COVER PAGE

Title: *Acinetobacter baumannii* - related osteomyelitis: clinical and epidemiological characterization

NCT number: NCT03559530

Date: 08/18/2020

FINAL REPORT

Study title: *Acinetobacter baumannii* - related osteomyelitis: clinical and epidemiological characterization

Pfizer Tracking Number: WI176466

The initial database consisted of 262 patients with bone tissue culture positive for *Acinetobacter baumannii* submitted to surgical procedures to treat osteomyelitis at the *Instituto de Ortopedia e Traumatologia da HCFMUSP* from January 2007 to December 2015. From this total, it was possible to collect data for 171 patients for analysis. Here is a description of the reason for not including 91 patients:

- non-location of medical records: 44 patients;

- culture results were not considered for treatment: 29 patients;

- duplicate cases in the database: 8 patients;

- cultures showing other species of *Acinetobacter*: 7 patients;

- cultures harvested at the time of initial treatment of cases of exposed fractures and considered as contamination / colonization: 3 patients.

The descriptive analysis of the total sample (171 patients) and the result of the comparison between the cases of patients with extensively drug resistant (XDR) isolates treated with tigecycline and colistin (65 patients) are described in the following report and represents the largest case series of osteomyelitis related to *A. baumannii* ever described. The study protocol was registered in clinicaltrials.gov (NCT03559530).

1. Descriptive analysis of the Acinetobacter baumannii osteomyelitis database

1.1. Demographics of 171 patients (percentage and absolute numbers)

- Average age: 43.2 years
- Male sex: 78.4% (134)
- Any comorbidity present: 33.9% (58)
    - Sistemic hypertension: 21.1% (36)
    - Neoplasia: 3.5% (6)
    - Diabetes mellitus: 10.5% (18)
    - HIV infection: 1.2% (2)
    - Rheumatoid arthritis: 4.7% (8)
    - Systemic lupus erythematosus: 0.6% (1)
    - Other rheumatological conditions: 1,2% (2)
    - Use of immunosuppressive drugs: 3.5% (6)
- Epidemiological background
    - Smoking: 6.4% (11)
    - Alcohol abuse: 5.8% (10)
    - Ilicit drug use: 0.6% (1)
    - Previous surgical site infection in the affected segment: 25.1% (43)
    - Prior orthopedic surgery: 43.3% (74)
- Affected segment
    - Hip: 24.6% (42)

- Leg: 21.6% (37)
- Thigh: 15.8% (27)
- Spine: 14.6% (25)
- Foot and ankle: 9.4% (16)
- Knee: 8.2% (14)
- Arm: 2.3% (4)
- Forearm: 1.8% (3)
- Hand and wrist: 1.2% (2)
- elbow: 0.6% (1)

• Co-infection agents present: 72.5% (124)

- *S. aureus*: 19.4% (24)
- Coagulase-negative *Staphylococcus* spp.: 19.4% (21)
- *Klebsiella pneumoniae*: 16.1% (20)
- *Pseudomonas aeruginosa*: 17.7% (22)
- *Candida* spp .: 0.8% (1)
- *Enterococcus* spp .: 28.2% (35)

• Antibiogram of *A. baumannii* isolates for the 171 patients included (table 1).

Table 1 –Antibiogram for *A. baumannii* samples from the 171 patients included.

Antimicrobial	**Susceptibility**	**Not tested**
Amikacin	61,4% (105)	0,6% (1)
Ampicillin/sulbactam	43,3% (74)	0% (0)
Cefepime	15,8% (27)	1,2% (2)
Ceftazidime	14% (24)	5,8% (10)
Ciprofloxacin	14,6% (25)	5,8% (10)
Imipenem	35,1% (60)	0,6% (1)
Meropenem	33,3% (57)	4,1% (7)
Colistin	63,7% (109)	33,9% (58)
Tigecycline	47,4% (81)	38% (65)
Gentamicin	58,5% (100)	0% (0)

Table 2 and Figures 1 to 7 below show the evolution of the susceptibility profiles of *A. baumannii* isolates against the main antimicrobials tested during the period in which the patients included in the study were treated. Tigecycline is not included in this analysis because A. baumannii susceptibility to this antimicrobial was extrapolated from breakpoints for enterobacteria during the study period, according to Clinical and Laboratory Standards Institute (CLSI) criteria.

