SCCI 2023 APPROACH TO XDR SEPSIS

NAI AN LAI
DIRECTOR
INTENSIVE CARE SERVICES
MATER HEALTH

COI DECLARATION

- Conference sponsorship from Biomerieux
- Research on BioFire Pneumonia Panel Plus with equipment support from Biomerieux
- Sponsored attendance at Clinical ID Forum by Pfizer
- Sponsored participation at Expert Forum for MDR Gram Negative Pathogens at the 14th World Congress of Intensive Care by Merck, Sharp & Dohme

DEFINITIONS: MDR, XDR, PDR

ORIGINAL ARTICLE BACTERIOLOGY

Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

A.-P. Magiorakos[1], A. Srinivasan[2], R. B. Carey[2], Y. Carmeli[3], M. E. Falagas[4,5], C. G. Giske[6], S. Harbarth[7], J. F. Hindler[8], G. Kahlmeter[9], B. Olsson-Liljequist[10], D. L. Paterson[11], L. B. Rice[12], J. Stelling[13], M. J. Struelens[1], A. Vatopoulos[14], J. T. Weber[2] and D. L. Monnet[1]

2012

TABLE 6. Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria

Bacterium	MDR	XDR	PDR
Staphylococcus aureus	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 1[a]	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1–5
Enterococcus spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 2	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 2.	
Enterobacteriaceae	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 3	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 3.	
Pseudomonas aeruginosa	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 4	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 4.	
Acinetobacter spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 5	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 5.	

[a]All MRSA isolates are defined as MDR because resistance to oxacillin or cefoxitin predicts non-susceptibility to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until 25 January 2011).
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

to all agents in all antimicrobial categories. To ensure correct application of these definitions, bacterial isolates should be tested against all or nearly all of the antimicrobial agents within the antimicrobial categories and selective reporting and suppression of results should be avoided.

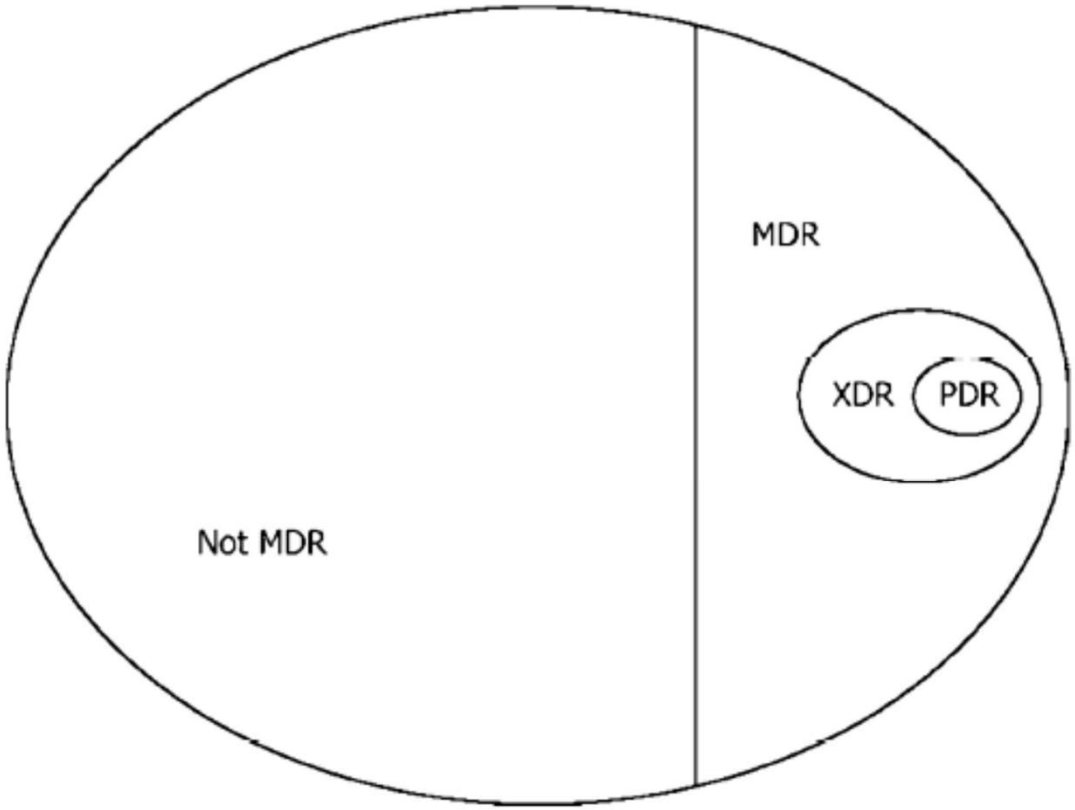

FIG. 1. Diagram showing the relationship of MDR, XDR and PDR to each other.

