

# Outcome of Initial Antibiotic Treatments among Hospitalized Patients with Hospital- and Healthcare-Associated Bacterial Infections in Brazil: Findings of the RECOMMEND Study

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## Introduction

- In recent years, increased rates of multidrug-resistant (MDR) Gram-negative bacterial infections have been observed globally.
- Increasing rates of MDR nosocomial pathogens may lead the clinicians to treat patients empirically with combinations of multiple broad-spectrum antibiotics, which can increase the risk of adverse events (AEs) and perpetuate the cycle of emerging resistance.<sup>1,2</sup>
- Brazil, and Latin American countries in general, have higher levels of bacterial resistance among key pathogens compared with Europe and the United States, particularly among non-fermentative Gram-negative bacilli and Enterobacteriaceae, but also among Gram-positive organisms (including *Staphylococcus aureus*).<sup>3,4</sup>
- Consequently, high consumption of last-resort drugs is quite frequent in Brazilian intensive care units, after many isolates have become resistant to the majority of currently available antibiotics.<sup>3-5</sup>
- Inadequate antibiotic therapy is an antibiotic regimen not including agents active against the etiological agents causing a documented infection.<sup>1</sup> Failure of active initial empiric antibiotic therapy in severe infections is associated with increased morbidity, mortality, and may generate additional healthcare resource utilization and costs.<sup>6-8</sup>
- Recent real-world data on initial antibiotic treatment (IAT) and associated outcomes among hospitalized patients with complicated infections is lacking in Brazil and other Latin American countries.

## Objectives

- The primary objective of this study was to document the IAT and associated outcomes among hospitalized patients with complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI) and nosocomial pneumonia (NP) in Brazil.
- The secondary objectives of this study involved assessing potential risk factors associated with IAT failure, and evaluating healthcare utilization and costs among hospitalized patients with cUTI, cIAI, and NP.

## Materials and methods

- This was a retrospective observational study (NCT02364284) involving medical chart review of adult patients (≥18 years) hospitalized with any of the three infections of interest (hospital-acquired or healthcare-associated cUTI, cIAI, NP [including ventilator-associated pneumonia]) during the period from July 1, 2013 through June 30, 2014.
- Enrolled patients were followed from index date (defined as the date of index diagnosis) until 30 days post-discharge, death while hospitalized or within 30 days post-discharge, or follow-up end date December 31, 2014.
- The study has been completed and included 26 hospital sites across the following five countries: Brazil (n=4), France (n=6), Italy (n=6), Spain (n=6) and Russia (n=4). Only the results from Brazil are presented here (results for other countries have been presented elsewhere).

## Study measures

- IAT was defined as all antibiotic agents received during the 48 h post-initiation of antibiotic therapy.
  - A line of therapy was considered complete if: an antibiotic within the treatment regimen was discontinued, the dose was increased, treatment was switched to an oral therapy, or a new antibiotic was added.
- Similar definitions were used to define subsequent lines of therapy. Data was captured for up to five antibiotic treatment lines.

- The primary measure of interest was the outcome of the IAT, classified as success, failure or indeterminate.
  - IAT failure was defined as any of the following: (a) discontinuation of the antibiotic regimen for reasons other than cure, de-escalation or streamlining; (b) dose increase or addition of another antibiotic beyond 48 h of treatment; (c) in-hospital death of any cause; (d) readmission due to recurrence of the same infection within 30 days of discharge; or (e) need for an additional source control procedure (applicable only for patients with cIAI).
- Patient (e.g., age, gender, comorbidity burden) and pathogen (e.g., pathogens identified, MDR pathogens) characteristics were assessed.
  - MDR pathogen infection was defined as resistance to at least one drug in any three of the following drug classes – aminoglycosides, amphenicol, β-lactams, carbapenems, cephalosporins, glycopeptides, glycylicycline, macrolides, monobactams, nitroimidazole, oxalolidinones, penicillins, penicillins + β-lactamase inhibitors, quinolones, streptogramins, tetracycline, lipopeptides
- All study measures were documented descriptively.