Table 2 – Percentage of *A. baumannii* isolates susceptible to main antimicrobials tested during the study period

	Amikacin	Ampi/Sulb	Cefepime	Ceftazidime	Ciprofloxacin	Carbapenem	Gentamicin
2007	29	79	14	14	14	43	50
2008	23	73	14	9	9	55	45
2009	29	59	18	18	12	47	76
2010	79	37	5	11	11	37	53
2011	58	27	19	15	15	27	65
2012	80	50	25	20	25	45	55
2013	84	29	16	16	16	26	68
2014	91	18	9	9	9	9	36
2015	82	18	18	9	18	18	64

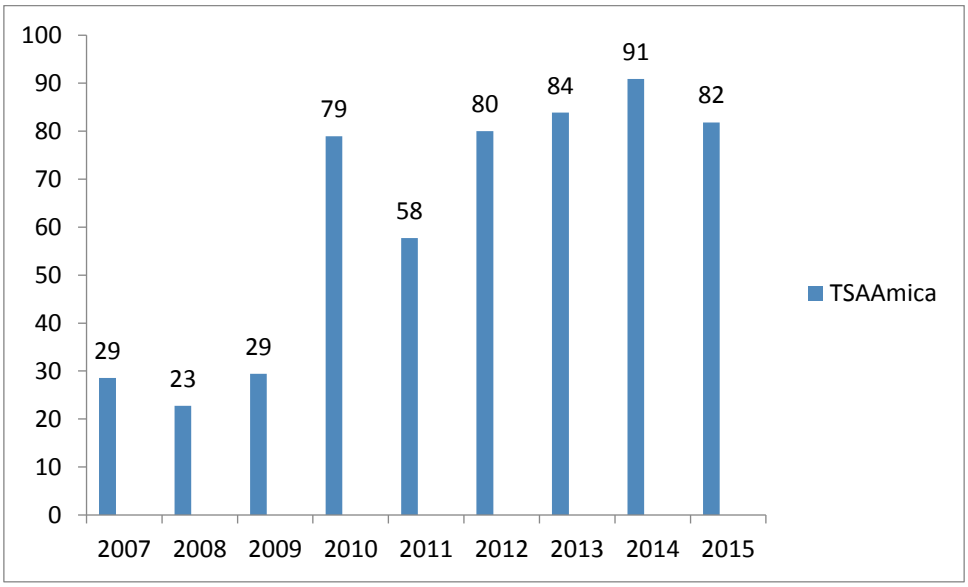

Figure 1 – Evolution of the susceptibility profile of isolates of *A. baumannii* to amikacin over study period

