29 Novembre 2016

Lo Scenario Attuale dell'Antibioticoterapia

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Disclosures

Consultant/Advisory Board/Speaker fee

- Pfizer, MSD, AstraZeneca
- Angelini, Basilea
- Astellas Pharma, Basilea
- Sanofi Aventis, Thermofisher

Antibiotic Resistance: Progress, Problems, and Prospects

Nathan C & Carls O NEJM 2014; Nov 6

- **Golden period**
- **Golden era**
- **These issues concern everyone**
  - Partnership
  - Return
  - Prevention
  - Leadership
  - Rewards
  - Access
  - Conservation through prioritization of medical use
  - Conservation through prescription tailored to diagnosis
  - Conservation through controlled access

Frailty at the Front Door

Wyrko Z. Clin Med (Lond) 2015;15(4):377-81

- **Frailty**
  - Multi-component syndrome
  - Many manifestations
  - Poorer outcomes
    - Mortality, morbidity and institutionalisation
- **Challenging recognition and management**
- **Multidisciplinary approach**
- **→ Appropriate assessment and subsequent intervention**

Infectious Diseases View

- **Complementary to Internal Medicine**
  - Frail infected
  - Infected frail or infected “frailing”
  - COPD
- **Chronically critical patients**
  - Independently of age and comorbidities
  - i.e prolonged ECMO support
- **Frail Microbiome**
- **Frail due to**
  - Fragmented therapies & toxicities
  - Treatment interruption
  - Recurrences
  - HIV infection
  - SOT or HSCT
  - Multiple surgeries

Antimicrobial Heteroresistance: An Emerging Field in Need of Clarity

El-Halfawy OM & Valvano MA Clin Microbiol Rev 2015; 28 (1): 191-207

- **"Heteroresistance"**
  - Subpopulations of seemingly isogenic bacteria have a range of susceptibilities to the same antibiotic
  - Lack of standard methods
  - Inappropriate use of this term
- **Recognized since at least 1947**
  - In Gram-positive and Gram-negative bacteria
  - Its clinical relevance may be considerable
  - More resistant subpopulations may be selected during antimicrobial therapy
- **Clinical magnitude difficult to explore because of:**
  - Nonstandard and costly methods
- **Need to develop uniform guidelines**

Progress in the Fight Against MDR Bacteria? A Review of U.S. FDA-Approved Antibiotics, 2010-2015

Deak D et al Ann Intern Med 2016;165:363-72

- **2010-2015: 8 new antibiotics:**
  - Ceftaroline, dalbavancin, tedizolid, oritavancin, ceftolozane-tazobactam, ceftazidime-avibactam, fidaxomicin, bedaquiline
  - 4 antibiotics were approved for ABSSSIs
  - 7 had similar mechanisms of action to those of previously approved drugs
  - 6 were initially developed by small to midsized companies
  - 7 are currently marketed by 1 of 3 large companies
- **Seven of them**
  - Substantially more expensive than their trial comparators

Asia CAP Ceftaroline Study

Clinical Cure at TOC by Patient Subgroup (CE)

	Ceftaroline 600 mg q12h n/N (%)	Ceftriaxone 2 g q24h n/N (%)	Difference % (95% CI)
Age group (cut-off 65 years)			
<65 years	84/107 (78.5)	67/85 (78.8)	–0.3 (–11.9, 11.7)
≥65 years	133/151 (88.1)	111/155 (71.6)	16.5 (7.6, 25.3)
Age group (cut-off 75 years)			
<75 years	146/177 (82.5)	118/161 (73.3)	9.2 (0.4, 18.1)
≥75 years	71/81 (87.7)	60/79 (75.9)	11.7 (–0.3, 23.9)
Sex			
Male	151/181 (83.4)	124/169 (73.4)	10.1 (1.4, 18.7)
Female	66/77 (85.7)	54/71 (76.1)	9.7 (–3.1, 22.6)
PORT risk class			
Class III	148/173 (85.5)	126/169 (74.6)	11.0 (2.6, 19.5)
Class IV	69/85 (81.2)	52/71 (73.2)	7.9 (–5.2, 21.4)
Previous systemic antibiotics			
No	175/209 (83.7)	143/195 (73.3)	10.4 (2.4, 18.4)
Yes	42/49 (85.7)	35/45 (77.8)	7.9 (–7.9, 24.2)

Zhong NS, et al. Lancet Infect Dis 2015;15:161-71.

Ceftobiprole: A European Perspective
Liapikou, Cilloniz & Torres
Drug Design, Development & Therapy 2015:9;4565-72

- **CAP:**
  - Non-inferiority met Vs. ceftriaxone±linezolid
  - Pathogens isolated in one third of patients
  - Ceftobiprole: more polymicrobial infections (20% Vs. 8%, p=0.016)
  - When switched to oral cefuroxime, microbiological eradication rates were significantly lower with ceftobiprole (89% Vs. 100%)
- **HAP:**
  - Non-inferiority met
- **VAP:**
  - Ceftobiprole had lower clinical cure rate (38.5% Vs. 56.7%, $p<0.05$)
  - Small sample size, heterogeneity, PK variations
  - In MV patients with non-VAP, clinical outcomes favoured ceftobiprole, suggesting that MV by itself is not associated with poor outcomes

