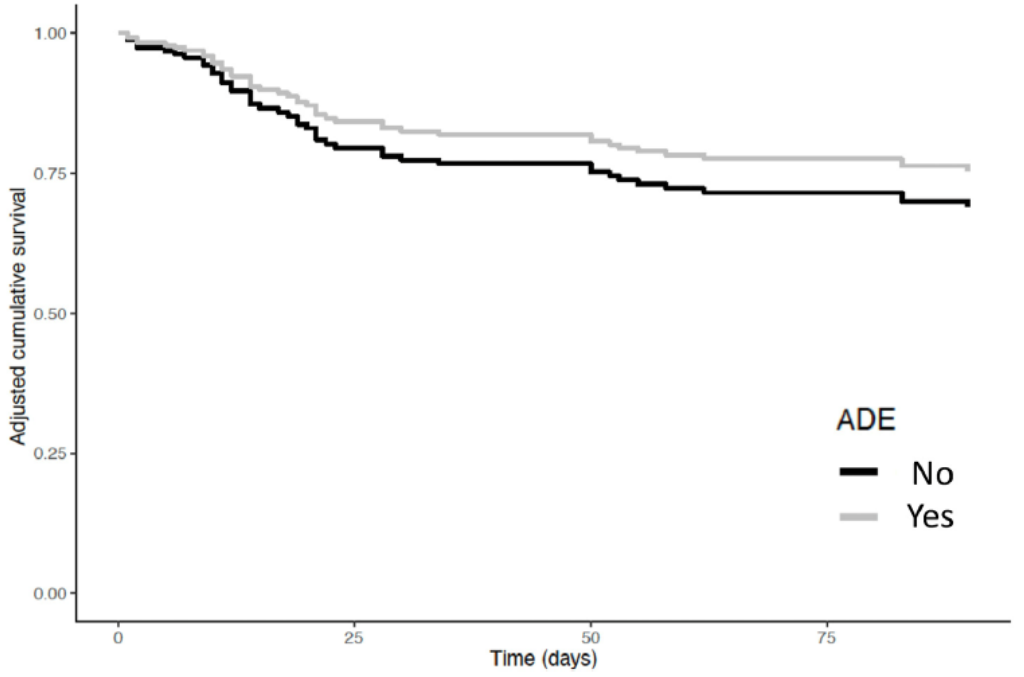


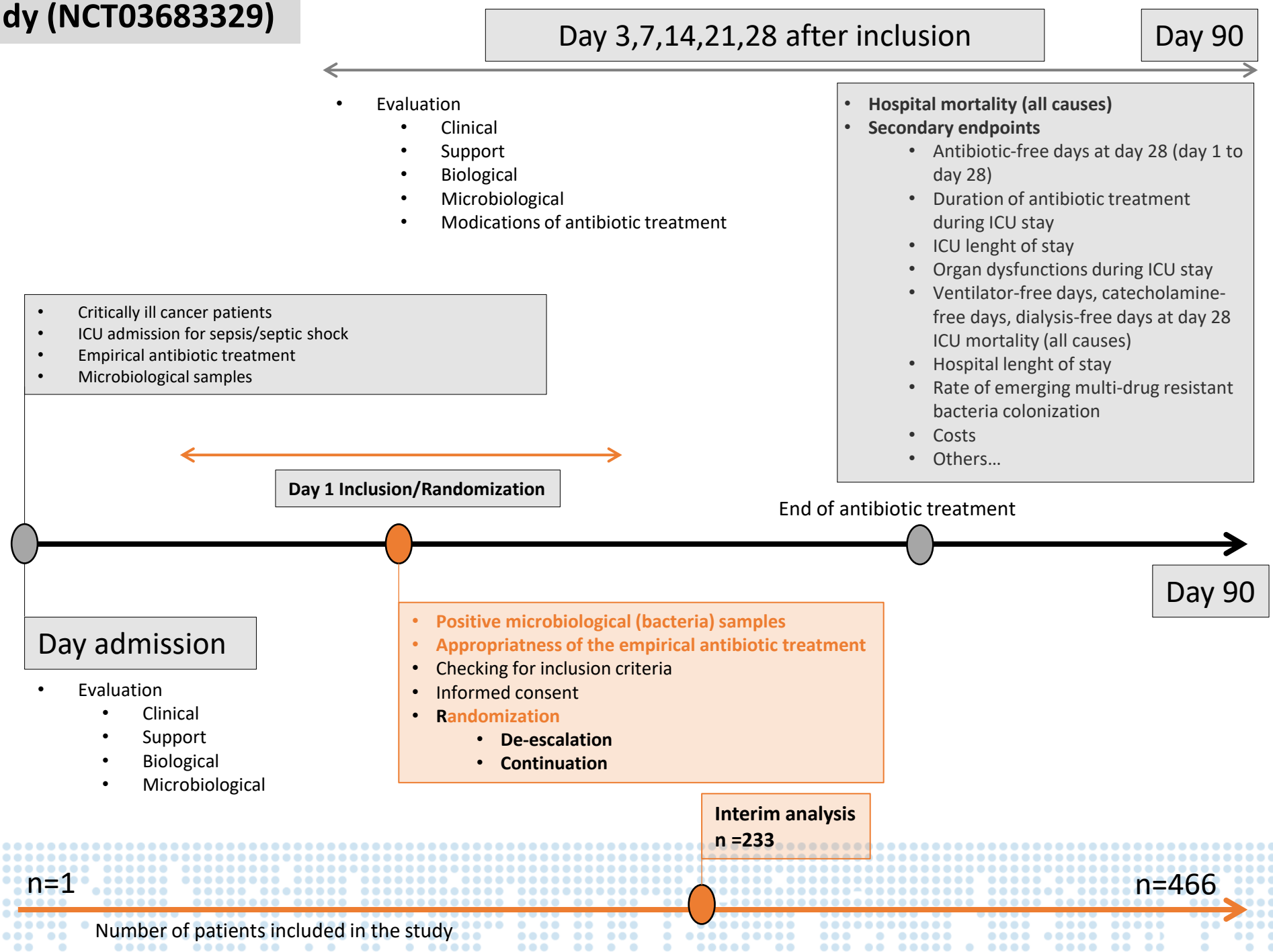
Table 3 Independent factors associated with 90-day mortality (multivariate analysis)

	HR	95% CI	P value
Age	1.034	0.996–1.072	0.078
Performans Status >2	15.93	3.487–72.74	<0.001
Metastatic stage	3.495	1.509–8.096	0.004
Recent cancer surgery	0.052	0.012–0.220	<0.001
Tumour compression	4.642	1.899–11.345	0.001
Lactate at ICU admission	1.294	1.131–1.480	<0.001
Renal replacement therapy	3.302	1.361–1.480	0.008
Factor V < 50%	2.294	1.317–6.761	0.009
MDR bacteria colonisation at ICU admission	2.343	1.008–5.443	0.048
Pivotal antibiotic de-escalation	0.370	0.142–0.962	0.041

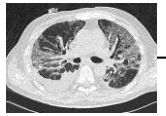
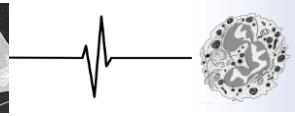


HPB (Oxford) 2024 Feb;26(2):270-281

The DéPOH study (NCT03683329)



Regarding antibiotic de-escalation

- RCTs have been unable to show convincing evidence that ADE is definitely safe in general population
- Systematic reviews have indicated a positive influence of ADE on mortality
  - Biases
- In neutropenic critically ill patients:
  - ADE seems to be safe
  - Infections with MDR germs are probably high-risk situations that are poorly assessed.
  - Infections known to be polymicrobial are probably an obstacle to performing ADE.
  - The results of the ongoing RCT Dépoh (NCT03683329) should provide some insights.

Antimicrobial Stewardship in a Hematological Malignancy Unit: Carbapenem Reduction and Decreased Vancomycin-Resistant Enterococcus Infection

Brandon J. Webb,[1,2] Jacob Majers,[3] Regan Healy,[3] Peter Bjorn Jones,[1] Allison M. Butler,[4] Greg Snow,[4] Sandra Forsyth,[1] Bert K. Lopansri,[1] Clyde D. Ford,[3] and Daanish Hoda[3]

2434 Patients with FN and empirical ATB

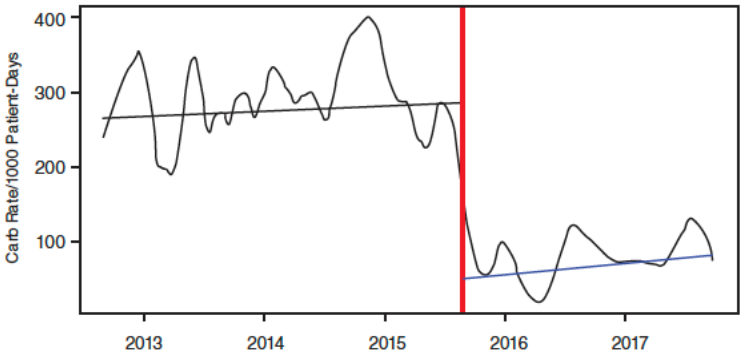
- Cycling program for cefepime or PTZ
- Strict rules for Daptomycine
- Strict rules for carbapenem

Table 2. Antibiotic Usage

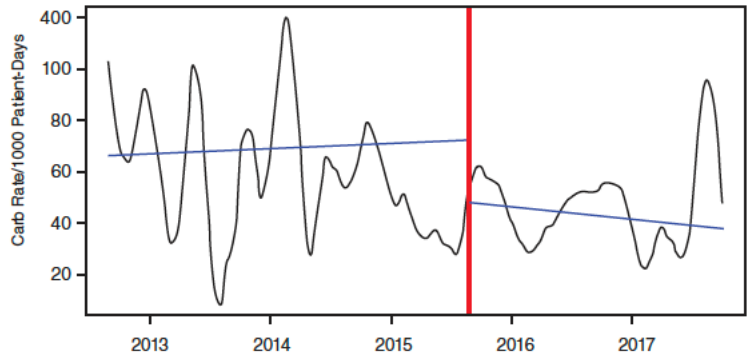
	Preimplementation		Postimplementation		
Antibiotic	DOT	DOT/1000 Patient-days	DOT	DOT/1000 Patient-days	*P* Value
Anti-pseudomonal carbapenem	8658	396.4	1371	123.4	<.001
Cefepime	1093	44.3	1837	165.4	.001
Piperacillin-tazobactam	1116	45.2	2183	196.5	<.001
Ceftazidime	175	7.1	217	19.5	<.001
Metronidazole	1702	68.9	739	66.5	.45
Ceftriaxone	222	9.0	127	11.4	.04
Levofloxacin	7190	291.1	3082	277.5	<.001
Daptomycin	1905	77.1	694	62.5	<.001
Linezolid	251	10.2	92	8.3	.11
Tigecycline	276	11.2	3	0.3	<.001
Vancomycin (intravenous only)	4564	184.8	1936	174.3	.05

Abbreviation: DOT, days of therapy.

