

Serious Infections Caused by Carbapenem Susceptible and Carbapenem Resistant *Acinetobacter baumannii-calcoaceticus* Complex – A Retrospective Review

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Abstract

Background: Increasing resistance to available antibiotics, including carbapenems, is limiting effective treatment options for serious *Acinetobacter baumannii-calcoaceticus* (ABC) complex infections that are associated with high mortality. This multi-center retrospective analysis is to describe the natural history and outcomes of serious ABC infections.

Materials/methods: This was a retrospective review of 125 cases of ABC infections from United States (US), Israel, Turkey and Russia. Baseline, microbiologic, treatment and outcomes data were collected from patients who were infected with hospital-acquired (HABP, n=23) or ventilator-associated bacterial pneumonia (VABP, n=26), bacteremia (n=36), urinary tract infection/acute pyelonephritis (n=16), and wound ABC infections (n=24) between 2017-2019.

Results: Fifty percent of cases reviewed were from the US. The median age of patients was 63 years (range 18-93), 46% were > 65 years old, 69% were male, 31% had renal failure, and 22% had septic shock. The most common co-morbidities observed were cardiac disease (41%), diabetes (32%) and moderate or severe renal disease (26%). Rates of resistance were observed as follows: ciprofloxacin 74%, ceftazidime 67%, amikacin 52% and colistin 0%. Carbapenem resistance (CR) was observed in 49% of patients. Most patients (73%) received combination therapy with 37% receiving at least 4 antibiotics. Carbapenems (40%) and penicillin/β-lactamase inhibitors (42%) were mostly used for treatment. Polymyxins were used in 18% of cases. Overall, the 28-day mortality was 34% and was highest in bacteremia (56%) and VABP (50%). CR appears to be a factor in mortality and other outcomes, as well as hospital days (table). In patients who received monotherapy, all 5 patients with CR infection died compared to 29% mortality in patients with carbapenem sensitive (CS) infection. Mortality was 70% in 20 cases when colistin was used for treatment.

Category	CR (n=60)	CS (n=63)
28-day Mortality	45%	24%
<i>A. baumannii</i> Eradicated	38%	56%
Clinical Cure	50%	63%
Hospital Days (mean)	16.9 d	13.7 d

Conclusions: Serious ABC infections are associated with substantial comorbidities and a high mortality rate despite treatment with combination therapy. CR appears to be a major factor in mortality. New antibiotics are urgently needed to treat serious ABC infections.

Introduction

- Acinetobacter baumannii-calcoaceticus* complex (ABC) is increasingly causing severe infections that are associated with high mortality in compromised hospital patients
- Increasing resistance to available antibiotics, including carbapenems, is limiting effective treatment options for serious ABC infections
- Many ABC isolates are either multi-drug resistant (MDR) or extremely drug resistant (XDR) which are susceptible to two or fewer classes of antibiotics
- Treatment options are also limited by antibiotics with poor pharmacokinetic properties and toxicity profiles
- This multi-center retrospective analysis describes the natural history and outcomes of serious ABC infections

Methods

Primary Objective

- To characterize ABC infections describing demographics, comorbidities, antimicrobial treatment, and outcomes

Secondary Objectives

- To describe the differences between patients with carbapenem-sensitive (CS) and carbapenem-resistant (CR) infections
- To compare the sensitivity of ABC isolates to antibiotics
- To assess the number of hospital days for ABC infections

Study Design

- An observational and retrospective analysis of 125 patients at 19 medical centers in the United States, Israel, Turkey and Russia between 2017-2019
- De-identified data was collected from chart reviews of patients (≥18years) infected with ABC and diagnosed with either hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), bacteremia, urinary tract infections or acute pyelonephritis (UTI/AP), and post-traumatic wound or surgical wound infections
- Clinical cure was defined as resolution of signs and symptoms

