Antimicrobico-resistenza: cure e ambiente #8

Antibiotici: troppi o troppo pochi?

CONVEGNO ACCREDITATO ECM: **crediti n. 7**

17 giugno 2025 ore 10.00-18.00

Auditorium di Sant'Apollonia via S. Gallo, 25/a - Firenze

Antimicrobial stewardship in Italia e in Europa

Mario Tumbarello

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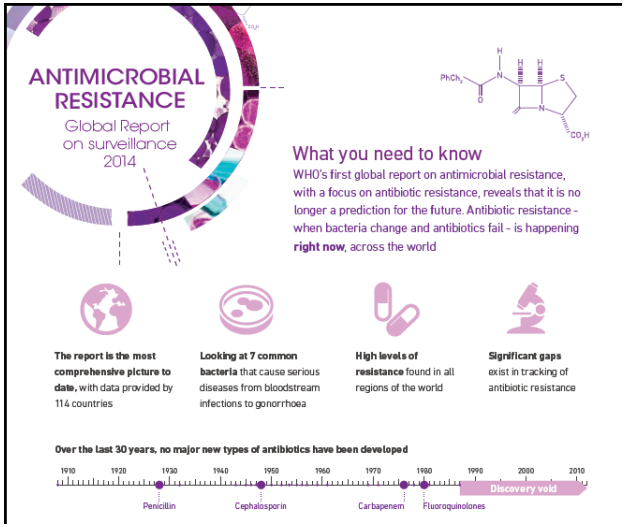
UNIVERSITÀ DI SIENA 1240



TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:

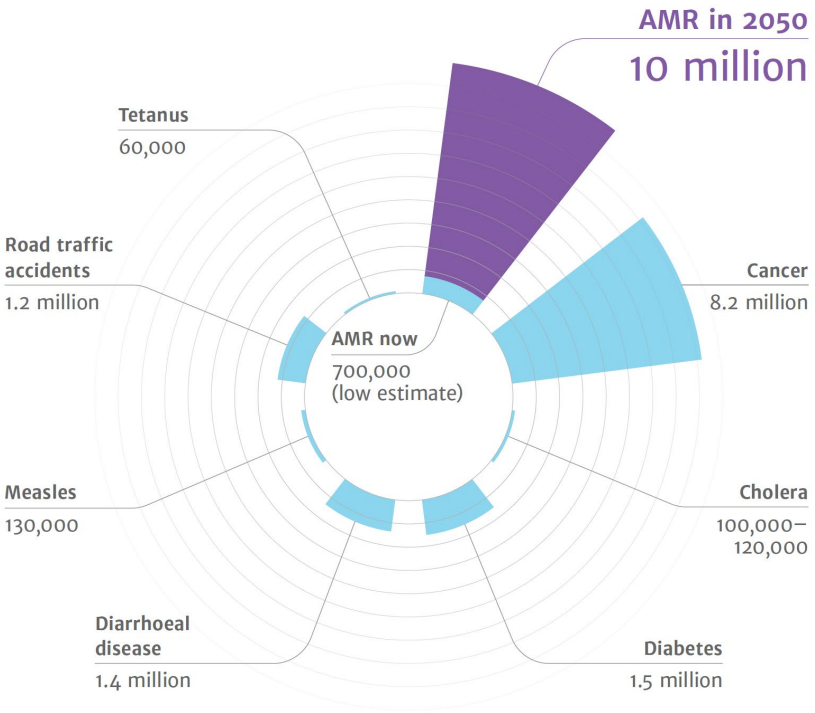
FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

MAY 2016

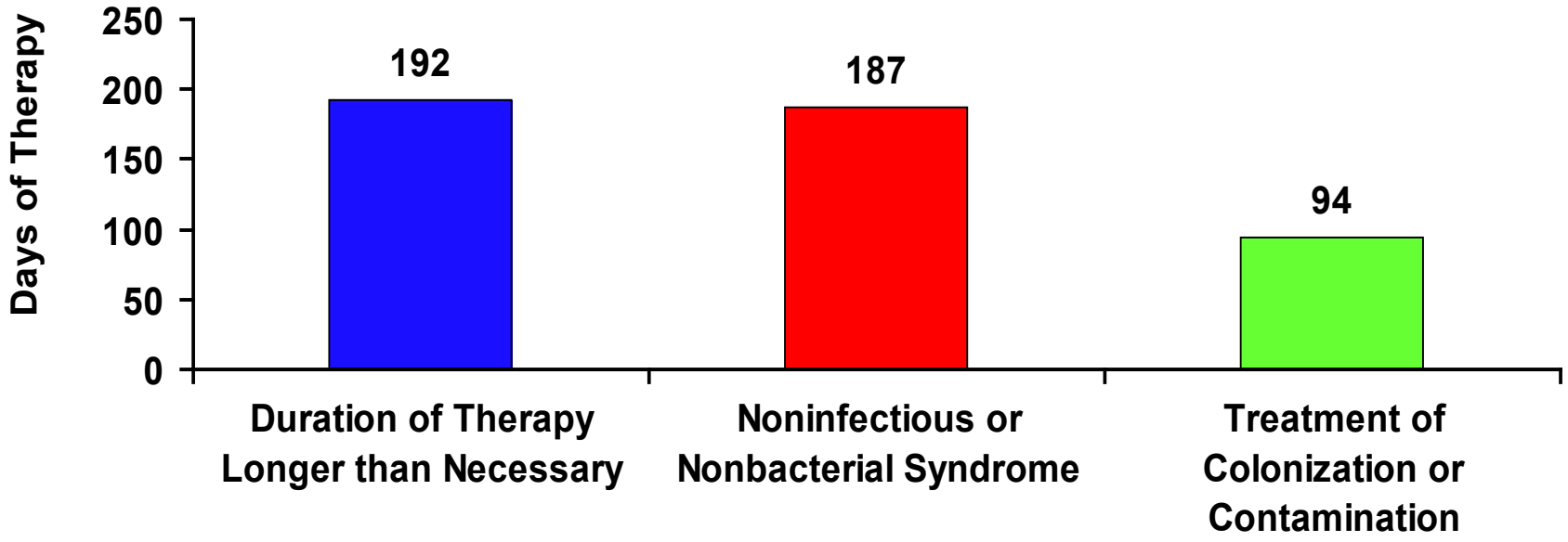
DEATHS ATTRIBUTABLE TO AMR EVERY YEAR



Unnecessary Use of Antimicrobials in Hospitalized Patients

- Prospective observational study in ICU
- 576 (30%) of 1941 antimicrobial days of therapy deemed unnecessary

Most Common Reasons for Unnecessary Days of Therapy



Hecker MT et al. *Arch Intern Med*. 2009;163:972-978.

15% antimicrobial days of therapy deemed unnecessary in hospitalized patients

Clinical Infectious Diseases
INVITED ARTICLE
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD
REVIEWS OF ANTI-INFECTIVE AGENTS: Louis D. Saravolatz, Section Editor

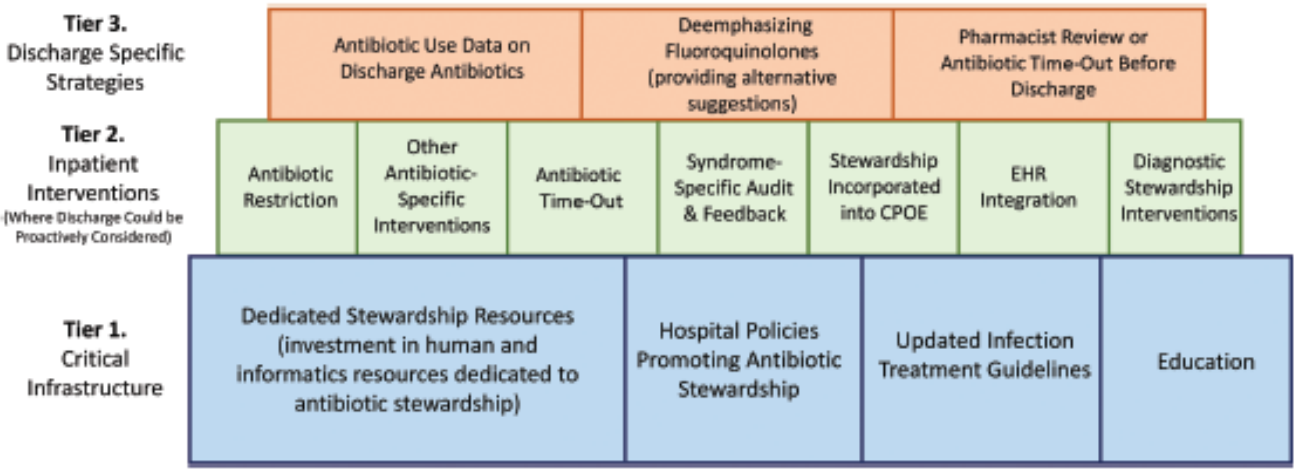
Antibiotic Overuse and Stewardship at Hospital Discharge: The Reducing Overuse of Antibiotics at Discharge Home Framework