Carbapenem use



Daptomycine use



CID 2020:71 (15 August) • Webb et al

Antimicrobial Stewardship in a Hematological Malignancy Unit: Carbapenem Reduction and Decreased Vancomycin-Resistant Enterococcus Infection

Brandon J. Webb,[1,2,©] Jacob Majers,[3] Regan Healy,[3] Peter Bjorn Jones,[1] Allison M. Butler,[4] Greg Snow,[4] Sandra Forsyth,[1] Bert K. Lopansri,[1] Clyde D. Ford,[3] and Daanish Hoda[3]

Table 3. Infections by Pre- and Postimplementation Periods

Infection	Preimplementation n	Preimplementation Per 1000 Encounters	Preimplementation Per 1000 Patient-days	Postimplementation n	Postimplementation Per 1000 Encounters	Postimplementation Per 1000 Patient-days	*P* Value
Gram-positive infection	167	105.83	7.65	84	98.13	7.56	.598
Gram-negative infection	81	51.33	3.71	55	64.25	4.95	.218
Anaerobic infection	6	3.80	0.27	3	3.50	0.27	.99
VRE infection	52	32.95	2.38	12	14.02	1.08	.006
Vancomycin and daptomycin-resistant *Enterococcus* infection	12	7.60	0.55	3	3.50	0.27	.336
Methicillin-resistant *Staphylococcus aureus* infection	7	4.44	0.32	1	1.17	0.09	.319
Carbapenem-resistant gram-negative bacilli infection	8	5.07	0.37	3	3.50	0.27	.794
ESBL-producing *Enterobacteriaceae* infection	3	1.9	0.14	9	10.51	0.81	.010
Likely AmpC ESBL-gene harboring *Enterobacteriaceae* infection	19	12.04	0.87	17	19.86	1.53	.127
Clostridioides difficile (30 days)	78	49.43	3.57	45	52.57	4.05	.810
Colonization (per encounter)							
VRE colonization	480	(30.4%)	…	172	(20.1%)	…	$P < .001$
Candida colonization	759	(48.1%)	…	460	(53.7%)	…	$P = .009$
Specimen site							
Blood	281	798	11.38	115	846	10.35	.06
Urine	37	105	1.50	13	96	1.17	.32
Respiratory	24	68	0.97	7	51	0.63	.26
Skin–soft tissue	5	14	0.20	1	7	0.09	.67
Intraabdominal	1	3	0.04	0	0	0	.99
Other	4	11	0.16	0	0	0	.31

Abbreviations: ESBL, extended-spectrum beta-lactamase; VRE, vancomycin-resistant *Enterococcus*.

Table 4. Multivariable Logistic Regression for Vancomycin-resistant *Enterococcus* Colonization

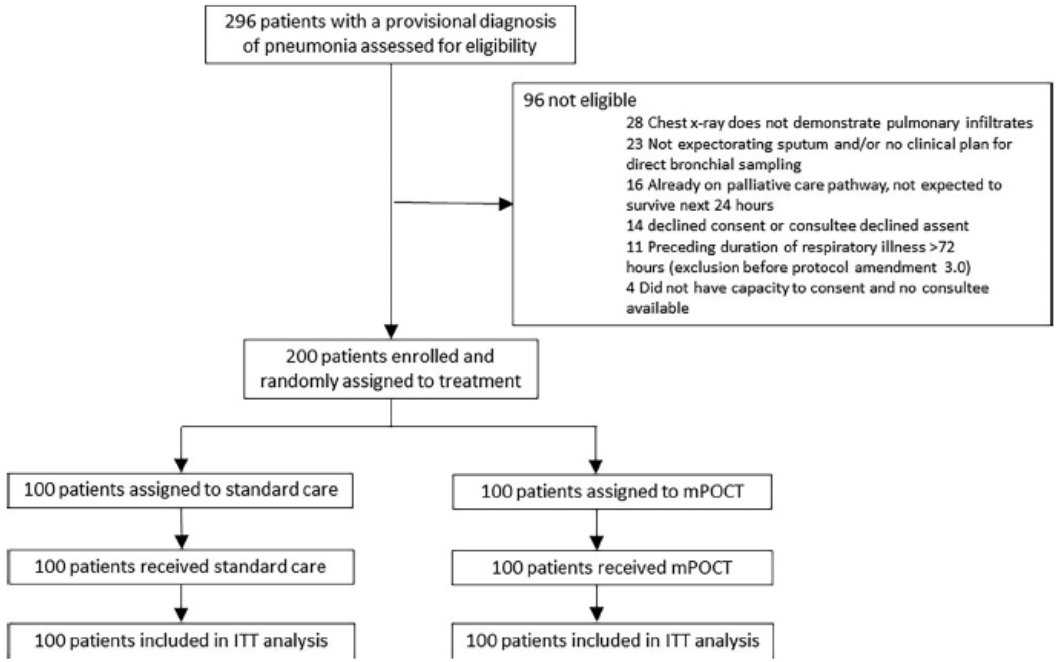
Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Intercept	0.23 (.19, .28)	<.001
Implementation of cycling program	0.64 (.51, .81)	<.001
Acute lymphoblastic leukemia	1.47 (1.14, 1.89)	.003
Chronic myeloid leukemia	0.76 (.30, 1.69)	.531
Non-Hodgkin lymphoma	0.94 (.71, 1.25)	.685
Length of stay (days)	1.02 (1.01, 1.03)	<.001
Haploidentical hematopoietic stem cell transplant	2.13 (1.28, 3.56)	.004
Metronidazole use (DOT)	1.02 (.99, 1.04)	.161
Carbapenem use (DOT)[a]	1.03 (1.01, 1.04)	<.001

Abbreviation: DOT, days of therapy/1000 patient-days.

[a]Carbapenem use was a found to be a significant contributor in the model by the full and reduced method.

Molecular point-of-care testing for lower respiratory tract pathogens improves safe antibiotic de-escalation in patients with pneumonia in the ICU: Results of a randomised controlled trial

Stephen Poole[a,b,*], Alex R Tanner[b], Vasanth V Naidu[b], Florina Borca[a,c], Hang Phan[c], Kordo Saeed[b,d], Michael P W Grocott[a,d,e], Ahilanandan Dushianthan[a,d,e], Helen Moyses[a], Tristan W Clark[a,b,d,f]



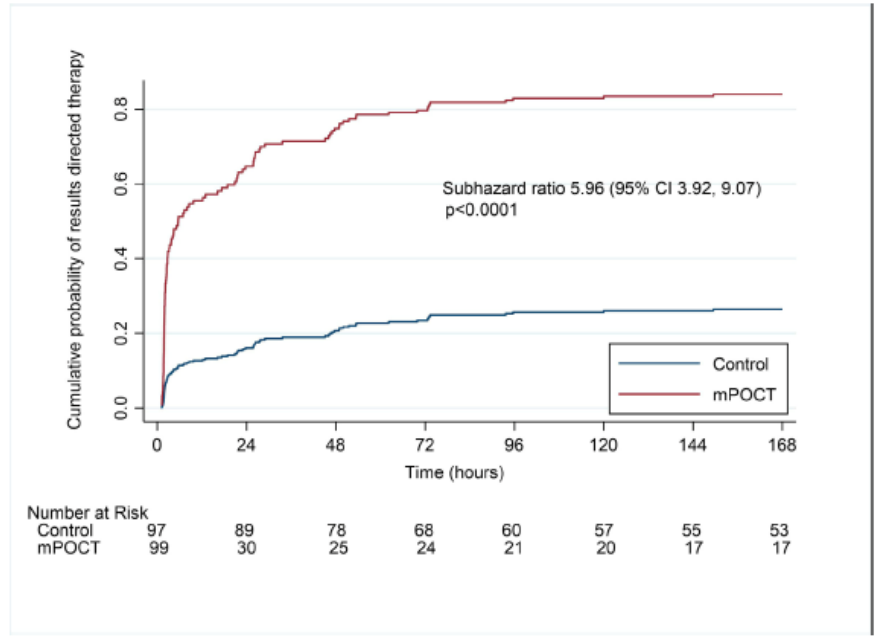


Fig. 3. Time-to-event curve for results-directed antimicrobial therapy.

Table 4
Antimicrobial use.

