

# The impact of initial antibiotic treatment failure: real-world insights in patients with complicated, health care-associated intra-abdominal infection

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**Purpose:** The RECOMMEND study (NCT02364284; D4280R00005) assessed the clinical management patterns and treatment outcomes associated with initial antibiotic therapy (IAT; antibiotics administered  $\leq 48$  hours post-initiation of antibiotic therapy) for health care-associated infections across five countries.

**Patients and methods:** Data were collected from a retrospective chart review of patients aged  $\geq 18$  years with health care-associated complicated intra-abdominal infection (cIAI). Potential risk factors for IAT failure were identified using logistic regression analyses.

**Results:** Of 385 patients with complete IAT data, bacterial pathogens were identified in 270 (70.1%), including Gram-negative isolates in 221 (81.9%) and Gram-positive isolates in 92 (34.1%). Multidrug-resistant (MDR) pathogens were identified in 112 patients (41.5% of patients with a pathogen identified). IAT failure rate was 68.3% and in-hospital mortality rate was 40.8%. Multivariate regression analysis demonstrated three factors to be significantly associated with IAT failure: patients admitted/transferred to the intensive care unit during index hospitalization, isolation of an MDR pathogen and previous treatment with  $\beta$ -lactam antibiotics.

**Conclusion:** We reveal the real-world insights into the high rates of IAT failure and mortality observed among patients with cIAI. These data highlight the challenges associated with choosing IAT, the impact of MDR pathogens on IAT outcomes and the importance of tailoring IAT selection to account for local epidemiology and patient history.

**Keywords:** complicated intra-abdominal infection, health care associated, initial antibiotic treatment, clinical outcome, real-world treatment patterns

## Introduction

Complicated intra-abdominal infections (cIAIs) occur when the infectious process of an intra-abdominal infection (IAI) extends beyond the limits of one organ, causing localized or diffuse infection of the peritoneum that is usually polymicrobial in nature.<sup>1</sup> The bacterial flora that comprise the infection are generally dependent on the specific location of the site of the perforation of the gastrointestinal tract in community-acquired cIAI.<sup>2</sup> Health care-associated cIAIs frequently result from previous intra-abdominal surgery, and therefore, the nature of the infecting nosocomial pathogen is typically defined by a combination of the site of the operation and the hospital.<sup>2</sup> cIAIs that occur in a health care-associated setting (hospital-acquired or acquired in another health care setting) are generally associated with higher mortality rates than community-acquired IAI. This increased mortality is due, in part, to the likely poorer underlying health status of patients in health care facilities and the impact of comorbidities on prognosis.<sup>3</sup> In addition, patients acquiring cIAI after surgery may have nutritional

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deficiency, altered intestinal flora and immune deficiency that also impact on prognosis.<sup>4</sup> There is also the potential for the involvement of a broader spectrum of microorganisms in health care-associated infection,<sup>5</sup> with an increased likelihood that the causative pathogens are multidrug resistant (MDR).<sup>6</sup> Pathogens typically isolated from health care-associated cIAIs are Gram-negative organisms, most commonly *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*; Gram-positive species, namely, *Enterococcus* spp.; and anaerobic species.<sup>7</sup> The increasing global prevalence of MDR pathogens in this setting, in particular, the continuing spread of extended-spectrum  $\beta$ -lactamase-producing Gram-negative Enterobacteriaceae, is a major concern for the treatment of cIAIs.<sup>8–10</sup>

Management of cIAI requires both timely surgical source control and empirical initial antibiotic therapy (IAT), followed by a switch to a more specific antibiotic regimen based on bacterial culture results.<sup>6,11,12</sup> To provide adequate coverage, IAT typically incorporates broad-spectrum antibiotics, sometimes in combination.<sup>12</sup> However, resistance rates in cIAI isolates are constantly changing and are also subject to regional variation; thus, local epidemiology must be accounted for to ensure that this empirical approach covers the relevant pathogens and does not contribute further to the development of antibiotic resistance.<sup>9,10,13–15</sup>

In severe health care-associated infections, delayed IAT and the administration of inappropriate antibiotics have both been linked with IAT failure, increased morbidity and mortality and an increased burden on health care resources.<sup>16–19</sup> There is a need, therefore, to gain a better understanding of the treatment patterns and risk factors associated with IAT failure, and the impact of IAT failure on patients in a real-world setting. To date, very few studies have looked, on an international scale, at the outcome of IAT in patients with health care-associated cIAI. Clinical trial eligibility criteria often restrict the inclusion of patients with comorbid diseases, so their findings may not be representative of real-world patients.<sup>20,21</sup> Furthermore, published observational studies have addressed mixed patient populations predominantly with community-acquired infections, rather than health care-associated infections.<sup>5,22</sup>

The RECOMMEND study (NCT02364284, D4280R00005) involved a comprehensive review of the medical records of patients with health care-associated cIAI, complicated urinary tract infection (cUTI) and nosocomial pneumonia (NP) across five different countries. The aim of the study was to evaluate the treatment patterns and clinical outcomes among these patients, including an assessment

of the IAT outcomes and risk factors associated with IAT failure. Analyses relating to patients with cIAI are reported here.

## Patients and methods

### Study design

RECOMMEND was an international, retrospective, multicenter, non-interventional cohort study based on a retrospective chart review of hospitalized adult patients with health care-associated cIAI, cUTI or NP from Brazil, France, Italy, Russia and Spain, between July 1, 2013 and June 30, 2014. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki. The study was consistent with the sponsor's policy on bioethics, the harmonized tripartite guideline E6(R1) from the International Conference on Harmonization, Good Clinical Practice and applicable regulatory requirements. The study protocol was reviewed and approved by an ethics committee (EC) or an institutional review board (IRB) at each site, except in France, where this is not required for retrospective studies, and Spain, where the national regional regulatory agency evaluated and classified the study in addition to EC approvals. The names of the ECs and IRBs providing their approval for the conduct of this study can be found in Table S1. Site investigators were responsible for obtaining informed consent from the patient or their legal representative in accordance with the local regulations.

Data were collected in an electronic case report form based on patient medical records covering the patient from diagnosis to 30 days' post-discharge, death, loss to follow-up or the end of the study period (December 31, 2014) if not discharged by the end of the study.

### Patients

For inclusion in the current analysis, patients had to be aged  $\geq 18$  years and have a clinical diagnosis of health care-associated cIAI requiring surgical intervention as previously defined,<sup>21</sup> with evidence of involvement of more than one organ causing peritonitis, and parenteral antibiotic therapy during the hospital stay beyond the 24-hour regimen associated with surgery. Health care-associated infection was defined as hospital acquired (developed  $\geq 48$  hours after hospital admission) or acquired in another health care setting, including hospitals, nursing homes, long-term care facilities or hemodialysis clinics,  $\leq 3$  months prior to or during in-patient admission. Patients were excluded from the study if they had taken part in any clinical trial during the patient selection or follow-up period.

Patients were identified using the ICD-10th revision codes or diagnosis-related group codes from the hospital discharge records, the health care-associated infection registry or other site-specific sources. Inclusion and exclusion criteria were applied to the corresponding medical charts and the final selection of eligible patients was at the discretion of the investigator, applying the criteria used in routine practice to identify patients with complicated infections. Each site could accrue a maximum of 40 patients per type of infection.

## Study measures

The primary objective of the study was to document the association of clinical outcomes with IAT (defined as all antibiotic agents administered during the 48 hours post-initiation of antibiotic therapy) and determine the factors associated with IAT success and failure. Success was defined as discontinuation of IAT, including de-escalation or streamlining, because of clinical cure or improvement, with no further need for an antibiotic; or a switch to oral antibiotic; and no readmission due to the same infection within 30 days of discharge. Failure was defined as discontinuation of the antibiotic regimen for reasons other than cure, de-escalation or streamlining; a change in IAT due to perceived clinical failure; a dose increase or addition of another antibiotic beyond 48 hours of treatment; the requirement of an additional source control procedure performed >48 hours post-IAT; in-hospital death of any cause; or readmission due to recurrence of the same infection within 30 days of discharge. In cases in which there was insufficient information to conclude whether the IAT outcome was a failure or a success, an indeterminate outcome was concluded. Data were collected for IAT and up to four additional lines of antibiotic treatment following IAT. A new line of antibiotic treatment was defined as any change occurring after 48 hours of initiation of antibiotic therapy, including discontinuation, an increase in dose, a switch to oral therapy or the addition of a new antibiotic.