Valerie M. Vaughn,[1,2,3] Adam L. Hersh,[4] and Emily S. Spivak[5]

- Discharge from acute hospitalization is an increasingly recognized source of antibiotic overuse

- Antimicrobials are prescribed to more than 10% of patients at hospital discharge

- Key targets for antibiotic stewardship at discharge include unnecessary antibiotics, excess duration, avoidable fluoroquinolones, and improving (or avoiding) intravenous antibiotic therapy



Antibiotic are misused in a variety of ways

- Given when they are not needed
- Continued when they are no longer necessary-duration
- Given at the wrong dose-renal and weight-based dosing
- Broad spectrum agents are used to treat very susceptible bacteria
- The wrong antibiotic is given to treat an infection

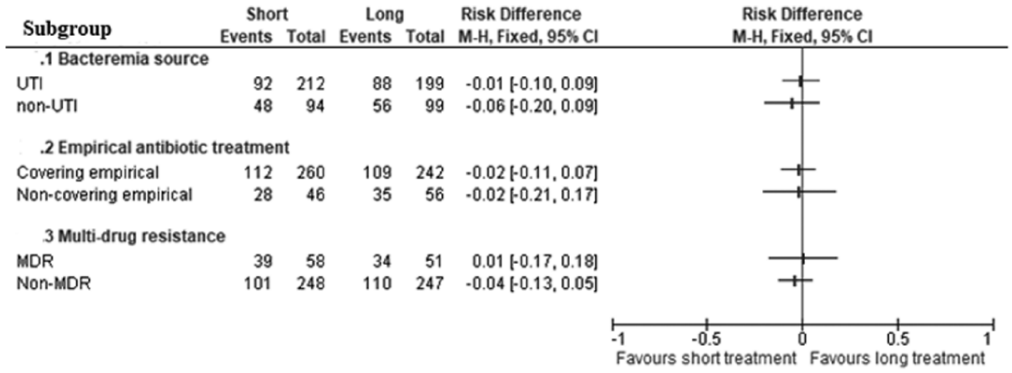
Clinical Infectious Diseases
MAJOR ARTICLE

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

604 patients with Gram negative bact

Dafna Yahav,[1,2] Erica Franceschini,[3] Fidi Koppel,[4] Adi Turjeman,[2,5] Tanya Babich,[2,5] Roni Bitterman,[4] Ami Neuberger,[4,6] Nesrin Ghanem-Zoubi,[4] Antonella Santoro,[3] Noa Eliakim-Raz,[1,2] Barak Pertzov,[5] Tali Steinmetz,[5] Anat Stern,[4] Yaakov Dickstein,[4] Elias Maroun,[4] Hiba Zayyad,[4] Jihad Bishara,[1,2] Danny Alon,[7] Yonatan Edel,[2,8] Elad Goldberg,[9] Claudia Venturelli,[3] Cristina Mussini,[3] Leonard Leibovici,[2,5] Mical Paul[4,6]; for the Bacteremia Duration Study Group[a]

Variable	Short-duration Arm (7 d) (n = 306)	Long-duration Arm (14 d) (n = 298)
Bacteria type[c]		
Escherichia coli	186 (60.8)	194 (65.1)
Klebsiella spp	47 (15.3)	33 (11.1)
Other Enterobacteriaceae	40 (13.1)	43 (14.4)
Acinetobacter spp	2 (0.7)	4 (1.3)
Pseudomonas spp	28 (9.2)	20 (6.7)
Other	3 (1)	4 (1.3)
MDR gram-negative bacteremia[d]	58 (18.9)	51 (17.1)



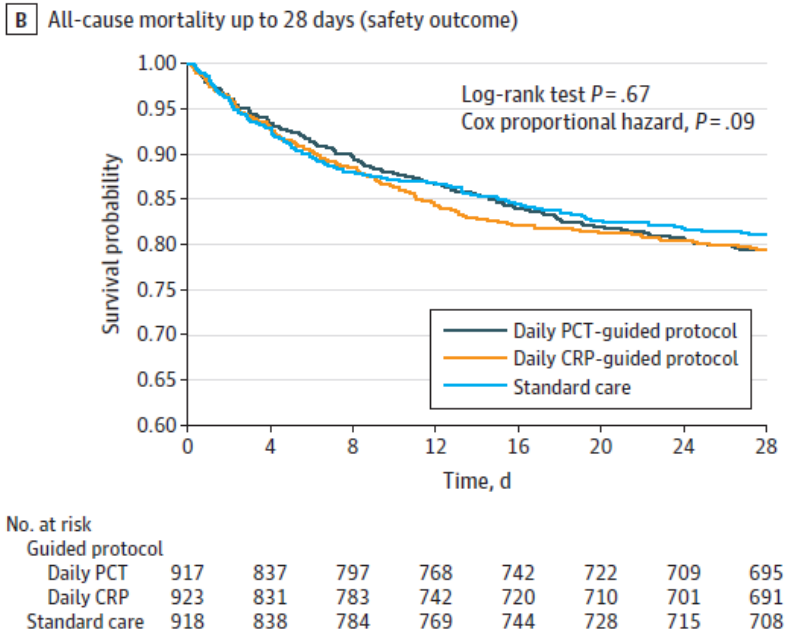
In patients hospitalized with gram-negative bacteremia achieving clinical stability before day 7, an antibiotic course of 7 days was noninferior to 14 days.

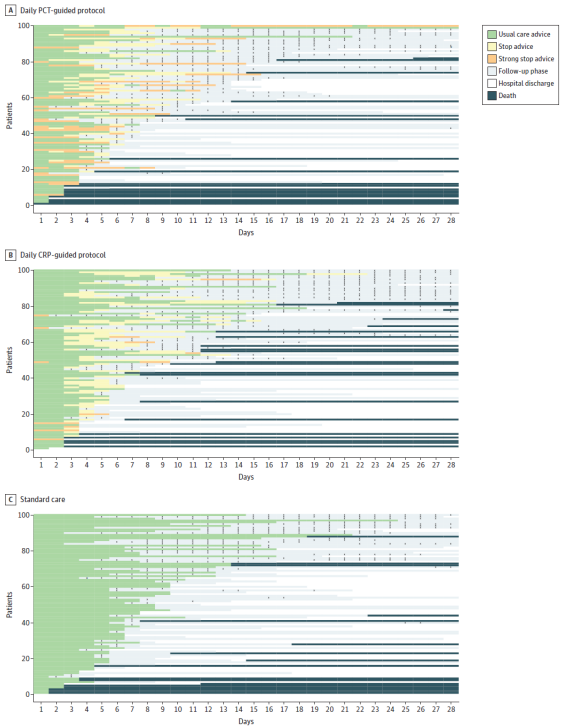
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis

The ADAPT-Sepsis Randomized Clinical Trial

918 patients were assigned to the daily PCT-guided proto
924 to the daily CRP-guided protocol
918 assigned to standard care





The daily PCT-guided protocol reduced total antibiotic duration and had noninferior all-cause mortality compared with standard care.

No difference was found in total antibiotic duration between standard care and daily CRP-guided protocol, and CRP showed inconclusive results for all-cause mortality.