## Results

- In total, 1321 patients (across the three conditions) were included in the study, of which 1244 (94.2%) had complete start and stop dates for IAT and comprised the full analytical set (FAS).
- In Brazil, the FAS for each indication was comprised of 82 patients with cUTI, 89 patients with cIAI, and 100 patients with NP, respectively (n=271 patients across the three indications).

### Patient characteristics

#### cUTI

- The study enrolled 82 patients with cUTI in Brazil with a mean age observed at hospital admission of 58.0 years (95% CI: [53.5; 62.6 years]) and the majority of patients were female (58.5%).
- The majority (79.3%) of patients had at least one comorbid condition requiring hospitalization, chronic or current drug therapy (including antibiotic use) or surgical treatment, with a mean number of 2.9 comorbidities per patient.
  - The most frequent comorbid conditions were hypertension (64.6%), diabetes (35.4%), malignancy (26.2%), renal insufficiency (18.5%), and cerebrovascular disease (13.8%).

#### cIAI

- The study enrolled 89 patients with cIAI with a mean age at hospital admission of 57.9 years (95% CI: [54.3; 61.6 years]) and a slight majority of patients were female (51.7%).
- The majority of patients (80.9%) had at least one comorbid condition requiring hospitalization, chronic or current drug therapy (including antibiotic use) or surgical treatment, with a mean number of 2.0 comorbidities per patient.
  - The most frequent comorbid conditions were hypertension (47.2%), malignancy (30.6%), diabetes (27.8%), and renal insufficiency (11.1%).

#### NP

- The study enrolled 100 patients with NP with a mean age at hospital admission of 64.7 years (95% CI: [61.5; 67.8 years]) and a majority of patients were male (75.0%).
- Almost all patients (94.0%) had at least one comorbid condition requiring hospitalization, chronic or current drug therapy (including antibiotic use) or surgical treatment, with a mean number of 2.8 comorbidities per patient.
  - The most frequent comorbid conditions were hypertension (68.1%), malignancy (24.5%), diabetes (22.3%), renal insufficiency (17.0%), COPD and cerebrovascular disease (12.8% each).