Additional information captured from medical records comprised baseline details relating to patients, pathogens and sites, including patient age, sex, comorbidity burden, pathogen type and the presence of MDR pathogens. To be classified as MDR, pathogens had to display resistance to at least one antibiotic in a minimum of three of any of the following drug classes: aminoglycosides, chloramphenicol, carbapenems, cephalosporins, glycopeptides, penicillins ±  $\beta$ -lactamase inhibitors, quinolones, tetracyclines, macrolides or streptogramins for all pathogens; or glycopeptides, oxazolidinones and lipopeptides for Gram-positive pathogens; or mono-bactams for Gram-negative pathogens; or

nitroimidazole for anaerobic pathogens. The incidence of IAT failure, in-hospital mortality rate, mortality rate at 30 days' post-discharge, incidence of hospital readmissions within 30 days' post-discharge, incidence of secondary infections, hospital length of stay, and total number of days on IAT and four additional lines of antibiotic treatment were also noted. Details of treatment were recorded, including antibiotic type(s), monotherapy or a combination of antibiotics, and the physician-reported reason for ending treatment.

## Statistical analyses

All variables were reported using descriptive statistics, and data were analyzed overall and by country. The association of IAT failure with potential risk factors (characteristics of patients [demographic and clinical], pathogens, sites and treatment) was explored using univariate and multivariate logistic regression analyses. For the regression analyses, indeterminate outcomes were grouped with treatment successes. The multivariate regression analysis included variables from the univariate analysis with  $P < 0.25$  as the potential confounders. ORs, corresponding 95% CIs and  $P$ -values were calculated. All analyses were performed by Quintiles using SAS® (SAS Institute Inc., Cary, NC, USA) version 9.4.

## Results

### Patient demographic and clinical characteristics

Data from 26 hospital sites across the five participating countries were collected (Brazil,  $n=4$ ; France,  $n=6$ ; Italy,  $n=6$ ; Russia,  $n=4$ ; Spain,  $n=6$ ). Across all three indications of interest, 1,708 potential patients were identified, and 1,321 patients were enrolled based on the inclusion criteria for each indication and patient consent, where applicable (not required in Spain). Complete start and stop records for IAT were available for 1,244 patients (cIAI,  $n=385$ ; cUTI,  $n=408$ ; NP,  $n=451$ ).

In total, 385 (30.9%) out of 1,244 patients were included with health care-associated cIAI as their index infection, with a mean (SD) age at hospital admission of 64.4 (15.7) years and a relatively even split of male to female patients (56.4% male overall), as shown in Table 1.

The majority (62.1%) were enrolled with hospital-acquired cIAI. The most common cIAI conditions ( $\geq 10\%$  of patients) were secondary peritonitis (37.4%), intra-abdominal abscess (30.4%) and cholecystitis (16.4%). The mean (SD) Deyo-Charlson comorbidity score (DCCS) was 2.4 (2.5),

**Table 1** Patient demographic and clinical characteristics at index hospitalization, overall and by country

Parameters	Brazil (n=89)	France (n=65)	Italy (n=68)	Russia (n=74)	Spain (n=89)	Total (N=385)
Age, years						
Mean (SD)	57.9 (17.4)	67.3 (12.4)	67.5 (14.3)	62.7 (15.6)	67.7 (15.3)	64.4 (15.7)
Sex						
Male, n (%)	43 (48.3)	40 (61.5)	41 (60.3)	36 (48.6)	57 (64.0)	217 (56.4)
Weight, kg						
n (non-missing)	76	63	41	52	34	266
Mean (SD)	71.9 (21.1)	70.6 (15.7)	73.9 (12.0)	84.0 (19.1)	73.3 (13.4)	74.5 (17.9)
Patients with comorbidity requiring hospitalization or treatment (surgery/ chronic or current drug therapy), n (%)	72 (80.9)	52 (80.0)	61 (89.7)	60 (81.1)	82 (92.1)	327 (84.9)
DCCS, mean (SD)	1.7 (1.9)	2.5 (2.7)	3.7 (3.1)	1.9 (2.0)	2.4 (2.4)	2.4 (2.5)
DCCS, n (%)						
0	36 (40.4)	23 (35.4)	11 (16.2)	20 (27.0)	23 (25.8)	113 (29.4)
1–2	30 (33.7)	13 (20.0)	18 (26.5)	35 (47.3)	31 (34.8)	127 (33.0)
3–4	15 (16.9)	17 (26.2)	14 (20.6)	10 (13.5)	19 (21.3)	75 (19.5)
≥5	8 (9.0)	12 (18.5)	25 (36.8)	9 (12.2)	16 (18.0)	70 (18.2)
Number of comorbidities by patient						
n (non-missing)	72	52	61	60	82	327
Number, mean (SD)	2.0 (1.0)	2.8 (1.6)	3.2 (2.1)	2.1 (1.2)	2.5 (1.6)	2.5 (1.6)
Comorbidity (≥10% of overall patients), n (%)						
N	72	52	61	60	82	327
Hypertension	34 (47.2)	30 (57.7)	28 (45.9)	38 (63.3)	43 (52.4)	173 (52.9)
Malignancy	22 (30.6)	13 (25.0)	29 (47.5)	11 (18.3)	26 (31.7)	101 (30.9)
Diabetes	20 (27.8)	13 (25.0)	15 (24.6)	11 (18.3)	25 (30.5)	84 (25.7)
COPD	2 (2.8)	11 (21.2)	7 (11.5)	8 (13.3)	9 (11.0)	37 (11.3)
Renal insufficiency	8 (11.1)	5 (9.6)	14 (23.0)	0 (0.0)	9 (11.0)	36 (11.0)
Liver disease	3 (4.2)	5 (9.6)	10 (16.4)	8 (13.3)	9 (11.0)	35 (10.7)
Hospitalized within 90 days prior to the index hospitalization, n (%)						
Yes	28 (31.5)	17 (26.2)	32 (47.1)	15 (20.3)	30 (33.7)	122 (31.7)
No	52 (58.4)	33 (50.8)	30 (44.1)	54 (73.0)	56 (62.9)	225 (58.4)
Unknown	9 (10.1)	15 (23.1)	6 (8.8)	5 (6.8)	3 (3.4)	38 (9.9)
Patient administered any antibiotics within 90 days prior to the index diagnosis, n (%)						
Yes	29 (32.6)	19 (29.2)	21 (30.9)	1 (1.4)	48 (53.9)	118 (30.6)
No	43 (48.3)	21 (32.3)	32 (47.1)	50 (67.6)	33 (37.1)	179 (46.5)
Unknown	17 (19.1)	25 (38.5)	15 (22.1)	23 (31.1)	8 (9.0)	88 (22.9)
If yes, antibiotic class, n (%)						
β-lactam antibacterials, penicillins	5 (17.2)	9 (47.4)	5 (23.8)	0 (0.0)	23 (47.9)	42 (35.6)
Other β-lactam antibacterials	12 (41.4)	8 (42.1)	5 (23.8)	1 (100)	13 (27.1)	39 (33.1)
Quinolone antibacterials	10 (34.5)	1 (5.3)	5 (23.8)	0 (0.0)	4 (8.3)	20 (16.9)
Other antibacterials	0 (0.0)	0 (0.0)	3 (14.3)	0 (0.0)	5 (10.4)	8 (6.8)
Aminoglycoside antibacterials	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	2 (4.2)	3 (2.5)
Sulfonamides and trimethoprim	2 (6.9)	0 (0.0)	1 (4.8)	0 (0.0)	1 (2.1)	4 (3.4)
All other therapeutic products	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	2 (1.7)
Acquisition of cIAI, n (%)						
Hospital-acquired	48 (53.9)	42 (64.6)	38 (55.9)	55 (74.3)	56 (62.9)	239 (62.1)
Health care-associated	41 (46.1)	23 (35.4)	30 (44.1)	19 (25.7)	33 (37.1)	146 (37.9)

**Note:** Percentages are calculated with numbers of patients for whom data were available as the denominator for each category as the denominator for each category.

