Hospital Acquired Infection Case Presentation

Adel Mohamad Alansary, MD

Patient

- 72 years old male undergoing left knee replacement on 2 August 2018.
- Diabetic on Glimepiride 4 mg daily.
- Hypertensive on Amlodipine 10 mg daily.
- History of appendectomy 40 years ago which was uneventful.

Patient

- He was admitted to the ICU due to occurrence of intraoperative hypotension and major bleeding.
- He received 2 units PRBCs in OR and another 2 units in ICU.
- On day 1 his Hb was 8.8 and he received another 2 units PRBCs
- BP was supported using low dose noradrenaline.

Do you need more info?

A. No we physicians know everything.
B. Yes if we want to reach a proper diagnosis and management.
C. No I am busy give her some blood and antimicrobials that's all we have.

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Do you need more info?

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Do you need more info?

- HBA1C
- WBCs and other labs
- Other drug history.
- Ambulation status. 6minute walk test.
- Any other history of hospitalization.

Other info

- BP 100/60
- Spontaneously breathing
- Pain treated with epidural Bupivacaine.
- WBCs 25000
- CRP 22
- Prophylactic antimicrobial: Cefazoline

Day 2

- Noradrenaline weaned gradually
- Hb 9.8
- Physiotherapy started
- WBCs 12000
- CRP 10

Day 3

Hb 9.5

WBCs 11000

CRP 10

Cefazolin stopped

Transfer to the ward

Hospital Course

- Uneventful hospital course.
- Patient was noncompliant with physiotherapy.

Day 7

- Patient has dyspnea on mild effort.
- SpO2 on room air 88%, 96% on O2 nasal cannula
- What to do?

What to Do?

A. Transfer to ICU, add supplemental oxygen
B. Watch for more deterioration.
C. Non of the above

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What to Do?

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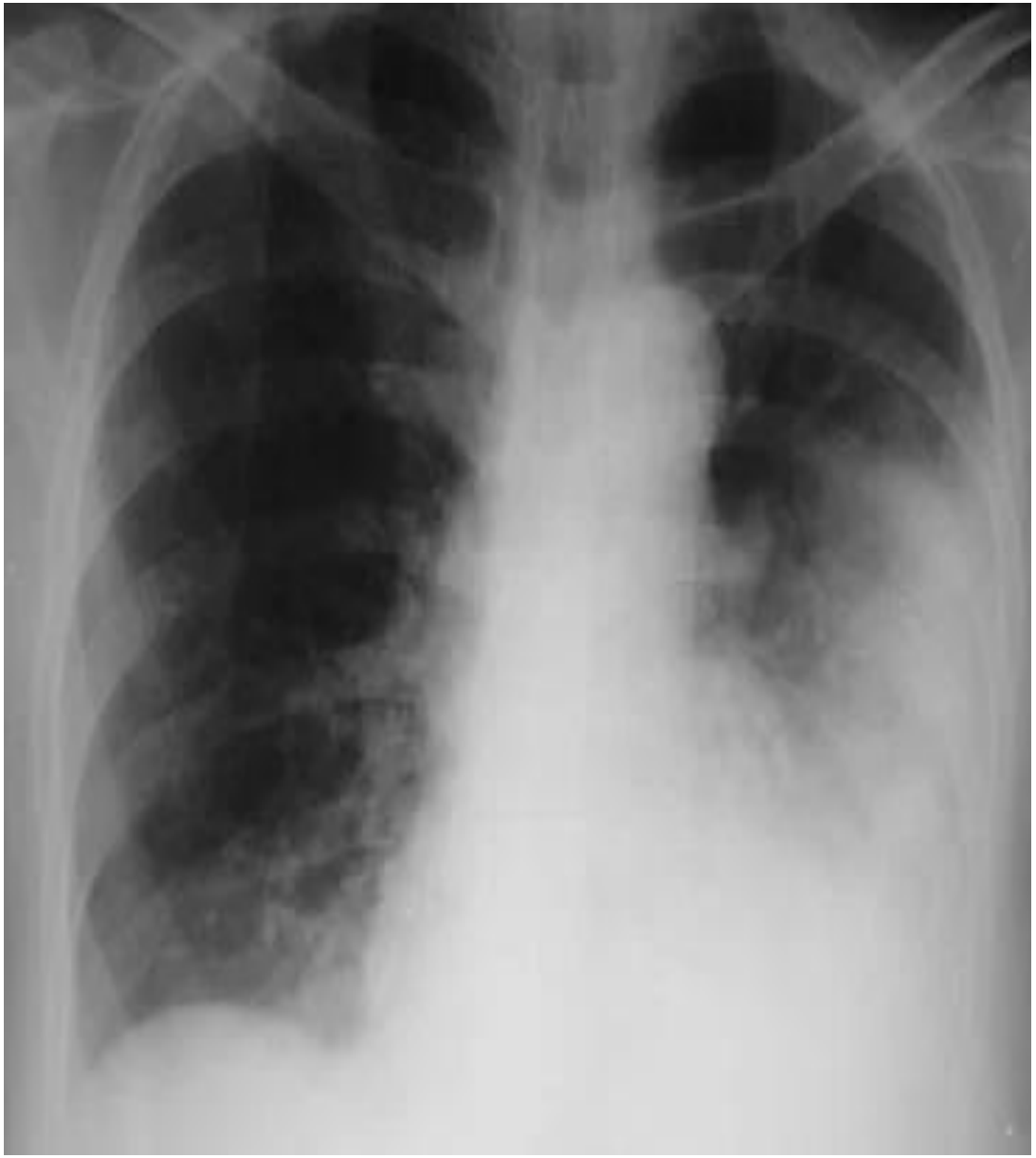
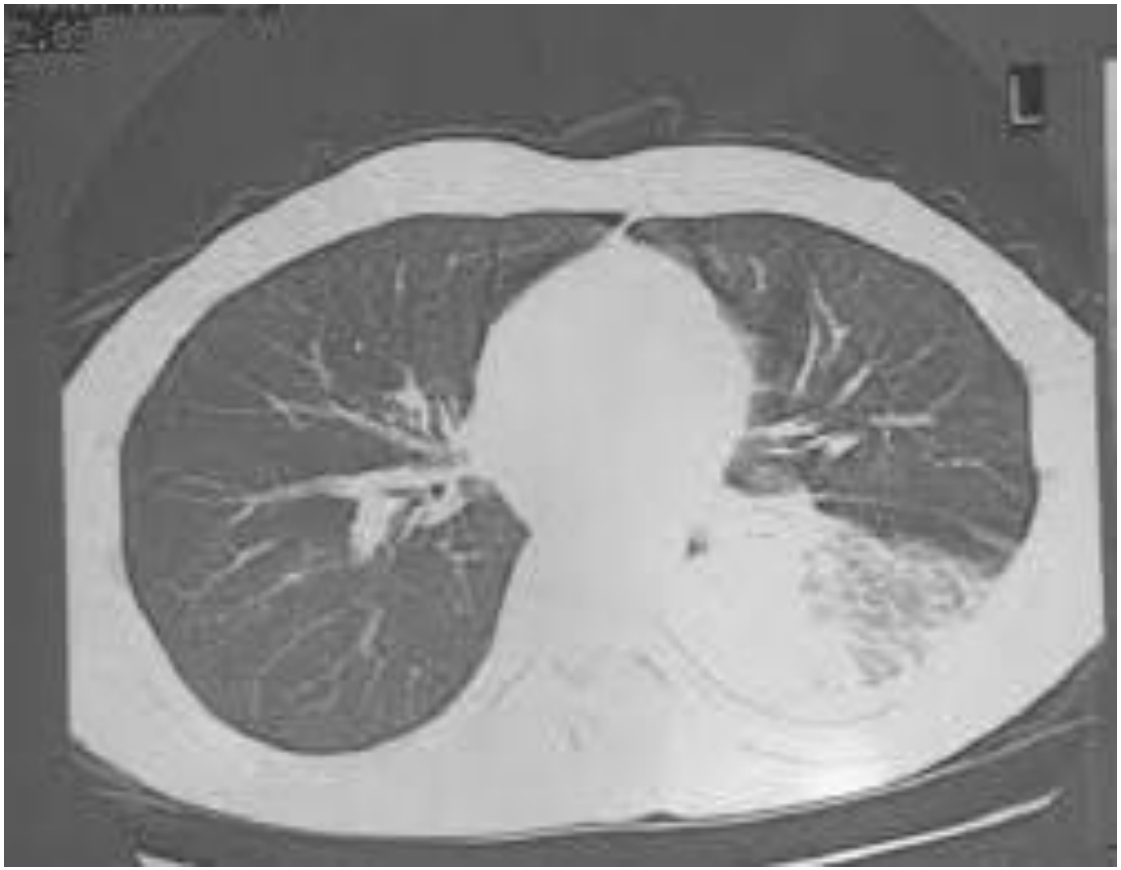
- Anticoagulation enoxaparin 40 mg OD given
- CXR unilateral consolidation shadow
- ECG 90 RSR
- BP 120/55
- LL venous duplex: NAD
- Cr 0.9



- WBCs 13000
- CRP 211
- Cultures were sent



PA angiography

- NAD
- Lung CT shows left lower lobe consolidation
- Dyspnea deteriorated and patient readmitted to ICU

CTPA should be done?

- Yes
- No

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CTPA should be done?

ⓘ Start presenting to display the poll results on this slide.

Geneva Score (Revised)

- Age> 65 1
- Previous VTE 3
- Surgery under GA or bone fracture within 1 month 2
- Cancer within 1 year 2

Geneva Score (Revised)

- Unilateral leg pain 3
- Hemoptysis 2
- HR 65-94 3
- HR >94 5
- Unilateral tenderness or leg edema 4
- 0-3 low, 4-10 moderate, >10 high

Wells Criteria for CT Pulmonary Angiography Deferral

- Developed scoring system to combine with D dimer to avert need for further tests
  - Clinical symptoms of DVT (3)
  - No alternative diagnosis (3)
  - Heart rate > 100 beats/min (1.5)
  - Immobilization or surgery in < 4 weeks (1.5)
  - Prior DVT/PE (1.5)
  - Hemoptysis (1.0)
  - Malignancy (1.0)

Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED-D-dimer. *J Thromb Haemost.* 2000 Mar;83(3):416-420.