Clinical Microbiology and Infection 31 (2025) 147–151

Contents lists available at ScienceDirect

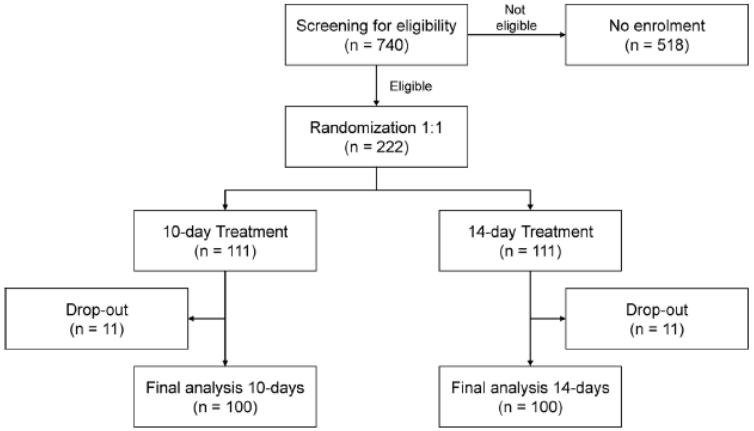
Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

Which trial do we need? Shorter antifungal treatment for candidemia – challenging the 14-day dogma

Nico Bekaan [1,2], Oliver A. Cornely [1,2,3,4,*], Tim Friede [5], Jürgen Prattes [6], Rosanne Sprute [1,2,3], Martin Hellmich [7], Philipp Koehler [1,2,8], Jon Salmanton-García [1,2,3], Jannik Stemler [1,2,3], Ilana Reinhold [1,2]



It remains to be seen how much we can shorten the duration of therapy. Could we even use a 7-day treatment regimen?
This would lead to an earlier randomization on day 7. An adaptive trial design could be used to randomize patients to receive either 7, 10, or 14 days of treatment.
A 7-day treatment arm would be added once interim analysis would demonstrate noninferiority of 14-day vs.10-
day treatment.
This would of course need a very well-defined patient population to avoid undertreatment.

The ‘shorter is better’ approach proved successful in a variety of infectious diseases, it is now time to evaluate and apply it to candidemia

Clinical Infectious Diseases
MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Clinical Infectious Diseases® 2025;80(1):108–17

Epidemiology and Outcomes of Antibiotic De-escalation in Patients With Suspected Sepsis in US Hospitals

Kai Qian Kam,[1,2,3] Tom Chen,[1] Sameer S. Kadri,[4,5] Alexander Lawandi,[4,6] Christina Yek,[4,5] Morgan Walker,[4,5] Sarah Warner,[4,5] David Fram,[7] Huai-Chun Chen,[7] Claire N. Shappell,[8] Laura DelloStritto,[1] Robert Jin,[1] Michael Klompas,[1,9] and Chanu Rhee[1,9]; for the Centers for Disease Control and Prevention Epicenters Program

124577 patients with suspected sepsis who were initially treated with ≥2 days of anti–MRSA and anti-pseudomonal antibiotics but had no resistant organisms that required these agents identified through hospital day 4.

Antibiotics were de-escalated in 36 806 (29.5%): narrowing in 27 177 (21.8%), cessation in 9629 (7.7%)

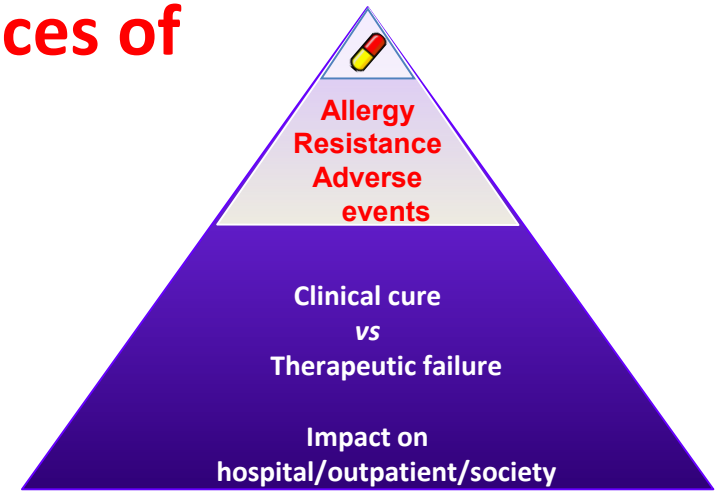
Table 2. Propensity Matching Analysis for Clinical Outcomes of Antibiotic De-escalation, Narrowing, and Cessation

	Odds Ratio (95% Confidence Interval), *P* Value[a]		
Outcome	De-escalation[b]	Narrowing[c]	Cessation[d]
Hospital onset Acute kidney injury	0.80 (.76–.84), .001	0.80 (.75–.85), .001	0.78 (.71–.85), .001
Clostridioides difficile infection after day 4	0.84 (.71–1.01), .062	0.97 (.81–1.16), .731	0.56 (.39–.79), .001
In-hospital mortality	0.92 (.86–.996), .039	0.65 (.60–.70), .001	1.57 (1.39–1.78), .001
Intensive care unit admission after day 4	0.59 (.52–.66), .001	0.61 (.54–.70), .001	0.56 (.46–.69), .001

De-escalation was associated with lower adjusted risks for AKI, ICU admission after day 4, and in-hospital mortality.

Antimicrobial stewardship is a package of measures to obtain…

- **Primary Goal: to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use**
  - Consequences
    - Toxicity
    - Selection of pathogenic organisms
    - Emergence of resistant pathogens

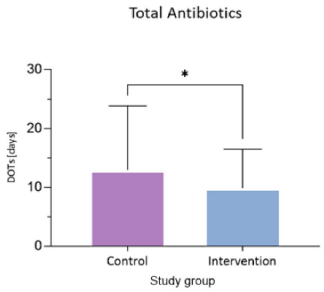


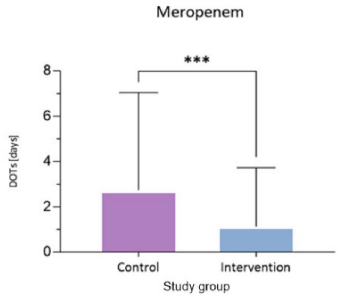
- **Secondary goal: to reduce health care costs without adversely affecting the quality of care**

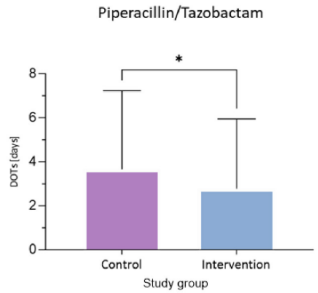
TYPE Original Research
PUBLISHED 22 May 2025
DOI 10.3389/fmed.2025.1549355

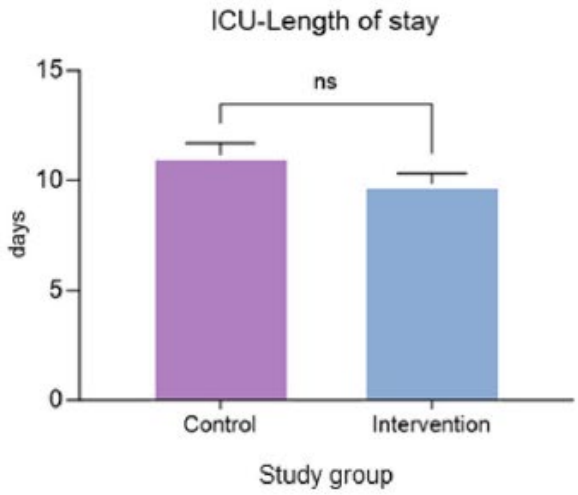
Reduced antimicrobial consumption through enhanced pneumonia management in critically ill patients: outcomes of an antibiotic stewardship program in the intensive care unit

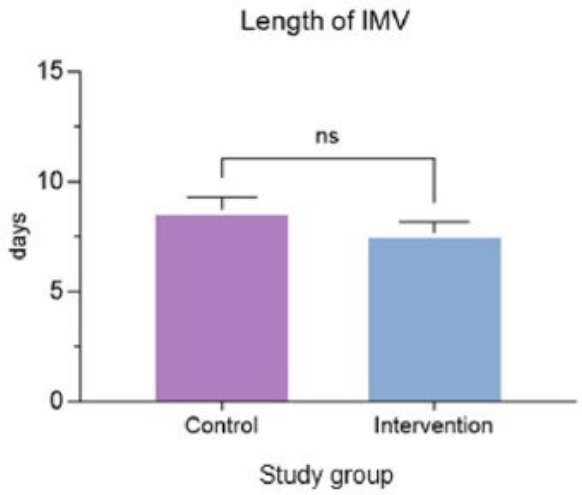
Asieb Sekandarzad[1*†], Annabelle Flügler[1†], Anne Rheinboldt[1], David Rother[1], Gesche Först[2], Siegbert Rieg[2], Alexander Supady[1], Achim Lother[1], Dawid Leander Staudacher[1], Tobias Wengenmayer[1], Winfried V. Kern[2] and Paul Marc Biever[1]