Microbiology

- Each clinical site conducted organism identification and susceptibility testing according to their own protocols
 - Isolates were considered “susceptible” or “resistant” to antimicrobial agents based on the reports by the local microbiology laboratories
 - Carbapenem-resistance was defined as resistant to imipenem and/or meropenem
- ### Data Collection
- Included baseline demographics and characteristics, medical histories, comorbidities, risk factors in the 90 days prior to diagnosis, antibiotic treatment for the index infection
 - The primary outcome was 28-day mortality and secondary outcomes included clinical cure, microbiologic eradication, and duration of hospitalization

Analyses

- Collected data was summarized and reported in aggregate form
- For CS and CR infections, data is described from 123 patients with *A. baumannii* at diagnosis

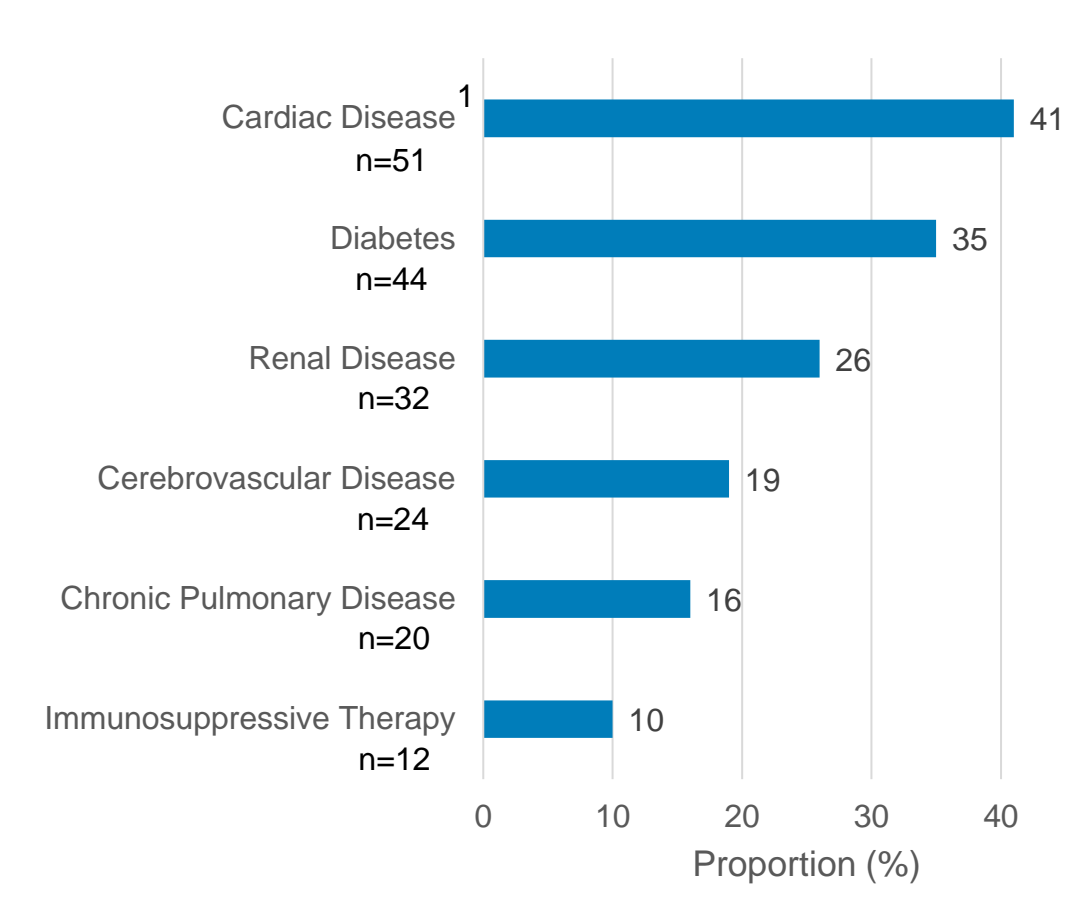
Results

Table 1. Baseline Characteristics by Infection Site

Category	Bacteremia (N=36)	HABP (N=23)	VABP (N=26)	UTI/AP (N=16)	Wound (N=24)	All (N=125)
ABC Identified at Diagnosis						