S. aureus CAP: Prevalence, Clinical Characteristics, and Outcomes

Self WH et al Clin Infect Dis Clin Infect Dis 2016;63(3):300-9

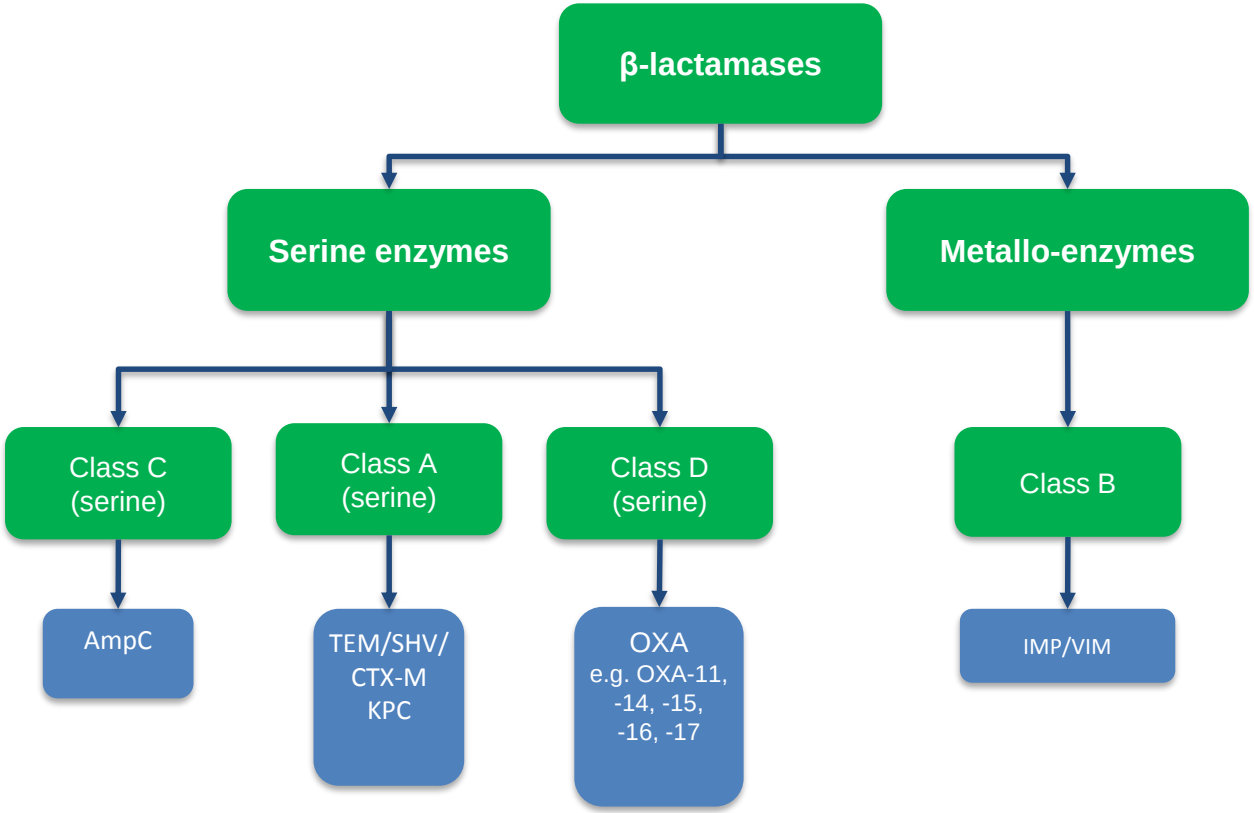
- **Multicenter prospective surveillance of adults hospitalized with CAP**
- **Comparison of *S. aureus* CAP with those of pneumococcal and all-cause non-*S. aureus* CAP**
  - 2,259 adults hospitalized for CAP
    - 37 (1.6%) had *S. aureus* identified, including 15 (0.7%) with MRSA
    - 115 (5.1%) had *S. pneumoniae*
    - Vanco or linezolid was used in 674 (29.8%) patients within the first three days
- **Chronic hemodialysis**
  - More common with MRSA (20.0%) than pneumo (2.6%) and others (3.7%)
- **Otherwise, clinical features at admission were similar:**
  - Concurrent influenza infection and hemoptysis
  - Multilobar infiltrates and pre-hospital antibiotics

S. aureus CAP:
Prevalence, Clinical Characteristics, and Outcomes
Self WH et al Clin Infect Dis Clin Infect Dis 2016;63(3):300-9

- **Clinical outcomes in MRSA Vs. pneumococcal CAP, respectively:**
  - ICU admission 86.7% vs 34.8%
  - In-patient mortality 13.3% vs 4.4%
- **Clinical relevance:**
  - Very low prevalence of *S. aureus*, and specifically MRSA
  - However, nearly one-third of hospitalized CAP received anti-MRSA antibiotics
  - The clinical presentation of MRSA CAP overlapped substantially with pneumococcal CAP
    - Current available medical tools should be implemented
  - Challenge of accurately targeting empirical anti-MRSA antibiotics
  - Need for new diagnostic strategies