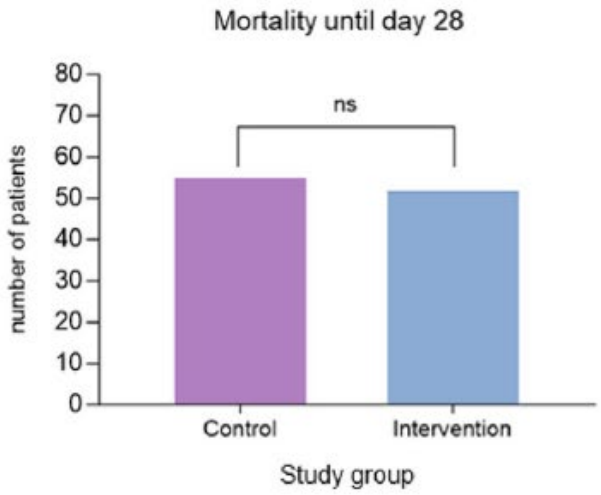








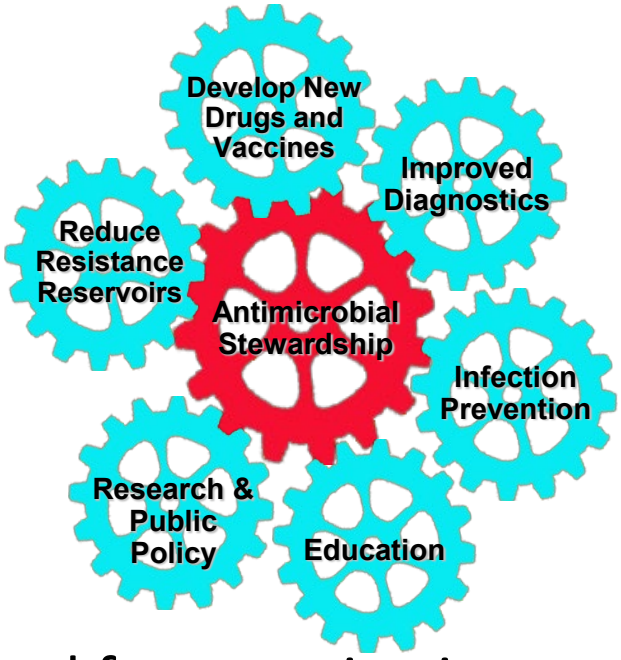




Implementation of an ASP in the ICU effectively reduces broad- spectrum antimicrobial consumption in critically ill patients with pneumonia without compromising patient safety.

Who is involved in an AS Program?

- Antimicrobial Stewardship Team - multidisciplinary
- ID physician
- Clinical microbiologist
- ID pharmacist
- IT support
- IC/epidemiology support



- Antimicrobial Stewardship Committee
- Members of the AS team
- Director for Infection Prevention & Control for organisation
- Other clinical members
  - Intensivists, physicians, surgeons, paediatricians

Antimicrobial Stewardship Strategies

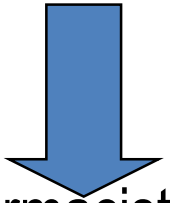
- Front end: Formulary restriction and preauthorization
- Back end: Interventions after antimicrobials have been prescribed
- BOTH: Prospective audit with intervention and feedback

Supplemental Strategies

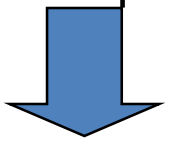
- Education, guidelines, clinical pathways
- Dose optimization via PK-PD
- De-escalation/Streamlining
- Antimicrobial order forms/order sets if CPOE
- IV-PO switch
- Computerized decision support
- Antimicrobial cycling
- Combination therapy

Front-end Approach

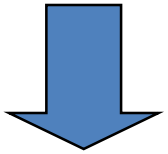
Physician writes order for “restricted drug”



Order arrives in pharmacy; pharmacist informs physician that drug is “restricted”/“not part of the pathway”/“nonformulary”



Prescribing physician and the “GATE KEEPER” converse



Approval or alternative antibiotic selected

Formulary Restriction/Preauthorization Front-end Approach

- **Advantages**
  - Direct control over antimicrobial use
  - Effective control of antimicrobial use during outbreaks
  - Decreased inappropriate use of antimicrobials (and thus costs)
- **Disadvantages**
  - Personnel needs
  - Antagonistic relationship (loss of autonomy)
  - Therapy may be delayed
  - De-escalation not addressed
  - ID physicians often exempt
  - Effectiveness in decreasing resistance is less clear

“Back end”

- Prescribers are allowed to order antibiotics upon admission
- Antibiotic orders are reviewed at specified intervals after initiation
- May be restricted to particular patient populations
    - Ex: Meropenem in ICU for up to 72 hours
    - Ex: Echinocandins in Febrile Neutropenia
- May be restricted to formulary drugs or by using a clinic pathway or protocol
    - Ex: Pneumonia protocol

Prospective Audit and Feedback
Back-end Approach

Physician writes order

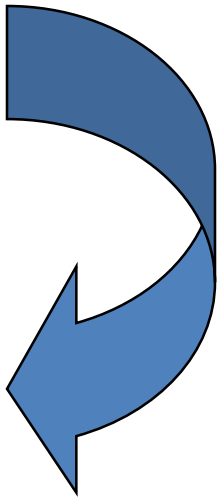
Antibiotic is Dispensed

At a later date, antibiotics are reviewed

(Targeted list of antibiotics, C/S mismatches, ICU patients, duration)

1.) Antibiotic Change/Continued based on Practice Guidelines

2.) Prescribing physician contacted and recommendation made



Prospective Audit and Feedback

- **Advantages**
  - Prescriber autonomy maintained
  - Educational opportunity provided
  - Patient information can be reviewed before interaction
  - Inappropriate antimicrobial use decreased
  - De-escalation
- **Disadvantages**
  - Compliance voluntary
  - Identification of patients may require computer support
  - Prescribers may be reluctant to change therapy if the patient is doing well
  - Some inappropriate antimicrobial use permitted (with retrospective audit)

Persuasive AMS strategies: Post prescription review

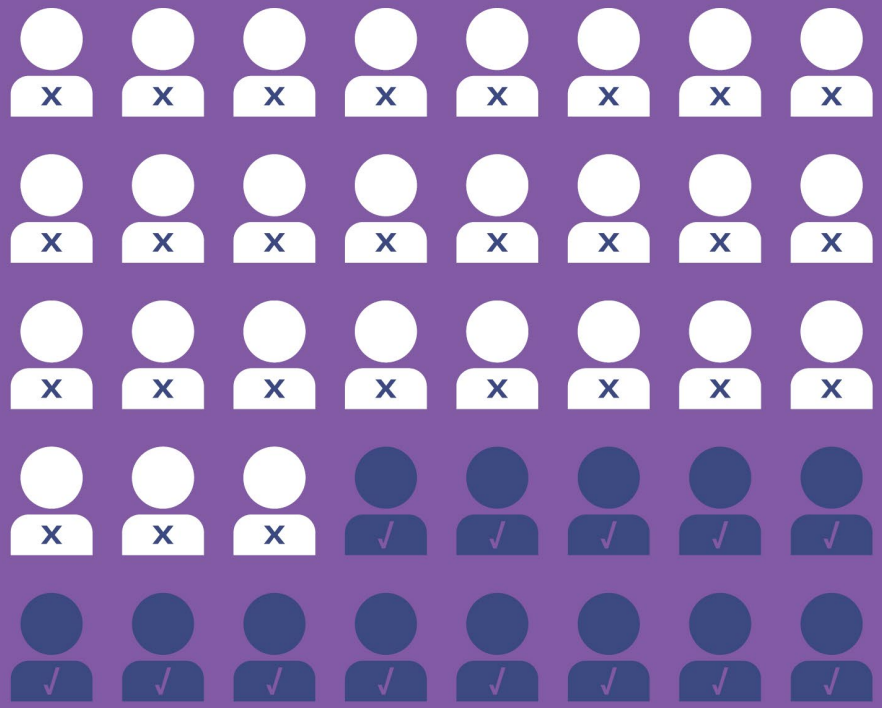
* Feedback directly to prescribers (preferably face-to-face).
  * Provides a mechanism of dialogue with opportunity for 'academic detailing'
  * May lead to a reduction of unnecessary antimicrobial use

RAPID DIAGNOSTICS WOULD REDUCE UNNECESSARY PRESCRIPTION

Out of 40m people who are given antibiotics for respiratory issues, annually in the U