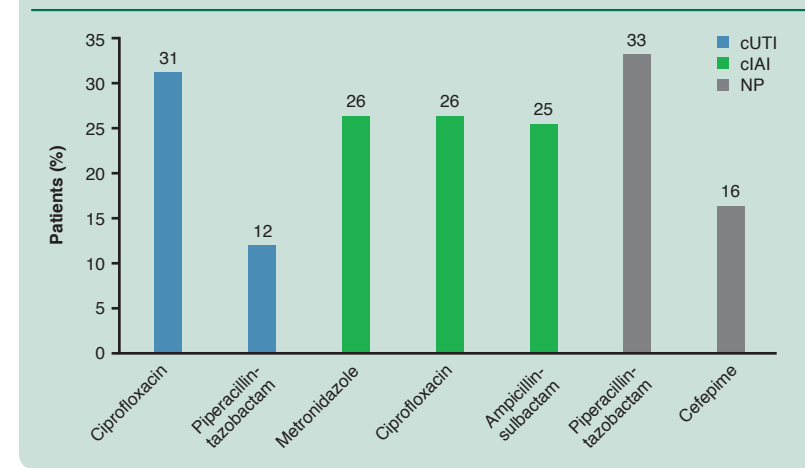
### Pathogen characteristics

- For cUTI, one or more bacterial pathogens were identified in 80 patients (97.6%). Two patients (2.4%) had no bacterial pathogen identified.
  - Gram-negative pathogens were isolated in 70 patients (87.5%). The most frequent pathogens were *Escherichia coli* (38.8% of patients with microbiological documentation), *Klebsiella* species (33.8%), *Pseudomonas aeruginosa* (8.8%), and *Enterobacter* spp. (6.3%).
  - Gram-positive pathogens were identified in 14 patients (17.5%), consisting of mostly *Enterococcus* spp. (15.0%).
- For cIAI patients, information on pathogen identification was missing for 22 patients and three patients (4.5%) had no bacterial pathogen identified. One or more bacterial pathogens were identified in 64 patients (71.9%).
  - Gram-negative pathogens were isolated in 50 patients (78.1%). The most frequent pathogens were *E. coli* (48.4%), *Klebsiella* spp. (17.2%), *Enterobacter* spp. (10.9%), and *P. aeruginosa* and *Acinetobacter* spp. (6.3% each).
  - Gram-positive pathogens were identified in 20 patients (31.3%), including *Staphylococcus* spp. (17.2%) and *Enterococcus* spp. (12.5%).
- For NP patients, information on pathogen identification was missing for 18 patients, and 16 patients (19.5%) had no bacterial pathogen identified. One or more bacterial pathogens were identified in 66 patients with microbiological documentation (66.0%).
  - Gram-negative pathogens were isolated in 49 patients (74.2%). The most frequent pathogens were *Klebsiella* spp. (24.2%), *P. aeruginosa* (19.7%), *Acinetobacter* spp. (19.7%), and *E. coli* (7.6%).
  - Gram-positive pathogens were identified in 17 patients (25.8%), consisting mainly of *Staphylococcus* spp. (19.7%).
- An MDR pathogen was identified in 37.5% of cUTI patients with microbiological documentation (36.5% of total), 31.3% of cIAI patients with microbiological documentation (22.5% of total), and 42.9% of NP patients with microbiological documentation (27.0% of total).

### Treatment patterns and associated outcomes

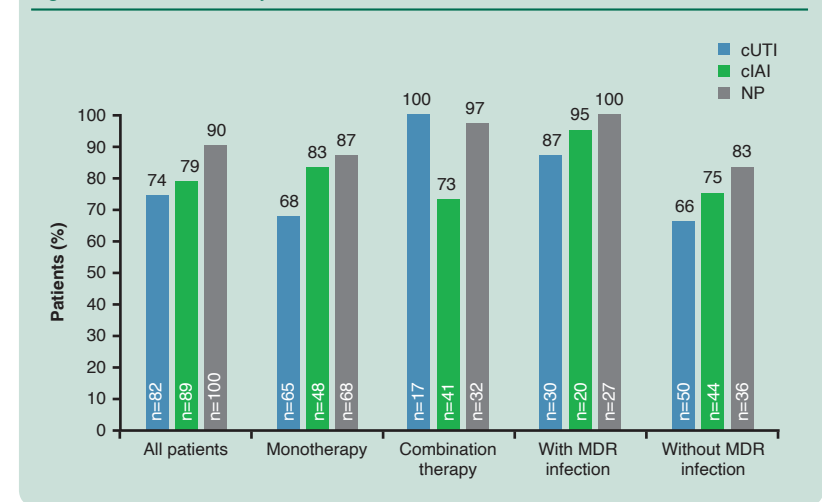
- IAT as monotherapy was observed in 79.3% of cUTI patients, 53.9% of cIAI patients, and 68.0% of NP patients.
- The most commonly used antibiotics (all regimens) by index infection are presented in Figure 1.
- The average IAT duration (all regimens) was 6.7 days (median: 5.5, range 1–31, n=82) for cUTI patients, 8.6 days (median: 7.0, range 1–54, n=89) for cIAI patients, and 7.5 days (median: 6.0, range 1–37, n=100) for NP patients.