Outcome	mPOCT group n = 100	Control group n = 100	Absolute difference (95% CI)	p value
Primary outcome				
Results-directed therapy	80 (80)	29/99 (29)	51 (39-63)	<0.0001
Secondary outcomes				
Time to results-directed therapy, hours*	2.3 [1.8-7.2]	46.1 [23.0-51.5]	-43.8 (-48.9 to -38.6)	<0.0001
Results-directed de-escalation	42 (42)	8/98 (8)	34 (23-45)	<0.0001
Time to results-directed de-escalation, hours†	4.8 [2.4- 13.0]	46.5 [26.3-48.9]	-41.4 (-53.0 to -29.7)	<0.0001
Results-directed escalation	9 (9)	1/98 (1)	8 (2 to 14)	0.034
Time to results-directed escalation, hours‡	5.1 [2.7-26.0]	27.5 [27.5-27.5]	-22.4 (-165.0 to 120.3)	0.38
Ineffective antimicrobial therapy at recruitment	14/100 (14)	14/99 (14)	-0.1 (-10 to 10)	0.98
Ineffective antimicrobial therapy at 48 hours post recruitment	12/99 (12)	8/95 (8)	4 (-5 to 12)	0.40
Duration of ineffective therapy, hours§	71.5 [46.0-113.0]	60.5 [18.5-127.5]	26.8 (-35.0 to 88.5)	0.38
De-escalatable therapy at recruitment	58 (58)	58/99 (59)	-0.6 (-14 to 13)	0.93
De-escalatable therapy at 48 h post-recruitment	29/99 (29)	40/95 (42)	-13 (-26 to 0.6)	0.063
Duration of all antimicrobial therapy, days¶	7.6 [5.0- 10.8]	7.0 [4.7-9.8]	0.6 (-0.7 to 1.9)	0.35
Number of antimicrobial classes used¶	2 (1-3)	2 (1-2)	0.1 (-0.2 to 0.2)	1.00
Antimicrobial free hours in following 14 days¶	145.6 [77.4-233.4]	170.9 [82.3-239.5]	-24.9 (-65.4 to 15.6)	0.23

Rapid molecular tests for detection of antimicrobial resistance determinants in Gram-negative organisms from positive blood cultures: a systematic review and meta-analysis☆

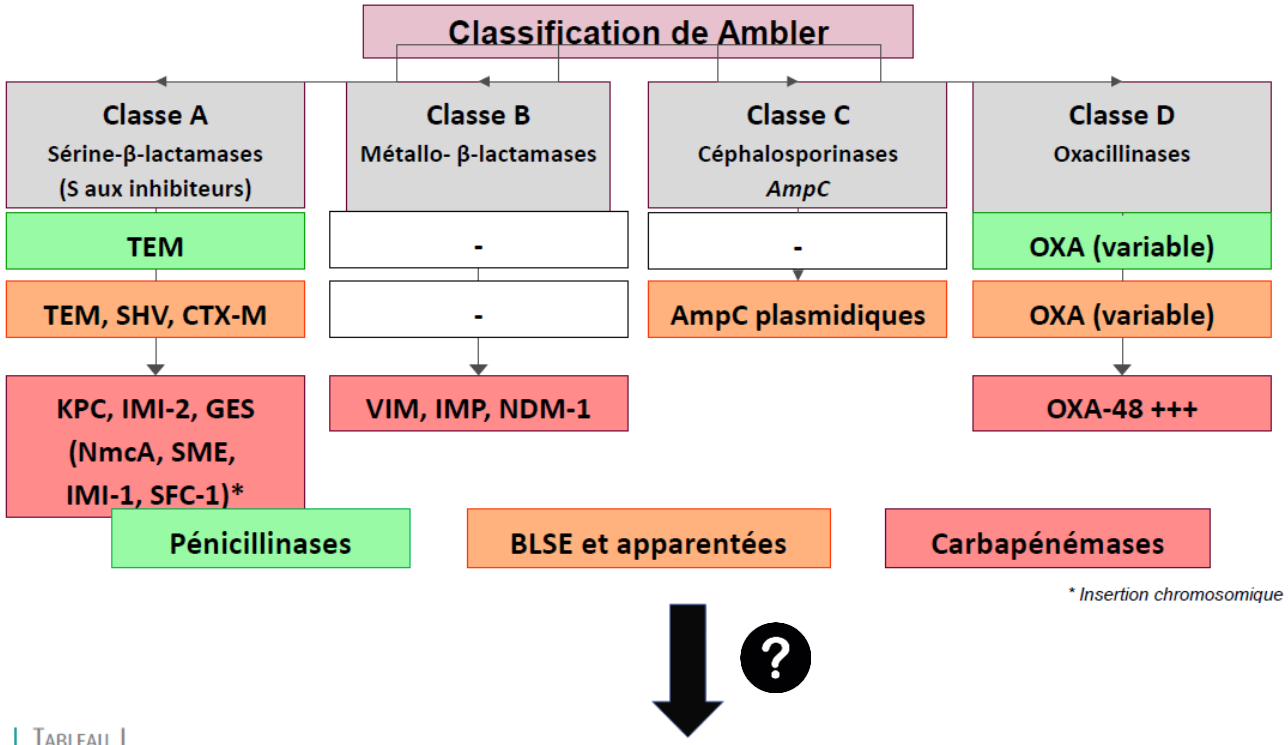
G. De Angelis [1], A. Grossi [2], G. Menchinelli [1], S. Boccia [2, 3], M. Sanguinetti [1, 4, *], B. Posteraro [5, 6]

Table 2
Summary of the subgroup analysis of the 20 included studies[a]

Resistance determinants investigated	No. of isolates[b] (no. of studies)	No. of isolates with Verigene and/or FilmArray results of			Sensitivity (95% CI), %	Specificity (95% CI), %
		Correct detection	Misdetection	No detection		
Studies using genotypic methods as comparators						
CTX-M	836 (3)	62	0	1	96.0 (87.1–98.8)	99.7 (98.6–99.9)
IMP	0 (0)	–	–	–	–	–
KPC	1181 (3)	27	0	0	93.5 (72.9–98.7)	99.8 (99.3–100.0)
NDM	637 (1)	1	0	0	75.0 (10.9–98.7)	99.9 (98.8–100.0)
OXA	747 (2)	7	0	1	79.9 (45.7–94.9)	99.8 (98.7–100.0)
VIM	89 (1)	1	0	0	75.0 (10.9–98.7)	99.6 (91.7–100.0)
Total	1380 (5)	98	0	2	95.5 (89.2–98.2)	99.7 (99.1–99.9)
Studies using phenotypic methods as comparators						
CTX-M	1832 (15)	199	2	14	89.2 (83.7–93.0)	99.3 (98.7–99.7)
IMP	305 (3)	3	0	3	49.1 (18.3–80.6)	99.5 (97.5–99.9)
KPC	641 (5)	18	0	11	59.8 (42.3–75.2)	99.3 (97.5–99.8)
NDM	0 (0)	–	–	–	–	–
OXA	1104 (6)	31	0	9	69.5 (42.1–87.7)	99.7 (89.9–99.9)
VIM	197 (2)	5	0	3	57.7 (26.5–83.8)	99.5 (96.7–99.9)
Total	1930 (16)	256	2	30[c]	85.3 (79.9–89.4)	99.1 (98.2–99.5)

Quel traitement des infections à BLSE en réanimation ?

Benoît Pilmis, Thibaud Delerue, Frédéric Mechai, Jean-Ralph Zahar, Françoise Jaureguy



1

Carbapenems

?

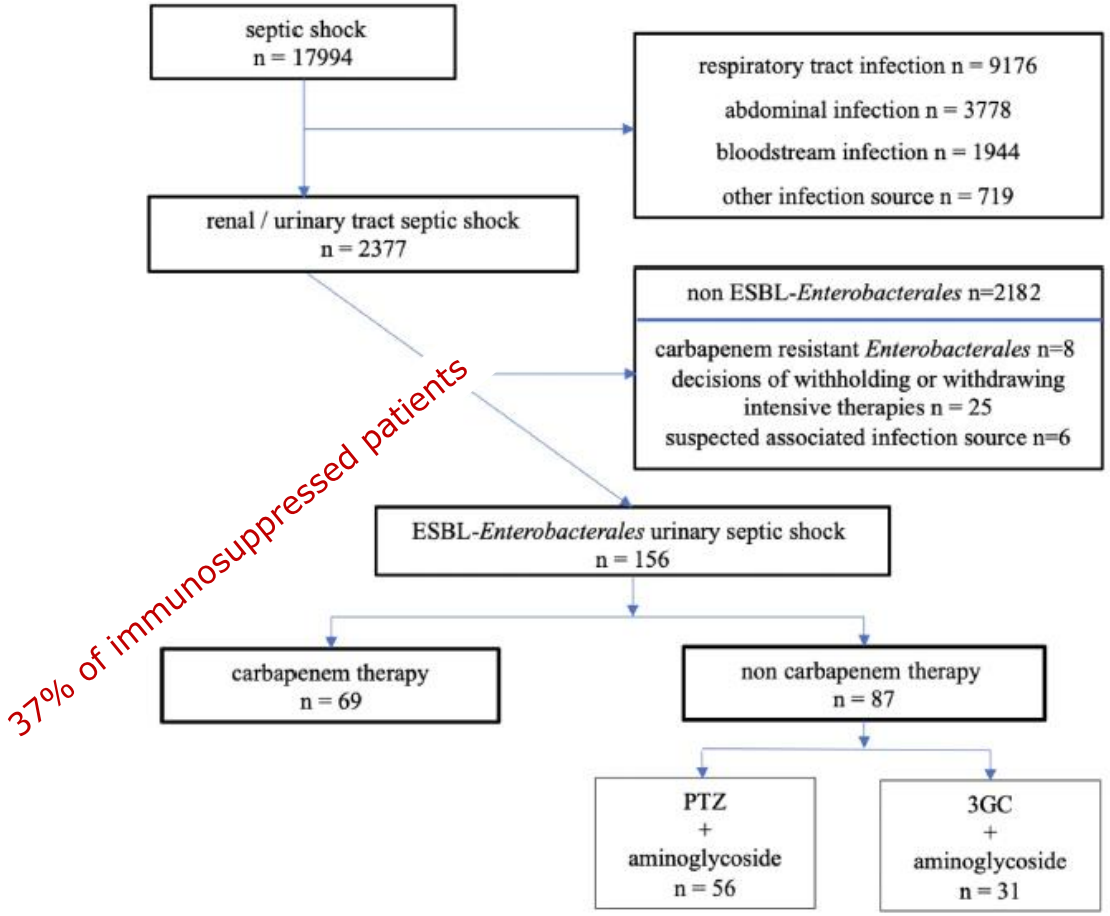
TABLEAU I

Prérequis pour l'utilisation d'une molécule autres que les carbapénèmes dans le traitement documenté des infections à Entérobactéries productrices de bêtalactamase.