Wells Criteria for CT Pulmonary Angiography Deferral

- Score < 4: PE unlikely
- Prevalence of PE 7.8% if score < 4
- Score < 4 **and** negative D dimer test
  - Prevalence 2.2% in derivation set
  - Prevalence 1.7% in validation set
- Score 2–6: 2.9% with negative D dimer test in validation set
- Score > 6
  - 20% with negative D dimer test
  - 60%–80% with positive D dimer test

Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED-D-dimer. *J Thromb Haemost.* 2000 Mar;83(3):416-420.

Day 1 readmission

- RR 32
- SpO2 on face mask 88
- BP 100/50
- WBCs 15000
- CRP 320

DD should include?

A. IPF, Pneumonia.
B. Pneumonia, PE.
C. Obesity hypoventilation, Pneumonia.
D. Fat embolism, IPF
E. Non of the above

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DD should include?

ⓘ Start presenting to display the poll results on this slide.

Definitions

- Pneumonia: new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation.

(Management of Adults With HAP/VAP, CID, 2016)

Definitions

- HAP is defined as a pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission.
- VAP is defined as a pneumonia occurring >48 hours after endotracheal intubation.

(Management of Adults With HAP/VAP • CID, 2016)

Which organisms should be targeted?

A. Enterobacteriaceae
B. Pseudomonas
C. MSSA
D. MRSA
E. All of the above

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Which organisms should be targeted?

ⓘ Start presenting to display the poll results on this slide.

- Escherichia coli, Klebsiella pneumoniae, Acinetobacter and Pseudomonas aeruginosa are the most common pathogens causing nosocomial infections.

The Egyptian Society of Chest Diseases and Tuberculosis
Egyptian Journal of Chest Diseases and Tuberculosis
www.elsevier.com/locate/ejcdt
www.sciencedirect.com

ORIGINAL ARTICLE

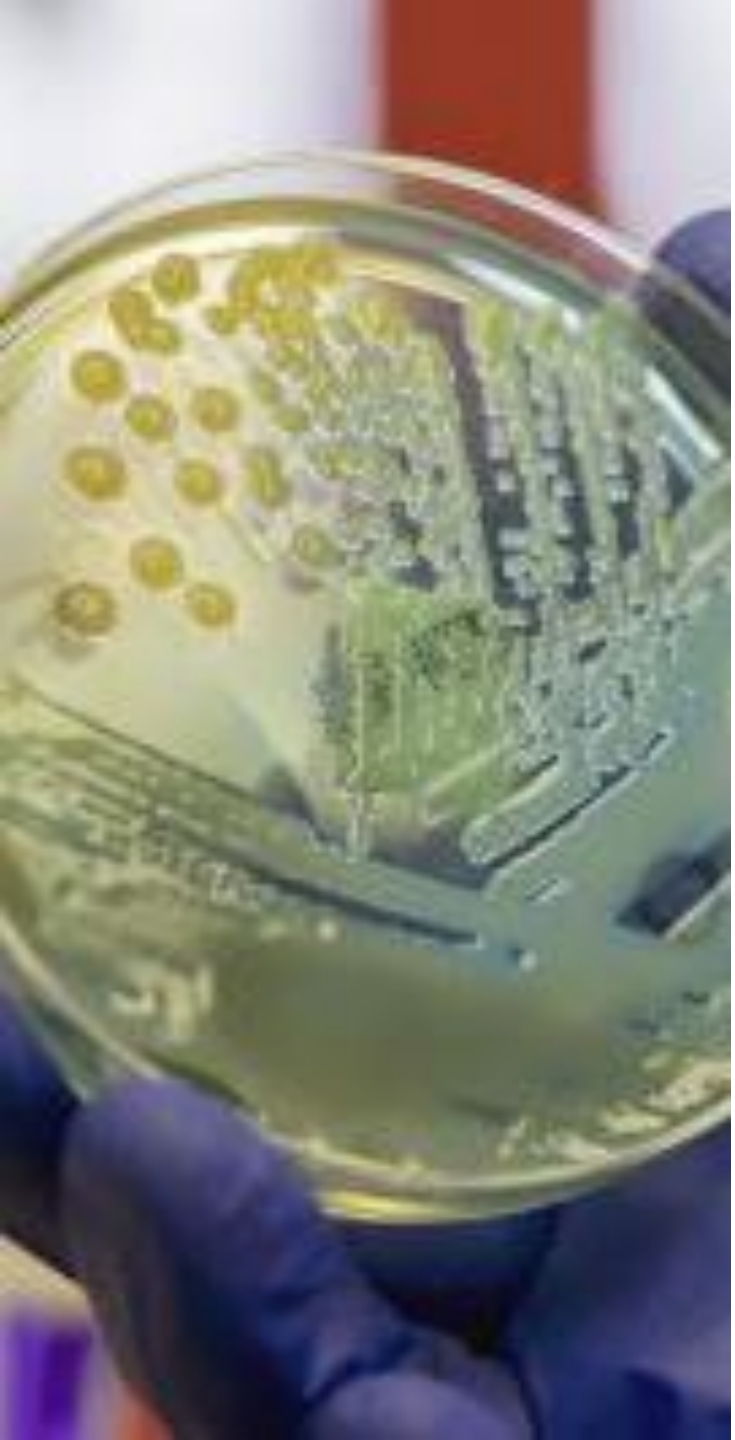
Pattern of hospital-acquired pneumonia in Intensive Care Unit of Suez Canal University Hospital

Mohamed Eida [a], Mohamed Nasser [b], Nermine El-Maraghy [c,*], Khaled Azab [a]

Table 4 The relation between the isolated organisms and the mechanical ventilation.

Isolated organisms	Total No.	Mechanical ventilation (n = 100)			
		Ventilated (VAP)		Non ventilated (HAP)	
		Freq.	% of column	Freq.	% of column
Methicillin resistant *Staph.aureus* (MRSA)	36	32	35.9	4	36.35
Klebsiella pneumoniae	29	25	28.1	4	36.35
Pseudomonas aeruginosa	6	5	5.7	1	9.1
Proteus spp.	6	6	6.8	0	0.0
E. coli	5	5	5.6	0	0.0
Strept. viridans	3	2	2.2	1	9.1
Methicillin sensitive *Staph.aureus* (MSSA)	2	2	2.2	0	0.0
No growth	13	12	13.5	1	9.1
Total	100	89	100	11	100

P value = 0.88.



Causative organisms

- Staphylococcus aureus (MRSA)
- Klebsiella oxytoca
- Escherichia coli
- Pseudomonas aeruginosa
- Staphylococcus aureus (MSSA)
- Enterobacter cloacae

BAL is

A. Mandatory in all HAP cases.
B. Mandatory in all VAP cases.
C. Correlates with improved outcome in HAP cases.
D. Correlates with improved outcome in VAP cases.
E. Non of the above.

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BAL is

ⓘ Start presenting to display the poll results on this slide.

Respiratory Samples

Invasive:

- BAL
- PSB
- Mini BAL

Noninvasive:

- Sputum
- Nasotracheal suction
- Endotracheal suction

Start Antimicrobial based on

A. Clinical criteria.
B. CRP.
C. PCT.
D. sTREM.
E. All of the above.

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Start Antimicrobial based on

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Choose the initial antimicrobial(s) based on

A. Physician preference.
B. Price.
C. Culture and sensitivity results.
D. Risk factors, and Local antibiogram

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Choose the initial antimicrobial(s) based on

ⓘ Start presenting to display the poll results on this slide.

Risk Factors for MDR HAP/VAP

- Prior antimicrobial within 90 days
- 5 or more days of hospitalization prior to VAP
- Shock at presentation of VAP
- ARDS preceding VAP
- Associated acute renal failure with RRT

Risk factors for MRSA HAP, Pseudomonas HAP/VAP

Prior IV antimicrobials within 90 days.

Treatment in units where any of these organism has an incidence of 10% or more, OR the incidence is unkown.

Colonization with OR prior isolation of any of these organisms.

When to use 2 antipseudomonal drugs

1. Any of MDR risk factors.

2. In units where > 10% of Gram negative isolates are resistant to one of the used antimicrobials.

3. In units where the antibiogram is unavaialble.

4. If patient has structural lung disease favouring infections. Bronchiectasis, IPF, Cystic fibrosis.

Course

- Levofloxacin was started empirically after taking:
  - Nasotracheal sample
  - Blood culture sample

Mechanical ventilation

Was started due to progressive dyspnea and hypoxemia.

After 6 hours hypoxemia improved and FIO2 reduced from 1- 0.7

Mechanical Ventilation

- Day 2 another patch appeared on CXR
- FIO2 increased to 0.9
- PEEP increased to 12
- Noradrenaline introduced due to hyptension

Course

- BAL was done revealing inflamed mucosa and several mucus plugs.
- Lavage fluid was sent to culture
- Previous cultures were still negative

Change/ Add antimicrobial

- Add Imipenem/ Cilastatin
- Inhaled colistin/ Amikacin

CRE?