**Abbreviations:** cIAI, complicated intra-abdominal infection; DCCS, Deyo-Charlson comorbidity score.

with 327 (84.9%) of 385 patients having at least one comorbidity that required hospitalization, chronic or ongoing drug therapy, or surgical treatment (Table 1).

Within the 90 days prior to index hospitalization, 122 (31.7%) patients had been hospitalized at least once and 118 (30.6%) had received antibiotics. Of those who had received prior antibiotics, the majority had received either  $\beta$ -lactam-based penicillin or another  $\beta$ -lactam-based antibacterial (Table 1).

The majority of patients in this cIAI cohort underwent a surgical intervention (295/385, 76.6%), with the majority of those surgeries being for the purpose of source control of the infection (218/295, 73.9%). A second surgical intervention to control the source infection was required by 20.2% of those who underwent surgery, and 13.3% required three or more surgical interventions. Of note, the proportion of patients who underwent surgery and required three or more surgical interventions to control the source infection was numerically higher in Brazil and Russia (22.0% and 19.7%, respectively) than in other countries ( $\leq 10.0\%$ ), as shown in Table 2.

## Pathogen characteristics

At least one bacterial pathogen was identified in 270 (70.1%) patients. Among the 454 bacterial pathogens isolated, 46 were isolated before the start of IAT, 309 were isolated within 0–6

days of the start of IAT and 133 were isolated 7 days or more after the start of IAT. Of the 270 patients, 221 (81.9%) had a Gram-negative pathogen isolated, 92 (34.1%) had a Gram-positive pathogen and 21 (7.8%) had an anaerobic pathogen (a patient could have more than one pathogen type identified; Figure 1 and Table S2). The most commonly isolated Gram-negative pathogens ( $\geq 10\%$  of patients) were *E. coli* (47.0%), *Klebsiella* spp. (17.0%) and *P. aeruginosa* (11.1%); however, differences were noted across countries (Figure 1 and Table S2). The most commonly isolated Gram-positive pathogens overall were *Enterococcus* spp. (20.0% of patients in the overall cIAI cohort), although again, differences were noted across countries.

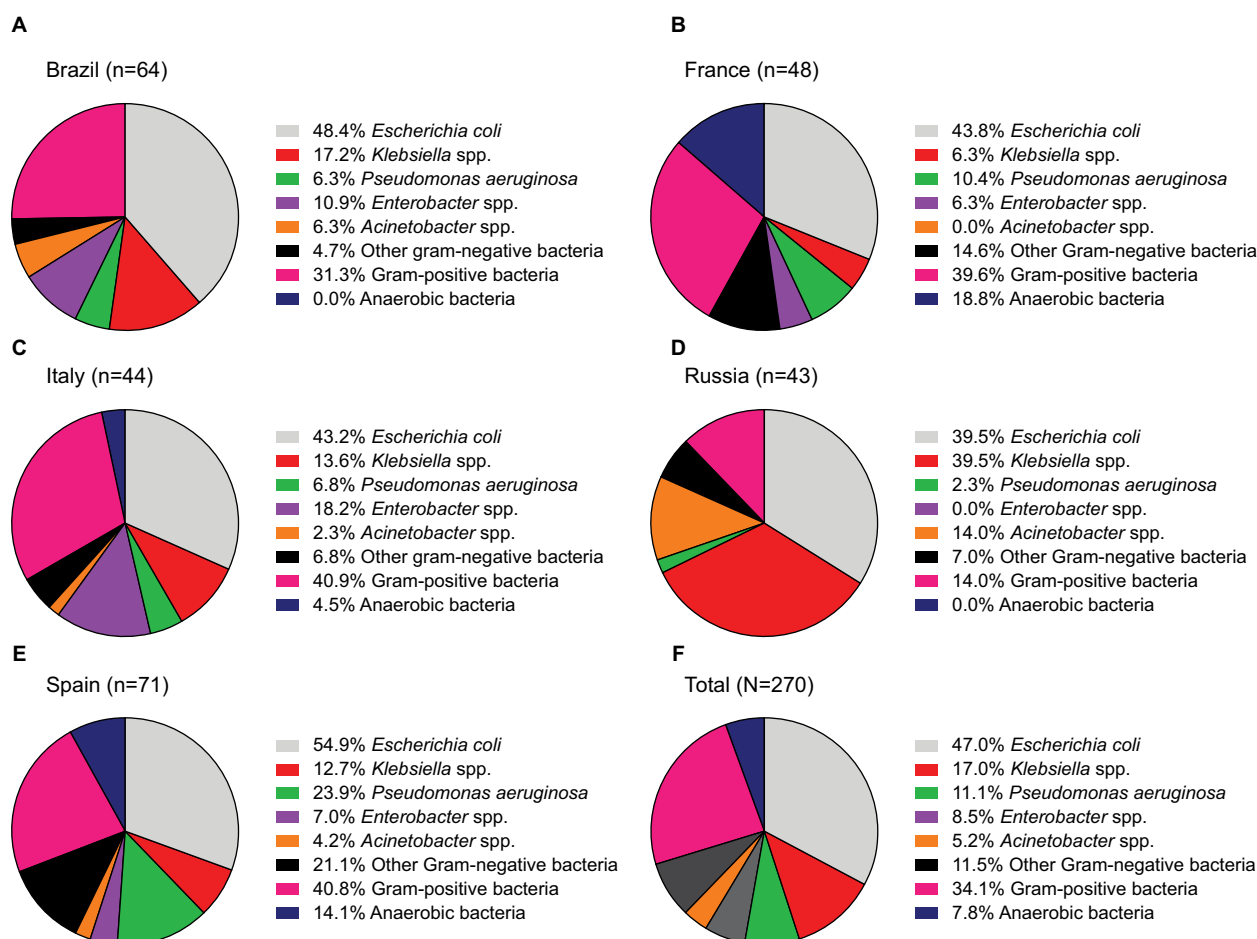
MDR pathogens were isolated in 41.5% of all patients who had a pathogen identified, with the highest incidence observed in Russia and the lowest in Brazil and Italy (Figure 1 and Table S2). Among individual species, MDR isolates were identified in 32 (25.2%) out of 127 patients for *E. coli*, 25 (54.3%) out of 46 patients for *Klebsiella* spp., 9 (30.0%) out of 30 patients for *P. aeruginosa*, 27 (50.0%) out of 54 patients for *Enterococcus* spp., 12 (41.4%) out of 29 patients for *Staphylococcus* spp. and 13 (92.9%) out of 14 patients for *Acinetobacter* spp. In patients in whom any MDR pathogen was isolated, resistance was most common to penicillins either with or without  $\beta$ -lactamase inhibitors (63.4% and 73.2%, respectively), quinolones