Site infectieux	Extirpable (drainage, chirurgie, retrait du cathéter)
Contrôle de la source	Effectué
Évolution clinique du patient	Stabilisation clinique, absence de gravité, absence d'immunodépression
Type d'enzymes et niveau phénotypique d'expression	CTX-M
CMI	Strictement inférieure à 8 mg/L pour la tazocilline
Espèce microbienne concernée	*Escherichia coli*

Anesth Reanim. 2019; 5: 310-314

Efficacy of carbapenem vs non carbapenem β-lactam therapy as empiric antimicrobial therapy in patients with extended-spectrum β-lactamase-producing *Enterobacterales* urinary septic shock: a propensity-weighted multicenter cohort study



PTZ : piperacillin / tazobactam. 3GC : 3rd generation cephalosporin.

Fig. 1 Flow chart

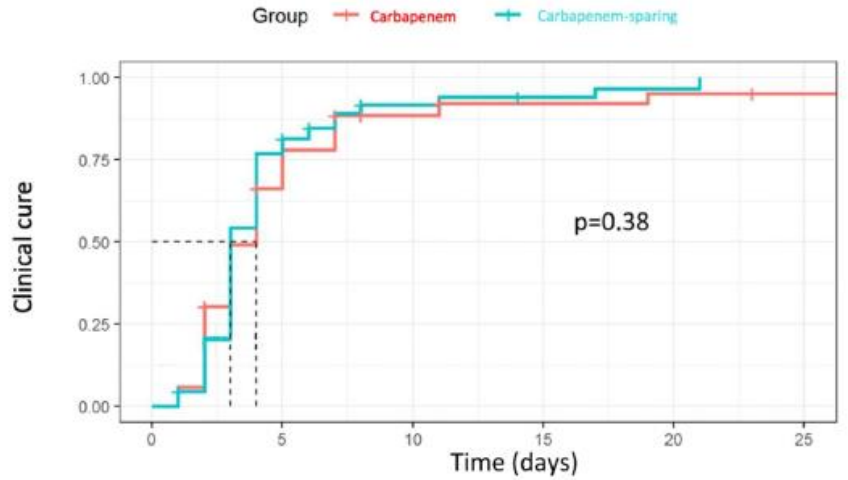


Fig. 2 Kaplan–Meier curves of reflecting the probability of clinical cure according to the empirical antimicrobial therapy group (carbapenem vs non carbapenem regimen). Kaplan–Meier curves was weighted with the propensity score. For patients with treatment failure, data were censored for length of hospitalization. *P*-value results from the Log Rank Test

Cariou et al. Annals of Intensive Care (2023) 13:22

Rationale and evidence for the use of new beta-lactam/beta-lactamase inhibitor combinations and cefiderocol in critically ill patients

François Barbier[1,2*], Sami Hraiech[3], Solen Kernéis[4], Nathanaël Veluppillai[4], Olivier Pajot[5], Julien Poissy[6], Damien Roux[2,7] and Jean-Ralph Zahar[2,8] On behalf of the French Intensive Care Society

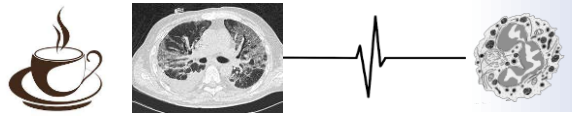


Table 1 In vitro activity of novel β-lactam/β-lactamase inhibitor combinations and cefiderocol against carbapenem-resistant Gram-negative bacteria

Main mechanisms of carbapenem resistance	**Enterobacterales**			***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
	Class A carbapenemase (KPC)	**Class D carbapenemase (OXA-48-like[a])**	**Class B carbapenemase (MBL[b])**	***OprD2* mutation Efflux[c] MBL[d]**	**OXA[e]**	**Chromosomal MBL**
Ceftolozane–tazobactam	–	–	–	+++ 75%-90%[f]	–[g]	–[g]
Ceftazidime–avibactam	+++ 96%-99%	+++ 96%-99%	–	++ 60%-70%	–[g]	–[g]
Ceftazidime–avibactam plus aztreonam	+++ 96–99%	+++ 96%-99%	+++ > 90%	± (MBL) 0–25%	–[g]	++[h] ~85%
Meropenem–vabor-bactam	+++ 95–99%	–	–	–	–	–[g]
Imipenem–relebactam	+++ 88%-95%	±	–	++ 70%-90%	–	–[g]
Cefiderocol	+++ 84–91%	+++ 88–93%	++ VIM: 79%-81% NDM: 41%-51%	+++ > 90%	+++[i] MIC ≤ 2 mg/L for > 90% of isolates	+++[i] MIC ≤ 2 mg/L for > 90% of isolates

Cefiderocol in Difficult-to-Treat Nf-GNB in ICU Settings

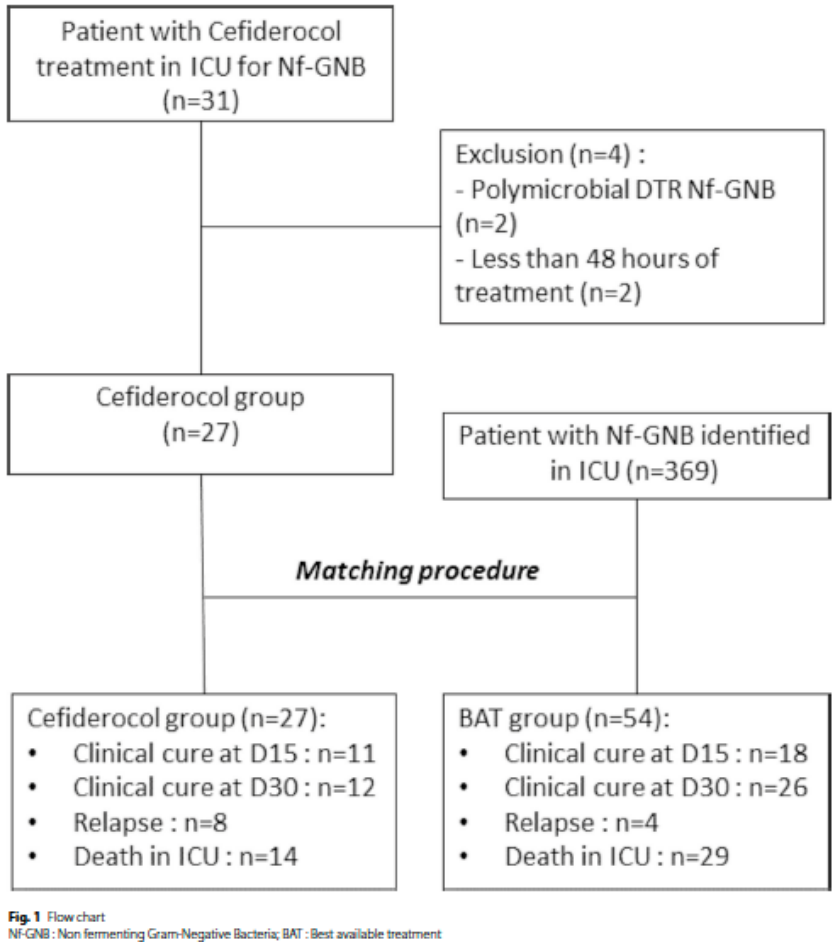
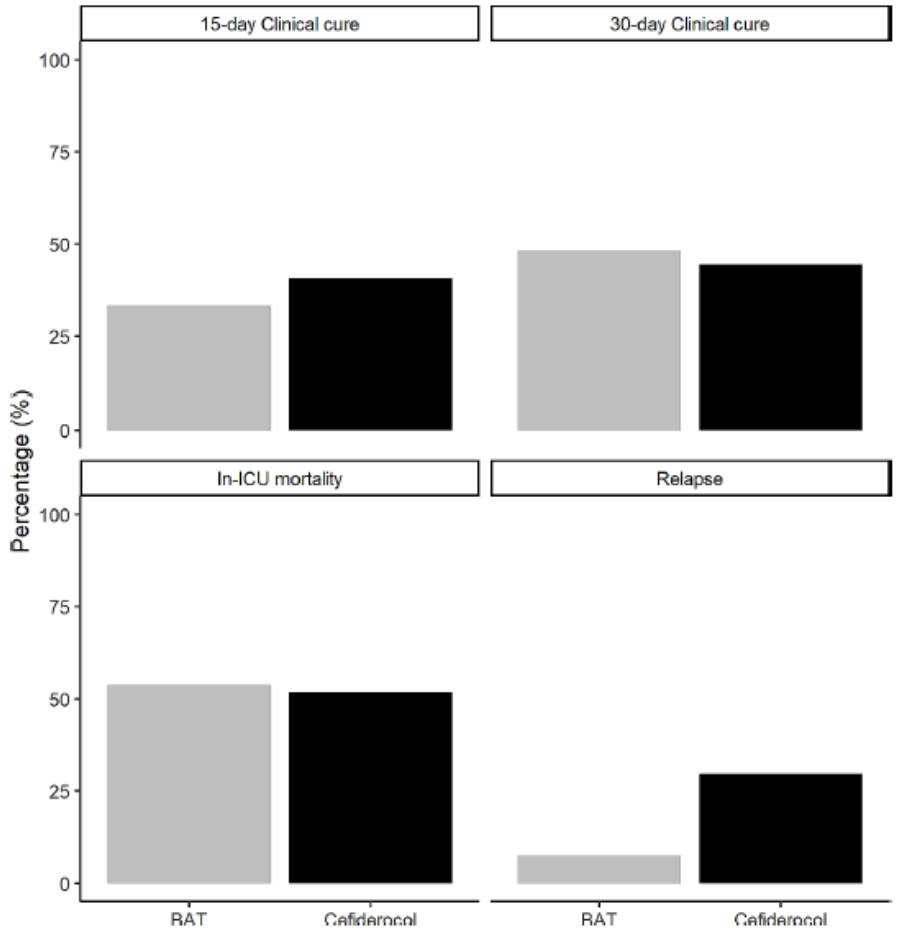