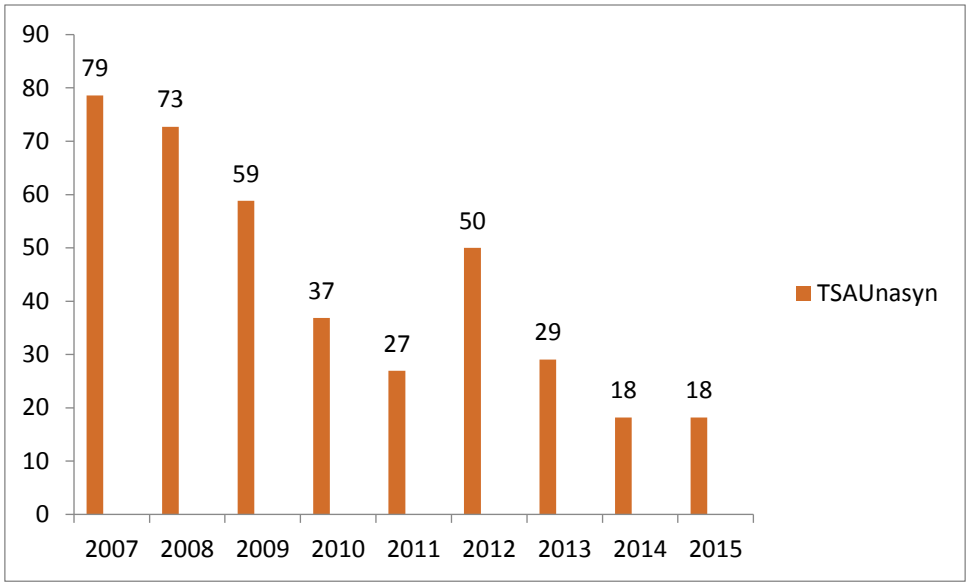

Figure 2 – Evolution of the susceptibility profile of isolates of *A. baumannii* to ampicillin/sulbactan over study period

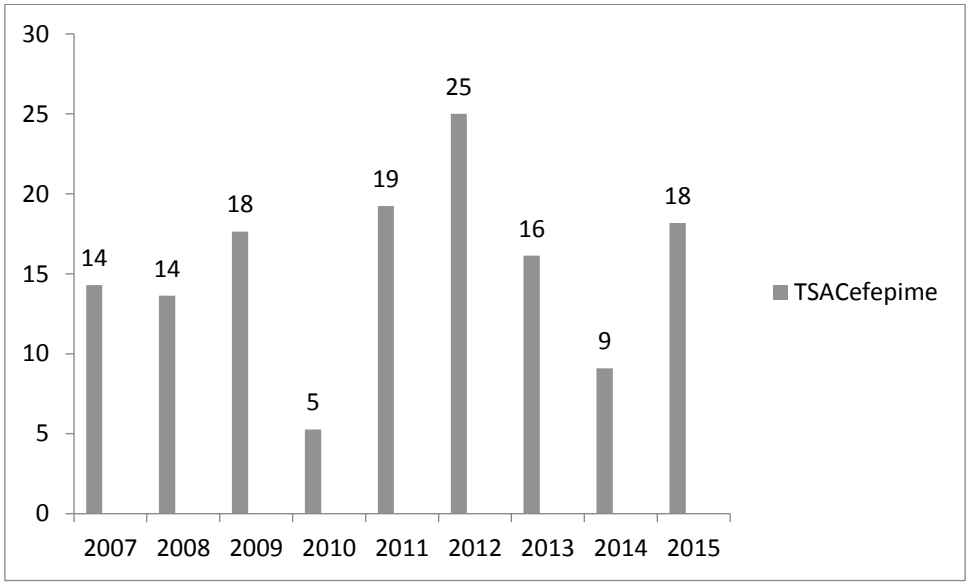

Figure 3 – Evolution of the susceptibility profile of isolates of *A. baumannii* to cefepime over study period