**Table 2** Summary of procedures performed during hospitalization for the index infection

Parameters	Brazil (n=89)	France (n=65)	Italy (n=68)	Russia (n=74)	Spain (n=89)	Total (N=385)
Patients with procedures undertaken during hospitalization for the index infection, n (%)						
Surgical intervention <sup>a</sup>	77 (86.5)	41 (63.1)	47 (69.1)	68 (91.9)	62 (69.7)	295 (76.6)
1 <sup>b</sup>	45 (58.4)	25 (61.0)	33 (70.2)	37 (54.4)	32 (51.6)	175 (58.3)
2 <sup>b</sup>	15 (19.5)	6 (14.6)	10 (21.3)	18 (26.5)	20 (32.3)	69 (23.4)
$\geq 3$ <sup>b</sup>	17 (22.1)	10 (24.4)	4 (8.5)	13 (19.1)	10 (16.1)	54 (18.3)
Mechanical ventilation	54 (60.7)	28 (43.1)	12 (17.6)	28 (37.8)	24 (27.0)	146 (37.9)
Other procedure	19 (21.3)	4 (6.2)	17 (25.0)	0 (0.0)	37 (41.6)	77 (20.0)
Endoscopy	6 (6.7)	7 (10.8)	7 (10.3)	6 (8.1)	11 (12.4)	37 (9.6)
None	0 (0.0)	20 (30.8)	8 (11.8)	2 (2.7)	5 (5.6)	35 (9.1)
Tracheostomy	10 (11.2)	0 (0.0)	1 (1.5)	17 (23.0)	6 (6.7)	34 (8.8)
Hemodialysis	11 (12.4)	9 (13.8)	3 (4.4)	3 (4.1)	4 (4.5)	30 (7.8)
Number of surgical interventions to control the source infection						
n	50	30	24	61	53	218
1	31 (62.0)	20 (66.7)	20 (83.3)	7 (60.7)	37 (69.8)	145 (66.5)
2	8 (16.0)	7 (23.3)	3 (12.5)	12 (19.7)	14 (26.4)	44 (20.2)
$\geq 3$	11 (22.0)	3 (10.0)	1 (4.2)	12 (19.7)	2 (3.8)	29 (13.3)

**Notes:** Percentages are calculated with numbers of patients for whom data were available as the denominator for each category as the denominator; total of percentages may exceed 100%. More than one procedure may apply for a single patient. <sup>a</sup>Surgical interventions refer to open abdomen procedures. Percutaneous interventions, interventional radiology and laparoscopic procedures were recorded as "other procedures", including those performed to control the infection. <sup>b</sup>n (%) of those undergoing a surgical intervention.





**Figure 1** Most common bacterial pathogens identified in specimen samples from patients in Brazil (A), France (B), Italy (C), Russia (D), Spain (E) and overall (F).

**Notes:** Patients could have more than one pathogen type identified. Data missing for 22 patients in Brazil. Percentages are calculated as a proportion of those patients with  $\geq 1$  bacterial pathogen identified.

(69.6%), aminoglycosides (64.3%), cephalosporins (62.5%), macrolides (33.0%), carbapenems (31.3%) and tetracyclines (21.4%).

## IAT treatment patterns

In the cIAI cohort, 48.6% of patients (187/385) received a single antibiotic as their IAT, while the remaining 51.4% (198/385) received a combination of antibiotics. The mean (SD) duration of IAT was 11.1 (20.2) days. Notably, IAT duration was shorter in patients receiving monotherapy than in those receiving combination therapy (Table 3). Large inter-country variation was observed in the antibiotics used throughout the study. The most common agents used either as a monotherapy or as part of a combination therapy are presented in Table 3 (all agents used as part of any IAT therapy in  $\geq 5\%$  of the total population). Across all countries, the most frequent monotherapy IATs ( $\geq 5\%$  of those receiving monotherapy) were  $\beta$ -lactams/ $\beta$ -lactamase inhibitors

(piperacillin–tazobactam, 33.2%; ampicillin–sulbactam, 13.4%, amoxicillin–clavulanic acid, 5.3%) or  $\beta$ -lactams on their own (ceftriaxone, 10.2%; cefotaxime, 6.4%; meropenem, 5.3%). The most frequent combination IATs ( $\geq 5\%$  of those receiving combination therapy) were ceftriaxone + metronidazole (11.6%), ciprofloxacin + metronidazole (11.1%), meropenem + vancomycin and amikacin + ceftriaxone + metronidazole (6.1% each).

The most common reasons for IAT discontinuation reported by physicians were cure (32.9%), perceived failure (28.5%), de-escalation (18.8%) and death (14.9%), as shown in Table 3. Notably, discontinuation due to cure was numerically higher in patients receiving combination therapy than monotherapy (39.3% vs 26.2%, respectively).

In the overall cIAI cohort, 37.9% received only the IAT. Meanwhile, 62.1% had a second line of treatment, 34.5% a third, 19.5% a fourth and 9.6% a fifth line. Most treatment lines given after IAT were monotherapies: 64.0% (153/239),

**Table 3** Characteristics of IAT overall and by country

Parameter	Brazil (n=89)	France (n=65)	Italy (n=68)	Russia (n=74)	Spain (n=89)	Total (N=385)
Type of therapy, n (%)						
Monotherapy	48 (53.9)	25 (38.5)	34 (50.0)	26 (35.1)	54 (60.7)	187 (48.6)
Combination therapy	41 (46.1)	40 (61.5)	34 (50.0)	48 (64.9)	35 (39.3)	198 (51.4)
IAT duration, days, mean (SD)						
All IAT	8.6 (8.1)	14.0 (45.9)	11.0 (7.8)	10.8 (7.4)	11.8 (9.1)	11.1 (20.2)
Monotherapy	8.5 (8.9)	5.7 (3.8)	10.7 (7.4)	6.9 (4.1)	11.6 (9.0)	9.2 (7.9)
Combination therapy	8.6 (7.0)	19.2 (58.1)	11.3 (8.2)	13.0 (8.0)	12.0 (9.3)	12.8 (27.1)
Most common IAT given as a monotherapy or as a part of a combination therapy (≥5% of the total population), n (%)						
Piperacillin–tazobactam	11 (12.4)	32 (49.2)	25 (36.8)	0 (0.0)	42 (47.2)	110 (28.6)
Metronidazole	23 (25.8)	15 (23.1)	19 (27.9)	41 (55.4)	12 (13.5)	110 (28.6)
Ceftriaxone	6 (6.7)	11 (16.9)	4 (5.9)	38 (51.4)	2 (2.2)	61 (15.8)
Ciprofloxacin	23 (25.8)	5 (7.7)	7 (10.3)	2 (2.7)	9 (10.1)	46 (11.9)
Amikacin	0 (0.0)	15 (23.1)	0 (0.0)	16 (21.6)	6 (6.7)	37 (9.6)
Meropenem	9 (10.1)	1 (1.5)	11 (16.2)	1 (1.4)	12 (13.5)	34 (8.8)
Ampicillin + sulbactam	22 (24.7)	0 (0.0)	8 (11.8)	3 (4.1)	0 (0.0)	33 (8.6)
Vancomycin	10 (11.2)	7 (10.8)	5 (7.4)	0 (0.0)	8 (9.0)	30 (7.8)
Cefotaxime	0 (0.0)	0 (0.0)	3 (4.4)	14 (18.9)	5 (5.6)	22 (5.7)
Imipenem	1 (1.1)	8 (12.3)	5 (7.4)	0 (0.0)	6 (6.7)	20 (5.2)
Reason for IAT discontinuation, n (%) <sup>a</sup>						
Cure	20 (22.7)	29 (44.6)	27 (40.3)	24 (32.4)	26 (29.2)	126 (32.9)
Perceived clinical failure	49 (55.7)	9 (13.8)	15 (22.4)	17 (23.0)	19 (21.3)	109 (28.5)
De-escalation	4 (4.5)	17 (26.2)	14 (20.9)	5 (6.8)	32 (36.0)	72 (18.8)
Death	14 (15.9)	11 (16.9)	8 (11.9)	19 (25.7)	5 (5.6)	57 (14.9)
Isolation of a resistant pathogen	4 (4.5)	3 (4.6)	11 (16.4)	2 (2.7)	15 (16.9)	35 (9.1)
Secondary infection requiring regimen change	6 (6.8)	3 (4.6)	3 (4.5)	12 (16.2)	4 (4.5)	28 (7.3)
Switch to oral therapy	0 (0.0)	2 (3.1)	4 (6.0)	0 (0.0)	5 (5.6)	11 (2.9)
Adverse event	0 (0.0)	1 (1.5)	2 (3.0)	0 (0.0)	3 (3.4)	6 (1.6)

**Note:** <sup>a</sup>Patient might report more than one reason for stopping IAT.

**Abbreviation:** IAT, initial antibiotic treatment.

75.9% (101/133), 84.0% (63/75) and 48.6% (18/37) of the patients in the second to fifth treatment lines, respectively. Overall, the mean (SD) total number of days of antibiotic therapy, including all lines of treatment, was 26.3 (53.8) days (Table 4). This was shorter in cases of IAT success than IAT failure or indeterminate outcome. However, variation in overall treatment duration was observed across the different countries (Table 4).