APPROACH TO XDR-ASSOCIATED SEPSIS

Empirical Phase (XDR possible)	Targeted Phase (XDR identified)	Refractory Phase (Therapeutic failure and/or clinical deterioration)
• Do we need to treat? (Sepsis vs non-infective causes)	• Do we need to treat? (Infection vs colonisation)	• Timing of escalation
• XDR risk factors	• Source control	• Source control
• Diagnostic modalities	• Severity of illness	• Choice of antimicrobial agent(s) and Dose optimisation: MIC, TDM
• Empirical antimicrobial therapy: site, illness severity, likelihood of XDR, local antibiogram, organ function, guidelines, allergies • Source control	• Targeted antimicrobial therapy: pathogen susceptibility, site, organ function, allergies, guidelines	• "Non-antibiotic" options: Bacteriophage, IVIG, monoclonal antibodies, pilicides, siderophores
Organisational level:	• Dose optimisation: MIC, TDM	Outbreak management:
• Building design, materials		• Isolation and cohorting
• Infection control: transmission-based precautions, surveillance		• Secondary surveillance – contact tracing and management
• Data: including antibiogram		• Decontamination, decolonisation

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The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Considerations for Empiric Antimicrobial Therapy in Sepsis and Septic Shock in an Era of Antimicrobial Resistance

Jeffrey R. Strich,[1,2] Emily L. Heil,[3] and Henry Masur[1]

[1]Critical Care Medicine Department, National Institutes of Health Clinical Center, Bethesda, Maryland, USA, [2]United States Public Health Service, Commissioned Corps, Rockville, Maryland, USA, [3]Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, Maryland, USA

Niederman *et al. Crit Care* (2021) 25:307
https://doi.org/10.1186/s13054-021-03736-w

Critical Care

REVIEW Open Access

Initial antimicrobial management of sepsis

Michael S. Niederman[1*], Rebecca M. Baron[2], Lila Bouadma[3], Thierry Calandra[4], Nick Daneman[5], Jan DeWaele[6], Marin H. Kollef[7], Jeffrey Lipman[8,9] and Girish B. Nair[10]

Mokrani *et al. Annals of Intensive Care* (2023) 13:39
https://doi.org/10.1186/s13613-023-01134-9

Annals of Intensive Care

REVIEW Open Access

Antibiotic stewardship in the ICU: time to shift into overdrive

David Mokrani[1], Juliette Chommeloux[1], Marc Pineton de Chambrun[1], Guillaume Hékimian[1] and Charles-Edouard Luyt[1,2*]

Zilahi *et al. Ann. Intensive Care* (2016) 6:96
DOI 10.1186/s13613-016-0199-4

Annals of Intensive Care

REVIEW Open Access

What's new in multidrug-resistant pathogens in the ICU?

Gabor Zilahi[1], Antonio Artigas[2,3] and Ignacio Martin-Loeches[1,3,4,5*]

REVIEW

Appropriate antimicrobial therapy in the era of multidrug-resistant human pathogens