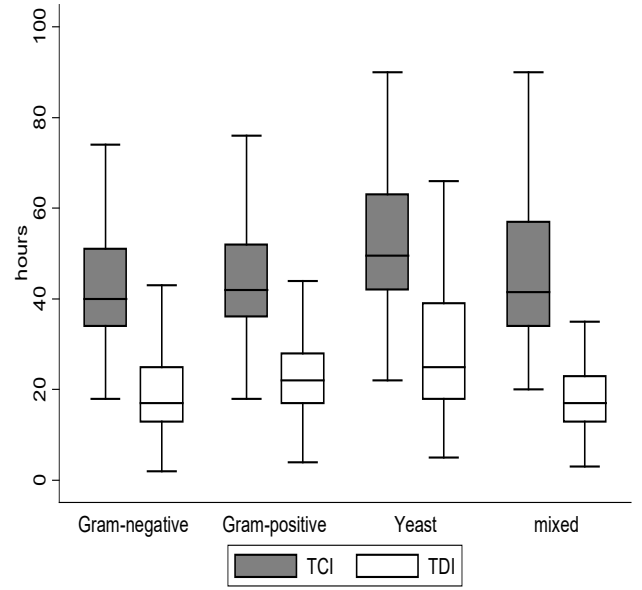
27m
get antibiotics unnecessarily

13m
who need antibiotics get them



Clinical Infectious Diseases
MAJOR ARTICLE

Rapid Diagnostic Tests and Antimicrobial Stewardship Programs for the Management of Bloodstream Infection: What Is Their Relative Contribution to Improving Clinical Outcomes? A Systematic Review and Network Meta-analysis

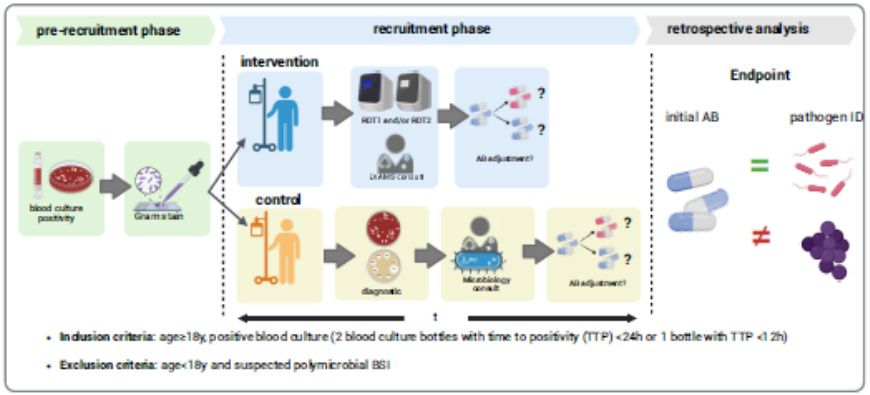


TCI, time to culture-based identification results ; TDI, time to direct identification results.

The use of RDT + ASP may lead to a survival benefit even when introduced in settings already adopting effective ASP in association with conventional BC

Rapid diagnostic testing combined with an immediate infectious disease consultation increases the rate of septic intensive care unit patients on targeted antibiotic therapy

Evelyn Kramme[1*†], Nadja Käding[2,3†], Tobias Graf[4], Karolin Schmoll[4], Heidi Linnen[5], Katharina Nagel[2], Esther Grote-Levi[2], Susanne Hauswaldt[2], Dennis Nurjadi[2,3] and Jan Rupp[1,2,3]



	Standard of care group, n=44	Intervention group, n=77	p-value[a]
	n (%)	n (%)	
Clinical outcome			
Mortality[c]	20 (45.5)	43 (56)	0.3[b]
LOS (days), ICU, median (IQR), non-fatal cases	29.5 (13.5-37)	15.52 (6-25)	0.06
LOS (days), ICU, median (IQR), all cases	15 (10-34.5)	12 (6-23)	0.07

Integration of an RDT system in the microbiological workflow for septic patients in ICU combined with a standardized ID intervention led to a significantly higher percentage of adequate antimicrobial treatment and greater adherence to local antibiotic therapy recommendations, even in a setting where 24/7 service is not available

Clinical impact of an educational antimicrobial stewardship program associated with infectious diseases consultation targeting patients with cancer: Results of a 9-year quasi-experimental study with an interrupted time-series analysis

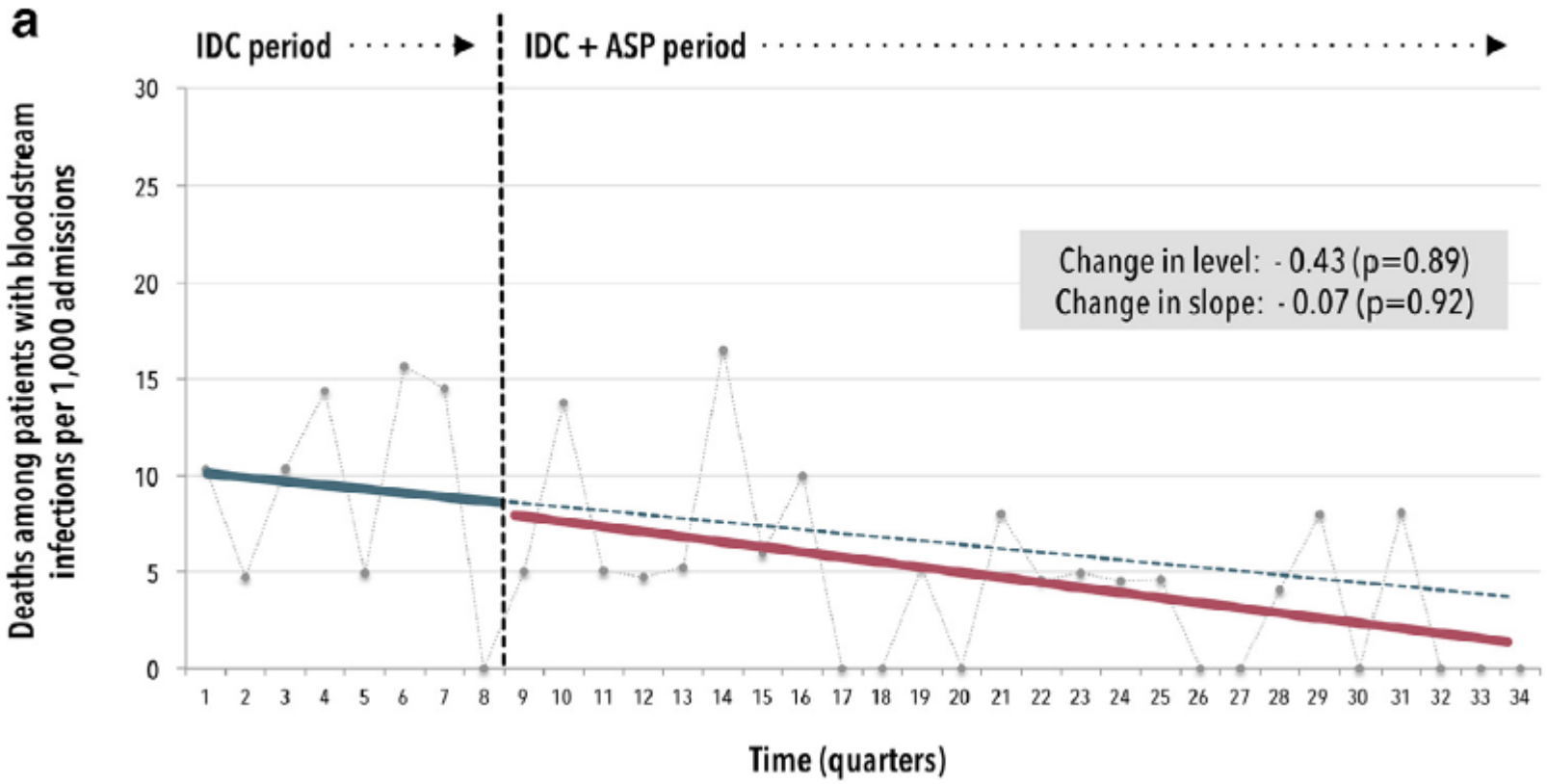
José Molina[a], Manuel Noguer[b], José Antonio Lepe[a], María Antonia Pérez-Moreno[c], Manuela Aguilar-Guisado[a], Roberto Lasso de la Vega[b], Germán Peñalva[a], Juan Carlos Crespo-Rivas[a], María Victoria Gil-Navarro[c], Javier Salvador[b], José Miguel Cisneros[a,*]

Journal of Infection 79 (2019) 206–211

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf



The combination of an ASP with IDC improved antibiotic use among patients with cancer, and was accompanied by a reduction of mortality of bacteraemic infections.