## Clinical outcomes of IAT

IAT failure was identified in 263 (68.3%) patients in the overall cIAI cohort, with similar rates across all countries (Table 4). Patients receiving monotherapy had numerically higher rates of IAT failure compared to those receiving combination therapy (70.6% vs 66.2%, respectively; Figure 2). IAT success and indeterminate outcomes were observed in 22.5% and 7.0%, respectively, of patients receiving monotherapy

and in 28.8% and 5.1%, respectively, of patients receiving combination therapy.

For all patients, the overall mean (SD) length of hospital stay from admission to discharge was 28.8 (30.8) days. Length of hospital stay did not differ greatly by IAT treatment outcome, except in Brazil, where patients with IAT success had a numerically shorter length of hospital stay than those with IAT failure (Table 4). The overall in-hospital mortality rate was 40.8%, although this varied across the participating countries, being highest in Brazil and lowest in Spain and Italy. The 30-day post-discharge mortality rate was 41.0% (Table 4).

There was a numerically higher rate of IAT failure in patients with MDR pathogens identified (81.3%) than those without (62.7%) in the overall cohort; this was observed consistently across all participating countries except France, where the IAT failure rates in patients with or without an

**Table 4** Treatment outcome measures, overall and by country

Parameter	Brazil (n=89)	France (n=65)	Italy (n=68)	Russia (n=74)	Spain (n=89)	Total (N=385)
IAT outcome, n (%)						
Failure <sup>a</sup>	70 (78.7)	42 (64.6)	42 (61.8)	53 (71.6)	56 (62.9)	263 (68.3)
Success	18 (20.2)	20 (30.8)	22 (32.4)	19 (25.7)	20 (22.5)	99 (25.7)
Indeterminate	1 (1.1)	3 (4.6)	4 (5.9)	2 (2.7)	13 (14.6)	23 (6.0)
Treatment duration (all lines of therapy), mean (SD) days	18.0 (15.3)	19.7 (46.0)	24.3 (47.9)	26.2 (61.6)	41.0 (75.0)	26.3 (53.8)
Duration by IAT outcome, mean (SD) days						
Failure	20.5 (16.3)	14.4 (12.2)	20.1 (12.0)	32.2 (72.0)	52.6 (92.1)	28.7 (55.8)
Success	8.2 (3.4)	32.2 (81.0)	31.6 (83.1)	11.5 (5.7)	16.1 (14.4)	20.5 (53.9)
Indeterminate	15.0 (NA)	9.7 (5.5)	27.8 (14.9)	7.5 (0.7)	29.3 (14.6)	24.0 (15.0)
LOS (from admission to discharge), mean (SD) days	22.2 (17.3)	28.5 (23.8)	34.3 (48.4)	19.6 (14.5)	39.2 (34.9)	28.8 (30.8)
LOS by IAT outcome, mean (SD) days						
Failure	25.5 (17.8)	29.6 (27.8)	25.2 (14.9)	21.6 (16.1)	43.9 (39.2)	29.3 (26.0)
Success	9.1 (6.3)	28.7 (13.9)	51.5 (80.4)	15.2 (7.2)	27.9 (26.7)	27.5 (42.4)
Indeterminate	22.0 (NA)	13.0 (9.5)	34.3 (25.4)	8.0 (1.4)	36.2 (20.3)	29.7 (20.8)
In-hospital mortality rate, n (%)	50 (56.2)	30 (46.2)	18 (26.5)	40 (54.1)	19 (21.3)	157 (40.8)
With MDR pathogen, n/N (%)	15/20 (75.0)	8/23 (34.8)	5/14 (35.7)	16/22 (72.7)	6/33 (18.2)	50/112 (44.6)
Without MDR pathogen, n/N (%)	20/44 (45.5)	12/25 (48.0)	7/30 (23.3)	9/21 (42.9)	9/38 (23.7)	57/158 (36.1)
30-day mortality rate, n (%)	50 (56.2)	30 (46.2)	18 (26.5)	40 (54.1)	20 (22.5)	158 (41.0)
With MDR pathogen, n/N (%)	15/20 (75.0)	8/23 (34.8)	5/14 (35.7)	16/22 (72.7)	7/33 (21.1)	51/112 (45.5)
Without MDR pathogen, n/N (%)	20/44 (45.5)	12/25 (48.0)	7/30 (23.3)	9/21 (42.9)	9/38 (23.7)	57/158 (36.1)
Number of days from initiation of IAT to patient's death (within 30 days of discharge), mean (SD)	19.6 (17.2)	18.7 (20.7)	15.8 (13.0)	18.4 (15.5)	41.6 (47.9)	21.5 (24.2)

**Notes:** <sup>a</sup>IAT failure defined as discontinuation of the antibiotic regimen for reasons other than cure/improvement in symptoms, including dose increase or addition of another antibiotic beyond 48 hours of treatment, in-hospital death of any cause or readmission due to recurrence of the same infection within 30 days of discharge. Streamlining, de-escalation or switch to oral antibiotics was not considered as treatment failure.

**Abbreviations:** IAT, initial antibiotic treatment; LOS, length of hospital stay; MDR, multidrug resistant, NA, not applicable.

MDR pathogen identified were roughly similar (Figure 3). In the overall cohort of patients with an MDR pathogen identified, the in-hospital and 30-day post-discharge mortality rates were also slightly higher than in those with no MDR pathogen identified. However, this was not consistently reflected across countries (Table 4).