<i>Acinetobacter baumannii</i> , n (%)	36 (100)	23 (100)	26 (100)	15 (93.8)	23 (95.8)	123 (98.4)
<i>Acinetobacter calcoaceticus</i> , n (%)	0 (0)	0 (0)	0 (0)	1 (6.2)	1 (4.2)	2 (1.6)
Gender, n (%)	M 24 (66.7) F 12 (33.3)	M 15 (65.2) F 8 (34.8)	M 19 (73.1) F 7 (26.9)	M 11 (68.7) F 5 (31.3)	M 17 (70.8) F 7 (29.2)	M 86 (68.8) F 39 (31.2)
Age, years, mean (SD)	66.9 (18.6)	60.9 (19.6)	57.0 (14.3)	56.8 (18.8)	49.5 (17.0)	59.1 (18.5)
Country of Residence, n (%)						
Israel	17 (47.2)	1 (4.3)	3 (11.5)	0 (0)	0 (0)	21 (16.8)
Russia	4 (11.1)	6 (26.1)	8 (30.8)	1 (6.7)	7 (29.2)	26 (20.8)
Turkey	5 (13.9)	4 (17.4)	2 (7.7)	2 (12.5)	3 (12.5)	16 (12.8)
United States	10 (27.8)	12 (52.2)	13 (50.0)	13 (86.7)	14 (58.3)	62 (49.6)
Spent time in ICU, n (%)	5 (13.9)	3 (13.0)	10 (38.5)	3 (18.8)	2 (8.3)	23 (18.4)
Mechanically ventilated, n (%)	19 (52.8)	14 (60.9)	26 (100)	0 (0)	4 (16.7)	63 (50.4)
Septic shock at diagnosis, n (%)	15 (41.7)	2 (8.7)	7 (26.9)	0 (0)	3 (12.5)	27 (21.6)

Comorbidities and Risk Factors

Fig.2 Reported Comorbidities*



*A patient could have more than 1 comorbidity
 *Includes myocardial infarction and congestive heart failure