A. Colistin inhalation and Polymixin B IV.
B. Tigecycline
C. Combine colistin with Carbapenem
D. Aminoglycoside monotherapy
E. New Blactam/ BLactamases

History

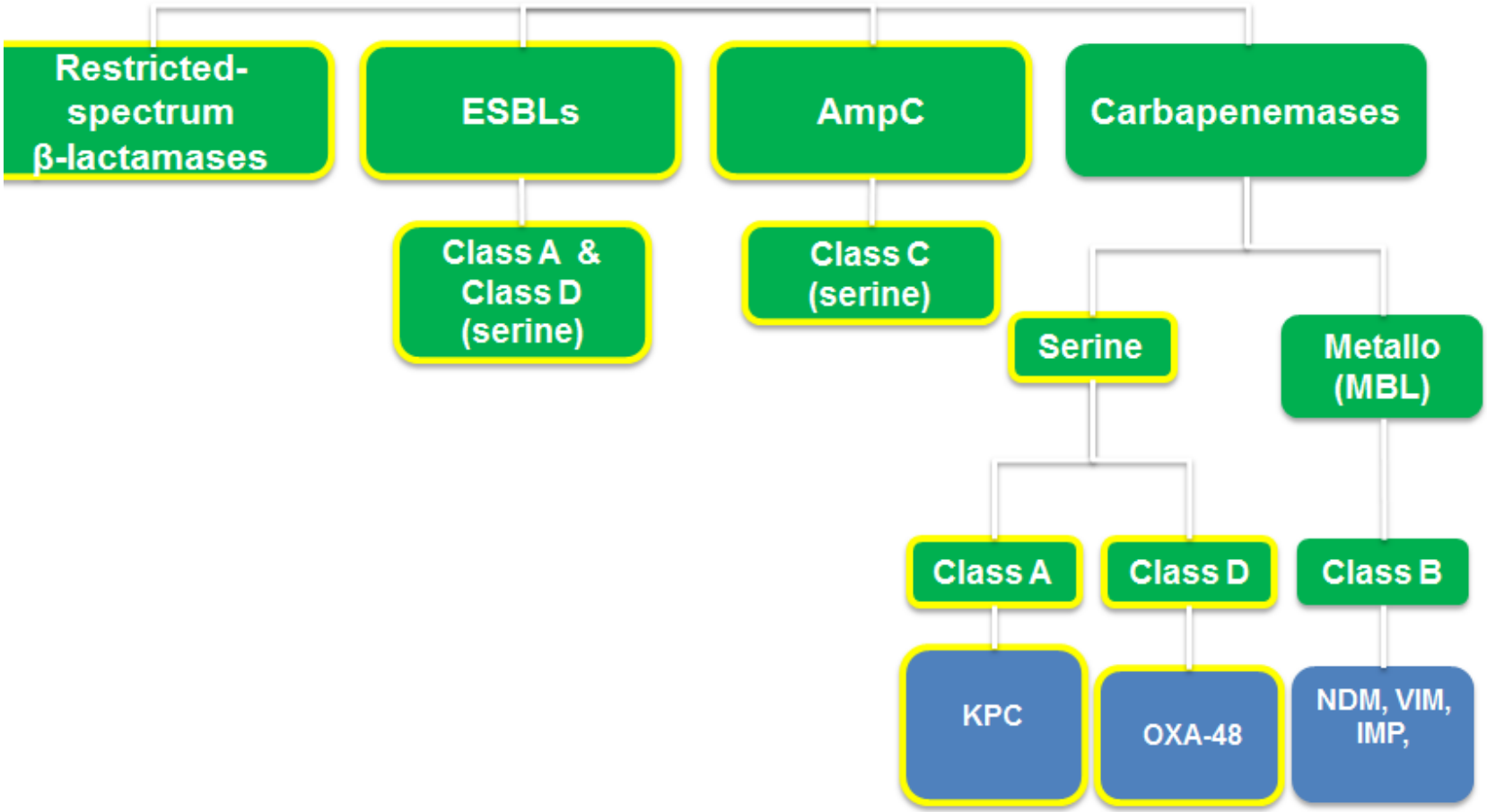
- 2000 KPC.
- 2005 K producing Oxacillinase OXA 48 Turkey.
- 2007 E. Coli New Delhi metallobetalactamases (NDM MBLs)

(Youhi D, CID: 2019)

Mechanisms of CR

- Hydrolyzing enzymes:
  - KPC
  - OXA
  - MBL
    - NDM
    - VIM
- Efflux pump upregulation. Pseudomonas
- Porin mutation. Pseudomonas

Beta Lactamases



Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Aztreonam-avibactam						
Cefiderocol						
Ceftazidime-avibactam[1]						
Ceftolozane-tazobactam[1]						
Eravacycline[1,2]						
Fosfomycin (intravenous)						
Imipenem-relebactam[3]						
Meropenem-vaborbactam[1]						
Plazomicin[1,4]						
Polymyxin B[1,5] or Colistin[1,5]						
Tigecycline[1,2]						

CEFTOLOZANE/TAZOBACTAM ACTIVITY VS *P. AERUGINOSA*

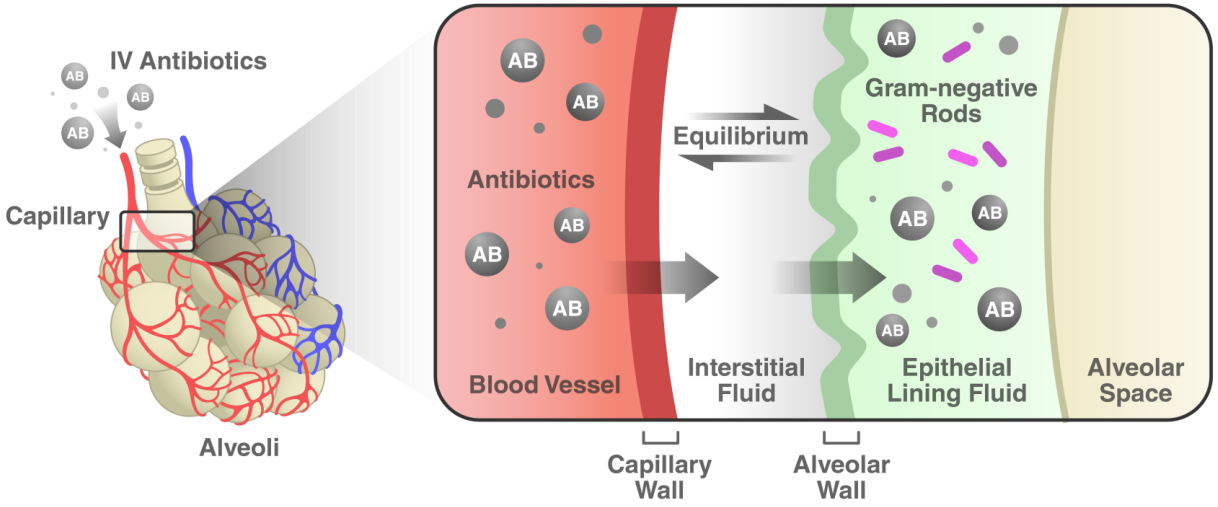
- Ceftolozane is stable against common *P. aeruginosa* resistance mechanisms, including loss of outer membrane porin (OprD), chromosomal AmpC, and up-regulation of efflux pumps (MexXY, MexAB)
- Isolates resistant to other cephalosporins may be susceptible, although cross-resistance may occur

Resistance Mechanisms	Outer Membrane Porin Loss	β-lactamase Enzyme	Efflux Pump	Efflux Pump
	OprD	AmpC	MexXY	MexAB
Ceftolozane	●	○	○	○
Ceftazidime	●	○	●	○
Cefepime	○	●	●	●
Piperacillin/tazobactam	◐	●	○	◐
Imipenem	●	●	●	●
Meropenem	●	●	●	●

○ **Activity greatly decreased > >** ● **Retains activity**

- **Castanheira M *et al.* Antimicrob Agents Chemother 2014;58:6844**

LUNG PENETRATION IS AN IMPORTANT CONSIDERATION IN TREATMENT SELECTION



Successful lung penetration expressed as ELF:plasma concentration ratio is critical in HABP/VABP treatment

AB, antibiotic; HABP, hospital-acquired bacterial pneumonia; IV, intravenous; VABP, ventilator-associated bacterial pneumonia.

1. Välitalo PAJ, et al. *Pharm Res*. 2016;33:856-867.

PATHOLOGICAL MODIFICATIONS IN THE LUNG OF PATIENTS ITH PNEUMONIA MAY INFLUENCE LUNG PENETRATION

Patient

Changes in lung may impact the ability to achieve target ELF concentrations[1]

Inflammatory responses to bacterial infections result in changes to lung parenchyma[1,2]

- Leakage at the alveolar-capillary membrane
- Serous exudate in alveoli
- Congested capillaries
- Fibrin deposits
- Accumulation of pathogens, neutrophils, and macrophages
- Thickened alveolar walls
- Suppurative and exudative-filled alveoli

ELF, epithelial lining fluid.

1. Jamal J-A, et al. *Clin Pulm Med*. 2013;20:121-128. **2**. Sattar SBA, Sharma S. Bacterial Pneumonia. StatPearls. Updated December 28, 2021. Accessed February 5, 2022.

AUGMENTED RENAL CLEARANCE IS PREVALENT IN CRITICALL ILL PATIENTS AND MAY IMPACT CLINICAL OUTCOMES

Patient

Augmented renal clearance[1-3]

Commonly seen in critically ill patients **(14%-80%)** and must be assessed

Individualized dosing based on PK/PD principles is recommended[1,2]

Increases probability of treatment success

Minimizes the emergence of resistance

Reduces adverse effects

Using conventional dosing regimens in critically ill patients can increase the likelihood of therapeutic failures[2]

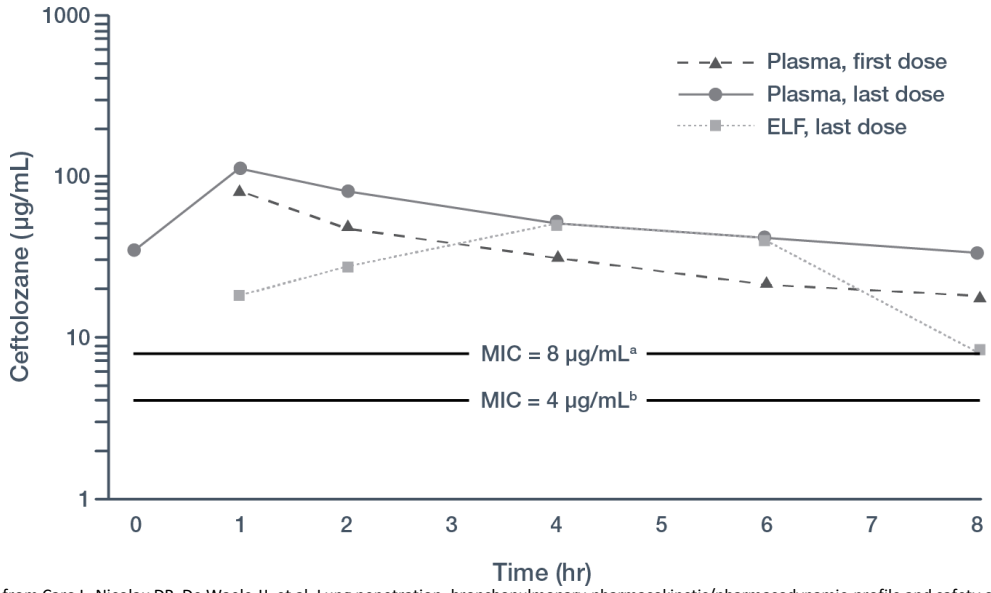
PD, pharmacodynamic; PK, pharmacokinetic.