## Univariate and multivariate factors associated with IAT failure

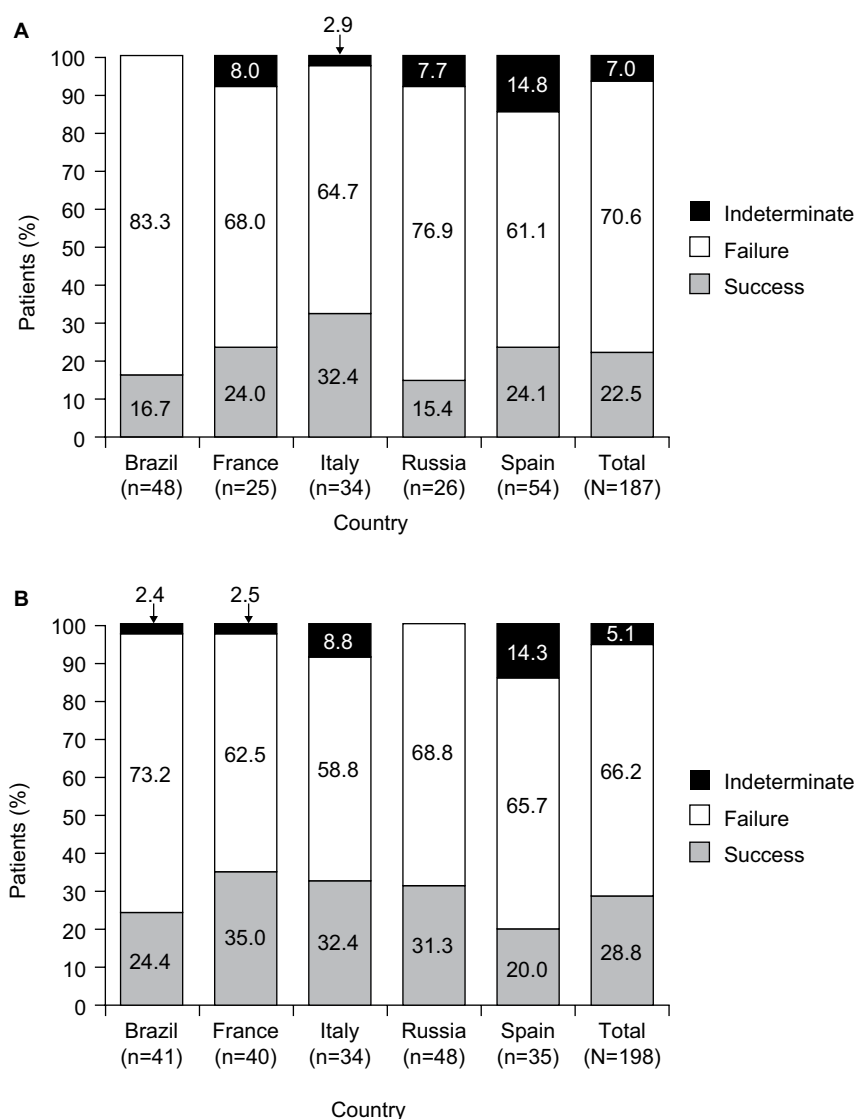
Factors associated with IAT failure identified by the univariate (unadjusted) analysis ( $P \leq 0.25$ ) for consideration in the multivariate analysis were age; country; intensive care unit (ICU) admission; DCCS; site-level resistance to third-generation cephalosporins, third-generation carbapenems, or combined site-level resistance to both; patient-level presence of MDR pathogens; prior hospitalization within 90 days prior to the index hospitalization and treatment with  $\beta$ -lactams within 90 days prior to the index hospitaliza-

tion (Table 5). Accounting for these confounding factors, a multivariate model was developed. The final model had a Hosmer–Lemeshow  $\chi^2$  value of 1.3467 with five degrees of freedom ( $P=0.9301$ ), indicating no evidence of lack of fit. The final model also had deviance and Pearson  $\chi^2$  values of 138.01 and 128.03 with 116 degrees of freedom ( $P=0.0799$  and  $P=0.2097$ ), respectively, indicating no evidence to reject the fitted model. Using this model, three predictive factors with a statistically significant association with IAT failure ( $P \leq 0.05$ ) were identified: patients admitted or transferred to an ICU setting during their index hospitalization ( $P=0.024$ ), patient-level isolation of an MDR pathogen ( $P<0.001$ ) and treatment with  $\beta$ -lactam antibiotics within 3 months prior to the index diagnosis ( $P=0.025$ ).

## Discussion

IAT treatment patterns, outcomes and potential risk factors for IAT failure in patients with health care-associated





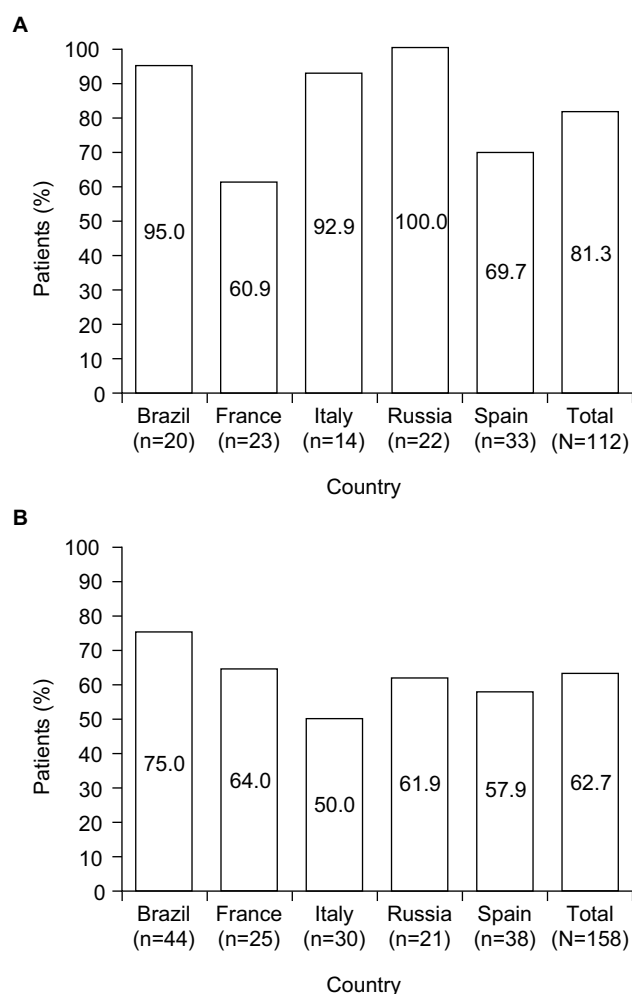
**Figure 2** Clinical outcomes of initial antibiotic therapy in patients receiving (A) monotherapy or (B) combination therapy.

infections, including cIAI, were assessed with a view to presenting a practicable insight into clinical management across Brazil, France, Italy, Spain and Russia. This is one of the first studies to look at the real-world outcomes and treatment patterns across these countries in patients with health care-associated cIAI.

Patient and disease characteristics and pathogen identification documented here were in line with the few other observational studies that have looked at clinical, microbiological and treatment profiles of community- and health care-acquired cIAIs.<sup>5,22</sup> Importantly, the frequency of comorbidities and previous number of admissions were high in this cohort. The most commonly observed pathogens (*E. coli*, *Klebsiella* spp. and *P. aeruginosa*)

were reflective of those that have previously been associated with cIAI in more stringently selected populations within clinical trials<sup>21,23</sup> and those observed in surveillance studies.<sup>9</sup> Of note, the proportion of patients from whom anaerobes were isolated was heterogeneous, which may reflect differences in sampling and microbiological procedures.

Across all countries in this study, IAT failure was observed in over two-thirds of patients. Failure rates were high (>60%) in each individual country, with higher rates observed in Brazil and Russia. The percentage of patients with an indeterminate outcome was low across all countries and unlikely to have affected the results observed. The high rate of failure may be due, in part, to the patient population



**Figure 3** Initial antibiotic therapy failure in patients (A) with and (B) without multi-drug-resistant pathogens identified.

included and the definition of IAT failure used. However, such criteria reflect real-world antibiotic use in this group of patients.

In critically ill patients, empiric IAT has an integral role in the success of treating health care-associated infections.<sup>16–19</sup> Appropriate IAT choice is an important contributing factor to the likelihood of treatment success.<sup>1</sup> Treatment guidelines advise that IAT for IAI should comprise a spectrum covering possible etiological pathogens, including Gram-negatives and anaerobes.<sup>12,24</sup> This can be monotherapy active against both or combination therapies that provide the coverage required. IAT should also be tailored to account for known local intrinsic resistance mechanisms of likely etiological pathogens and, in the health care-associated setting, coverage for *P. aeruginosa* and Gram-positive bacteria such as *Enterococcus* spp. is recommended.<sup>1,25</sup>

In the present study, large inter-country variation was observed in the specific antibiotics used, potentially due to differences in the availability and cost of antibiotics across the different countries or the prescribing patterns accounting for local resistance patterns. However, from the relatively high level of IAT failure observed and the proportion of patients with perceived clinical failure requiring subsequent lines of antibiotic therapy, IAT selection in some of these patients might have been suboptimal, providing limited or compromised efficacy against the subsequently identified pathogens.