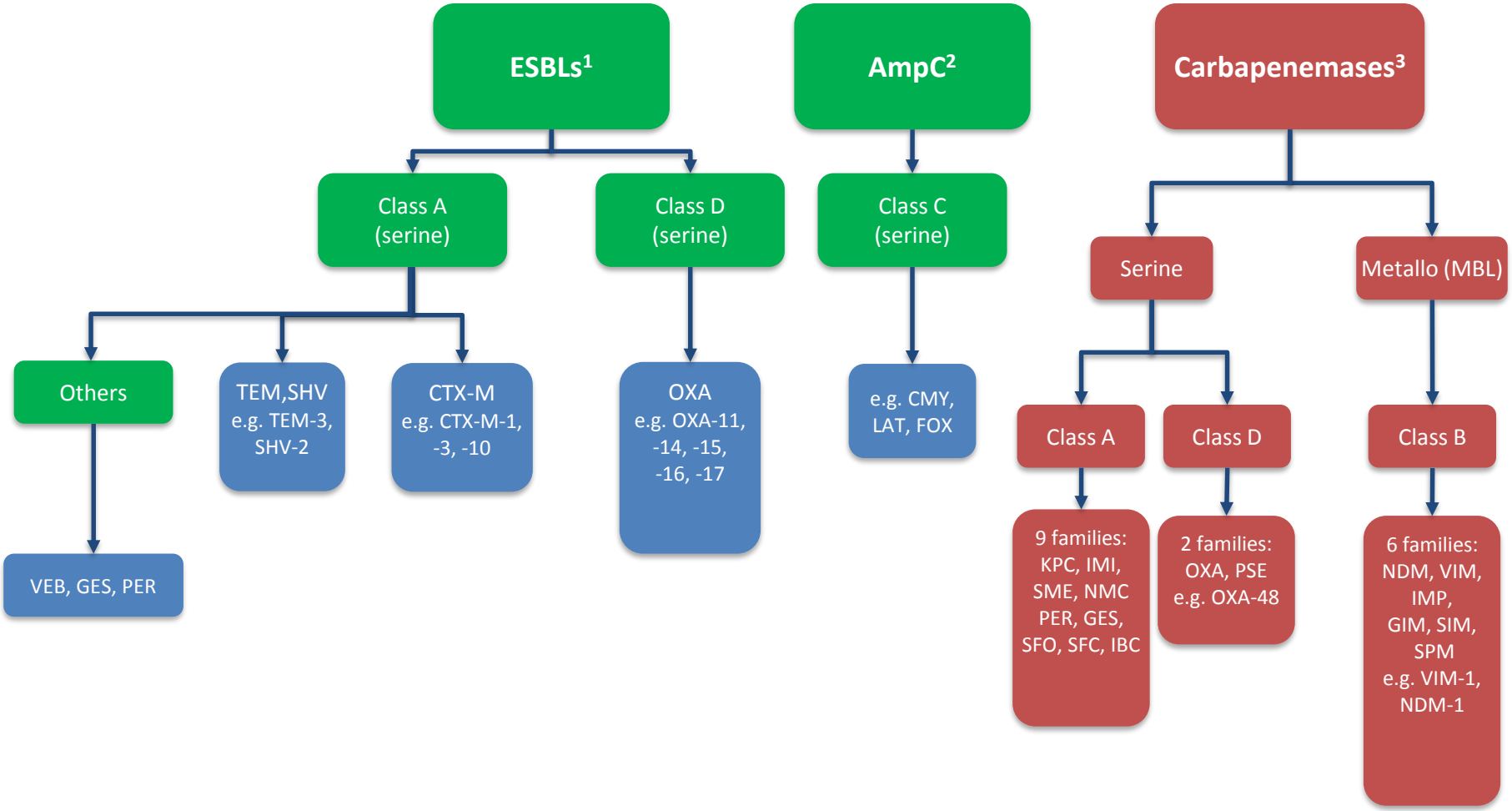
Classifying β-lactamases

Bush. Rev Inf Dis 1987;10:681; Bush et al. Antimicrob Agents Chemother 1995;39:; Bush. Curr Opin Investig Drugs 2002;3:1284



The β-lactamase Family

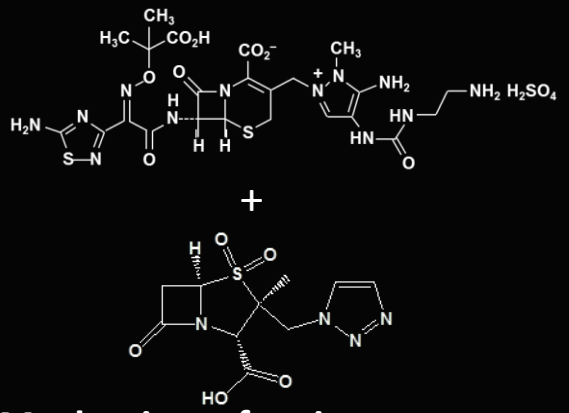
Bradford PA. Clin Microbiol Rev 2001;14:933–51;
Jacoby GA. Clin Microbiol Rev 2009;22:161–82;
Stuart JC, Leverstein-Van Hall MA. Int J Antimicrob Agents 2010;36:205–10



Ceftolozane/Tazobactam Overview

Class

- Antipseudomonal cephalosporin + β-lactamase inhibitor
- Fixed 2:1 ratio



Mechanism of action

- Rapidly bactericidal
- Inhibits cell wall synthesis
- Active against organisms with porin deficiencies or mutations
- Inhibits β-lactamases, broadens coverage to most ESBL-producing Enterobacteriaceae

In vitro activity

- *Pseudomonas aeruginosa*, including drug-resistant strains
- *Escherichia coli*, including ESBL-positive strains
- *Klebsiella pneumoniae*, including ESBL-positive strains
- Minimal activity against Gram-positive bacteria
- Limited activity against anaerobes
- No activity against KPC, MBL

Development stage

- Completed Phase 3 trials for treatment of cIAI and cUTI
- Phase 3 trial underway for nosocomial pneumonia

In vivo efficacy

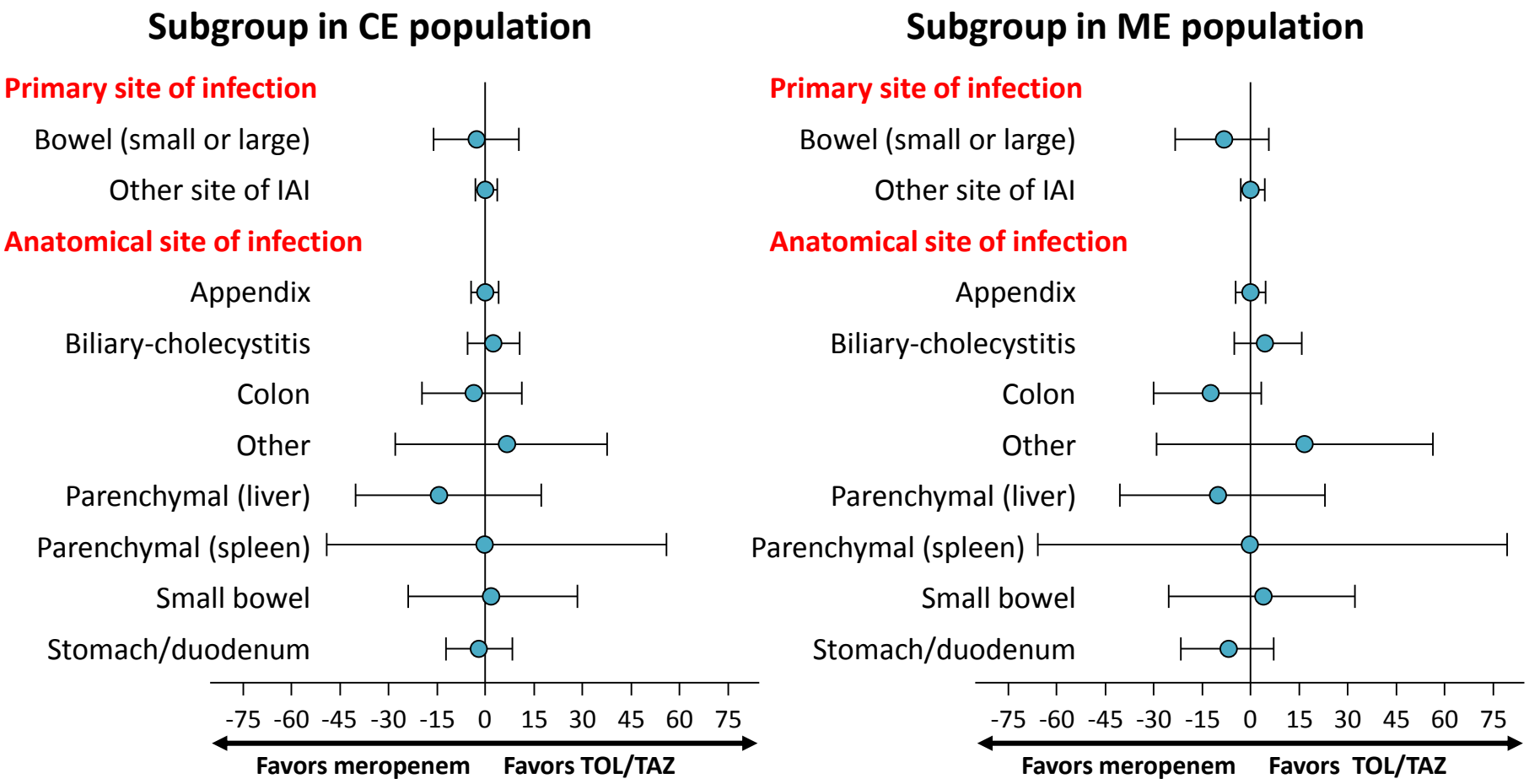
- Activity in mouse models of sepsis, pneumonia, urinary tract infection, burn wound infection, and thigh infection
- Positive outcomes and adhered to an expected safety profile in Phase 2 and 3 trials in adult patients with cUTI and cIAI