1. Bilbao-Meseguer I, et al. *Clin Pharmacokinet*. 2018;57(9):1107-1121. **2.** Mahmoud SH, et al. *Pharmaceutics*. 2017;9(3):36. **3.** Roberts JA, et al. *Lancet Infect Dis.* 2014;14(6):498-509.

PK/PD DATA IN PATIENTS WITH PNEUMONIA RECEIVING MECHANICAL VENTILATION

Prospective, multicenter, open-label, phase 1 study

Ceftolozane concentration



Ceftolozane/tazobactam 3 g achieved therapeutic concentrations above MIC in the ELF over 100% of the dosing interval

Objective:

- To characterize the plasma PK, intrapulmonary penetration, and safety of Ceftolozane/tazobactam 3 g in critically ill patients with pneumonia receiving mechanical ventilation

Adapted from Caro L, Nicolau DP, De Waele JJ, et al. Lung penetration, bronchopulmonary pharmacokinetic/pharmacodynamic profile and safety of 3 g of ceftolozane/tazobactam administered to ventilated, critically ill patients with pneumonia. *J Antimicrob Chemother*. 2020;75(6):1546-1553. Available at https://academic.oup.com/jac/article-abstract/75/6/1546/5811380.

[a]The MIC of unbound ceftolozane for intermediate susceptible *P. aeruginosa* is 8 µg/mL.

[b]The MIC of unbound ceftolozane for *P. aeruginosa* is 4 µg/mL.

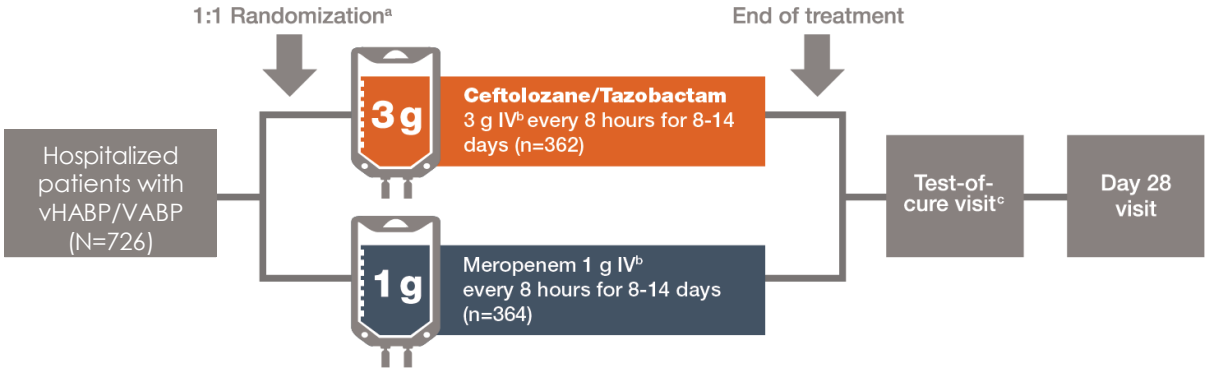
ELF, epithelial lining fluid; MIC, minimum inhibitory concentration; *P. aeruginosa, Pseudomonas aeruginosa*; PD, pharmacodynamic; PK, pharmacokinetic.

1. Caro L, et al. *J Antimicrob Chemother*. 2020;75(6):1546-1553.

The clinical data supporting (ceftolozane and tazobactam) in patients with HABP/VABP

ASPECT-NP: STUDY DESIGN

Phase 3, double-blind, multinational, noninferiority study



Primary efficacy end point:

- All-cause mortality at day 28

Secondary end point:

- Clinical response, defined as complete resolution or significant improvement in signs and symptoms of the index infection at the test-of-cure visit, which occurred 7 to 14 days after the end of treatment. The analysis population for both the primary and key secondary end points was the ITT population, which included all randomized patients

[a]Stratified by vHABP/VABP diagnosis and age (≥65 years and <65 years).
[b]Over a 1-hour period.
[c]7–14 days after the end of treatment.
ITT population included all randomized patients.
ASPECT-NP, Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia; ITT, intent-to-treat; IV, intravenous; VABP, ventilator-associated bacterial pneumonia; vHABP ventilated hosptial-acquired bacterial pneumonia.
1. Kollef MH, et al. *Lancet Infect Dis*. 2019;19(12):1299-1311.

- Why meropenem as comparator in ASPECT-NP

- Meropenem has a broad spectrum of activity against a range of bacterial organisms, including most of the expected pathogens for this indication
- Meropenem is generally considered one of the best available antibiotics for this indication, and appears in evidence-based guidelines as the first- line treatment option for nosocomial pneumonia
- Meropenem is recommended at a dose of 1 g every 8 hours by the ATS/IDSA for the treatment of HAP, including VAP and HCAP in patients with late-onset disease or risk factors for multidrug resistant pathogens

Kollef M *et al.* Lancet Infect Dis 2019;19:1299

ASPECT-NP: COMPARABLE BASELINE CHARACTERISTICS BET EEN ARMS

Baseline characteristic[1]	Ceftolozane/Tazobactam (n=362)	Meropenem (n=364)
Male, n (%)	262 (72)	255 (70)
Median age, y (range)	63 (50-72)	62 (49-73)
Creatinine clearance, mL/min, n[a] (%) ≥150 (augmented renal clearance) ≤50 to ≥15 <15	 67 (19) 52 (14) 0 (0)	 64 (18) 47 (13) 1 (<1)
In the ICU, n (%)	334 (92)	334 (92)
Mean APACHE II score (SD) ≥20, n (%)	17.5 (5.2) 124 (34)	17.4 (5.7) 115 (32)
Primary diagnosis, vHABP (%)	99 (27)	108 (30)
Failed current antibacterial therapy for vHABP/VABP[b] (%)	53 (15)	40 (11)

Patients were[1]:

- 100% ventilated (71.5% VABP; 28.5% vHABP)
- 92% in the ICU[1]
- Patients had a median baseline APACHE II score of 17.5, indicating ~24% mortality rate (1/3 of patients had a score of ≥20, a 40% mortality rate)[1,2]
- ~13% of patients were deteriorating on their current therapy[1]
- 14% of patients had moderate or severe renal impairment[1]

[b]Data were missing for 1 patient in the meropenem group.

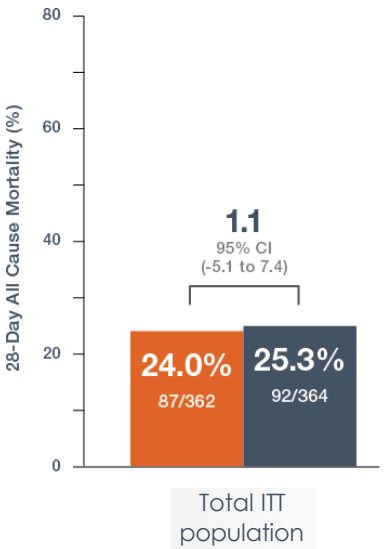
APACHE II, Acute Physiological Assessment and Chronic Health Evaluation II; ASPECT-NP, Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; SD, standard deviation; VABP, ventilator-associated bacterial pneumonia; vHABP, ventilated hospital-acquired bacterial pneumonia.

1. Kollef MH, et al. *Lancet Infect Dis*. 2019;19(12):1299-1311. **2.** Godinjak A, et al. *Acta Med Acad.* 2016;45(2):97-103.

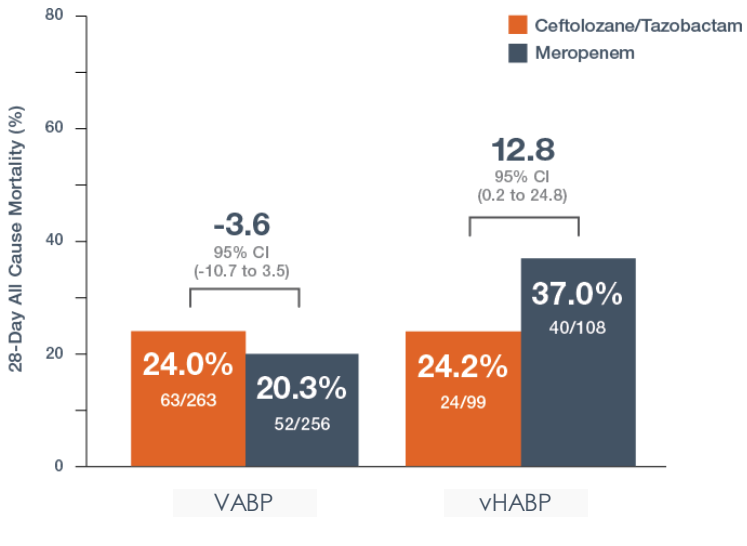
ASPECT-NP: DEMONSTRATED NONINFERIORITY VS MEROPENEM IN 28-DAY ALL-CAUSE MORTALITY

28-day all-cause mortality in the ITT population

Primary end point



Data by strata



In the vHABP subgroup of patients (~28.5%), there was a favorable response for ZERBAXA: 24.2% (24/99) versus 37.0% (40/108) for meropenem