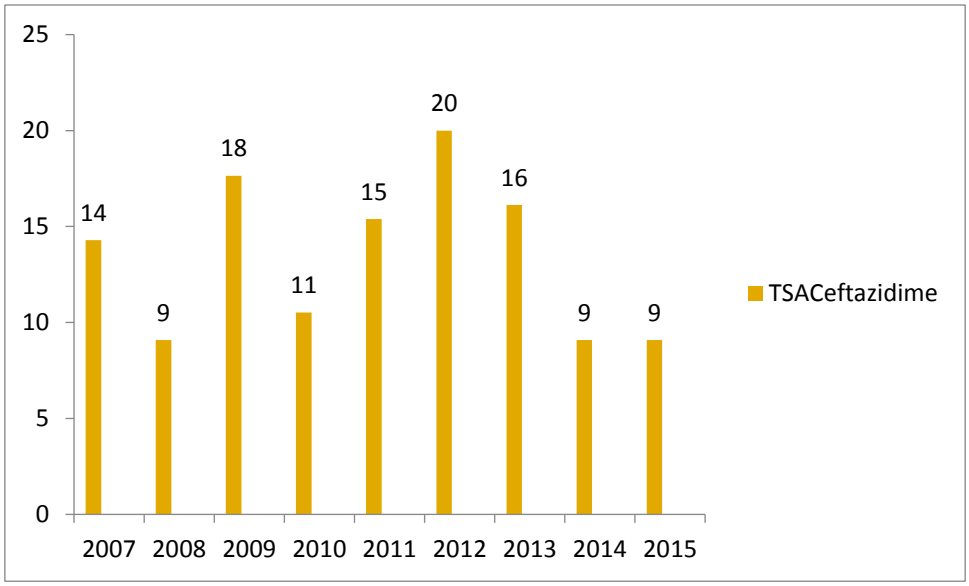

Figure 4 – Evolution of the susceptibility profile of isolates of *A. baumannii* to ceftazidime over study period

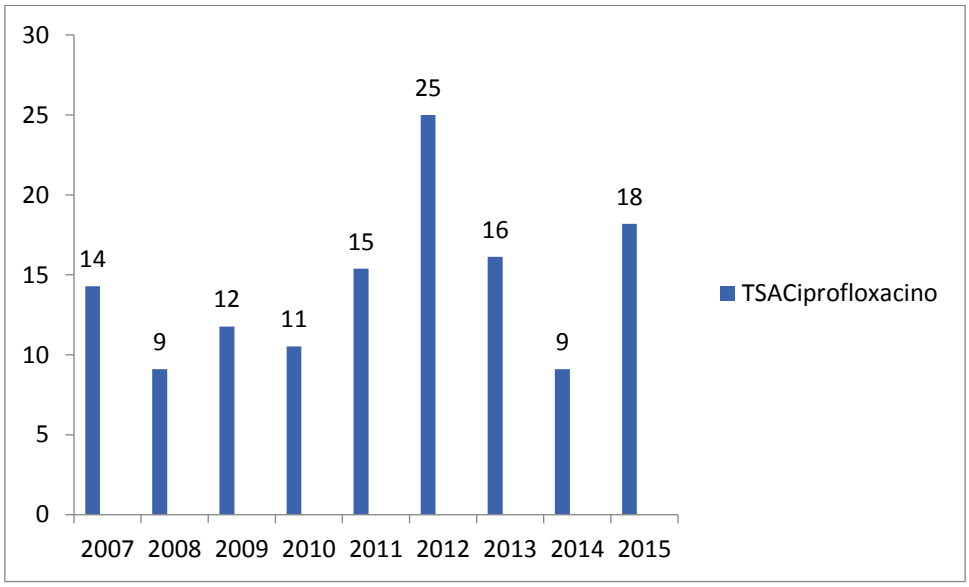

Figure 5 – Evolution of the susceptibility profile of isolates of *A. baumannii* to ciprofloxacin over study period