Pharmacokinetics

- Linear PK
- Lung penetration
- Rapid tissue distribution
- Minimal accumulation
- Extensive renal excretion
- Low protein binding
- Minimal CYP450 drug-drug interactions

ASPECT-cIAI

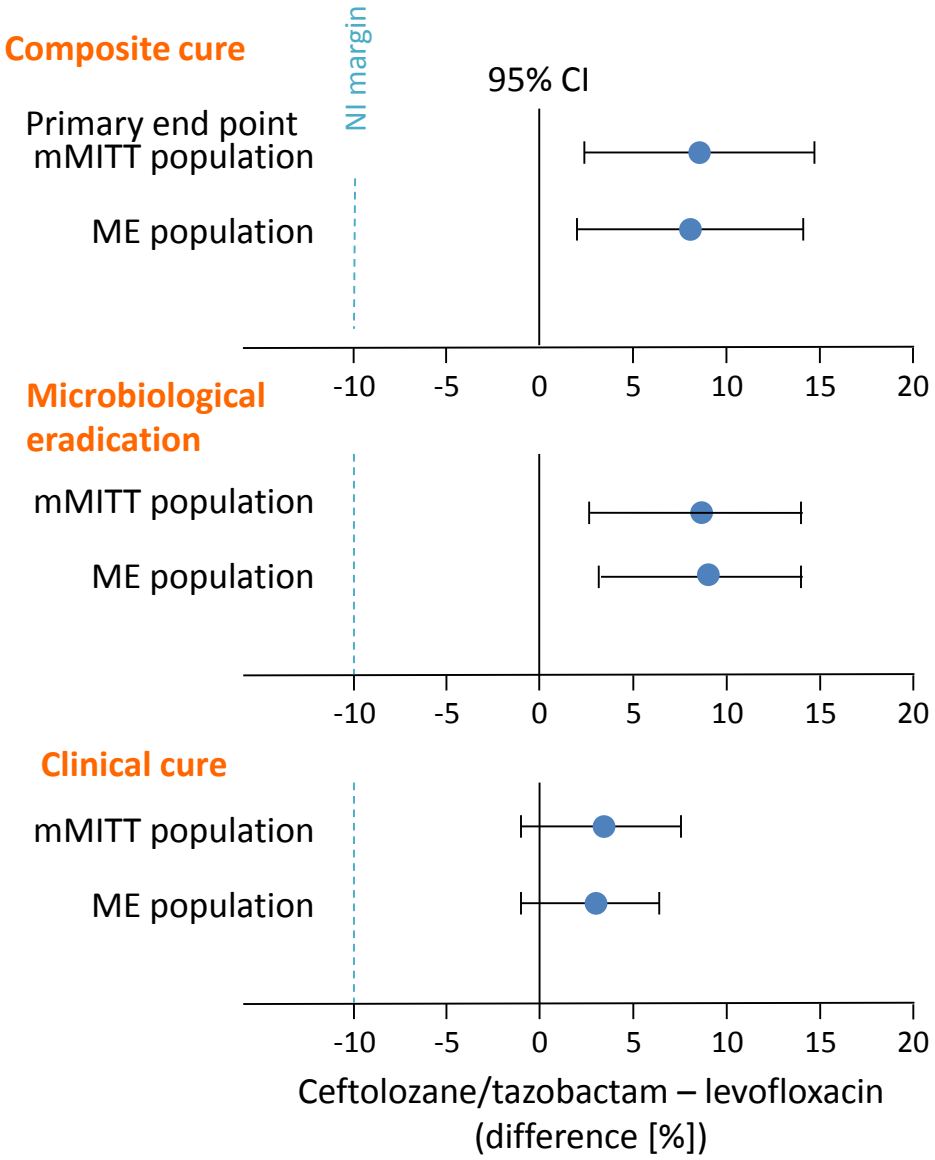
Clinical Response at TOC Visit by Infection Site



95% CI for the difference of ceftolozane/tazobactam [TOL/TAZ] + metronidazole – meropenem are calculated as Wilson score CIs. A patient can have more than 1 anatomical site of infection. Data as-observed approach used for calculation of Wilson score CIs.

Eckmann et al. ECCMID 2014. Poster P0266a.

ASPECT-cUTI
Key Primary and Secondary Analysis Endpoints at TOC Visit



Ceftolozane/ tazobactam n/N (%)	Levofloxacin n/N (%)	Percentage difference (95% CI)	Percentage difference (99% CI)
306/398 (76.9)	275/402 (68.4)	8.5 (2.3 to 14.6)	8.5 (0.4-16.5)
284/341 (83.3)	266/353 (75.4)	8.0 (2.0 to 14.0)	8.0 (0.01-15.8)

n/N (%)	n/N (%)	(95% CI)
320/398 (80.4)	290/402 (72.1)	8.3 (2.4 to 14.1)
294/341 (86.2)	274/353 (77.6)	8.6 (2.9 to 14.3)

n/N (%)	n/N (%)	(95% CI)
366/398 (92.0)	356/402 (88.6)	3.4 (-0.7 to 7.6)
327/341 (95.9)	329/353 (93.2)	2.7 (-0.8 to 6.2)

Wagenlehner et al. ECCMID 2014. Poster eP449.