Diagnostic Microbiology and Infectious Disease 91 (2018) 282–283

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Diagnostic Microbiology and Infectious Disease 91 (2018) 282–283

Automatic notification and infectious diseases consultation for patients with *Staphylococcus aureus* bacteremia☆

Lucas Djelic [a], Nisha Andany [a,b], Jeffrey Craig [a], Nick Daneman [a,b], Andrew Simor [a,b,c], Jerome A. Leis [a,b,d,*]

- 3-year quasi-experimental evaluation on patients with SAB
- standardize timely ID consultation through automatic notification by the Microbiology laboratory.
- increased ID consultation for SAB (70% versus 100%, P=0.001) and decreased time to consultation (14.5 versus 4 h, P<0.001).
- Adherence to Quality of Care Indicators (QCIs) increased (45% versus 87%, P<0.001), transfer to intensive care

Journal of Infection 77 (2018) 503–508

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Unsolicited consultation by infectious diseases specialist improves outcomes in patients with bloodstream infection: A prospective cohort study

Patricia Jiménez-Aguilar[a,b,*], Alberto Romero-Palacios[a,b], Iría-Jesus De-la-Calle[a], María-Carmen Martínez-Rubio[a,b], José-Antonio Girón-González[b,c,d], Jesus Rodríguez-Baño[e,f,g]

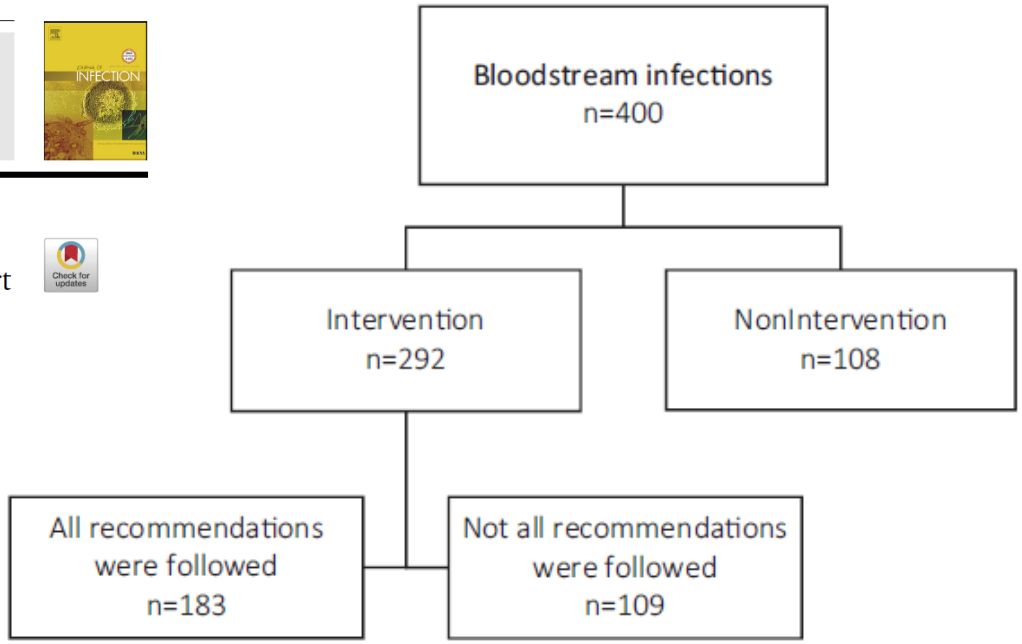


Fig. 1. Algorithm of included patients.

- Unsolicited consultation by an IDS for patients with BSI was performed only on days when an IDS was available.
- The intervention was independently associated with a higher percentage of days on optimal antimicrobial treatment ($p < 0.001$) but not with mortality.
- Adherence to recommendations was associated

Clinical Infectious Diseases
MAJOR ARTICLE

A Retrospective Cohort Study to Assess the Impact of an Inpatient Infectious Disease Telemedicine Consultation Service on Hospital and Patient Outcomes

Daniel Monkowski,[1] Luther V. Rhodes III,[1] Suzanne Templer,[2] Sharon Kromer,[3] Jessica Hartner,[4] Kimberly Pianucci,[5] and Hope Kincaid[6]

Inpatient ID consultations using real-time interactive telemedicine assessments

- 244 patients managed at 1 remote hospital
- 171 patients were seen via teleID
- all 73 patients in the pre-teleID group were transferred from the remote hospital to the hub hospital, only 14 (8.2%) of all remote hospital patients assessed by teleID were transferred.
- Patient LOS across both facilities decreased when patients were seen via teleID, compared to pre-teleID

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Antibiotic Stewardship in Outpatient Telemedicine: Adapting Centers for Disease Control and Prevention Core Elements to Optimize Antibiotic Use

Authors: Guillermo V. Sanchez, Sarah Kabbani, Sharon V. Tsay, Destani Bizune, Adam L. Hersh, Angelina Luciano, and Lauri A. Hicks | AUTHORS INFO & AFFILIATIONS

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Abstract

The rapid expansion of telemedicine has highlighted challenges and opportunities to improve antibiotic use and effectively adapt antibiotic stewardship best practices to outpatient telemedicine settings. Antibiotic stewardship integration into telemedicine is essential to optimize antibiotic prescribing for patients and ensure health care quality. We performed a narrative review of published literature on antibiotic prescribing and stewardship in outpatient telemedicine to inform the adaptation of the Core Elements of Outpatient Antibiotic Stewardship *framework to outpatient telemedicine settings. Our narrative review suggests that in-person antibiotic stewardship interventions can be adapted to outpatient telemedicine settings. We present considerations for applying the* Core Elements of Outpatient Antibiotic Stewardship *to outpatient telemedicine which builds upon growing evidence describing care delivery and quality improvement in this setting. Additional applied implementation research is necessary to inform the application of effective, sustainable, and equitable antibiotic stewardship interventions across the spectrum of outpatient telemedicine.*

Primary care physicians' attitudes and perceptions towards antibiotic resistance and outpatient antibiotic stewardship in the USA: a qualitative study

Rachel M Zetts ,[1] Andrea Stoesz,[1] Andrea M Garcia,[2] Jason N Doctor,[3] Jeffrey S Gerber,[4] Jeffrey A Linder,[5] David Y Hyun[1]

Strengths and limitations of this study

- This study presents new data on US-based primary care physicians attitudes towards antibiotic resistance, inappropriate antibiotic prescribing and outpatient antibiotic stewardship approaches.
- Eight focus groups with internal medicine physicians, family medicine physicians and paediatricians were held in four geographically dispersed US cities, which allowed for a wide-range of viewpoints to be represented in the dataset.
- The focus groups did not include some types of clinicians that provide primary care in the USA (eg, nurse practitioners, physician assistants).
- Although physicians from across the USA were included in this study, the small sample size limits the generalisability of these findings.

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From: **Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis: The BLING III Randomized Clinical Trial**

JAMA. 2024;332(8):629-637. doi:10.1001/jama.2024.9779

JAMA

QUESTION Is there a difference in mortality between continuous and intermittent infusions of β-lactam antibiotics in critically ill patients with sepsis?

CONCLUSION In critically ill patients with sepsis, continuous vs intermittent β-lactam antibiotic infusions did not significantly reduce 90-day mortality in the primary analysis. A clinically important benefit with continuous infusions is possible.