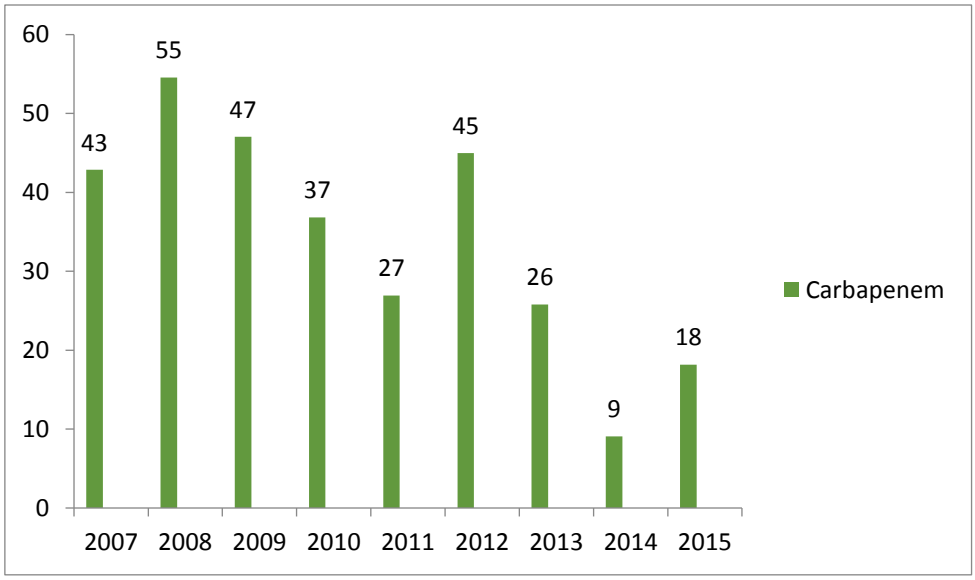

Figure 6 – Evolution of the susceptibility profile of isolates of *A. baumannii* to carbapenems (imipenem and meropenem) over study period

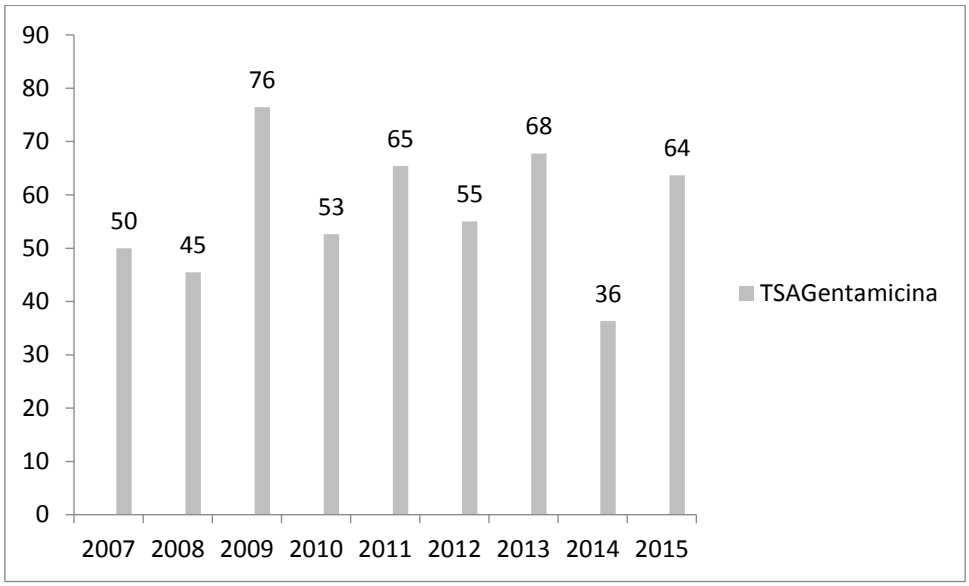

Figure 7 – Evolution of the susceptibility profile of isolates of *A. baumannii* to gentamicin over study period

- Classification of osteomyelitis
    - Post traumatic: 64.9% (111)
    - Contiguous: 29.8% (51)
    - Spine osteomyelitis: 2.9% (5)

- Hematogenic: 2.3% (4)
- Acute: 52.6% (90)
- Chronic: 47.4% (81)

• Previous open fracture: 36.8% (63). Open fracture classification according to Gustilo and Anderson

- No registeredclassification : 22.2% (14)
- II: 4.8% (3)
- IIIa: 14.3% (9)
- IIIb: 44.4% (28)
- IIIc: 14.3% (9)

• Neuropathic foot infection: 2.9% (5)

• Decubitus ulcer infection: 16.4% (28)

• Closed fracture: 9.4% (16)

• ASA score:

- ASA I: 35.1% (60)
- ASA II: 51.5% (88)
- ASA III: 13.5% (23)

• need for muscle or skin flap repair during osteomyelitis treatment: 32.2% (55)

• Negative pressure therapy: 25.1% (43)

• Hyperbaric oxygen therapy: 1.2% (2)