Ceftolozane-Tazobactam: Place in Therapy

- **Official Indications**
  - **IAI**
  - **Complicated UTI**
- **Microbiological activity**
  - ***P. aeruginosa***
  - **ESBL**
- **PK Advantages**
- **Carbapenem-sparing strategies**
- **Piperacillin-tazobactam alternatives**
  - **Data from clinical trial vs ESBL-producing bacteria**

Future
MICROBIOLOGY

REVIEW

Critical issues for *Klebsiella pneumoniae* KPC-carbapenemase producing *K. pneumoniae* infections: a critical agenda

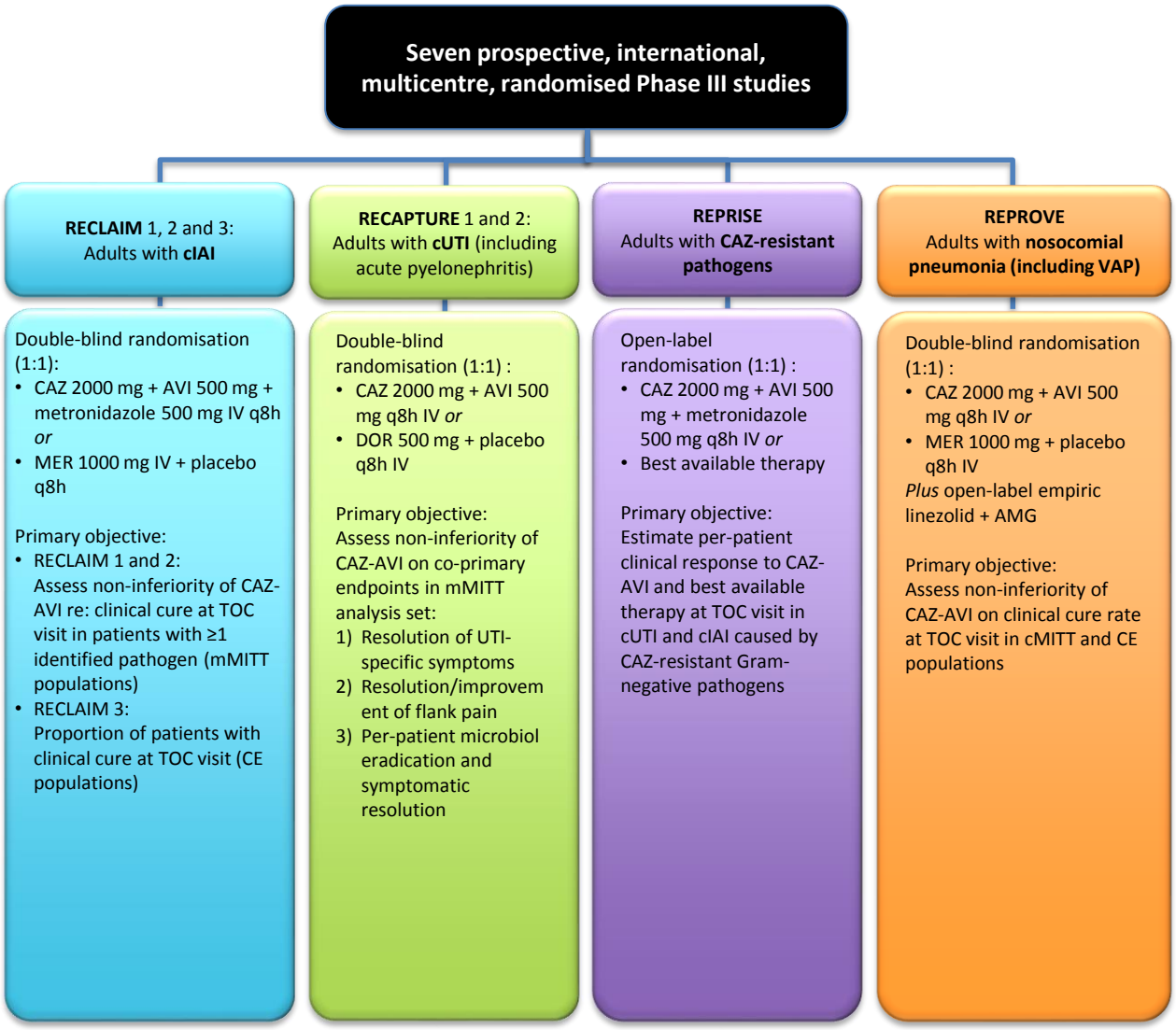
Francesco G De Rosa*[1], Silvia Corcione[1], Rossana Cavallo[2], Giovanni Di Perri[1] & Matteo Bassetti[3]

ABSTRACT The wide dissemination of carbapenemase producing *K. pneumoniae* (KPC-Kp) has caused a public health crisis of global dimensions, due to the serious infections in hospitalized patients associated with high mortality. In 2014, we aim to review clinical data on KPC-Kp at a time when a pro-active strategy (combating the problem before it is established) is no longer useful, focusing on epidemiology, patient risk profile, infection control, digestive tract colonization and treatment issues such as the role of carbapenems or carbapenem sparing strategies, colistin and resistance, dual carbapenem administration and the role of tigecycline. All these issues are illustrated prospectively to provide a forum for a Consensus strategy when not only intensive care units but also medical and surgical wards are affected by the epidemics.

In Vitro Susceptibility to Ceftazidime-Avibactam of Carbapenem-Nonsusceptible Enterobacteriaceae Isolates Collected during the INFORM Global Surveillance Study (2012- 2014) de Jonge BL et al AAC 2016; 60(5): 3163-9

- **Susceptibility to CAZ-AVI**
  - **98%**
    - Meropenem-nonsusceptible & MBL-negative isolates
  - **98%**
    - Isolates with KPC or OXA-48-like β-lactamases both alone and in combination with ESBLs and/or AmpC β-lactamases
  - **95%**
    - Meropenem-nonsusceptible, carbapenemase-negative isolates
- **CAZ-AVI activity compromised only in isolates with metallo-β-lactamases**