Fig. 1 Flow chart
Nf-GNB : Non fermenting Gram-Negative Bacteria; BAT : Best available treatment



28% with immunosuppression

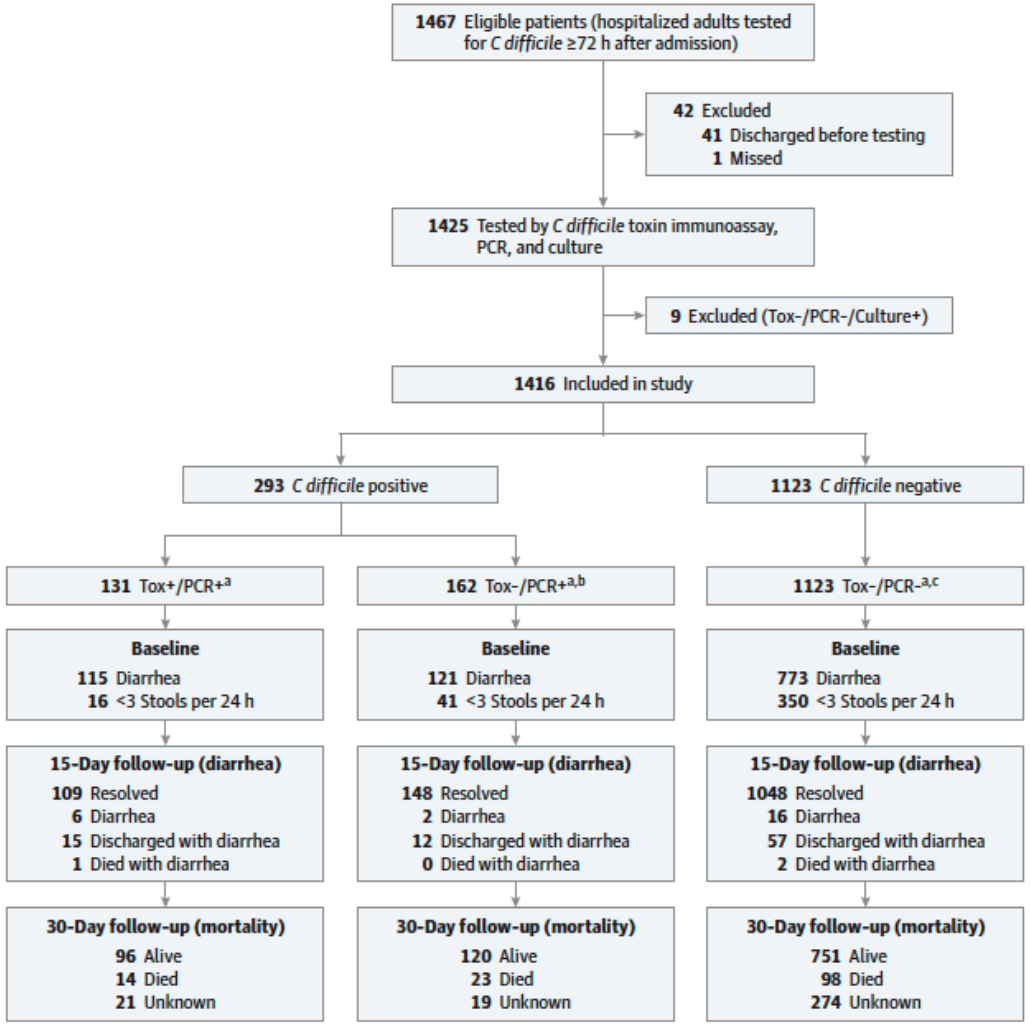
Vacheron *et al. Annals of Intensive Care* (2024) 14:73

Original Investigation

Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era

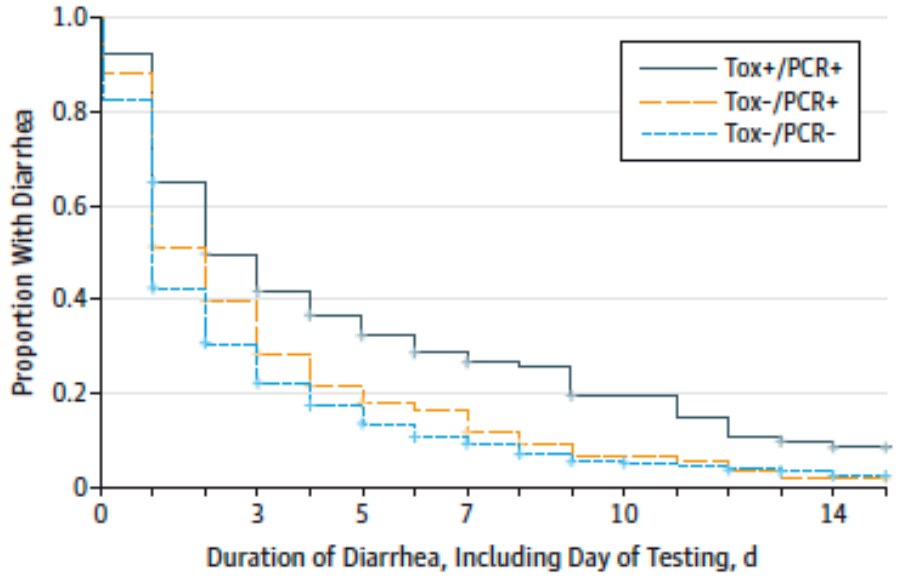
Christopher R. Polage, MD, MAS; Clare E. Gyorke, BS; Michael A. Kennedy, BS; Jhansi L. Leslie, BS; David L. Chin, PhD; Susan Wang, BS; Hien H. Nguyen, MD, MAS; Bin Huang, MD, PhD; Yi-Wei Tang, MD, PhD; Lenora W. Lee, MD; Kyoungmi Kim, PhD; Sandra Taylor, PhD; Patrick S. Romano, MD, MPH; Edward A. Panacek, MD, MPH; Parker B. Goodell, BS, MPH; Jay V. Solnick, MD, PhD; Stuart H. Cohen, MD

Figure 1. Flow of Patients Through Testing and Follow-up



Patients undergoing C difficile testing were grouped by US Food and Drug Administration–approved toxin and PCR tests as Tox+/PCR+, Tox−/PCR+, or Tox−/PCR−. Toxin results were reported clinically. Polymerase chain reaction results were not reported.

Figure 2. Kaplan-Meier Curves of Time to Resolution of Diarrhea by *Clostridium difficile* Test Group



No. at risk

Tox+/PCR+	131	62	41	29	25	8
Tox-/PCR+	162	60	29	21	10	2
Tox-/PCR-	1123	328	172	99	42	23

JAMA Intern Med 2015;175(11):1792–801.

Clinical Outcomes of Treated and Untreated *C. difficile* PCR-Positive/Toxin-Negative Adult Hospitalized Patients: a Quasi-Experimental Noninferiority Study

Catherine A. Hogan,[a,b]* Matthew M. Hitchcock,[c,d] Spencer Frost,[e] Kristopher Kapphahn,[f] Marisa Holubar,[g,h] Lucy S. Tompkins,[g] Niaz Banaei[a,b,g]

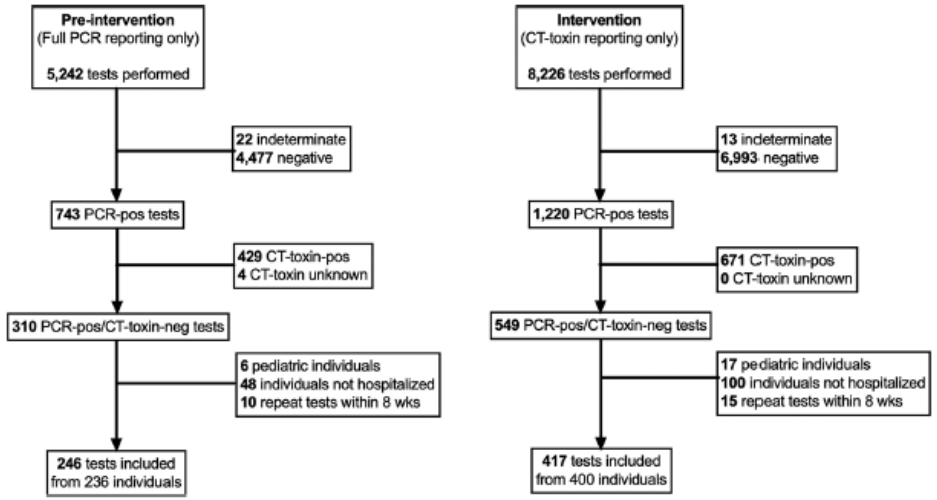


FIG 1 Flowchart of the study. CT-toxin, cycle threshold-based toxin. Indeterminate refers to an indeterminate PCR result.