• Average number of surgical procedures for treatment: 3.5

- Antimicrobial use
    - Prior to diagnosis of *A. baumannii* infection: 90.6% (155)
    - Use of combination therapy (two active drugs) for *A. baumannii*: 2.9% (5)
    - Treatment groups:
        - **Colistin: 19.9% (34)**
        - Ampicillin / Sulbactam: 18.7% (32)
        - **Tigecycline: 18.1% (31)**
        - Aminoglycosides: 15.2% (26)
        - Quinolone: 14% (24)
        - Carbapenem: 10.5% (18)
        - Aminoglycoside + tigecycline: 1.2% (2)
        - Aminoglycoside + Colistin: 0.6% (1)
        - 3th and 4th generation cephalosporins: 0.6% (1)
        - Sulfamethoxazole / trimethoprim: 0.6% (1)
        - Tigecycline + Colistin: 0.6% (1)
- OPAT: 14% (24)
- Average length of antimicrobial treatment time: 72.6 days
- Average length of hospital stay: 77.9 days
- Adverse events
    - Some adverse event: 21.6% (37)
    - Change of microbial drug due to adverse event: 3.5% (6)

• Outcome

- After 1 year (favorable X unfavorable)
    - Favorable: 53.8% (92)
- After 1 year (detailed)
    - Remission: 53.8% (92)
    - Relapse: 15.2% (26)
    - Amputation: 14.6% (25)
    - Loss of follow-up: 12.3% (21)
    - Death related to *A. baumannii* infection: 3.5% (6)
    - Death not related to *A. baumannii* infection: 0.6% (1)

2. Comparative analysis of cases of osteomyelitis by A. baumannii XDR treated with either colistin or tigecycline

For this analysis, the 65 patients with XDR A. baumannii -related osteomyelitis, always resistant to carbapenems, treated with colistin or tigecycline were included. The choice of antimicrobial was at the discretion of the attending physicians responsible for each patient during their hospitalization and was not influenced by this study, since this is a retrospective analysis.

Baseline characteristics of each group were compared, according to :

- demographic variables and clinical characteristics already described above,
- tincidence of adverse events related to the treatment and
- outcomes of the patients according to the antimicrobial used.

Quantitative characteristics were described according to groups using summary measures (mean ± standard deviation or median (minimum; maximum) and compared between groups using Student's t-tests or Mann-Whitney tests. Qualitative characteristics of the patients

were described according to groups using absolute and relative frequencies, association between groups were tested using chi-square or exact tests (Fisher's exact test or likelihood ratio test). The software used for the analysis was Microsoft-SPSS for Windows version 20.0. Microsoft Excel 2003 was the software used for data tabulation. Tests were performed at a significance level of 5%.

Table 3 shows the distribution of the 65 patients according to each treatment group (colistin or tigecycline) regarding demographic variables and clinical characteristics. In the group of patients treated with tigecycline, the frequency of men was statistically lower than in the group treated with colistin (p = 0.028). In the group of patients treated with tigecycline, there were also predominance of smokers (p = 0.021) and patients with chronic osteomyelitis (p = 0.036).

Table 3 - Distribution of patients with XDR *A. baumannii* osteomyelitis according to demographic and clinical characteristics and comparison according to treatment group (colistin or tigecycline).