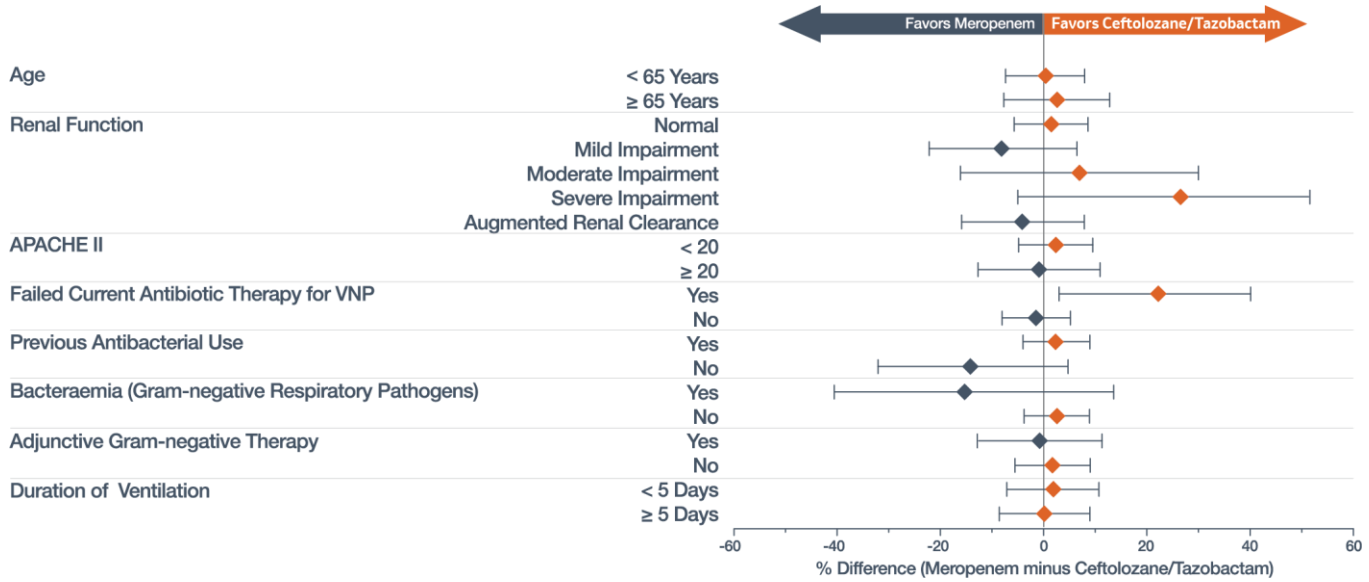
The analysis population for both the primary and secondary end points was the ITT population, which included all randomized patients.

ASPECT-NP, Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia; CI, confidence interval; ITT, intent-to-treat; VABP, ventilator-associated bacterial pneumonia; vHABP, ventilated hospital-acquired bacterial pneumonia.

1. Kollef MH, et al. *Lancet Infect Dis*. 2019;19(12):1299-1311.

ASPECT-NP: DAY 28 MORTALITY BY SELECT SUBGROUPS IN THE ITT POPULATION (ALL RANDOMIZED PATIENTS)

Results analyzed by subgroup were consistent with overall efficacy end points



Descriptive statistics are provided on selected subgroups to characterize an ITT population with severe nosocomial pneumonia (diagnosis of either VABP or ventilated HABP), and are not adjusted for multiplicity.

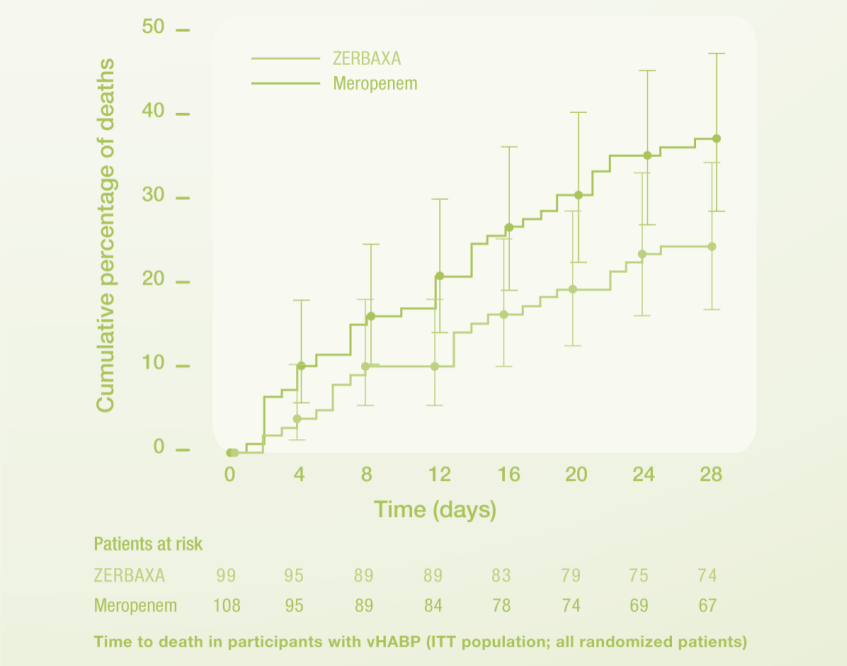
APACHE II, Acute Physiological Assessment and Chronic Health Evaluation II; ASPECT-NP, Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia; ITT, intent-to-treat; VABP, ventilator-associated bacterial pneumonia; vHABP, ventilated hospital-acquired bacterial pneumonia; VNP, ventilated nosocomial pneumonia.

1. Kollef MH, et al. *Lancet Infect Dis*. 2019;19(12):1299-1311.

ASPECT-NP: DAY 28 MORTALITY IN PATIENTS WITH VHABP

ZERBAXA showed a favorable mortality rate vs meropenem in adult patients with vHABP

Subgroup analysis ASPECT-NP



Time to death in participants with vHABP (ITT population; all randomized patients)

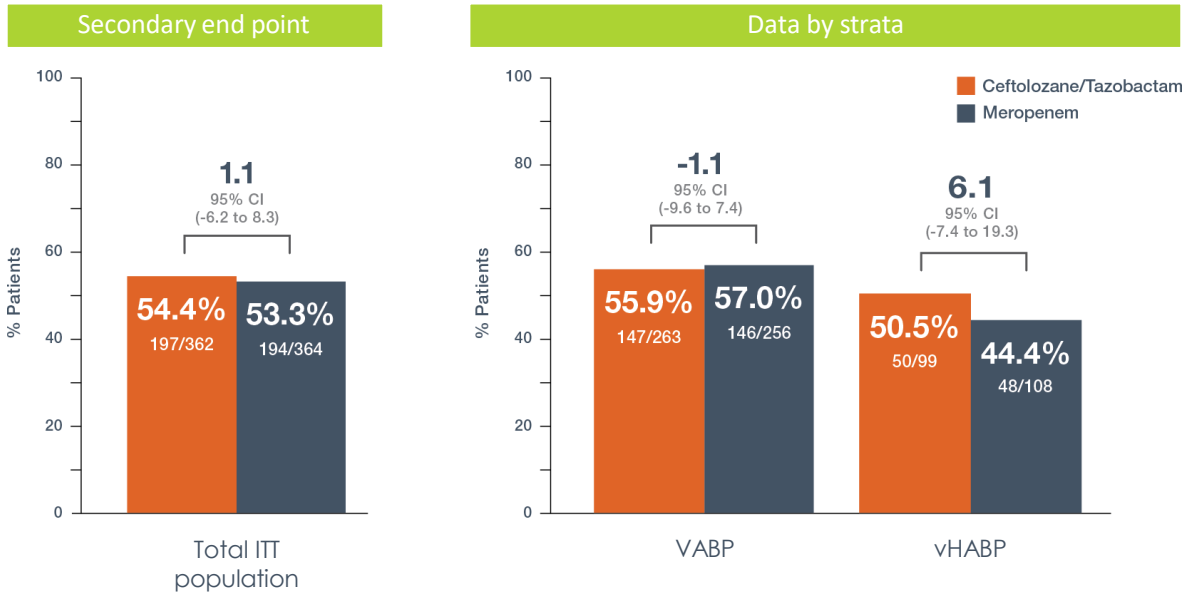
Treatment with Ceftolozane/Tazobactam showed a relative mortality difference of 34.6% compared to treatment with meropenem

ASPECT-NP, Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia; ITT, intent-to-treat; vHABP, ventilated hospital-acquired bacterial pneumonia.

1. Timsit JF, et al. *Crit Care.* 2021;25:290.

ASPECT-NP: DEMONSTRATED NONINFERIORITY VS MEROPENEM IN CLINICAL CURE RATES AT TEST OF CURE (TOC)

Clinical cure rates at TOC in the ITT population



The analysis population for both the primary and secondary end points was the ITT population, which included all randomized patients.

ASPECT-NP, Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia; CI, confidence interval; ITT, intent-to-treat; TOC, test-of-cure; VABP, ventilator-associated bacterial pneumonia; vHABP, ventilated hospital-acquired bacterial pneumonia.

1. Kollef MH, et al. *Lancet Infect Dis*. 2019;19(12):1299-1311.

ASPECT-NP: ADVERSE REACTIONS IN VHABP/VABP

Adverse event rates in the safety population		
	Ceftolozane/tazobactam[a] (n=361)	Meropenem (n=359)
At least one AE, n (%)	310 (86%)	299 (83%)
Severe	143 (40%)	136 (38%)
Serious	152 (42%)	129 (36%)
Leading to study discontinuation	37 (10%)	42 (12%)
Resulting in death	105 (29%)	101 (28%)
At least one treatment-related AE, n (%)	38 (11%)	27 (8%)
Severe	5 (1%)	3 (1%)
Serious	8 (2%)	2 (1%)
Leading to study discontinuation	4 (1%)	5 (1%)
Resulting in death	0	0

[a]The ZERBAXA dose was 3 g administered every 8 hours, adjusted to match renal function when appropriate.
Safety population comprised all randomized patients with ≥1 dose of study treatment, according to actual treatment received.
AE, adverse event; vHABP, ventilated hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.
1. Kollef MH, et al. *Lancet Infect Dis*. 2019;19(12):1299-1311.

ASPECT-NP: TREATMENT-RELATED ADVERSE EVENTS IN VHABP/VABP

Adverse event rates in the safety population		
Most frequent treatment-related AEs reported in ≥0.5% of the ZERBAXA group	Ceftolozane/tazobactam[a] (n=361)	Meropenem (n=359)
Clostridioides difficile colitis	4 (1%)	1 (<1%)
Diarrhea	4 (1%)	6 (2%)
Liver function test abnormal	12 (3%)	5 (1%)
AST increased	3 (1%)	3 (1%)
Gamma-glutamyltransferase increased	3 (1%)	0
ALT increased	2 (1%)	4 (1%)
Atrial fibrillation	2 (1%)	0
Clostridioides difficile infection	2 (1%)	1 (<1%)
Erythema	2 (1%)	0
Vomiting	2 (1%)	1 (<1%)

[a]The ZERBAXA dose was 3 g administered every 8 hours, adjusted to match renal function when appropriate.
Safety population comprised all randomized patients with ≥1 dose of study treatment, according to actual treatment received.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; VABP, ventilator-associated bacterial pneumonia; vHABP, ventilated hospital-acquired bacteria pneumonia.
1. Kollef MH, et al. *Lancet Infect Dis*. 2019;19(12):1299-1311.