TABLE 2 Primary and secondary outcomes of the study in the intervention group (CT-toxin only reporting) compared to the preintervention group (PCR only reporting)

Outcome	No. (%) or median (IQR) in:		Unadjusted HR or OR (90% CI)	Unadjusted *P* value	aHR or OR (90% CI)	Adjusted *P* value[e]	Noninferiority margin	Evidence of noninferiority established
	Preintervention group	Intervention group						
Symptomatic *C. difficile* PCR$^+$/CT-toxin$^+$ conversion within 8 wk[a]	13 (5.3)	28 (6.7)	1.29 (0.73–2.28)	0.46	0.90 (0.37, 2.16)	0.84	1.15	No
Unresolved diarrhea at 7 days[b]	40 (20.0)	57 (13.7)	0.63 (0.44–0.92)	0.04	0.57 (0.32, 1.01)	0.10	1.15	Yes
Median hospital length of stay[c]	10.8 (4.2–22.1)	6.9 (3.0–17.8)	1.30 (1.11–1.53)	0.001	1.20 (0.88, 1.64)	0.26	1.15	No
30-Day all-cause mortality[d]	21 (8.6)	26 (6.5)	0.74 (0.45–1.22)	0.32	0.46 (0.20, 1.04)	0.12	1.10	Yes

J Clin Microbiol 2022;60(6):e0218721.

Advances in antibacterial treatment of adults with high-risk febrile neutropenia

Adrien Contejean [1,2,3]*, Alexis Maillard [2], Etienne Canouï [2], Solen Kernéis[3,4,5], Bruno Fantin[3,6], Didier Bouscary[3,7], Perrine Parize [8], Carolina Garcia-Vidal[9,10] and Caroline Charlier [2,3,11,12]

Table 3. Clinical hypotheses if patient is still febrile at Day 3

Hypotheses	Complementary investigations
Underdosed antibiotics	Therapeutic drug monitoring
Inappropriate antibiotic therapy	Repeat blood cultures
Uncontrolled focal infection	Full body tomography
	Consider [^{18}F]FDG-PET-CT scan
	Therapeutic drug monitoring
	Consider central venous catheter withdrawal and culture
	Search for *Clostridioïdes difficile* infection
Thrombosis (+/− septic) of central venous catheter	Central catheter Doppler ultrasound
	Repeat blood cultures
Undocumented MDR bacteria	Repeat blood cultures
Insufficient antibacterial spectrum	
Viral infection	Nasopharyngeal swab with PCR test
(flu, respiratory syncytial virus, SARS-CoV-2, etc.)	
Invasive fungal infection	Sinus and chest tomography
(aspergillosis, mucormycosis, invasive candidiasis, etc.)	Galactomannan antigen
	Aspergillus sp. blood PCR
	Mucor sp. blood PCR
	β-D-Glucan
	Repeat blood cultures

Invasive Fungal Diseases in Adult Patients in Intensive Care Unit (FUNDICU): 2024 consensus definitions from ESGCIP, EFISG, ESICM, ECMM, MSGERC, ISAC, and ISHAM

Intensive Care Med. 2024 Mar 21. doi: 10.1007/s00134-024-07341-7.

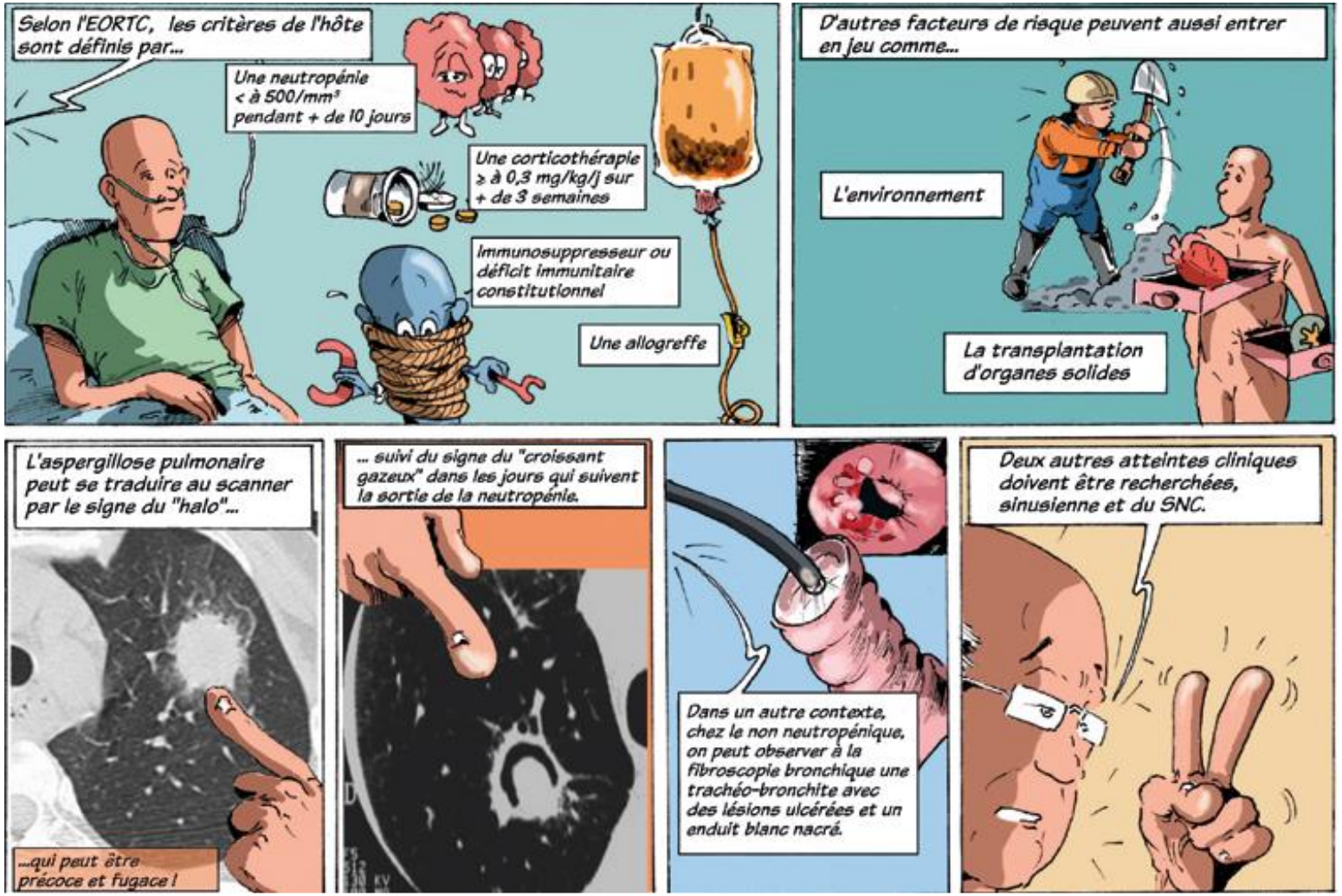
Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

J. Peter Donnelly,[1] Sharon C. Chen,[2] Carol A. Kauffman,[3] William J. Steinbach,[4] John W. Baddley,[5] Paul E. Verweij,[6] Cornelius J. Clancy,[7] John R. Wingard,[8]

CID 2020:71 (15 September) • 1367

- The EORTC/MSGERC recently revised and updated the consensus definitions of invasive fungal disease (IFD).
- These definitions primarily focus on patients with cancer and stem cell or solid-organ transplant patients.
- They may therefore not be suitable for intensive care unit (ICU) patients.
- **Diagnosis of IFD in the ICU presents many challenges, which are different for invasive candidiasis and for invasive aspergillosis**.

IPA during neutropenia (EORTC/MSG criteria)



Comic strip from the Grrr-OH

Bassetti, Clin Infect Dis 2021:72 (Suppl 2) • S121

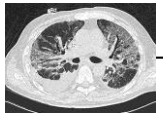
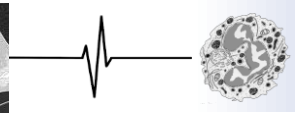
Donnelly J,Clin Infect Dis 2020; 71:1367–76

Core Recommendations for Antifungal Stewardship: A Statement of the Mycoses Study Group Education and Research Consortium

Melissa D. Johnson,[1,a] Russell E. Lewis,[2,a] Elizabeth S. Dodds Ashley,[1,a] Luis Ostrosky-Zeichner,[3] Theoklis Zaoutis,[4] George R. Thompson III,[5] David R. Andes,[6] Thomas J. Walsh,[7] Peter G. Pappas,[8] Oliver A. Cornely,[9,10,11,12] John R. Perfect,[1] and Dimitrios P. Kontoyiannis[13]; for the Mycoses Study Group Education and Research Consortium

Table 3. Sample Care Bundles for Invasive Candidiasis and Invasive Aspergillosis

Bundle	
Invasive candidiasis management bundle	
At the time therapy is being started	Perform 2 high-volume blood cultures (40 mL) prior to starting therapy
	Removal of existing CVCs within 24 h of diagnosis
	Initial appropriate selection and dosing of antifungals considering local epidemiology started within 12 h of culture
	Ophthalmological exam within the first week of diagnosis
After starting therapy	Follow-up blood cultures daily until clearance of candidemia is documented
	Echocardiography in patients with persistent fungemia, fever, or new cardiac symptoms
	Assessment of clinical efficacy 3–5 d after starting therapy and evaluating the need for alternative therapy based on culture identification and susceptibility results are available
	Administration of at least 2 wk of therapy after clearance of blood cultures (longer with organ involvement)
	Step-down to oral fluconazole therapy in patients with a favorable clinical course and an isolate with documented susceptibility
Invasive aspergillosis management bundle	
At the time therapy is being started	Serum galactomannan test repeated twice in patients not on mold-active azole prophylaxis
	CT imaging of chest and/or sinus/brain in patients with symptoms localized at these signs
	Early bronchoscopy (within 48 h) with cytology examination and culture of BAL fluid, measurement of galactomannan antigen titer in BAL; transbronchial biopsy if feasible
	Initial appropriate selection and dosing of antifungal agents considering previous antifungal exposure and local epidemiology
	Systematic screening for drug interactions using a computerized drug interactions database for any patient starting or stopping a triazole antifungal agent
After starting therapy	Periodic (eg, weekly) testing of serum galactomannan (if aspergillosis) as an adjunct criterion to assess treatment response
	TDM of voriconazole and posaconazole and possibly isavuconazole serum levels to document adequate drug exposures
	Assessment of therapy appropriateness based on microbiological, culture, or histological results
	Repeat chest CT imaging after 3–4 wk and periodically based on response, to assess infection status and/or progression
	Step-down to oral triazole therapy in patients with a favorable clinical course

Antiviral stewardship ?