Variable	Treatment group		Total (N = 65)	p
	Colistin (N = 34)	Tigecycline (N = 31)		
Sex (Male)	29 (85,3)	19 (61,3)	48 (73,8)	**0,028**
Age (years)	40,6 ± 19,1	46,8 ± 18,9	43,6 ± 19,1	0,193**
Length of hospital stay (days)	74,5 (13; 331)	64 (0; 226)	70 (0; 331)	0,948£
Charlson index	0 (0; 5)	1 (0; 7)	0 (0; 7)	0,083£
Presence of comorbidity	10 (29,4)	13 (41,9)	23 (35,4)	0,292
Systemic hypertension	6 (17,6)	9 (29)	15 (23,1)	0,277
Neoplasia	2 (5,9)	3 (9,7)	5 (7,7)	0,663*
Diabetes	4 (11,8)	2 (6,5)	6 (9,2)	0,674*
HIV	0 (0)	2 (6,5)	2 (3,1)	0,224*
Rheumatoid arthritis	2 (5,9)	1 (3,2)	3 (4,6)	>0,999*
Systemic lupus erythematosus	0 (0)	0 (0)	0 (0)	a
Ankylosing spondylitis	0 (0)	0 (0)	0 (0)	a
Other rheumatic diseases	0 (0)	1 (3,2)	1 (1,5)	0,477*
Use of immunosuppressive drugs	1 (2,9)	1 (3,2)	2 (3,1)	>0,999*
Chemotherapy	0 (0)	0 (0)	0 (0)	a
Chronic Renal Disease	0 (0)	0 (0)	0 (0)	a
Previous SSI in the affected segment	10 (29,4)	7 (22,6)	17 (26,2)	0,531
Injectable drug abuse	0 (0)	1 (3,2)	1 (1,5)	0,477*
Smoking	0 (0)	5 (16,1)	5 (7,7)	**0,021***
Alcohol abuse	2 (5,9)	4 (12,9)	6 (9,2)	0,413*
Previous orthopedic surgery in the affected segment	10 (29,4)	14 (45,2)	24 (36,9)	0,189
Affected Segment				0,414
Lower limbs	29 (85,3)	24 (77,4)	53 (81,5)	
Upper limbs	5 (14,7)	7 (22,6)	12 (18,5)	
Other agents detected	24 (70,6)	21 (67,7)	45 (69,2)	0,804

Classification of osteomyelitis Lima and Zumiotti				0,841#
Post-traumatic	23 (67,6)	19 (61,3)	42 (64,6)	
Contiguity	7 (20,6)	9 (29)	16 (24,6)	
Hematogenic	2 (5,9)	2 (6,5)	4 (6,2)	
Spine	2 (5,9)	1 (3,2)	3 (4,6)	
Time classification of osteomyelitis				**0,036**
Acute	22 (64,7)	12 (38,7)	34 (52,3)	
Chronic	12 (35,3)	19 (61,3)	31 (47,7)	
Antecedent of open fracture	17 (50)	10 (32,3)	27 (41,5)	0,147
Infection in pressure ulcer	6 (17,6)	4 (12,9)	10 (15,4)	0,736*
Antecedent of closed fracture	1 (2,9)	4 (12,9)	5 (7,7)	0,184*
ASA Classification				0,189
I	11 (32,4)	8 (25,8)	19 (29,2)	
II	20 (58,8)	15 (48,4)	35 (53,8)	
III	3 (8,8)	8 (25,8)	11 (16,9)	
Number of surgical procedures for treatment	3 (1; 12)	3 (1; 9)	3 (1; 12)	0,510£
Presence of implant	6 (17,6)	3 (9,7)	9 (13,8)	0,480*
Need to remove the implant	4 (11,8)	9 (29)	13 (20)	0,082
Need for soft tissue repair	10 (29,4)	8 (25,8)	18 (27,7)	0,746
Use of negative pressure therapy	12 (35,3)	6 (19,4)	18 (27,7)	0,151
Hyperbaric oxygen use	1 (2,9)	0 (0)	1 (1,5)	>0,999*
Pain	6 (17,6)	7 (22,6)	13 (20)	0,619
Hyperemia	9 (26,5)	4 (12,9)	13 (20)	0,172
Local elevated temperaure	2 (5,9)	1 (3,2)	3 (4,6)	>0,999*
Fistula	19 (55,9)	19 (61,3)	38 (58,5)	0,659
Edema	1 (2,9)	4 (12,9)	5 (7,7)	0,184*
Fever	4 (11,8)	9 (29)	13 (20)	0,082
Use of antimicrobial before A. baumannii infection	34 (100)	30 (96,8)	64 (98,5)	0,477*
Other antimicrobials used	29 (85,3)	23 (74,2)	52 (80)	0,264
Need for OPAT	4 (11,8)	9 (29)	13 (20)	0,082
Baseline Creatinine	0,69 ± 0,36	0,82 ± 0,54	0,75 ± 0,45	0,260**
Full treatment lenght (days)	42,5 (1; 193)	42 (9; 193)	42 (1; 193)	0,438£