Fig.3 Risk Factors 90 Days Prior to Diagnosis

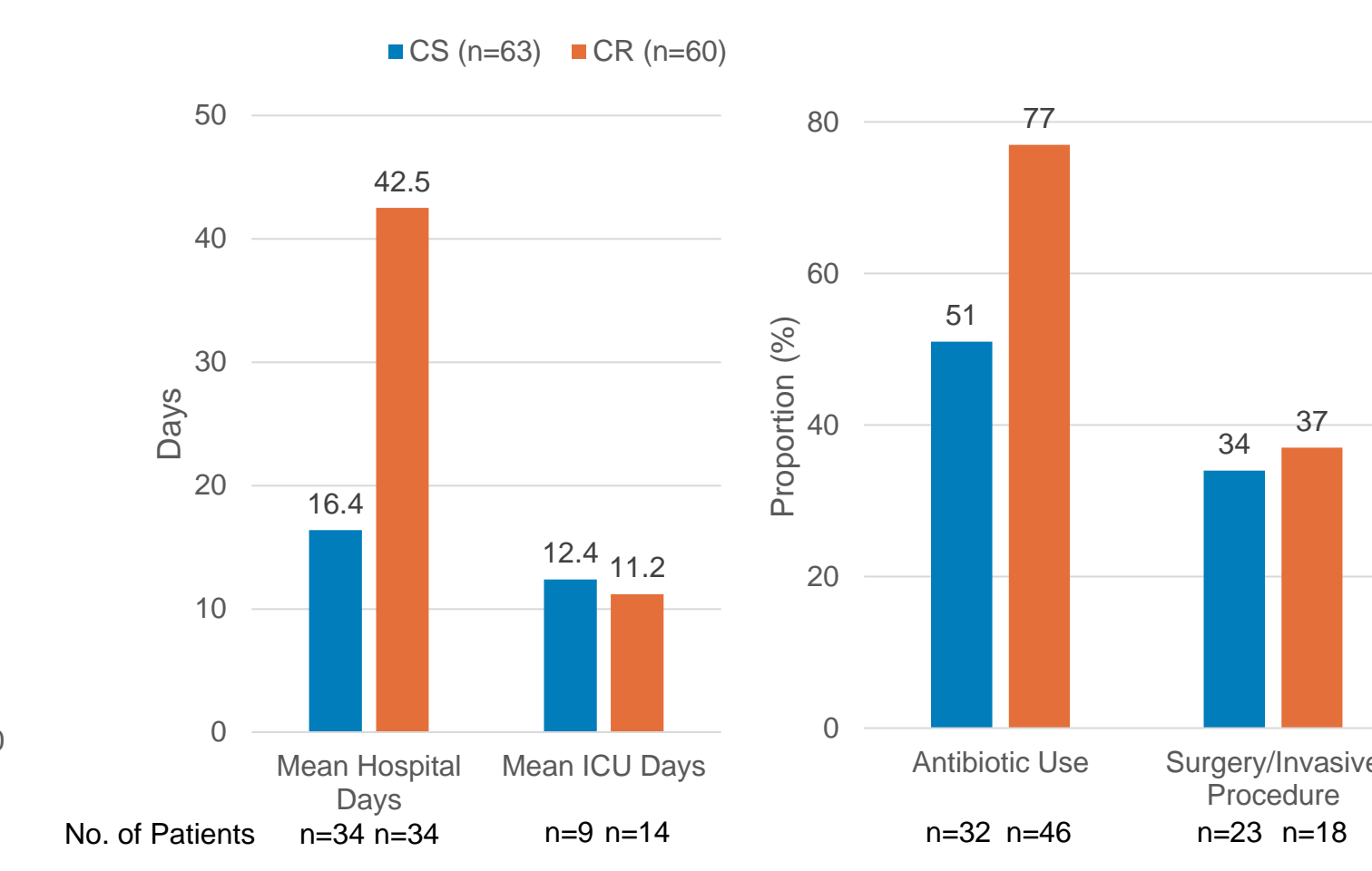
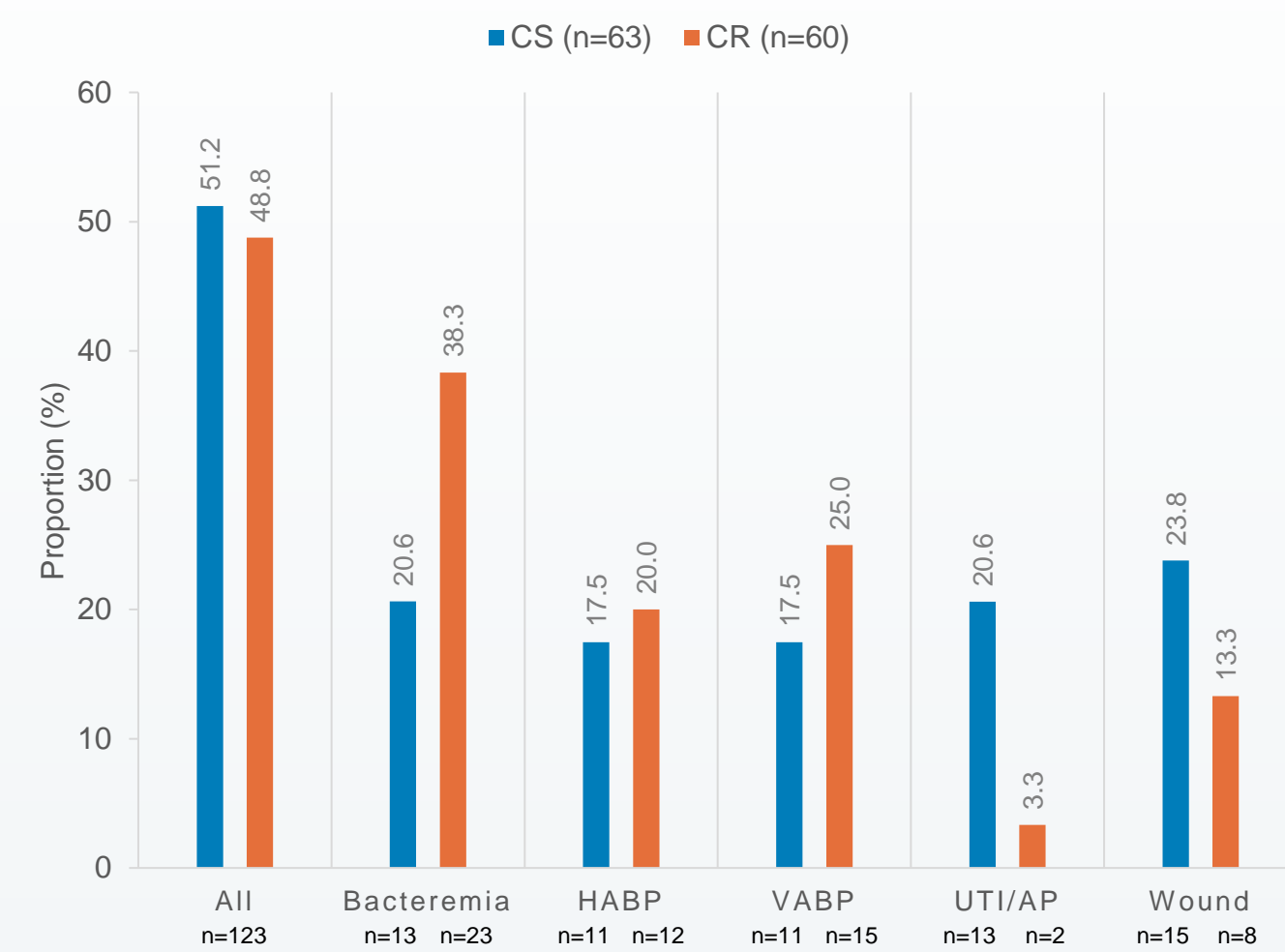