IN REAL-WORLD EVIDENCE STUDIES, 30-DAY MORTALITY AND CLINICAL CURE RATES WERE CONSISTENT WITH DATA FROM THE ASPECT-NP TRIAL

Mortality[a]	Clinical success[b]
0.0%-33.0% (10 multi-patient studies, N=498)	51.4%-100% (17 multi-patient studies, N=494)

[a]Mortality rate included, but not limited to, all-cause, inpatient, or infection-related

[b]Clinical success is typically defined as resolution of signs or symptoms of respiratory tract infection following therapy and survival

This systematic literature review is subject to several limitations, including:

- Variability in reported outcomes
- Inclusion of non–peer-reviewed conference proceedings
- Potential duplication of data or double counting of patients across studies
- Small sample size and retrospective design of many of the studies
- Publication bias due to potential non-publication of negative results

ASPECT-NP, Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia.

1. Puzniak L, et al. *Infect Dis Ther.* 2021;10:1227-1252.

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0

Published by IDSA, 3/7/2022

A Focus on **Extended-Spectrum β-lactamase Producing Enterobacterales**, **Carbapenem-Resistant Enterobacterales**, and ***Pseudomonas aeruginosa* with Difficult-to-Treat Resistance**

Pranita D. Tamma*, Samuel L. Aitken, Robert A. Bonomo, Amy J. Mathers, David van Duin, Cornelius J. Clancy

Question 4: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*?

Recommendation: Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam, as monotherapy, are preferred options for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*.

Rationale

Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam, as monotherapy, are preferred options for the treatment of infections outside of the urinary tract, based on *in vitro* activity [139, 141, 177, 227-268], observational studies [269], and clinical trial data [101, 127, 270-276]. The vast majority of patients in clinical trials receiving the novel β-lactam-β-lactamase inhibitors were not infected with DTR-*P. aeruginosa*.

Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)

Recommendations on the choice of antibiotic treatment for CRPA

In patients with severe infections due to difficult to treat CRPA, we suggest therapy with ceftolozane-tazobactam if active *in vitro*. Insufficient evidence is available for imipenem-relebactam, cefiderocol and ceftazidime-avibactam at this time.	Conditional	Very low
In patients with non-severe or low-risk CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use the old antibiotics, chosen from among the *in vitro* active antibiotics on an individual basis and according to the source of infection.	Good practice statement	Expert opinion

Recommendations on combination therapy for CRPA

Lacking evidence, we cannot recommend for or against the use of combination therapy with the new BLBLI (ceftazidime-avibactam and ceftolozane-tazobactam) or cefiderocol for CRPA infections.	No recommendation	
When treating severe infections caused by CRPA with polymyxins, aminoglycosides, or fosfomycin, we suggest treatment with two *in vitro* active drugs. No recommendation for or against specific combinations can be provided.	Conditional	Very low
In patients with non-severe or low-risk CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use monotherapy chosen from among the drugs active *in vitro*, on an individual basis and according to the source of infection.	Good practice statement	Expert opinion

Combinations

Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy

Mario Tumbarello,[1] Pierluigi Viale,[2] Claudio Viscoli,[3] Enrico Maria Trecarichi,[1] Fabio Tumietto,[2] Anna Marchese,[4] Teresa Spanu,[5] Simone Ambretti,[6] Francesca Ginocchio,[3] Francesco Cristini,[2] Angela Raffaella Losito,[1] Sara Tedeschi,[2] Roberto Cauda,[1] and Matteo Bassetti[3,7]

[1]Institute of Infectious Diseases, Catholic University of the Sacred Heart, A. Gemelli Hospital, Rome; [2]Clinic of Infectious Diseases, University

Variable	No. (%) of Patients		*P* Value
	Nonsurvivors (n = 52)	Survivors (n = 73)	
Postantibiogram antimicrobial regimens			
Monotherapy	25 (48.1)	21 (28.7)	.02
Tigecycline	10 (19.2)	9 (12.3)	.28
Colistin	11 (21.5)	11 (15.1)	.37
Gentamicin	4 (7.6)	1 (1.3)	.09
Combination therapy	27 (51.9)	52 (71.2)	.02
2-drug combinations	23 (44.2)	33 (45.2)	.91
Tigecycline + colistin	7 (13.4)	16 (21.9)	.22
Tigecycline + gentamicin	6 (11.5)	6 (8.2)	.53
Other 2-drug combinations[e]	10 (19.2)	11 (15.1)	.54
3-drug combinations	4 (7.7)	19 (26.1)	.009
Tigecycline + colistin + meropenem	2 (3.8)	14 (19.2)	.009
Other 3-drug combinations[f]	2 (3.8)	5 (6.8)	.47
Inadequate initial antimicrobial treatment	39 (75)	36 (49.3)	.003
Presentation with septic shock	13 (25)	4 (5.5)	.002
APACHE III score (mean ± SD)	40 ± 22	24 ± 15	<.001

J Antimicrob Chemother 2015; **70**: 2133–2143
doi:10.1093/jac/dkv086 Advance Access publication 21 April 2015

Journal of Antimicrobial Chemotherapy

Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

Variable	All infections ($n=661$)	BSIs ($n=447$)	Non-bacteraemic infections ($n=214$)	*P* value
Treatment variables				
inadequate empirical antimicrobial treatment	365 (55.2)	279 (62.4)	86 (40.2)	<0.001
post-antibiogram antimicrobial therapy				
monotherapy	307 (46.4)	156 (34.9)	151 (70.6)	<0.001
combination therapy	354 (53.5)	291 (65.1)	63 (29.4)	<0.001
two-drug combination	134 (20.3)	93 (20.8)	41 (19.2)	0.62

J Antimicrob Chemother 2015; **70**: 2133–2143
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Journal of Antimicrobial Chemotherapy

Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

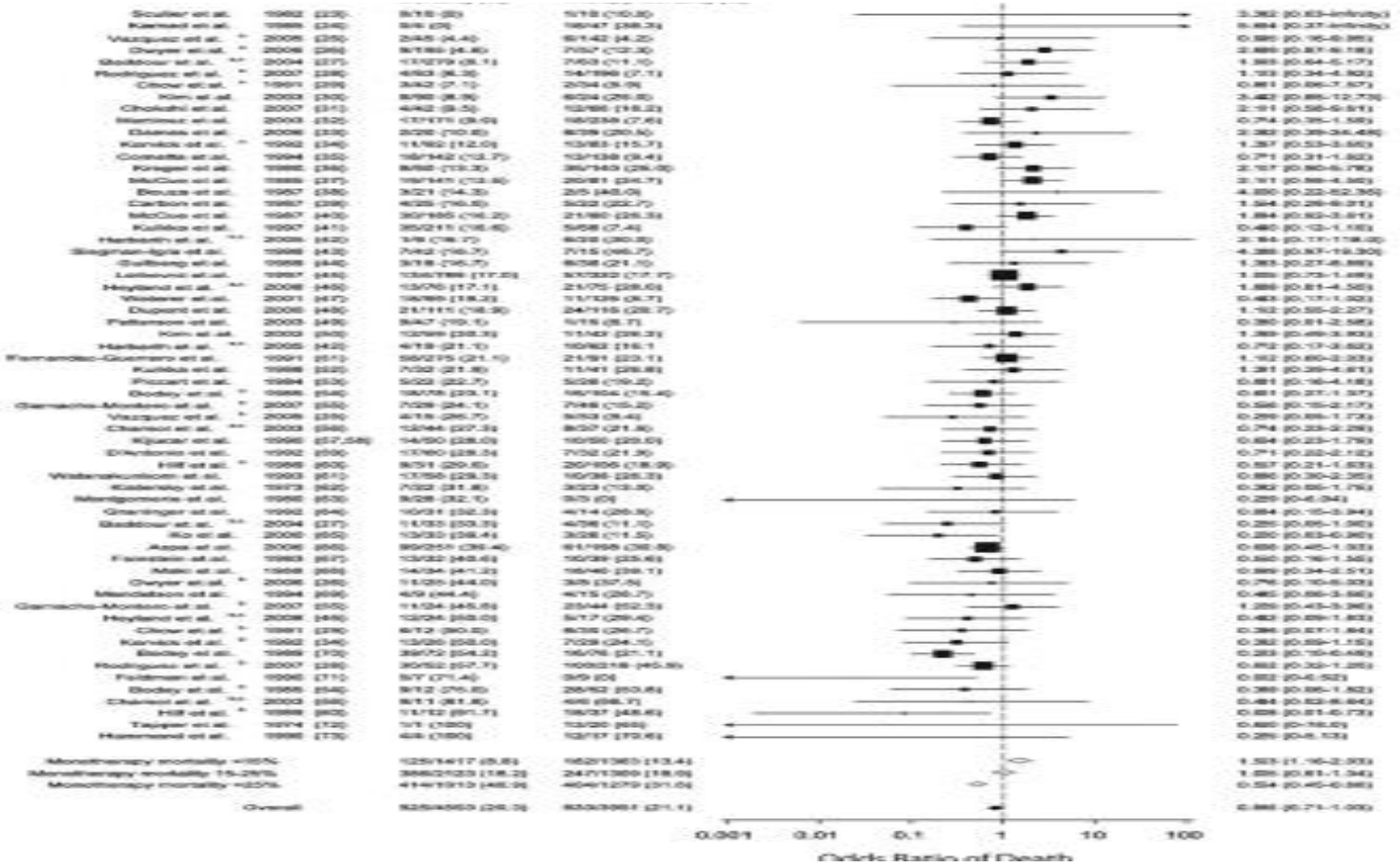
Variable	All infections ($n=661$)	BSIs ($n=447$)	Non-bacteraemic infections ($n=214$)	*P* value
three-drug combination	217 (32.8)	196 (43.8)	21 (9.8)	<0.001
combination including a carbapenem[d]	205 (31.0)	177 (39.6)	28 (13.1)	<0.001
double-carbapenem combination	8 (1.2)	8 (1.8)	0	0.049
combination without a carbapenem	149 (22.5)	114 (25.5)	35 (16.4)	0.008
combination plus rifampicin	12 (1.8)	6 (1.3)	6 (2.8)	0.19