Data expressed as n (%), mean ± SD or median (min, max.); Chi-square test; * Fisher's exact test; # Likelihood ratio test; ** Student's t-test; £ Mann-Whitney test; a There are no cases to estimate

Regarding the registered adverse events, table 4 shows the comparison between the two treatment groups. It is possible to observe that the general incidence of adverse events was higher in the group of patients treated with colistin (p = 0.047), as well as the incidence of renal impairment (p = 0.003). The incidence of nausea and vomiting was higher in the group of patients treated with tigecycline (p = 0.046).

Table 4 - Comparison of incidence of adverse events during treatment for patients receiving colistin or tigecycline

Variable	Treatment group		Total (N = 65)	p
	Colistin (N = 34)	Tigecycline (N = 31)		
Overall adverse events	23 (67,6)	13 (41,9)	36 (55,3)	**0,047**
Renal impairment	20 (58,8)	7 (22,6)	27 (41,5)	**0,003**
Liver abnormalities	1 (2,9)	1 (3,2)	2 (3,1)	>0,999*
Nausea	0 (0)	4 (12,9)	4 (6,2)	**0,046***
Neural alterations	0 (0)	0 (0)	0 (0)	a
Skin rash	1 (2,9)	0 (0)	1 (1,5)	>0,999*
Other	5 (14,7)	2 (6,4)	7 (10,7)	0,430

Data expressed as n (%) or mean ± SD; Chi-square test; * Fisher's exact test; ** Student's t-test; a There are no cases to estimate

Due to the characteristics of the osteomyelitis evolution, the treatment outcome was assessed based on the patient's evaluation 12 months after the end of the treatment. Evaluated outcomes were remission of the infection (absence of signs and symptoms compatible with osteomyelitis activity), relapse (patient returning with signs and symptoms of infection up to 12 months after treatment), amputation, death and loss of follow-up. The outcomes were also evaluated in a dichotomous way, being considered remission as a favorable outcome and recurrence, amputation and death and as unfavorable outcomes. Patients who presented loss of follow-up were analyzed in two ways: as a separate outcome and as part of unfavorable outcomes. There were no significant differences between the two treatment groups in these analyzes, as can be seen in Tables 5 and 6.

Table 5 - Distribution of the outcomes after 12 months of treatment according to the antimicrobial group

Outcome	Treatment group		Total (N = 65)	p
	Colistin (N = 34)	Tigecycline (N = 31)		
Remission	15 (44,1)	12 (38,7)	27 (41,5)	0,801
Death	2 (5,8)	3 (9,6)	5 (7,7)	0,663
Recidive	5 (14,7)	6 (19,3)	11 (16,9)	0,744
Amputation	7 (20,6)	2 (6,45)	9 (13,8)	0,152
Loss of follow-up	5 (14,7)	8 (25,8)	13 (20)	0,355

Data expressed as n (%); Chi-square test to estimate

Table 6 - Dichotomic distribution of the outcomes after 12 months of treatment according to the antimicrobial group

Outcome	Treatment group		Total (N = 65)	p
	Colistin (N = 34)	Tigecycline (N = 31)		
Outcome				0,535
Unfavorable	14 (41,2)	11 (35,5)	25 (38,5)	
Favorable	15 (44,1)	12 (38,7)	27 (41,5)	
Loss of follow-up	5 (14,7)	8 (25,8)	13 (20)	
Outcome				0,659
Unfavorable	19 (55,9)	19 (61,3)	38 (58,5)	
Favorable	15 (44,1)	12 (38,7)	27 (41,5)	

Data expressed as n (%); Chi-square test to estimate

Analysis of presented data allows us to conclude that, in this sample of patients studied, tigecycline presented a better safety profile than colistin for the treatment of osteomyelitis related to XDR carbapenem resistant *A. baumannii*. Both antimicrobial presented similar efficacy. The data presented in this report will be submitted for scientific publication.