POPULATION

4608 Men
2423 Women

Critically ill adults aged ≥18 years treated for sepsis

Mean age: 59 years

LOCATION

104
ICUs worldwide

INTERVENTION

Continuous infusion
Continuous infusion (over 24 hours) of either piperacillin-tazobactam or meropenem

Intermittent infusion
Intermittent infusion (over 30 minutes) of either piperacillin-tazobactam or meropenem

PRIMARY OUTCOME

All-cause mortality within 90 days after randomization

FINDINGS

All-cause mortality at day 90

Absolute difference, **−1.9%** (95% CI, −4.9% to 1.1%)
Odds ratio, **0.91** (95% CI, 0.81 to 1.01); *P* = .08

Dulhunty JM, Brett SJ, De Waele JJ, et al; BLING III Study Investigators. Continuous vs intermittent β-lactam antibiotic infusions in critically ill patients with sepsis: the BLING III randomized clinical trial. *JAMA*. Published June 12, 2024. doi:10.1001/jama.2024.9779

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Table 2. Reporting of Primary, Secondary, and Tertiary Outcomes

Outcome	Continuous infusion (n = 3498)[a]	Intermittent infusion (n = 3533)[a]	Absolute difference, % (95% CI)	Odds ratio or mean difference (95% CI)	*P* value[b]
Primary outcome					
All-cause mortality at day 90, No./total (%)	864/3474 (24.9)	939/3507 (26.8)	−1.9 (−4.9 to 1.1)	0.91 (0.81 to 1.01)	.08
Adjusted analysis			−2.2 (−5.5 to 1.1)	0.89 (0.79 to 0.99)	.04
Secondary outcomes					
Clinical cure at day 14, No./total (%)	1930/3467 (55.7)	1744/3491 (50.0)	5.7 (2.4 to 9.1)	1.26 (1.15 to 1.38)	<.001
New acquisition, colonization, or infection with an MRO or *C difficile*, No./total (%)[c]	253/3498 (7.2)	266/3533 (7.5)	−0.3 (−1.9 to 1.4)	0.96 (0.80 to 1.15)	.65
All-cause ICU mortality, No./total (%)	595/3474 (17.1)	645/3507 (18.4)	−1.3 (−4.0 to 1.4)	0.92 (0.81 to 1.04)	.35
All-cause hospital mortality, No./total (%)	808/3474 (23.3)	878/3507 (25.0)	−1.8 (−4.8 to 1.2)	0.91 (0.81 to 1.02)	.27

Clinical cure was higher in the continuous vs intermittent infusion group (55.7% vs 50.0%). Other secondary outcomes were not statistically different.

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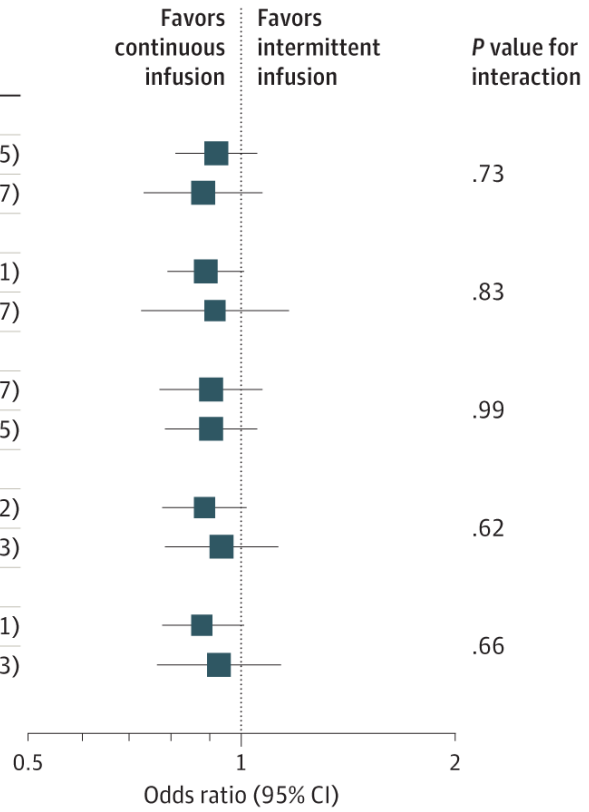
JAMA. 2024;332(8):629-637. doi:10.1001/jama.2024.9779

	Group, No./total (%)				
	Continuous infusion	Intermittent infusion	Absolute difference, % (95% CI)[a]	Odds ratio (95% CI)[b]	*P* value for interaction
Pulmonary infection					
Yes	593/2178 (27.2)	647/2249 (28.8)	-1.7 (-5.2 to 1.9)	0.92 (0.81 to 1.05)	.73
No	271/1296 (20.9)	292/1258 (23.2)	-2.1 (-6.0 to 1.7)	0.88 (0.73 to 1.07)	
β-Lactam antibiotic					
Piperacillin-tazobactam	667/2749 (24.3)	722/2746 (26.3)	-2.2 (-5.3 to 1.0)	0.89 (0.79 to 1.01)	.83
Meropenem	183/696 (26.3)	203/714 (28.4)	-1.7 (-7.0 to 3.7)	0.92 (0.73 to 1.17)	
Age, y					
<65	348/1935 (18.0)	375/1938 (19.3)	-1.5 (-4.5 to 1.6)	0.91 (0.77 to 1.07)	.99
≥65	516/1539 (33.5)	564/1569 (35.9)	-2.2 (-6.5 to 2.0)	0.91 (0.78 to 1.05)	
Sex					
Male	563/2290 (24.6)	612/2279 (26.9)	-2.3 (-5.7 to 1.1)	0.89 (0.78 to 1.02)	.62
Female	301/1184 (25.4)	327/1228 (26.6)	-1.2 (-5.4 to 3.0)	0.94 (0.78 to 1.13)	
APACHE II score					
<25	543/2599 (20.9)	610/2661 (22.9)	-2.2 (-5.2 to 0.8)	0.88 (0.77 to 1.01)	.66
≥25	320/872 (36.7)	328/842 (39.0)	-1.7 (-7.1 to 3.7)	0.93 (0.76 to 1.13)	



The Journal of Infectious Diseases
MAJOR ARTICLE

Impact of Attaining an Aggressive Pharmacokinetic-Pharmacodynamic Target on the Clinical Efficacy of Continuous Infusion β-Lactam Therapy for Early Posttransplant Gram-Negative Infections in Critically Ill Orthotopic Liver Transplant Recipients: An Interim Analysis of a 3-Year Prospective, Observational Study

Milo Gatti,[1,2] Matteo Rinaldi,[1,3] Cristiana Laici,[4] Cecilia Bonazzetti,[1,3] Luca Vizioli,[5] Simone Ambretti,[1,6] Maria Cristina Morelli,[5] Antonio Siniscalchi,[4] Maddalena Giannella,[1,3] Pierluigi Viale,[1,3] and Federico Pea[1,2]

Fifty critically ill OLT recipients were treated with CI BL therapy for documented Gram-negative infections.

Table 4. Univariate and Multivariate Analyses Assessing Predictor Factors for 30-Day Resistance

Variable	OLT Recipients, No. (%)[a]		*P* Value	
	No 30-d Resistance (n = 46)	30-d Resistance (n = 4)	Univariate Analysis	Multivariate Analysis
BL treatment and PK/PD target attainment				
Quasi-optimal/suboptimal PK/PD target attainment	3 (6.5)	2 (50.0)	.04	.02[d]
Combination therapy	14 (30.4)	2 (50.0)	.58	…

At multivariate analysis, failure in attaining an aggressive BL PK/PD target emerged as the only independent predictor of 30-day resistance development.

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From: **Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock: A Systematic Review and Meta-Analysis**