- Asymptomatic patients:
  - BK virus without symptoms in HCT
  - CMV in lower risk hosts
  - HHV-6 DNAemia

Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7)

*Per Ljungman, Rafael de la Camara, Christine Robin, Roberto Crocchiolo, Hermann Einsele, Joshua A Hill, Petr Hubacek, David Navarro, Catherine Cordonnier, Katherine N Ward, on behalf of the 2017 European Conference on Infections in Leukaemia group**

	European Society of Clinical Microbiology and Infectious Diseases recommendation grading[4]	Study	Comment
Aciclovir	CI	Prentice et al (1994)[52] Milano (2011)[53]	Less effective than valaciclovir
Valaciclovir	BI	Ljungman (2002)[54] Winston (2003)[55] Milano (2011)[53]	Used together with pre-emptive therapy
Ganciclovir	CI	Winston (1993)[56] Goodrich (1993)[57]	Used at engraftment
Valganciclovir	CIIh	Montesinos (2009)[58] Boeckh (2015)[59]	Cord blood HSCT used in Montesinos et al;[58] prophylaxis against late cytomegalovirus disease
Foscarnet	DIIu	Ordemann (2000)[100] Bregante (2000)[101]	NA
Letermovir	AI	Marty (2017)[102]	Only effective against cytomegalovirus

HSCT=haematopoietic stem cell transplantation. NA=not applicable.

Table: **Recommended drugs for antiviral prophylaxis after allogeneic HSCT**

www.thelancet.com/infection **Published online May 29, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30107-0**

Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7)

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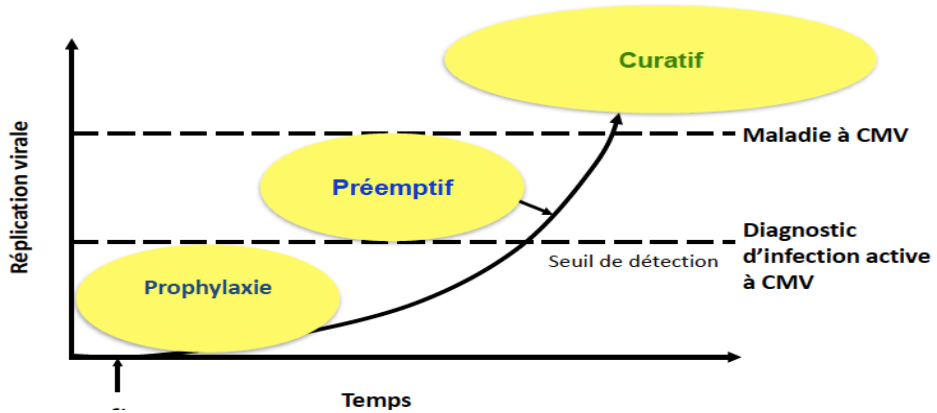
- **Pre-emptive strategy first line**
  - PCR+ or Ag+ and asymptomatic
  - Ganciclovir or Foscarnet (AI)
  - Valganciclovir (AII)
    - Unless digestive GVHD
- **Pre-emptive strategy 2nd line**
  - Cidofovir (BII)
  - Leflunomide or artesunate (CIII)
    - Resistance
    - Refractory disease
  - Immunoglobulins not recommended (DIII)

- **CMV disease**
- **1st line**
  - Ganciclovir (AII)
  - Foscarnet if ganciclovir toxicity or resistance (AIII)
  - Ig or hyperimmune Ig in combination with antiviral in CMV PNP (CIII)
    - No Ig or HivIg for other CMV diseases
- **2nd line**
  - Cidofovir or ganciclovir + foscarnet (BII)
  - Retinitis: intravitreal gancilovir or foscarnet
  - Valganciclovir instead of GCV or Foscarnet (BIII, except digestive GVHD)
  - Cidofovir +Ganciclovir or Foscarnet (BII)

www.thelancet.com/infection **Published online May 29, 2019** http://dx.doi.org/10.1016/S1473-3099(19)30107-0

Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

Raymund R. Razonable[1] | Atul Humar[2,3]



Antiviral drugs for cytomegalovirus prevention and treatment in solid organ transplant recipients

Drug	Treatment[a]	Prophylaxis	Comments on use and toxicity
Valganciclovir	900 mg[b] po twice daily	900 mg[b] po once daily	Ease of administration Leukopenia is major toxicity
IV ganciclovir	5 mg/kg IV every 12 h	5 mg/kg IV once daily	Intravenous access and its associated complications Leukopenia is major toxicity
Valacyclovir	NOT recommended	2 g po four times daily	For kidney transplant recipients only NOT recommended for heart, liver, pancreas, lung, intestinal, and composite tissue transplant recipients High pill burden Neurotoxicity NOT recommended for treatment of CMV disease or asymptomatic infection
Foscarnet	60 mg/kg IV every 8 h (or 90 mg/kg every 12 h)	NOT recom-mended	Second-line alternative agent for treatment Highly nephrotoxic Used for *UL97*-mutant ganciclovir-resistant CMV infection or disease NOT recommended for preemptive therapy
Cidofovir	5 mg/kg once weekly ×2, then every 2 wk thereafter	NOT recom-mended	Third-line agent Highly nephrotoxic May be used for *UL97*-mutant ganciclovir-resistant CMV infection or disease NOT recommended for preemptive therapy

Clinical Transplantation. 2019;33:e13512. https://doi.org/10.1111/ctr.13512

Cytomegalovirus antiviral stewardship in solid organ transplant recipients: A new gold standard

Margaret R. Jorgenson[1] | Jillian L. Descourouez[1] | Hanna Kleiboeker[1] | Kerry Goldrosen[1] | Lucas Schulz[1] | John P. Rice[2] | Jon S. Odorico[3] | Didier A. Mandelbrot[4] | Jeannina A. Smith[5] | Christopher M. Saddler[5]

TABLE 2 Enrollment type

	Historic (2018) N = 87	Current (2021) N = 93	*p*-Value
Treatment	26%	12%	.012
Prophylaxis (all)	62%	79%	.013
Ganciclovir-resistant-cytomegalovirus (GR-CMV)	5%	3%	.54

Note: Prophylaxis (all) = CMV, preemptive monitoring, surveillance.

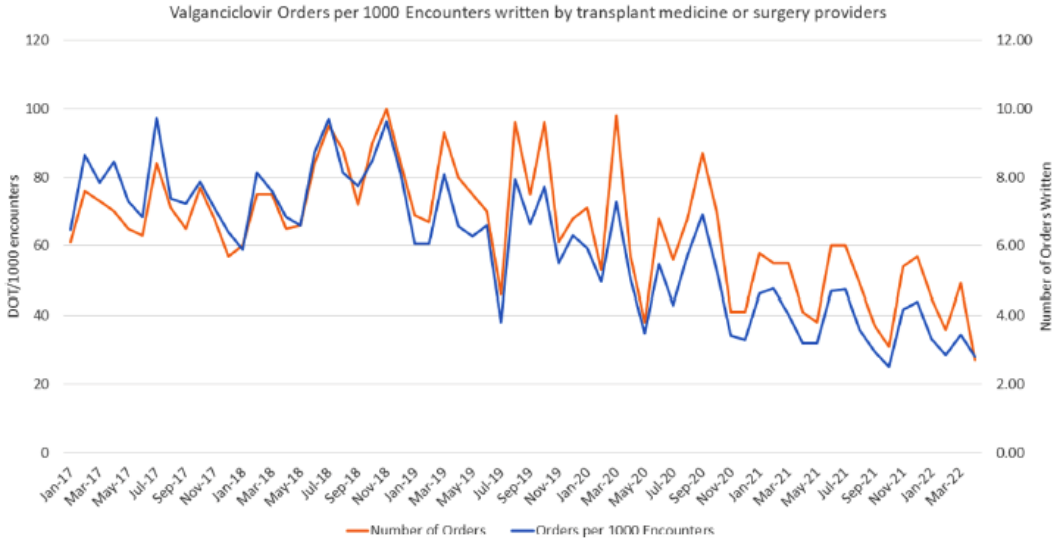


FIGURE 4 Vanganciclovir orders/1000 clinic encounters written by transplant medicine or transplant surgery providers