Fig.1 Distribution of CS and CR *A. baumannii* Infections



Incidence of CR infections was higher in bacteremia and pneumonia cases

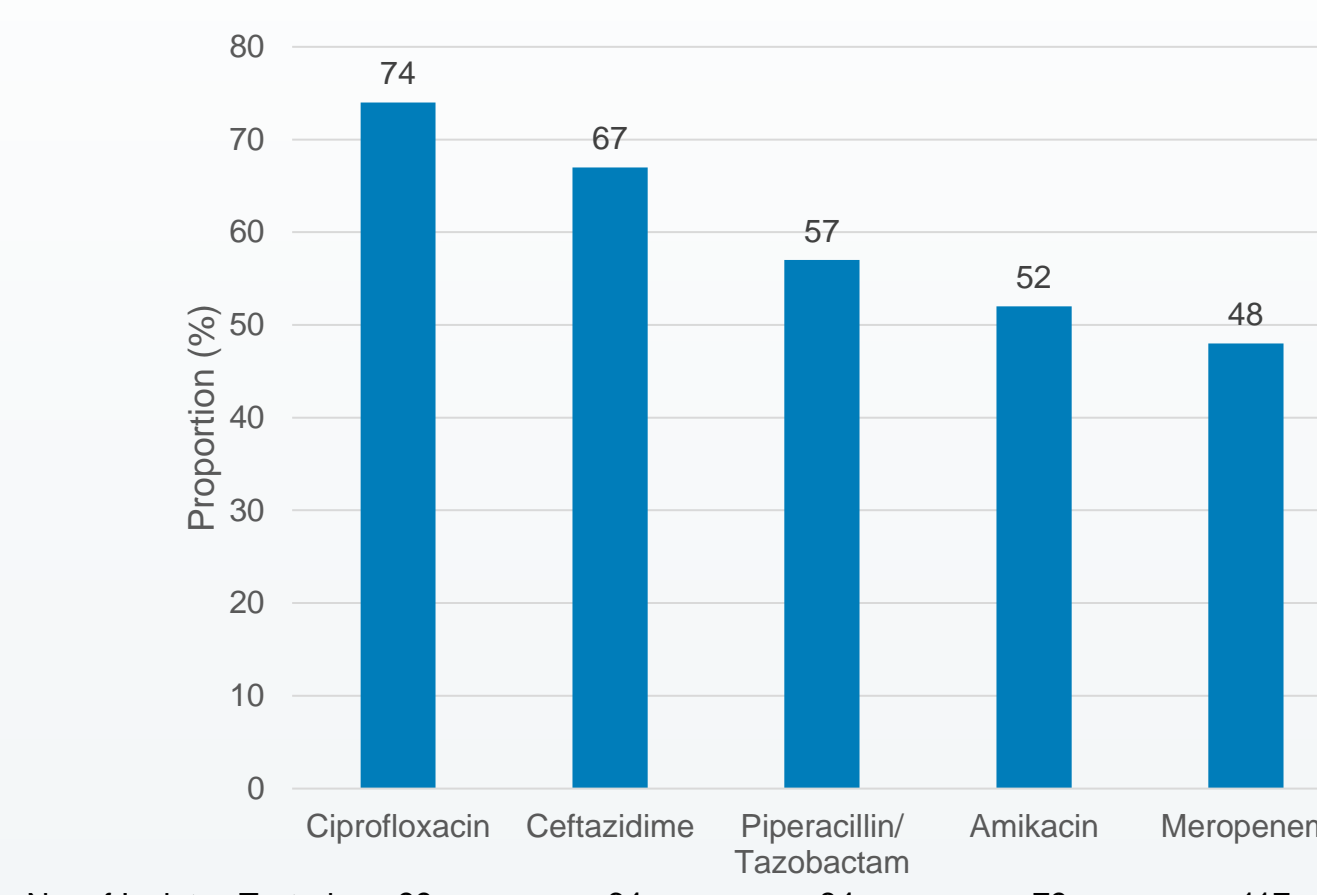
Table 2. Distribution of CR Infections by Country

Country	Patients, n/N (%)
Israel	20/21 (95.2)
Russia	16/26 (61.5)
Turkey	5/16 (31.3)
United States	19/62 (30.6)

Defined as resistant to imipenem and/or meropenem

Resistance

Fig.4 Rates of Resistance to All Isolates*



*Based on local microbiology lab reports. Only resistant isolates were recorded in the case report form

The vast majority of sites did not report on colistin resistance.

- 60 patients were reported to have carbapenem-resistant *A. baumannii* isolates (resistant to imipenem and/or meropenem)
- In this study, carbapenem-resistance is associated with resistance to other classes of antibiotics
- Of these carbapenem-resistant isolates,
 - 98% (59/60) were resistant to ciprofloxacin or levofloxacin
 - 85% (51/60) were resistant to β-lactams +/- β-lactamase inhibitor (ceftazidime, cefepime, ceftriaxone, cefotaxime or piperacillin/tazobactam)
 - 77% (46/60) were resistant to aminoglycosides (amikacin, gentamicin or tobramycin)