JAMA. 2024;332(8):638-648. doi:10.1001/jama.2024.9803

Study	Dead (prolonged)	Alive (prolonged)	Dead (intermittent)	Alive (intermittent)	Absolute difference (95% CI)	Risk ratio (95% CI)	Weight, %
Georges et al,[33] 2005	3	21	3	20	-0.01 (-0.20 to 0.19)	0.96 (0.21 to 4.27)	0.8
Rafati et al,[34] 2006	5	15	6	14	-0.05 (-0.33 to 0.23)	0.83 (0.30 to 2.29)	1.6
Roberts et al,[35] 2007	3	26	0	28	0.10 (-0.02 to 0.22)	6.77 (0.37 to 125.32)	0.2
Roberts et al,[36] 2009	2	3	0	5	0.33 (-0.12 to 0.79)	5.00 (0.30 to 83.69)	0.2
Chytra et al,[38] 2012	21	99	28	92	-0.06 (-0.16 to 0.04)	0.75 (0.45 to 1.24)	5.1
Dulhunty et al,[39] 2013	3	27	6	24	-0.10 (-0.28 to 0.08)	0.50 (0.14 to 1.82)	1.1
Dulhunty et al,[40] 2015	54	156	60	158	-0.02 (-0.10 to 0.07)	0.93 (0.68 to 1.28)	9.8
Jamal et al,[41] 2015	4	4	5	3	-0.12 (-0.61 to 0.36)	0.80 (0.33 to 1.92)	2.1
Jamal et al,[42] 2015	5	3	8	0	-0.33 (-0.69 to 0.02)	0.65 (0.38 to 1.12)	4.6
Abdul-Aziz et al,[43] 2016	18	52	26	44	-0.11 (-0.27 to 0.04)	0.69 (0.42 to 1.14)	5.2
Zhao et al,[44] 2017	7	18	8	17	-0.04 (-0.29 to 0.21)	0.88 (0.37 to 2.05)	2.2
Khan and Omar,[22] 2023	12	40	20	29	-0.18 (-0.36 to 0.00)	0.57 (0.31 to 1.03)	4.0
Mirjalili et al,[45] 2023	14	54	25	43	-0.16 (-0.31 to -0.01)	0.56 (0.32 to 0.98)	4.4
Monti et al,[14] 2023	127	176	127	177	0.00 (-0.08 to 0.08)	1.00 (0.83 to 1.21)	17.6
Saad et al,[46] 2024	8	22	12	18	-0.13 (-0.37 to 0.10)	0.67 (0.32 to 1.39)	2.8
Álvarez-Moreno et al,[47] 2024	2	10	2	11	0.01 (-0.28 to 0.30)	1.08 (0.18 to 6.53)	0.6
Dulhunty et al,[15] 2024	864	2610	939	2568	-0.02 (-0.04 to 0.00)	0.93 (0.86 to 1.01)	37.4
Bayesian							
Vague priors[a]					-0.03 (-0.08 to 0.00)	0.86 (0.72 to 0.98)	
Semi-informative priors[a]					-0.04 (-0.10 to 0.01)	0.86 (0.73 to 0.98)	
Frequentist							
Hartung-Knapp-Sidik-Jonkman					-0.05 (-0.10 to 0.00)	0.80 (0.67 to 0.94)	
DerSimonian-Laird					-0.03 (-0.07 to 0.00)	0.91 (0.85 to 0.97)	

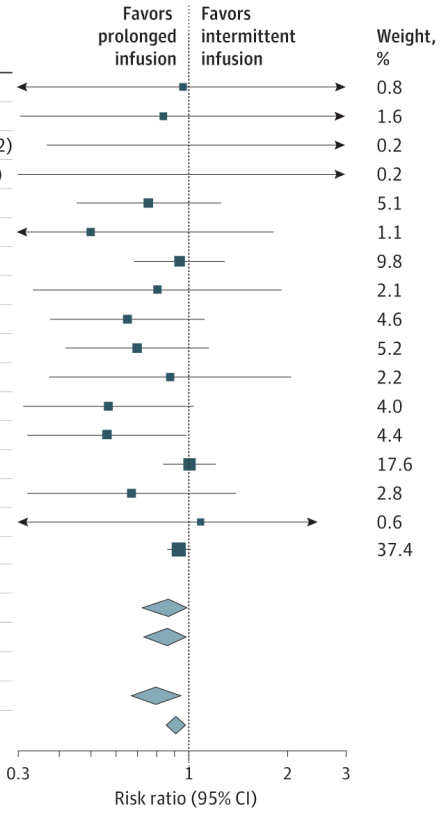

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Table 2. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Summary of Findings

Outcome	No. of trials/No. of participants	Certainty of evidence (quality of the evidence)[a]	Infusion, No./No. (%)		(95% CrI)	
			Prolonged	Intermittent	Absolute difference	Risk ratio
All-cause 90-d mortality	17/9014	High, ++++	1152/4488 (25.7)	1275/4526 (28.2)	−0.03 (−0.08 to 0.00)	0.86 (0.72 to 0.98)
ICU mortality	15/8967	High, ++++	806/4466 (18.0)	911/4501 (20.2)	−0.03 (−0.08 to 0.0)	0.84 (0.70 to 0.97)
Clinical cure	12/8301	Moderate,[b] +++-	2367/4137 (57.2)	2106/4164 (50.6)	0.11 (0.05 to 0.18)	1.16 (1.07 to 1.31)
Microbiologic cure	4/352	Very low,[c] +---	145/174 (83.3)	126/178 (70.8)	0.13 (−0.02 to 0.28)	1.18 (0.96 to 1.48)
Adverse events	4/7761	Very low,[d] +---	42/3868 (1.1)	49/3893 (1.3)	−0.00 (−0.06 to 0.04)	0.89 (0.51 to 1.57)
ICU length of stay, d	12/8935	Low,[e] ++-	12.6	13.1	−0.42 (−1.09 to 0.26)	NA

Among adults in the intensive care unit who had sepsis or septic shock, the use of prolonged β-lactam antibiotic infusions was associated with a reduced risk of 90-day mortality compared with intermittent infusions.

The current evidence presents a high degree of certainty for clinicians to consider prolonged infusions as a standard of care.

communications medicine

Perspective

https://doi.org/10.1038/s43856-024-00516-9

Overcoming challenges in the economic evaluation of interventions to optimise antibiotic use

Check for updates

Laurence S. J. Roope[1,2] ✉, Liz Morrell[1], James Buchanan[1,3], Alice Ledda[4,5], Amanda I. Adler[6], Mark Jit[7], A. Sarah Walker[2,5,8], Koen B. Pouwels[1,5,16], Julie V. Robotham[4,5,16], Sarah Wordsworth[1,2,5,16] & on behalf of the STEPUP team*

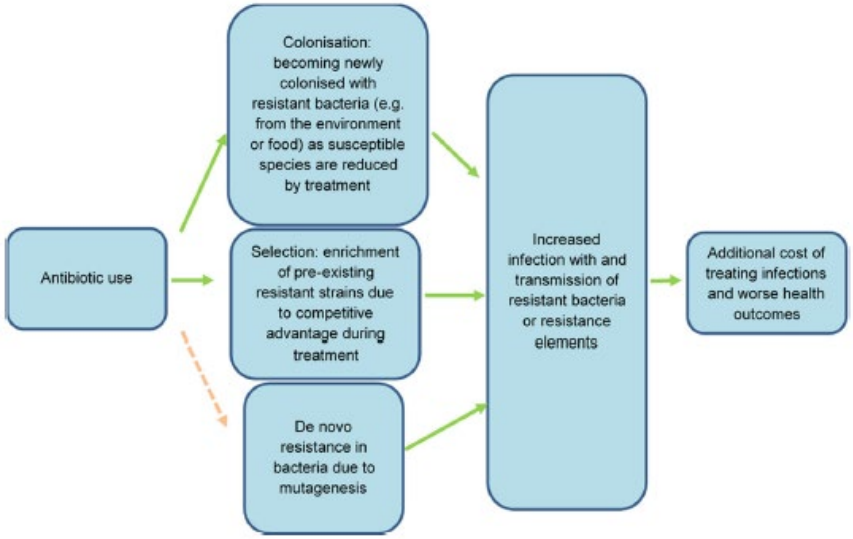

Table 1 | Summary of key elements that pose a challenge in economic evaluation of stewardship interventions

Elements	Comments
Impact of antibiotic use on spread of resistance	Resistant strains are typically enriched during antibiotic treatment, due to their competitive advantage over susceptible strains. However, the extent of this enrichment, for a given increase in antibiotic use, varies by bug-drug combination and is difficult to predict.
Extent to which resistance can be reversed by reducing antibiotic use	This probably depends on a variety of factors, including the fitness cost of the resistance mechanism, epidemic potential of bacteria/strain, cross-resistance with alternative antibiotics, and environmental considerations.
Effects of antibiotic use on susceptibility to colonisation with resistant bacteria	The impact of antibiotic use on subsequent risk of infection with resistant bacteria, and the associated health-economic outcomes, is poorly understood.
Lack of high-quality data on economic outcomes	This is especially problematic in the context of events without precedent, such as costs from being unable to perform invasive surgery if effective prophylactic antibiotics become unavailable, or if infections become substantially harder to treat than they have been previously.
Impact of antibiotic use on emergence of resistance in bacteria	While de novo resistance in bacteria, due to mutagenesis, may not be relevant for most infections with resistant bacteria, it is probably important for tuberculosis, gonorrhoea and specific bug-drug combinations. Predicting the emergence of resistance is notoriously difficult.

- The impact of all interventions that impact use of antibiotics must be considered
- Measuring the benefits of antibiotic optimization
- Adapting economic evaluation methods to evaluate interventions to improve antibiotic use
- Incorporating long-term costs of antibiotic resistance is complicated
- Learning from methods used in the economic evaluation of newly available antibiotics
- Economic evaluation of antibiotic interventions based on probability of costs exceeding a threshold