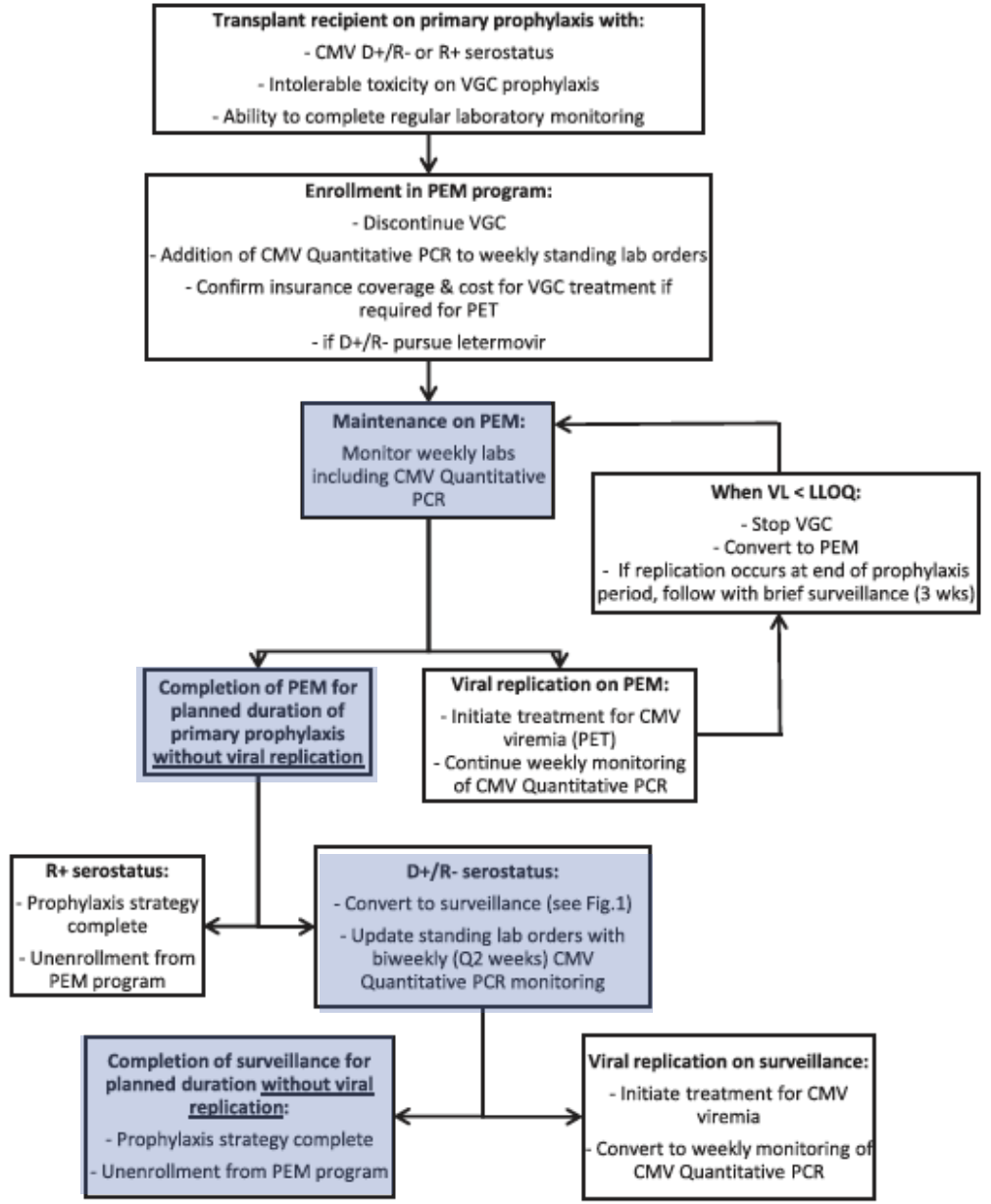


FIGURE 2 Center-specific algorithm for preemptive monitoring. CMV, cytomegalovirus; D, donor; LLOQ, lower limit of quantification; PCR, polymerase chain reaction; PEM, preemptive monitoring; PET, preemptive treatment; R, recipient; VGC, valganciclovir

Transpl Infect Dis. 2022;24:e13864.

Herpesviridae in critically ill hematology patients: HHV-6 is associated with worse clinical outcome

Frédéric Gonzalez [a,*], Samuel Beschmout [a], Laurent Chow-Chine [a], Magali Bisbal [a], Evelyne d'Incan [b], Luca Servan [a], Jean-Manuel de Guibert [a], Norbert Vey [b], Marion Faucher [a], Antoine Sannini [a], Djamel Mokart [a]

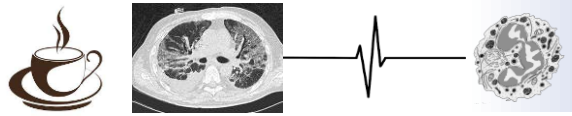


Table 4
Multivariable analysis for factors associated with hospital mortality.

	Odds Ratio	95% CI	p-value
Lines of chemotherapy	1.26	[1.06–1.52]	0.015
Corticosteroids	2.30	[1.21–4.36]	0.011
SAPS II	1.03	[1.01–1.04]	0.008
Septic shock	2.16	[1.20–3.89]	0.010
SOFA respiration score ≥ 2	2.66	[1.58–4.49]	<0.0001
Sepsis with bacteria identification	0.50	[0.29–0.87]	0.014
Invasive aspergillosis	4.87	[1.93–12.29]	0.001
HHV6 reactivation	2.35	[1.03–5.34]	0.042
EBV reactivation	3.33	[1.14–9.79]	0.028
Antiviral therapy (ICU stay)			
None	1	1	
Prophylactic	0.41	[0.18–0.95]	0.037
Curative	1.31	[0.75–2.28]	0.35

SAPS II = Simplified Acute Physiology Score II. SOFA = Sequential Organ Failure Assessment.

Table 6
Multivariable regression model for factors associated with 1-year mortality.

	Odds Ratio	95% CI	p-value
Lines of chemotherapy	1.33	[1.09–1.61]	0.005
Corticosteroids	1.72	[0.98–3.03]	0.06
Graft-versus-host disease	2.59	[1.11–6.05]	0.002
Charlson's comorbidity index	1.19	[1.03–1.36]	0.015
Invasive mechanical ventilation	4.50	[2.58–7.84]	<0.0001
Renal replacement therapy	2.38	[1.19–4.78]	0.015
Sepsis with bacteria identification	0.61	[0.34–1.10]	0.10
Non-fermenting Gram negative bacilli identification	2.68	[1.07–6.72]	0.036
Invasive aspergillosis	7.68	[2.03–29.01]	0.003
HHV-6 disease	0.25	[0.05–1.17]	0.08
HHV-6 pneumonitis	6.87	[1.09–43.3]	0.040

Human herpesvirus 6, 7, and 8 in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Rebecca Pellett Madan[1] | Jonathan Hand[2] | on behalf of the AST Infectious Diseases Community of Practice

- Most HHV6 infections are asymptomatic
- Routine HHV6 PCR in asymptomatic patients not recommended
- Prophylactic and pre-emptive treatment not recommended
- HHV6 PCR in blood and CSF recommended for diagnosis of infection
- In case of persistent high viral load, look for chromosomal integration of the virus
- Antiviral treatment should be initiated in case of encephalitis, and considered in case of other organ involvement
  - Foscarnet
  - Ganciclovir
  - Cidofovir

Clinical Transplantation. 2019;33:e13518.
https://doi.org/10.1111/ctr.13518

Metrics

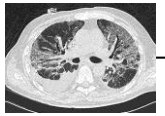
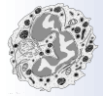
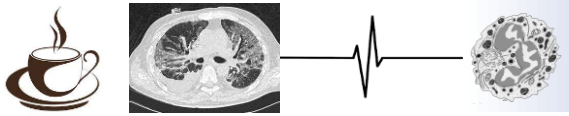




Table 2
Examples of potential antibacterial, antiviral and antifungal process, outcome, and balancing metrics

	Process	Outcome	Balancing
Antibiotic stewardship	Usage (DOT) Guideline adherence • ASB • MRSA-targeted antibiotic in FN • DOT for FN SAP selection, timing Intervention acceptance rates DOT in recipient of bacteremic donor First-line OI prophylaxis rate Cost Provider-specific usage	Infection rate Infection-related readmission Infectious mortality Infectious LOS ADE/toxicity Antimicrobial resistance • Antibiogram ◦ Hospital ◦ Unit ◦ Urine in KTR • Bacterial isolate trends • FQR in HM/HCT Surgical site infection	Infection rate Infectious readmission Recurrent infection after de-escalation/ cessation Infectious LOS Infectious mortality Surgical site infection DOOR/RADAR
Antifungal stewardship	Usage (DOT, LOT) Cost # Prescriptions reviewed Guideline adherence Diagnostic optimization TDM Intervention acceptance rate	Incidence of IFI IFI mortality Relapse EORTC/MSG IFI classification Causative organism tracking Effectiveness of AF prophylaxis ADE/toxicity	Infection rate Infectious readmission Recurrent infection after de-escalation/ cessation readmission Infectious mortality (fungal)
Antiviral stewardship	Usage (DOT) Cost Intervention acceptance rate Guideline adherence Diagnostic optimization RBV appropriateness	Infection rate: • CMV DNAemia • CMV disease Viral hospitalization ADE/toxicity Resistance rate Time-to-CMV eradication	Infection rate Infectious readmission Recurrent DNAemia/disease after de-escalation/cessation Readmission Infectious mortality (CMV, RSV)

Abbreviations: ADE, adverse drug event; ASB, asymptomatic bacteriuria; CMV, cytomegalovirus; DOOR/RADAR, desirability of outcome ranking/response adjusted for days of antibiotic risk; DOT, days of therapy; FN, febrile neutropenia; FQR, fluoroquinolone resistance; KTR, kidney transplant recipients; LOS, length of stay; LOT, length of therapy; OI, opportunistic infection; RBV, ribavirin; RSV, respiratory syncytial virus; SAP, surgical antibacterial prophylaxis; TDM, therapeutic drug monitoring.

Infect Dis Clin N Am 37 (2023) 823–851



Conclusion

- Safe ?
- Anti-microbial optimization in IC patients is challenging due to their recurring exclusion from clinical trials and guidelines for common clinical syndromes.
- There is an absolute need for antimicrobial stewardship in this high risk population.
- For these patients, the literature describes specific approaches in terms of diagnostic and therapeutic management that can form the basis for implementing safe antimicrobial stewardship strategies