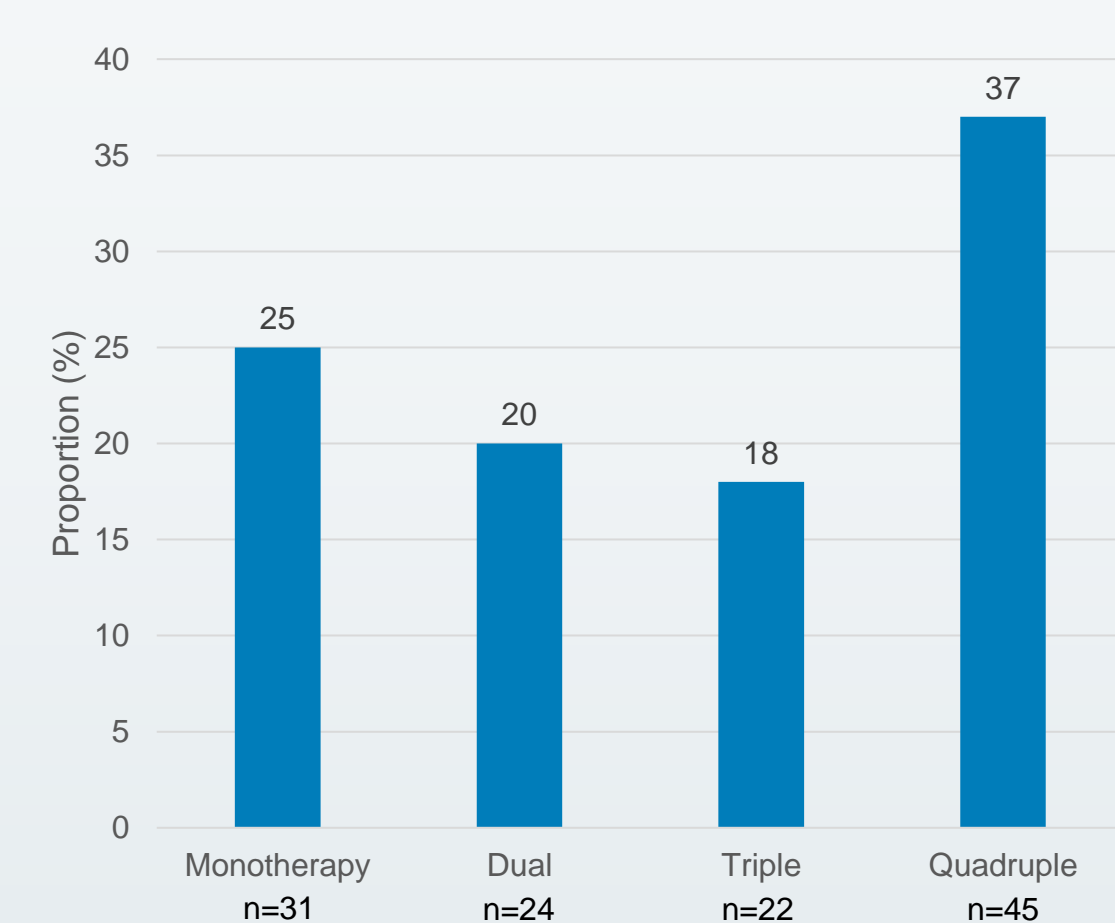
Antibiotic Treatment

Table 3. Antibiotics Used For Treatment

Antimicrobial Class	n (%)
Carbapenems	49 (40.2)
PCNs + BLIs	51 (41.8)
3G Cephalosporins	33 (27.0)
4G Cephalosporins	24 (19.7)
Fluoroquinolones	29 (23.8)
Polymyxins	22 (18.0)
Tetracyclines	27 (22.1)