J. M. Pogue[1], K. S. Kaye[2], D. A. Cohen[3] and D. Marchaim[3,4]

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EMPIRICAL ANTIMICROBIAL THERAPY IN POSSIBLE XDR SEPSIS

- Prediction of MRO is challenging

Clinical Microbiology and Infection, Volume 21 Number 4, April 2015

TABLE 3. Examples of prediction scores studies for certain ESKAPE pathogens

	VRE [86]	MRSA [87]	ESBL [88]	CRE [41]	*Acinetobacter baumannii* [89]	*Pseudomonas aeruginosa* [90]
Variable of interest	VRE carriage upon admission	MRSA carriage upon admission of elective surgical patients	ESBL infection upon admission	CRE vs. ESBL in nosocomial BSI	Colonization or infection with MDR *A. baumannii*	Mortality from *P. aeruginosa* BSI
Variables included in final score	Previous MRSA carriage, haemodialysis, transfer from LTCF, antibiotic exposure, prior hospitalization, age >60 years.	Recent antibiotic treatment, history of hospitalization, age >75 years.	Recent hospitalization, transfer from LTCF, Charlson Comorbidity Score ≥4, recent β-lactam or fluoroquinolone, recent urinary catheterization, age ≥70 years	Background neurological disease, dependent functional status on admission, diabetes, antibiotics exposure in the past 3 months, and ICU stay	Bedridden, ICU stay, Charlson score>3, recent β-lactam usage, MRSA isolation within 30 days	ICU stay, coagulopathy, septic shock, age ≥65 years (2 points each), and poor clinical condition (1 point)
Predictive score [a]	≥10	≥7	≥6	≥32	≥3	≥7
Sensitivity	44%	86%	55%	81%	NR	84%
Specificity	98%	41%	94%	70%	NR	85%
Positive predictive value	81%	NR	82%	21%	88%	NR
Negative predictive value	90%	NR	81%	97%	60%	NR

Abbreviations: BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase-producing Enterobacteriaceae; ESKAPE, an acronym displaying groups of multidrug resistant organisms set by the Infectious Diseases Society of America [1]; ICU, intensive care unit; LTCF, long-term care facility; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; VRE, vancomycin-resistant enterococci;.
[a]The Predictive score indicates the threshold number for defining higher risk for the condition being tested with the score.

TABLE 4. Examples of various matched cased-case-control analyses of ESKAPE pathogens predictors

Risk factor	VRE [91,92]	MRSA [93,94]	ESBL [95]	CRE [75,96,97]	*Acinetobacter baumannii* [98,99]	*Pseudomonas aeruginosa* [100]
Long-term care facility	X				X	
Recent exposure to antimicrobials	X	X	X	X	X	X
Dependent functional status				X		
Foreign invasive chronic devices				X	X	X
Recent surgery or invasive procedure				X		
Recent prior hospitalization					X	
Advanced age	X		X			
Complex comorbidities	X				X	
Immunosuppressive states	X				X	X
ICU stay		X		X		
Male sex		X			X	

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase-producing Enterobacteriaceae; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

EMPIRICAL ANTIMICROBIAL THERAPY IN POSSIBLE XDR SEPSIS

- Importance of timely, appropriate empirical antimicrobial therapy for Hospitalised adult patients with bacterial sepsis
  - Reduced mortality with appropriate therapy (OR 0.44, 95% CI 0.38 – 0.50). Associated with shorter LOS, lower rate of treatment failure, lower antibiotic exposure and lower hospital cost (Bassetti M, et al. Int J. Antimicrob Agents. 2020).
  - Reduced mortality with earlier/no delay in appropriate therapy (OR 0.57, 95% CI 0.45 – 0.72) (Zasowski EJ, et al. Chest 2020).
  - Prevalence-adjusted pathogen-specific number needed to treat for appropriate antimicrobial therapy to prevent one death for MDR bacteria NNT=20 (Vazquez-Guillamet C, et al. Crit Care Med. 2014).
  - In patients with septic shock, number needed to treat for appropriate initial antimicrobial therapy to prevent one death NNT=4 (Vazquez-Guillamet C, et al. Crit Care Med. 2014).

Open Forum Infectious Diseases

REVIEW ARTICLE

The Clinical Impact of Rapid Molecular Microbiological Diagnostics for Pathogen and Resistance Gene Identification in Patients With Sepsis: A Systematic Review

Valentino D'Onofrio,[1,2,8] Lene Salimans,[1] Branka Bedenić,[3] Reinoud Cartuyvels,[4] Ivan Barišić,[5] and Inge C. Gyssens[1,6]

[1]Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium, [2]Department of Infectious Diseases and Immunity, Jessa Hospital, Hasselt, Belgium, [3]Department of Microbiology, School of Medicine, University of Zagreb, Zagreb, Croatia, [4]Department of Clinical Biology, Jessa Hospital, Hasselt, Belgium, [5]Molecular diagnostics, Austrian Institute of Technology, Vienna, Austria, and [6]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, the Netherlands