	Numbers (%) of non-survivors				
	all	those who received combination therapy	those who received monotherapy	OR (95% CI)	*P*
Patient characteristics					
total	225/661 (34.0)	107/354 (30.2)	118/307 (38.4)	0.69 (0.49–0.97)	0.03
male	151/417 (36.2)	76/228 (33.3)	75/189 (39.7)	0.76 (0.50–1.16)	0.18
age >65 years	131/362 (36.2)	49/165 (29.7)	82/197 (41.6)	0.59 (0.37–0.94)	0.02
comorbidities					
COPD	57/106 (53.8)	24/48 (50.0)	33/58 (56.9)	0.76 (0.33–1.75)	0.48
cardiovascular disease	117/275 (42.5)	56/135 (41.5)	61/140 (43.6)	0.92 (0.55–1.52)	0.73
cerebrovascular disease or dementia	30/81 (37.0)	13/35 (37.1)	17/46 (37.0)	1.01 (0.36–2.75)	0.99
solid tumour	38/147 (25.8)	16/69 (23.2)	22/78 (28.2)	0.77 (0.34–1.72)	0.49
haematological malignancy	36/89 (40.4)	22/64 (34.4)	14/25 (56.0)	0.41 (0.14–1.17)	0.06
liver disease	30/72 (41.7)	13/37 (35.1)	17/35 (48.6)	0.57 (0.20–1.63)	0.25
solid organ transplantation	24/52 (46.1)	19/38 (50.0)	5/14 (35.7)	1.8 (0.43–8.10)	0.36
chronic renal failure	56/122 (45.9)	29/67 (43.3)	27/55 (49.1)	0.79 (0.36–1.72)	0.52
HIV infection or immunodeficiency	8/20 (40.0)	5/15 (33.3)	3/5 (60.0)	0.33 (0.02–4.17)	0.29
diabetes	70/168 (41.7)	39/90 (43.3)	31/78 (39.7)	1.16 (0.60–2.25)	0.64
neutropenia	26/70 (37.1)	17/52 (32.7)	9/18 (50.0)	0.48 (0.14–1.68)	0.19
Charlson comorbidity index ≥3	155/339 (45.7)	78/181 (43.1)	77/158 (48.7)	0.80 (0.51–1.25)	0.30
ward submitting index culture					
medical (all)	86/272 (31.6)	43/132 (32.6)	43/140 (30.7)	1.09 (0.63–1.88)	0.74
haematology	25/59 (42.4)	14/43 (32.6)	11/16 (68.7)	0.22 (0.05–0.87)	0.01
surgical (all)	50/159 (31.4)	22/81 (27.2)	28/78 (35.9)	0.66 (0.32–1.38)	0.23
transplants	7/18 (38.9)	3/10 (30.0)	4/8 (50.0)	0.43 (0.04–4.28)	0.39
ICU	89/230 (38.7)	42/141 (29.8)	47/89 (52.8)	0.38 (0.21–0.68)	<0.001
Infection characteristics					
BSI	173/447 (38.7)	93/291 (32.0)	80/156 (51.3)	0.45 (0.29–0.68)	<0.001
low-risk BSI	32/103 (31.1)	19/74 (25.7)	13/29 (44.8)	0.42 (0.16–1.16)	0.06
high-risk BSI	141/344 (41.0)	74/217 (34.1)	67/127 (52.8)	0.46 (0.29–0.74)	<0.001
non-bacteraemic infections (all)	52/214 (24.3)	14/63 (22.2)	38/151 (25.2)	0.85 (0.39–1.78)	0.65
lower respiratory tract	34/85 (40.0)	8/32 (25.0)	26/53 (49.1)	0.35 (0.11–0.99)	0.03
intra-abdominal	12/42 (28.6)	4/17 (23.5)	8/25 (32.0)	0.65 (0.12–3.16)	0.55
urinary tract	4/82 (4.9)	1/11 (9.1)	3/71 (4.2)	2.27 (0.04–31.22)	0.48
other	2/5 (40.0)	1/3 (33.3)	1/2 (50.0)	0.50 (0.004–78.17)	0.71
clinical presentation					
septic shock	57/100 (57.0)	30/67 (44.8)	27/33 (81.8)	0.18 (0.05–0.53)	<0.001
APACHE III score ≥15	208/481 (43.2)	98/267 (36.7)	110/214 (51.4)	0.55 (0.37–0.80)	0.001
KPC-Kp isolate characteristics					
colistin resistant	62/132 (47.0)	23/54 (42.6)	39/78 (50.0)	0.74 (0.35–1.58)	0.40
tigecycline resistant	51/152 (33.5)	29/91 (31.9)	22/61 (36.1)	0.83 (0.40–1.74)	0.59
gentamicin resistant	47/118 (39.8)	25/69 (36.2)	22/49 (44.9)	0.70 (0.31–1.57)	0.34
meropenem MIC ≤8 mg/L	79/243 (32.5)	43/154 (27.9)	36/89 (40.4)	0.57 (0.32–1.03)	0.04
meropenem MIC ≥16 mg/L	146/418 (34.9)	64/200 (32.0)	82/218 (37.6)	0.78 (0.51–1.19)	0.22
Inadequate empirical antibiotic therapy	144/365 (39.4)	71/212 (33.5)	73/153 (47.7)	0.55 (0.35–0.86)	0.006

	Numbers (%) of non-survivors				
	all	those who received combination therapy	those who received monotherapy	OR (95% CI)	*P*
total	225/661 (34.0)	107/354 (30.2)	118/307 (38.4)	0.69 (0.49–0.97)	0.03
ICU	89/230 (38.7)	42/141 (29.8)	47/89 (52.8)	0.38 (0.21–0.68)	<0.001
BSI	173/447 (38.7)	93/291 (32.0)	80/156 (51.3)	0.45 (0.29–0.68)	<0.001

A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A meta-analytic/meta-regression study