Figure 1. Commonly used initial antibiotics by index infection



- IAT failure rates by index infection for all patients and for patients receiving monotherapy or combination therapy are shown in Figure 2.
- In-hospital all-cause mortality rates for cUTI, cIAI and NP were 46.3%, 56.2% and 72.0% respectively.
- For all three infection types, both IAT failure and mortality rates were numerically higher in patients who suffered from an infection with an MDR pathogen, compared to patients without an MDR infection.
  - IAT failure rates in patients with or without an MDR infection are shown in Figure 2.
  - For the 30 cUTI patients infected with an MDR pathogen, in-hospital mortality rate was 70.0%, and 30-day mortality rate was 73.3%. For the 50 cUTI patients who did not have an MDR infection, in-hospital mortality rate and 30-day mortality rate were both 32.0%.
  - For the 20 cIAI patients infected with an MDR pathogen, in-hospital and 30-day mortality rates were both 75.0%. For the 44 cIAI patients who did not have an MDR infection, in-hospital mortality rate and 30-day mortality rate were both 45.5%.
  - For the 27 NP patients infected with an MDR pathogen, in-hospital mortality rate and 30-day mortality rate were both 85.2%. For the 36 NP patients who did not have an MDR infection, in-hospital mortality rate was 61.1%, and 30-day mortality rate was 69.4%.

Figure 2. IAT failure rates by index infection



## Conclusions

- High rates of IAT failure and all-cause mortality highlight an unmet need among hospitalized patients with common hospital-acquired or healthcare-associated Gram-negative infections.
- This study provides recent real-world practice patterns and outcomes associated with IAT among cUTI, cIAI and NP patients in Brazil.
- Approximately 30–40% of patients with microbiological documentation in all three indications had an MDR pathogen.
- MDR infection was numerically associated with a higher IAT failure rate and increased mortality in Brazil.
- High rates of IAT failure and in-hospital mortality were observed in this study in Brazil highlighting the significant challenges associated with treating nosocomial infections in an environment of growing resistance.

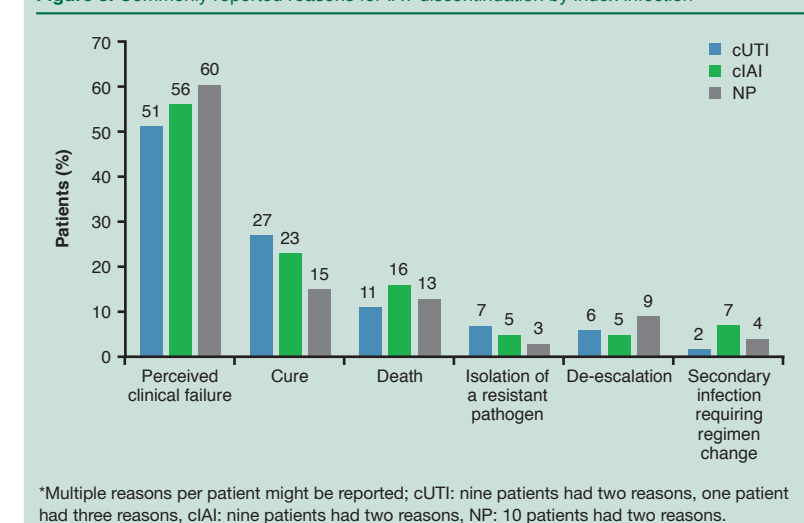
### Disclosures

KR, SK, DP, YT, and EP are all employees and shareholders of AZ. PP, EB and SRF are employees of Quintiles. JRB has been an advisor for AstraZeneca, MSD, Roche, Achaogen and Basilea; a speaker for MSD, Astellas, Pfizer and Novartis; and he has received grants for research from Gilead and the EFPIA partners of COMBACTE-CARE and COMBACTE-MAGNET (AstraZeneca, MedImmune, Acuris).

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Figure 3. Commonly reported reasons for IAT discontinuation by index infection\*



## Limitations

- This was a retrospective observational study and study data were abstracted from patient medical charts. Thus, missing or inaccurate data in the medical charts may have led to misclassification of patients and/or study measures.
- The definition of treatment failure included in-hospital death of any cause, which may have led to an overestimate of treatment failure.
- The retrospective design of the study may also have favored the selection of a severely ill patient population, which may have impacted the IAT failure rate and mortality rate.
  - A site in Brazil only included patients who were deceased at the time of data collection (with approximately 95% in-hospital death rate and 100% IAT failure rates for the three indications). The demographic and clinical characteristics did not vary between patients included at this site compared with other participating sites.
- The sites selected constituted a convenience sample and may or may not be representative of the geographic distribution or the hospital type or size in each of the participating countries.