Ceftazidime-avibactam Phase III Clinical Trial Programme



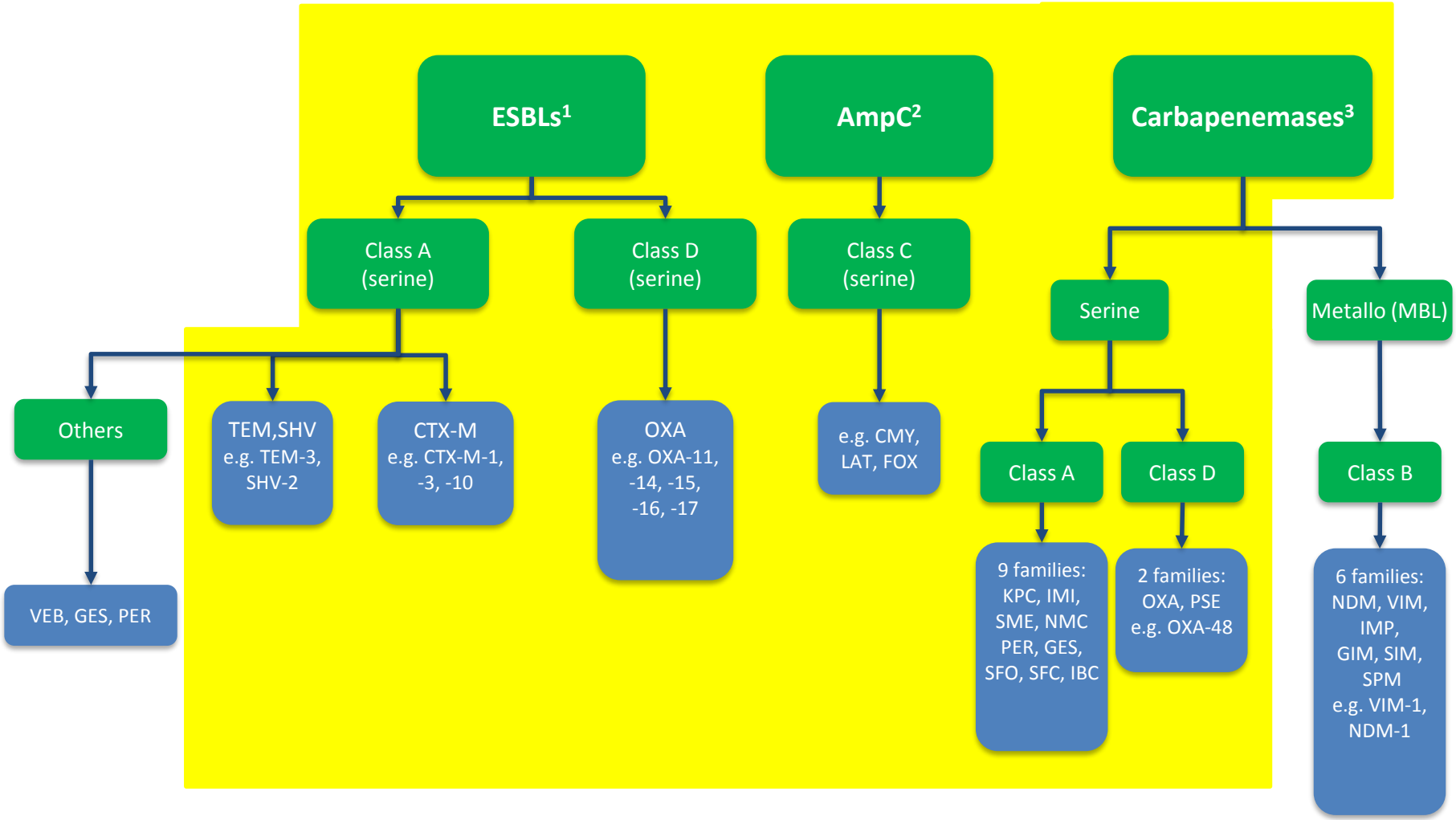
CE, clinically evaluable; cMMIT, clinically modified intent-to-treat; mMIITT, microbiological modified intent-to-treat

In vitro activity of Ceftazidime-avibactam Vs. Specific β-lactamases

Bradford PA. Clin Microbiol Rev 2001;14:933–51;

Jacoby GA. Clin Microbiol Rev 2009;22:161–82;

Stuart JC, Leverstein-Van Hall MA. Int J Antimicrob Agents 2010;36:205–10



Tedizolid

ESTABLISH-1 (TR701-112)[1]

- **A Phase 3 Randomized, Double-blind, Multicenter Study Comparing the Efficacy and Safety of 6-Day Oral Tedizolid Phosphate FA and 10-Day Oral Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections**

  Key endpoints

  - Early clinical response at the 48- to 72-hour assessment (defined as: no increase in lesion area from baseline and afebrile, confirmed by second temperature measurement within 24 hours)
  - Investigator-assessed clinical response at PTE

ESTABLISH-2 (TR701-113)[2,3]

- **A Phase 3 Randomized, Double-blind, Multicenter Study Comparing the Efficacy and Safety of IV to Oral 6-Day Tedizolid Phosphate FA and IV to Oral 10-Day Linezolid for the Treatment of ABSSSI**

  Key endpoints

  - Early clinical response at the 48- to 72-hour assessment (defined as: at least 20% decrease in lesion area from baseline)
  - Investigator-assessed clinical response at PTE

FA=free acid; PTE = post therapy evaluation; IV=intravenous; ABSSSI=acute bacterial skin and skin structure infections.

1. Prokocimer P, et al. JAMA. 2013;309(6):559-569; **2.** http://www.clinicaltrials.gov/ct2/show/NCT01421511; **3.** Fang E, et al. Efficacy and safety results from the ESTABLISH-2 ABSSSI study comparing IV and oral tedizolid phosphate and linezolid. Poster presented at: 23rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 27-30, 2013; Berlin, Germany. (LB2964).