With an ever-increasing prevalence of MDR pathogens isolated from cIAIs, antimicrobial resistance among health care-associated pathogens has been identified as one of the major challenges in the management of cIAI.<sup>7,9,22</sup> In the present study, just under half of the patients with pathogens identified had an MDR pathogen isolated. This is consistent with the literature, which shows a higher proportion of MDR pathogens among health care-associated infections than community-acquired infections.<sup>6</sup> The definition of MDR in this study was in line with that proposed in a European Center for Disease Prevention and Control and Centers for Disease Control and Prevention initiative.<sup>26</sup> The multivariate analyses performed demonstrate that the presence of an MDR pathogen and treatment with  $\beta$ -lactam antibiotics within the 3 months prior to index infection are associated with an increased risk of IAT failure. It is noteworthy that it was specifically pretreatment with  $\beta$ -lactam antibiotics and not any other pretreatment that was significantly associated with IAT failure. While it is expected that the use of previous antibiotics would select patients with drug-resistant pathogens, the effect of previous  $\beta$ -lactam use was independent of isolation of an MDR pathogen. These data support the importance of understanding and interpreting treatment guidelines to account for patient history and the local epidemiology.<sup>14,16,27,28</sup>

In addition to high IAT failure rates, the overall mortality rates observed here were higher than the average mortality rates seen in other observational studies (typically around 10% or less), which mostly included less-complicated community-acquired infections.<sup>5,22,29,30</sup> However, it is recognized that the cause of death has not been analyzed and may not be related to the index infection.

Limitations of this study pertained mostly to its retrospective design, which limited data availability to information in the patient record and, given the relative ease of enrolling deceased vs living patients, may have favored the selection of a more severely ill patient population. Severity of illness may be reflected in the relatively high proportion of patients who were admitted or transferred to the ICU and may explain the

**Table 5** Statistical predictors of initial antibiotic treatment failure – univariate and multivariate analyses

Potential risk factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, years				
18–44 <sup>a</sup>	Reference	0.050 <sup>b</sup>	–	–
45–64	1.42 (0.70, 2.89)		–	–
≥65	2.14 (1.07, 4.26)		–	–
Gender				
Female <sup>a</sup>	Reference	0.785		
Male	0.94 (0.61, 1.45)			
Country				
Spain <sup>a</sup>	Reference	0.093 <sup>b</sup>	–	–
Brazil	2.17 (1.12, 4.22)		–	–
France	1.08 (0.55, 2.09)		–	–
Italy	0.95 (0.50, 1.83)		–	–
Russia	1.49 (0.77, 2.89)		–	–
Number of days in hospital before the start of IAT				
0–7 <sup>a</sup>	Reference	0.393	–	–
8–14	0.67 (0.35, 1.28)		–	–
15–30	0.69 (0.31, 1.51)		–	–
>30	0.50 (0.15, 1.69)		–	–
ICU admission (initial admission or transfer)				
No <sup>a</sup>	Reference	<0.001 <sup>b</sup>	Reference	–
Yes	2.31 (1.48, 3.59)		2.49 (1.13, 5.51)	0.024
DCCS				
0 <sup>a</sup>	Reference	0.080 <sup>b</sup>	–	–
1–2	1.16 (0.68, 1.96)		–	–
3–4	2.10 (1.08, 4.06)		–	–
≥5	1.77 (0.92, 3.42)		–	–
Site-level resistance to third-generation cephalosporins <sup>c</sup>				
No <sup>a</sup>	Reference	0.132 <sup>b</sup>	–	–
Yes	0.99 (0.98, 1.00)		–	–
Site-level resistance to third-generation carbapenems <sup>c</sup>				
No <sup>a</sup>	Reference	0.032 <sup>b</sup>	–	–
Yes	0.99 (0.98, 1.00)		–	–
Combined site-level resistance to third-generation cephalosporins and carbapenems <sup>c</sup>				
No <sup>a</sup>	Reference	0.001 <sup>b</sup>	–	–
Yes	0.98 (0.96, 0.99)		–	–
Patient-level presence of MDR pathogen				
No <sup>a</sup>	Reference	<0.001 <sup>b</sup>	Reference	–
Yes	2.58 (1.46, 4.58)		5.45 (2.05, 14.52)	<0.001
Hospitalized within 90 days prior to the index hospitalization				
No <sup>a</sup>	Reference	0.019 <sup>b</sup>	–	–
Yes	1.78 (1.09, 2.91)		–	–
Treated with $\beta$ -lactam antibiotic within the past 3 months				
No <sup>a</sup>	Reference	0.008 <sup>b</sup>	Reference	–
Yes	2.03 (1.18, 3.52)		3.20 (1.15, 8.87)	0.025

**Notes:** In this analysis, treatment outcome is either failure or success/indeterminate. The logistic regression coding is: 1= failure, 0= success or indeterminate. <sup>a</sup>Reference category. <sup>b</sup>Variables identified as significant in the univariate logistic regression analysis ( $P \leq 0.25$ ) were analyzed by multivariate logistic regression analysis. Data shown are from the final model using the stepwise backward selection process; therefore, only significant data that remained in the final model for the multivariate analysis are shown. <sup>c</sup>On-site level of antibiotic resistance of Gram-negative isolates to third-generation cephalosporins, carbapenems or both combined.

**Abbreviations:** DCCS, Deyo-Charlson comorbidity score; IAT, initial antibiotic treatment; ICU, intensive care unit; MDR, multidrug resistant.

association of this factor with IAT failure during multivariate analysis, although this should be interpreted with caution due to differences in hospital requirements and practice patterns for admission to the ICU. Given a lack of consensus on the definition for IAT failure, the study used a composite definition, which included additional interventions for infection source control and death due to any cause. With the relatively high level of comorbid conditions in these patients and their underlying medical conditions, inclusion of all-cause death may have overestimated the rate of IAT failure and led to worse outcomes than those observed in other published literature in this area.

Despite these limitations, the present study provides a global, real-world insight into current treatment patterns for patients with cIAI, the impact of IAT failure in patients who have been treated according to current cIAI practice and the potential risk factors associated with IAT failure. These data reiterate the challenges presented when choosing IAT, as well as the need for ongoing epidemiological studies and communication between microbiologists and prescribing physicians that will assist in providing a more tailored approach to IAT selection. This study was unique in looking specifically at the risk factors associated with IAT failure and in using IAT failure as an endpoint. With the paramount importance of effective early antibiotic treatment in cIAI, a broader awareness of local resistance epidemiology and further understanding of the influence of these risk factors on IAT and overall clinical outcome will help guide IAT selection and cIAI management.

## Data sharing

Upon request, and subject to certain criteria, conditions and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices: 1) for indications that have been approved in the USA and/or European Union; or 2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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## Author contributions

EB was the project manager in charge of study delivery. PP was in charge of data interpretation and study report generation. SR-F was in charge of all data analyses from generation of the statistical analysis plan to creation of the final data tables and revision of the study reports. JR-B was the scientific coordinator of the study. Project management within AstraZeneca was provided at different time points by Kamil Jedynski, Yasmina Tazir and Dominic Lim. All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

## Disclosure

KR and DP are employees of and shareholders in AstraZeneca. SK is a former employee of and shareholder in AstraZeneca. EB and PP are employees of IQVIA (formerly QuintilesIMS), Real-World Insights. SR-F is a former employee of IQVIA (formerly QuintilesIMS), Real-World Insights. JR-B was a scientific consultant for AstraZeneca, Merck, Achaogen and InfectoPharm and has been a speaker in accredited educational activities for Merck. JR-B also receives funding for research