- 25 eligible studies involving 8 different molecular technologies
- Increase appropriateness of antimicrobial therapy (6 studies)
- Lower length of stay (2 studies)
- Decrease in antimicrobial use and cost (6 studies)
- Heterogeneity in mortality reporting (in-hospital, in-ICU, 7-day or 28-day). In-hospital mortality was lower in one study. All other studies found no significant differences in mortality. No study found higher mortality with the use of molecular diagnostic technology

2020

APPROACH TO XDR-ASSOCIATED SEPSIS

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APPROACH TO REFRACTORY XDR SEPSIS

- No uniform definition of what constitute refractoriness in sepsis and what is considered treatment failure
  - ID physicians: Failure to improve clinically after 7 to 10 days?
  - Microbiologists: Persistently positive cultures?
  - Intensivists: Worsening shock and/or organ function?
  - Surgeons: Increasing frequency of requests for reassessments and possibly source control?
  - Radiologists: More frequent and expensive scans +/- requests for radiological drainage?

- ICU caveats for non-ICU people (also relevant for ICU people):
  - Noradrenaline dose is not the only indicator of shock severity
  - Steroids, vasopressin, correction of acidosis, CRRT, changes in sedative agents, changes in ventilatory strategy and cardiac rhythm management all may impact noradrenaline requirement
  - CRRT makes almost everything looks better, including lowering of CRP!

ANTIMICROBIAL APPROACH TO PERSISTENT MRSA BACTERAEMIA

antibiotics

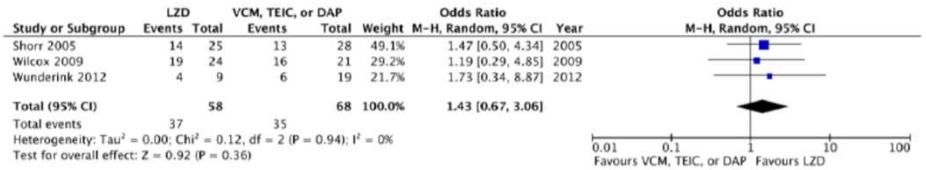
MDPI

Systematic Review

Effectiveness and Safety of Linezolid Versus Vancomycin, Teicoplanin, or Daptomycin against Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Systematic Review and Meta-Analysis

Hitoshi Kawasuji [1], Kentaro Nagaoka [1], Yasuhiro Tsuji [2], Kou Kimoto [1], Yusuke Takegoshi [1], Makito Kaneda [1], Yushi Murai [1], Haruka Karaushi [3], Kotaro Mitsutake [3] and Yoshihiro Yamamoto [1,*]

(A)



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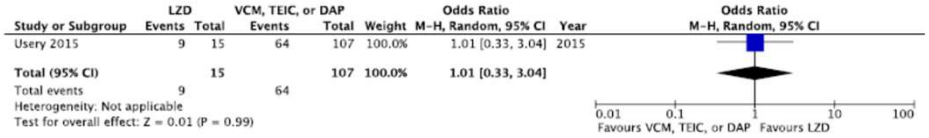


Received: 17 August 2022 | Revised: 5 November 2022 | Accepted: 7 November 2022

DOI: 10.1002/phar.2741

ORIGINAL RESEARCH ARTICLE

PHARMACOTHERAPY

Vancomycin plus ceftaroline for persistent methicillin-resistant *Staphylococcus aureus* bacteremia

Wesley D. Kufel[1,2,3] | Katie A. Parsels[2,3] | Bruce E. Blaine[4] | Jeffrey M. Steele[2,3] | Rahul Mahapatra[2,3] | Kristopher M. Paolino[2,3] | Stephen J. Thomas[2,3]

Salvage Treatment for Persistent Methicillin-Resistant *Staphylococcus aureus* Bacteremia: Efficacy of Linezolid With or Without Carbapenem

Hee-Chang Jang,[1] Sung-Han Kim,[1,a] Kye Hyoung Kim,[1] Choong Jong Kim,[1] Shinwon Lee,[1] Kyoung-Ho Song,[1] Jae Hyun Jeon,[1] Wan Beom Park,[1] Hong Bin Kim,[1] Sang-Won Park,[1] Nam Joong Kim,[1] Eui-Chong Kim,[2] Myoung-don Oh,[1] and Kang Won Choe[1]

Departments of [1]Internal Medicine and [2]Laboratory Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