Anand Kumar, MD; Nasia Safdar, MD; Shravan Kethireddy, MD; Dan Chateau, PhD



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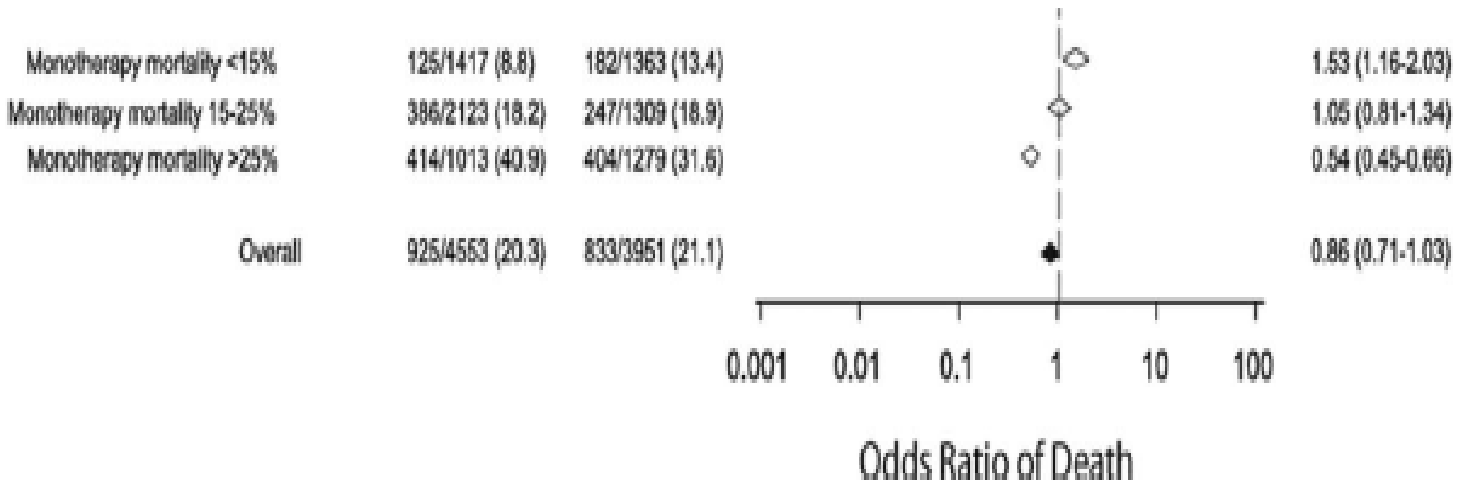
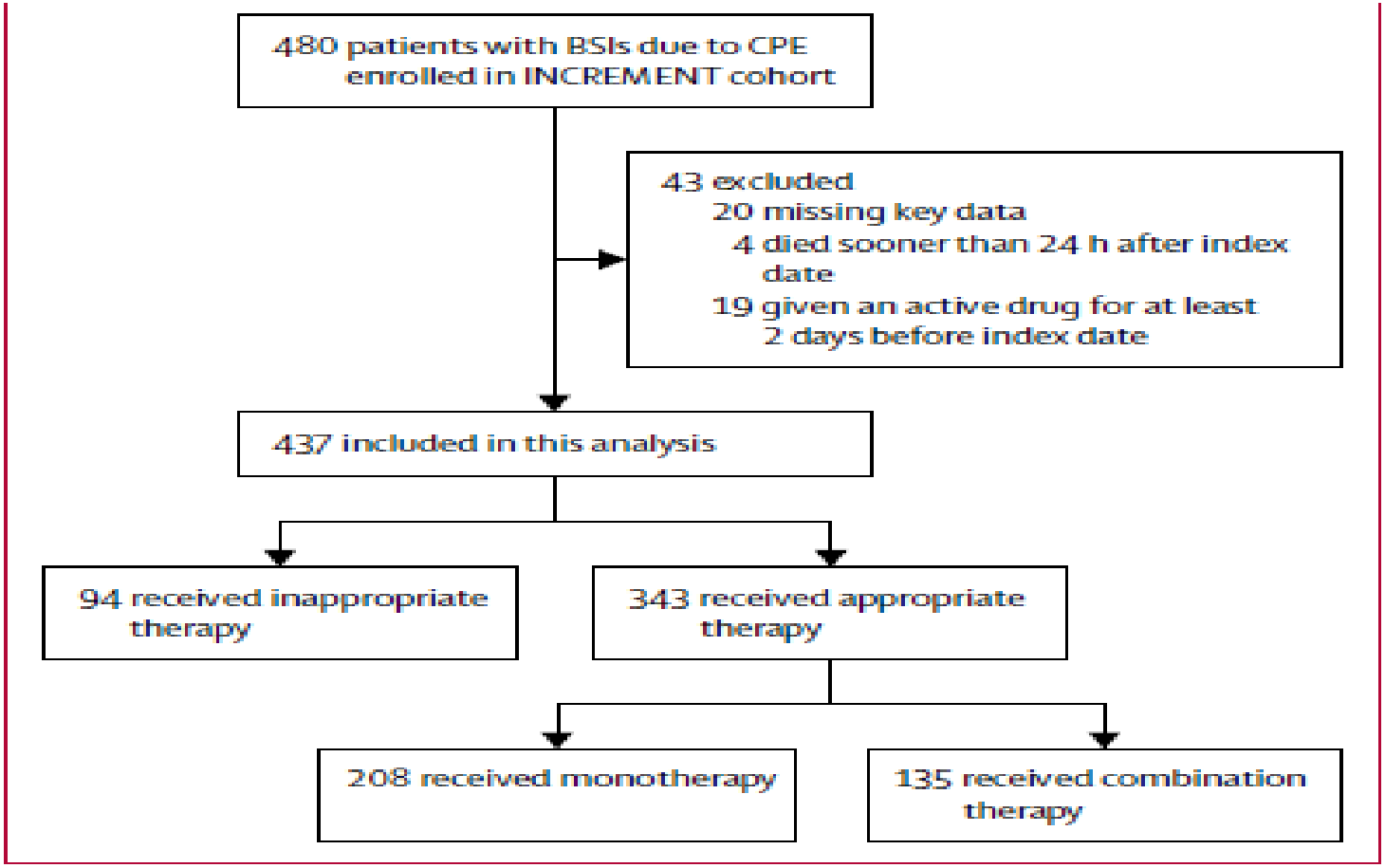
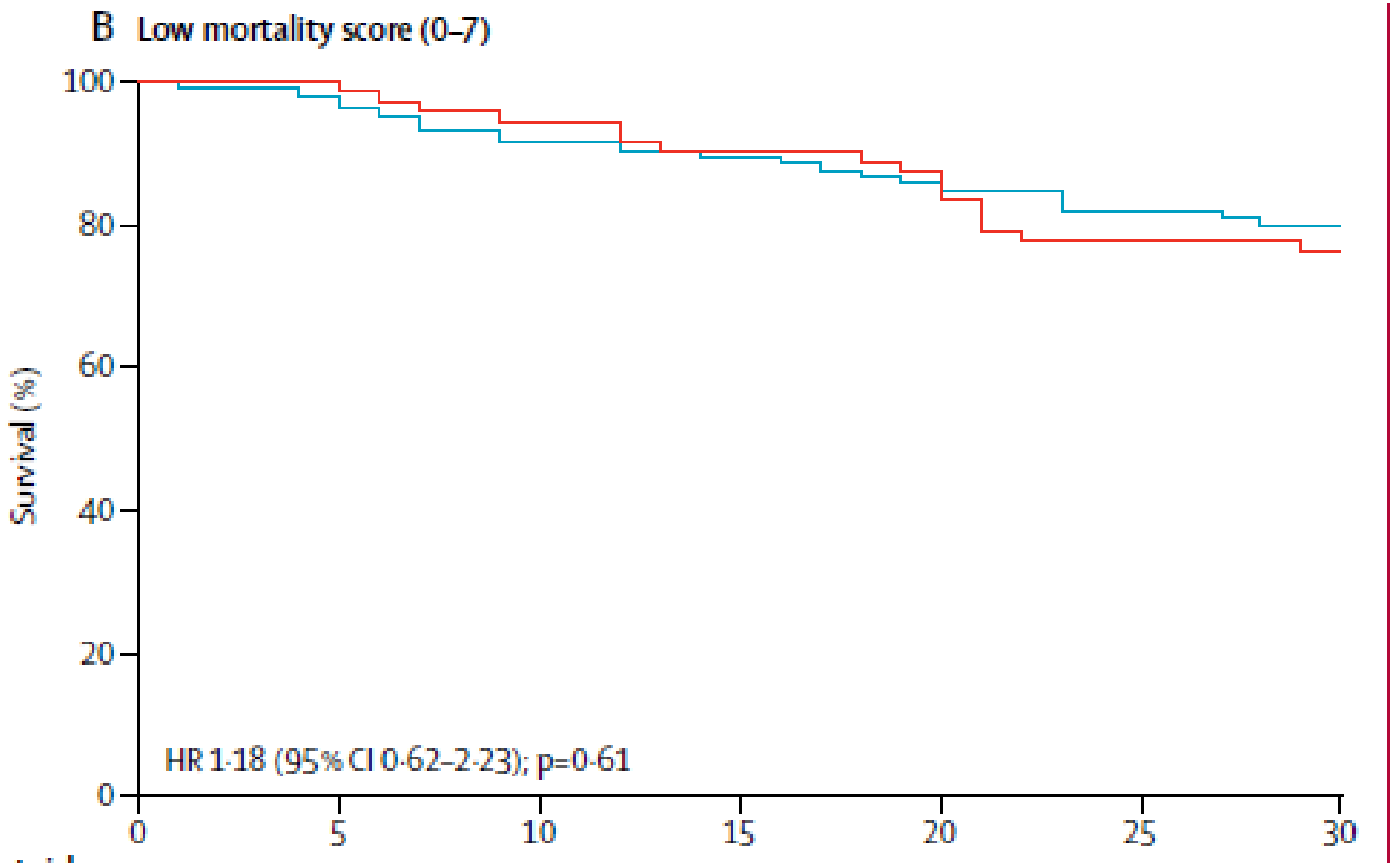


Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study



Low mortality scores



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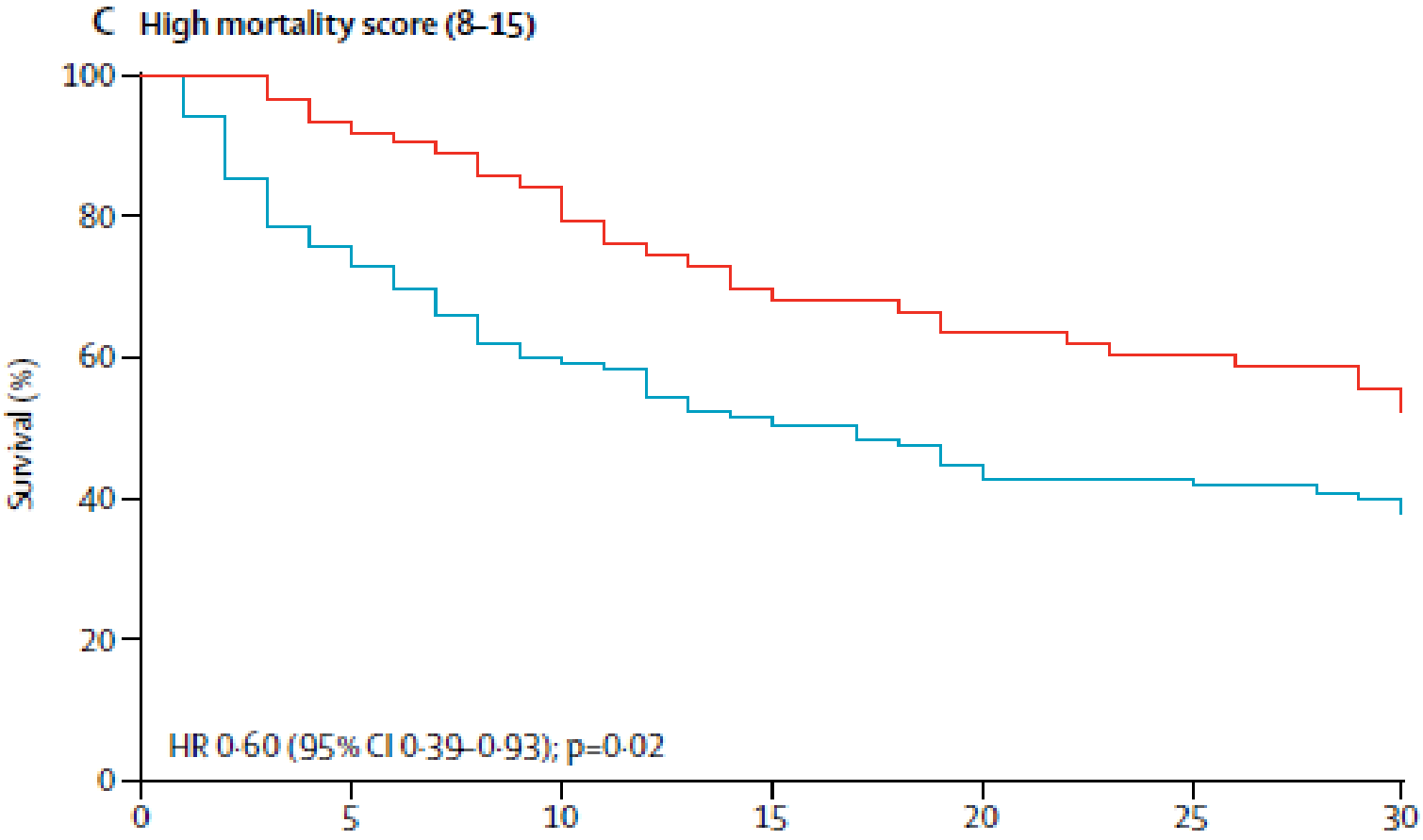

Steady Clinical improvement

- He went home after 2 weeks.

When to stop antimicrobials?

- 7 days
- Clinical, radiologic and lab parameters are more important than fixed time.
- You may add PCT to above parameters.

PCT in deescalation

- A single randomized trial (ProVAP) directly evaluated use of procalcitonin algorithms versus standard care in 101 patients with known or suspected VAP.
- In the procalcitonin group, stopping antibiotics when the procalcitonin level was <0.5 ng/mL or had decreased by ≥80 percent from peak resulted in a significant 27 percent reduction in antibiotic use (median 10 versus 15 days) without increasing adverse outcomes.