Tedizolid in ABSSSIs: ESTABLISH-2

Moran GJ et al Lancet Infect Dis 2014;14:696-705

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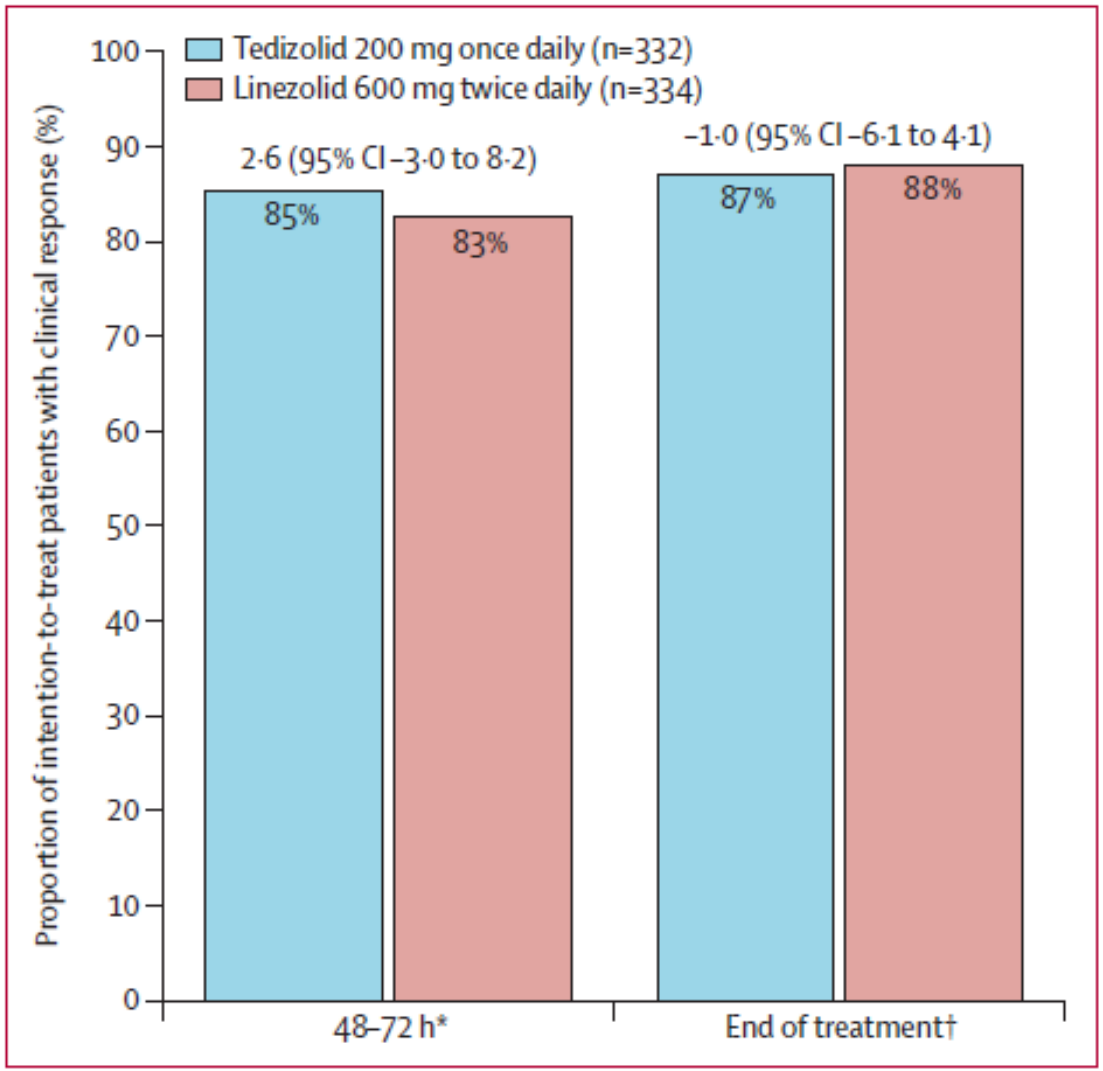

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Dalbavancin & Oritavancin: Features of Trial

Chambers HF et al, NEJM 2014; 370:2238-2239

- **Trials similar**
  - Dalbavancin iv 1000-mg dose, with a 500-mg dose administered 1 week later
  - Oritavancin was given as a one-time dose of 1200 mg
  - Vancomycin 15 mg/Kg q12h was the comparator in both drugs
    - Step-down option to oral linezolid in the dalbavancin trials
- **In accordance with the 2010 FDA draft guidance**
  - & the final October 2013 guidance for ABSSSIs
- **The primary efficacy end point:**
  - Clinical response of the wound, cellulitis, or major abscess (i.e., no progression and reduction in lesion size as compared with baseline in a patient who is alive and did not receive rescue therapy) determined 48 to 72 hours after the initiation of therapy
- **Substantial departure from most previous registrational trials**
  - Using the ABSSSI definition with more objective criteria of success