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## Supplementary materials

**Table S1** IECs and IRBs consulted

Center number	Name and address of IEC/IRB	Date of approval
0101	Conselho Municipal de Saúde de Porto Alegre (Porto Alegre Municipal Board of Health) Ramiro Barcelos, 2350 – Porto Alegre/RS 90035-903 Brazil	2 December 2015
0102	Local Ethics Committee for Human Research of the PUC-Campinas (C.E.P.S.H.P.) Rod. Dom Pedro I, Km 136 – Pq. das Universidades – Campinas – SP (São Paulo), Brazil	24 August 2015
0103	Local Ethics Committee of Santa Casa de Misericórdia de Belo Horizonte Rua Domingos Vieira 590, Santa Efigênia 30.150-240, MG (Minas Gerais) Belo Horizonte, Brazil	26 October 2015
0104	Pontifícia Universidade Católica do Rio Grande do Sul ("PUCRS") Research, Innovation & Development Pro-rector's Office Partenon 90.619-900 RS Porto Alegre, Brazil	15 November 2015
0201	Comitato Etico Università Sapienza Azienda Policlinico Umberto I Viale del Policlinico, 155 00162 Roma, Italy	12 February 2015
0202	Comitato Etico dell'IRCCS Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani di Roma Via Portuense 292-00149 Rome, Italy	17 February 2015
0203	Al Comitato Etico per la sperimentazione clinica della Provincia di Vicenza c/o Ospedale S. Bortolo viale Rodolfi 37 36100 Vicenza, Italy	10 April 2015
0204	Comitato Etico Indipendente dell'Azienda Ospedaliero- Universitaria di Bologna, Policlinico S. Orsola-Malpighi Padiglione 3 – Via Albertoni, 15-40138 Bologna, Italy	4 March 2015
0205	Spedali Civili – Brescia Comitato Etico Provinciale Provincia di Brescia P.le Spedali Civili, 1-25123 Brescia, Italy	14 January 2015
0206	Comitato Etico della Provincia Monza Brianza Via Pergolesi, 33-20090 Monza, Italy	2 March 2015
0301	Germans Trias i Pujol Hospital Research Ethics Committee Ctra. De Canyet, s/n – 08,916 Badalona, Spain	13 January 2015
0302	Clinical Research Ethics Committee of Hospital Universitari Mútua de Terrassa Plaza Dr Robert, 5 08221 Terrassa, Barcelona, Spain	18 December 2014
0303	CREC – Parc de Salut MAR Dr Aiguader, 88, 08003 Barcelona, Spain	13 January 2015
0304	Clinical Research Ethics Committee of Hospital Clínic de Barcelona Villarroel, 170-08036 Barcelona, Spain	12 January 2015
0305	Coordinating Biomedical Research Ethics Committee of Andalusia Hospital Universitario Virgen Macarena 2° Planta. Avda. Dr Fedriani, 3 41071 Sevilla, Spain	12 December 2014
0306	Research Ethics Committee of the Principality of Asturias C/ Celestino Villamil s/n 33006 Oviedo, Spain	29 January 2015
0501	Moscow City Health Department, The State-Financed Health care Institution Municipal Clinical Hospital No. 12 Ethics Committee, 26 Bakinskaya St., Moscow 115516, Russia	6 February 2015
0502	EXPERT Ethics Committee at SPB SBHI (St Petersburg State Budgetary Health care Institution) City Hospital No. 40 9 Borisova Street, Sestroretsk, St Petersburg 197706, Russia	19 January 2015
0503	The Local Ethics Committee of the St Petersburg State Budgetary Health Institution, Mariinskaya City Hospital Liteyny Ave, 56, St Petersburg, Russia	30 December 2014
0505	Ethics Committee, State Budgetary Institution of Health care (SBIH) of Novosibirsk Region (NR) City Clinical Hospital (CCH) No. 25 of Novosibirsk 630075, Novosibirsk, 1a Alexander Nevsky Street, Russia	16 February 2015

**Abbreviations:** IEC, independent ethics committee; IRB, institutional review board.

**Table S2** Bacterial pathogens identified in specimen samples, including multidrug-resistant organisms, overall and by country

Bacterial pathogen <sup>a</sup>	Brazil (n=67) <sup>b</sup>	France (n=65)	Italy (n=68)	Russia (n=74)	Spain (n=89)	Total (N=363) <sup>b</sup>
n	64	48	44	43	71	270
Gram-negative, n (%) <sup>c</sup>	50 (78.1)	35 (72.9)	34 (77.3)	39 (90.7)	63 (88.7)	221 (81.9)
<i>Escherichia coli</i>	31 (48.4)	21 (43.8)	19 (43.2)	17 (39.5)	39 (54.9)	127 (47.0)
<i>Klebsiella</i> spp.	11 (17.2)	3 (6.3)	6 (13.6)	17 (39.5)	9 (12.7)	46 (17.0)
<i>Pseudomonas aeruginosa</i>	4 (6.3)	5 (10.4)	3 (6.8)	1 (2.3)	17 (23.9)	30 (11.1)
<i>Enterobacter</i> spp.	7 (10.9)	3 (6.3)	8 (18.2)	0 (0.0)	5 (7.0)	23 (8.5)
<i>Acinetobacter</i> spp.	4 (6.3)	0 (0.0)	1 (2.3)	6 (14.0)	3 (4.2)	14 (5.2)
<i>Proteus</i> spp.	1 (1.6)	1 (2.1)	0 (0.0)	1 (2.3)	4 (5.6)	7 (2.6)
<i>Citrobacter</i> spp.	0 (0.0)	1 (2.1)	1 (2.3)	0 (0.0)	2 (2.8)	4 (1.5)
<i>Serratia</i> spp.	0 (0.0)	1 (2.1)	0 (0.0)	2 (4.7)	1 (1.4)	4 (1.5)
<i>Morganella morganii</i>	1 (1.6)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
<i>Haemophilus</i> spp.	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
<i>Salmonella</i> spp.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.4)
Other	1 (1.6)	2 (4.2)	2 (4.5)	0 (0.0)	7 (9.9)	12 (4.4)
Gram-positive, n (%) <sup>c</sup>	20 (31.3)	19 (39.6)	18 (40.9)	6 (14.0)	29 (40.8)	92 (34.1)
<i>Enterococcus</i> spp.	8 (12.5)	15 (31.3)	8 (18.2)	5 (11.6)	18 (25.4)	54 (20.0)
<i>Staphylococcus</i> spp.	11 (17.2)	4 (8.3)	7 (15.9)	0 (0.0)	7 (9.9)	29 (10.7)
<i>Streptococcus</i> spp.	2 (3.1)	2 (4.2)	4 (9.1)	1 (2.3)	7 (9.9)	16 (5.9)
Other	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	1 (1.4)	2 (0.7)
Anaerobic bacteria, n (%) <sup>c</sup>	0 (0.0)	9 (18.8)	2 (4.5)	0 (0.0)	10 (14.1)	21 (7.8)
<i>Bacteroides</i> spp.	0 (0.0)	6 (12.5)	2 (4.5)	0 (0.0)	7 (9.9)	15 (5.6)
<i>Clostridium</i> spp.	0 (0.0)	2 (4.2)	0 (0.0)	0 (0.0)	2 (2.8)	4 (1.5)
<i>Prevotella</i> spp.	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.4)
Other bacterial agent, n (%) <sup>c</sup>	1 (1.6)	2 (4.2)	0 (0.0)	0 (0.0)	3 (4.2)	6 (2.2)
Multidrug-resistant pathogen, n (%) <sup>c</sup>						
Yes	20 (31.3)	23 (47.9)	14 (31.8)	22 (51.2)	33 (46.5)	112 (41.5)
No	44 (68.8)	25 (52.1)	30 (68.2)	21 (48.8)	38 (53.5)	158 (58.5)
Missing	25	17	24	31	18	115
Fungal pathogen, n (%) <sup>d</sup>	2 (3.0)	8 (12.3)	5 (7.4)	0 (0.0)	15 (16.9)	30 (8.3)

**Notes:** <sup>a</sup>Patients could have more than one pathogen type identified. <sup>b</sup>Data missing for 22 patients in Brazil. <sup>c</sup>Percentages are calculated as a proportion of those patients with  $\geq 1$  bacterial pathogen identified. <sup>d</sup>Percentages are calculated as a proportion of the overall population.

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