GRAM NEGATIVE BACTERAEMIA- VALUE OF FOLLOW UP BLOOD CULTURE(FUBC)

Original Investigation | Infectious Diseases

Association of Follow-up Blood Cultures With Mortality in Patients With Gram-Negative Bloodstream Infections

A Systematic Review and Meta-analysis

Joshua T. Thaden, MD, PhD; Sarah Cantrell, MLIS, AHIP; Michael Dagher, MD; Yazhong Tao, PhD; Felicia Ruffin, PhD; Stacey A. Maskarinec, MD, PhD; Stacy Goins, BA; Matthew Sinclair, MD; Joshua B. Parsons, MD, PhD; Emily Eichenberger, MD; Vance G. Fowler Jr, MD, MHS

Figure 2. Association of Obtaining Follow-up Blood Cultures (FUBCs) With Mortality in Patients With Gram-Negative Bloodstream Infection

Source	HR (95% CI)
Amipara et al,[9] 2021	0.47 (0.24-0.91)
Giannella et al,[7] 2020	0.45 (0.22-0.92)
Maskarinec et al,[5] 2020	0.63 (0.53-0.75)
Green et al,[21] 2021	0.43 (0.17-1.08)
Mitaka et al,[22] 2021	0.37 (0.12-1.19)
Total	0.56 (0.45-0.71)

Heterogeneity: $\chi^2_4 = 2.57$ ($P = .63$); $I^2 = 0\%$

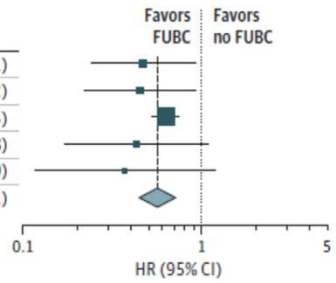
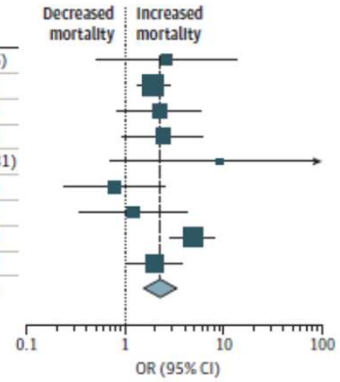


Figure 3. Association of Positive Follow-up Blood Cultures (FUBCs) With Mortality in Patients With Gram-Negative Bloodstream Infection

Source	OR (95% CI)
Amipara et al,[9] 2021	2.64 (0.51-13.55)
Maskarinec et al,[5] 2020	1.93 (1.33-2.80)
Chan et al,[11] 2021	2.22 (0.83-5.93)
Wiggers et al,[8] 2016	2.40 (0.93-6.19)
Groft et al,[32] 2021	9.00 (0.71-113.81)
Spaziante et al,[28] 2020	0.78 (0.24-2.53)
Mitaka et al,[29] 2020	1.21 (0.34-4.31)
Kim et al,[30] 2022	4.87 (2.90-8.17)
Kang et al,[31] 2013	1.98 (1.03-3.81)
Total	2.27 (1.54-3.34)

Heterogeneity: $\chi^2_8 = 14.48$ ($P = .07$); $I^2 = 45\%$



REFRACTORY GRAM-NEGATIVE BACTERAEMIA

J Antimicrob Chemother 2018; **73** Suppl 3: iii2–iii78
doi:10.1093/jac/dky027

Journal of Antimicrobial Chemotherapy

Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/ Healthcare Infection Society/British Infection Association Joint Working Party†

Peter M. Hawkey[1]*, Roderic E. Warren[2], David M. Livermore[3], Cliodna A. M. McNulty[4], David A. Enoch[5], Jonathan A. Otter[6] and A. Peter R. Wilson[7]

[1]Institute of Microbiology and Infection, University of Birmingham, Birmingham, UK; [2]Shrewsbury and Telford Hospital NHS Trust, Telford, UK; [3]Norwich Medical School, University of East Anglia, Norwich, UK; [4]Microbiology Department, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN, UK; [5]Public Health England, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [6]Imperial College London, UK; [7]Department of Microbiology and Virology, University College London Hospitals, London, UK

Clinical Infectious Diseases
IDSA GUIDELINES

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

Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

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THANK YOU

QUESTIONS?