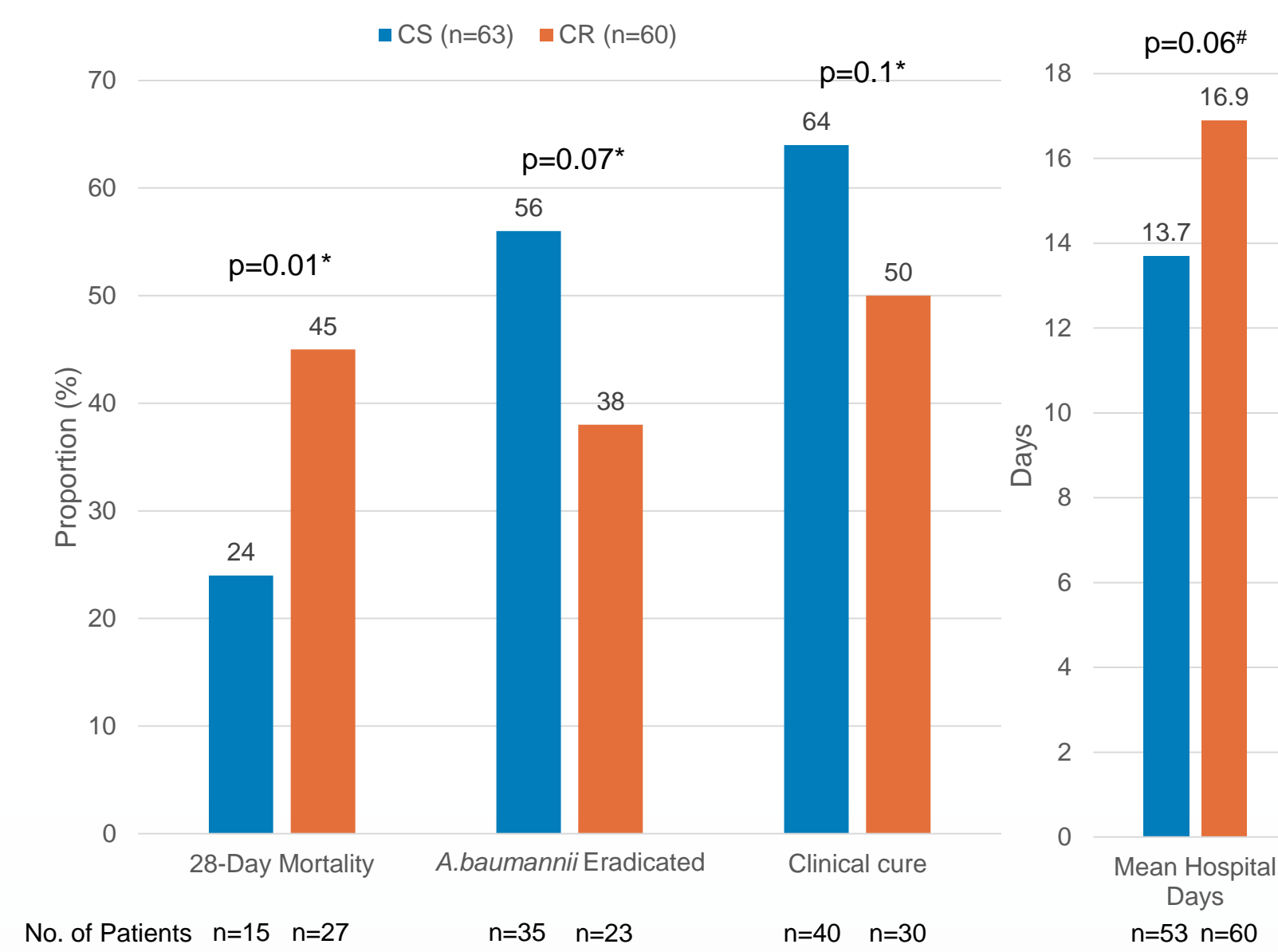
N=122 since 122/125 patients received antibiotic treatment
 PCN=penicillin; BLI=β-lactamase inhibitor; 3G=3rd generation; 4G=4th generation

Fig.5 Antibiotic Regimen For Treatment



Outcomes

Fig.6 Outcomes and Hospitalization by *A. baumannii* Carbapenem Susceptibility



* Fisher's Exact Test
 * t-test

- 28-Day mortality was:
 - 56% in bacteremia, 50% in VABP and 26% in HABP
 - 51% in mechanically-ventilated patients compared to 16% in non ventilated patients
 - 70% (14/20) in patients who received colistin for treatment
- Among patients treated with monotherapy, the likelihood of mortality was greater for patients with CR than CS infection (100% [5/5] vs 23% [6/26])
- The mortality among US patients was 15% compared to 56% in Ex-US patients; likely contributing to this was the difference in rates of carbapenem resistance

Conclusions

- Serious ABC infections are associated with substantial comorbidities and a high mortality rate despite treatment with combination therapy
- CR appears to be a major factor in mortality, other outcomes, and hospital days
- The majority of isolates that were resistant to carbapenem were also resistant to fluoroquinolones, β-lactams +/- β-lactamase inhibitors, and aminoglycosides
- Differences were observed in CR incidence and mortality between US and Ex-US regions
- New antibiotics are urgently needed to treat serious ABC infections

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