Dalbavancin & Oritavancin: Features of Trial

Chambers HF et al, NEJM 2014; 370:2238-2239

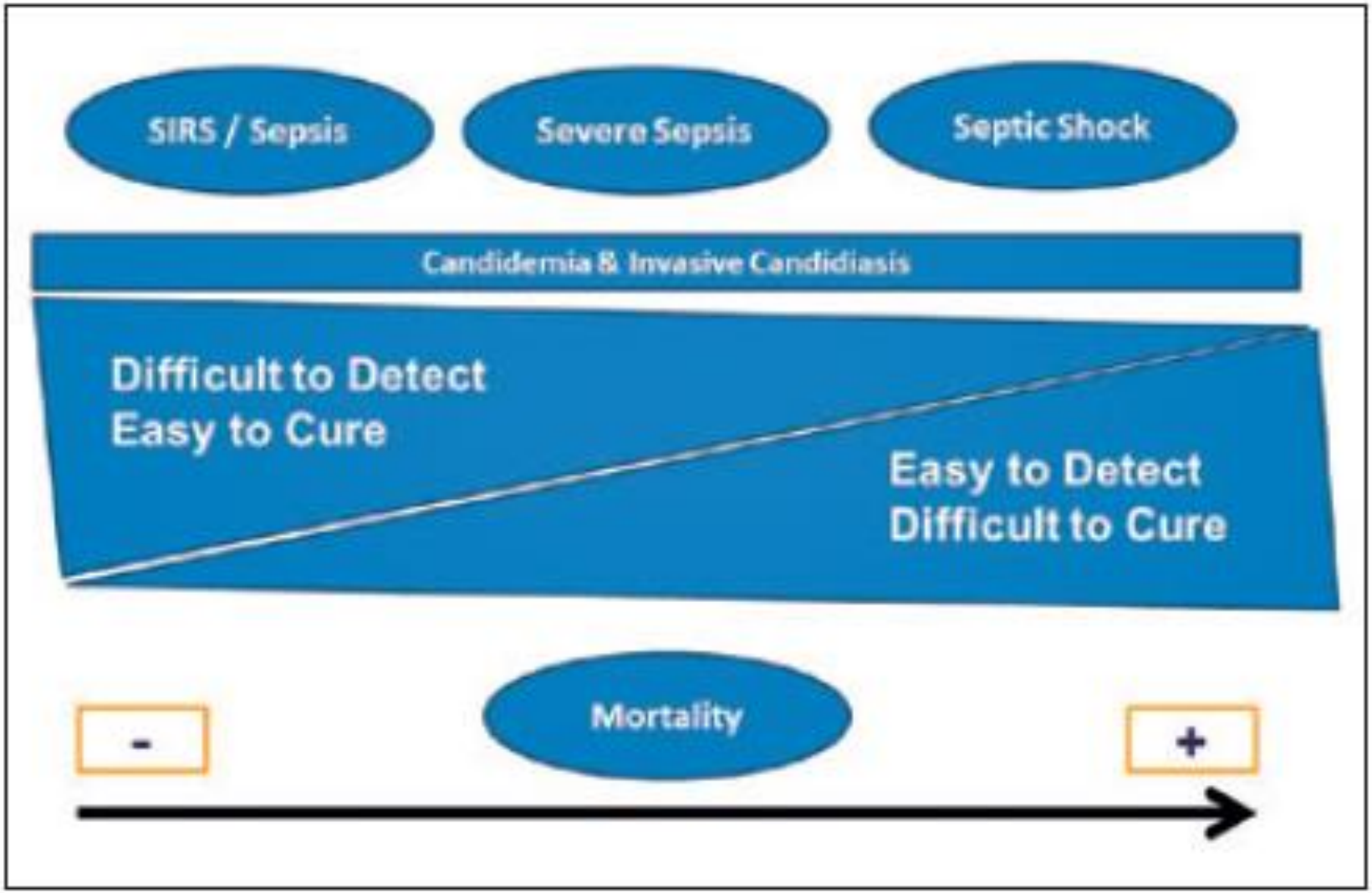
- **Dalbavancin trials**
  - Higher percentage of sicker patients
    - With fever 85% vs. 15%
    - With elevated WBC count 40% vs. 22%
    - With SIRS 51% vs. 18%
    - Patients' lesions were 46% larger on average (345 cm^2 vs. 237 cm^2)
- **Outcomes similar to vancomycin**
  - Both exceeded the noninferiority thresholds of 10% for the primary and secondary efficacy end points
  - There was 86% concordance of outcomes between lesion response at 48 to 72 hours and investigator-assessed success or failure of the treatment
- **The efficacy of vancomycin was remarkably similar**
  - No significant effect on outcome caused by differences in design or patients

Conclusioni

- Scenario Clinico
- Scenario Microbiologico
- Scenario Economico
- Scenario Metodologico

Invasive Candidiasis as A «Enteropathogenetic» Opportunistic Syndrome

De Rosa FG et al, Infez Med 2015; 2: 105-116



KPC → CCC

De Rosa FG et al Clin Infect Dis 2014

- **Candida**
- ***C. difficile***
- **Carbapenemasi**

- **Ruolo Patogenetico del tubo digerente**
- ….
- ….

Scenario Clinico-Microbiologico

- **Infezioni da batteri MDR**
  - **Ampio denominatore**
  - **Epidemiologia locale**
    - Gram-positivi
    - Gram-negativi
    - MDR, KPC-Kp, *A. baumannii,* MRSA, *P. aeruginosa*
- **Aree di intervento:**
  - **Antimicrobial Stewardship**
    - Carbapenem-sparing strategies
    - De-escalation
    - Ceftolozane-tazobactam
    - Ceftazidime-avibactam
  - **Infection Control**
    - Prevenzione CVC-BSI
    - KPC-Kp
- **Interdisciplinarietà**

Scenario HTA

Barbieri M et al HTA Focus 2016;2:45-93

Original Articles

Analisi di minimizzazione dei costi del trattamento delle infezioni batteriche acute di cute e struttura cutanea a livello del sito chirurgico in pazienti sottoposti ad intervento cardiochirurgico

Marco Barbieri, Paolo Bigliano, Diego Barilà, Alberto Clerici, Mauro Rinaldi, Giovanni Di Perri, Francesco G. De Rosa

Abstract

Background: Dalbavancin, a lipoglycopeptide antibiotic agent that is active against gram-positive pathogens, has a long plasma half-life, allowing for one single dosing (once shot) or once a week for 2 weeks for treatment of acute bacterial skin and skin-structure infections (ABSSSI). The objective of this analysis was to assess whether the use of dalbavancin would lead to a reduction of hospital costs for inpatients with ABSSSI after cardiosurgery compared to other antibiotic treatments.

Methods: We retrospectively reviewed 35 patients with definite, probable or possible ABSSSI after surgery in a Cardiac Surgery Department of the "Città della Salute e della Scienza" hospital in Turin during year 2014. Patients received several antibiotic treatments, including linezolid, vancomycin, daptomycin, tigecycline and teicoplanin. For each patient, we estimated whether the use of these antibiotic therapies increased the LOS (Length Of Stay) in cardiac surgery ward, namely whether they could have discharged earlier (at home or in a less expensive ward) with the use of dalbavancin. The cost savings associated with this potential reduction in LOS were estimated. Costs of each antibiotic option and laboratory costs were also considered. Unit costs and resource use were mainly taken from the internal hospital costs or from national tariffs, when not available. Univariate sensitivity analyses were performed on key parameters.

Results: The use of dalbavancin was associated with cost savings ranging from approximately € 3,200 compared to vancomycin to € 4,700 compared to daptomycin. Savings were mainly due to a reduction in LOS estimated equal to 2.34 days. Sensitivity analyses corroborated the base case results, and dalbavancin remained cost saving in every scenario.

Conclusions: Dalbavancin has the potential of being a cost saving option compared to other commonly used antibiotic therapies from a hospital perspective due to the reduction in LOS. Future studies with a larger number of patients treated with dalbavancin may confirm these findings.

Key words: Dalbavancin, ABSSSI, cost-minimisation, length of stay, cardiosurgery

Clinical Trials

Deak D et al Ann Intern Med 2016;165:363-72

- **Most trials were of non-inferiority**
  - No demonstration of superior outcomes on patient survival or disability
- **No trials evaluated direct patient outcomes as primary end-points**
  - Primary end-point with Dalba, orita and tedizolid:
    - Cessation of spread of the baseline lesion
    - Absence of fever
    - No rescue antibiotic medication
- **Some drugs did not have any confirmatory evidence from a second independent trial or did not have any confirmatory trials**