Observational Study Report Synopsis

Drug Substance Not Applicable

Study Code D4280R00005

EudraCT Number Not Applicable

RECOMMEND Study

Reporting patterns and results of initial antibiotic treatment in patients with complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI) and nosocomial pneumonia (NP) including ventilator-associated pneumonia (VAP)

Study dates: First subject enrolled: 18 February 2015
Last subject last visit: 10 February 2016

Phase of development: Not Applicable – Observational study

This study was performed in compliance with Good Pharmacoepidemiology Practices, including the archiving of essential documents.

Study centres

Twenty-six hospital sites from Brazil (n=4), France (n=6), Italy (n=6), Spain (n=6) and Russia (n=4). Except in Russia, the majority of participating sites were tertiary care hospitals.

Publications

- Karve S, Ryan K, Pascual, E, Peeters P, Rojas-Farreras S, Baelen E, Rodriguez-Baño J. IDWeek 2016, October 26–30, 2016, New Orleans, LA, USA (poster 319).
- Karve S, Ryan K, Peeters P, Baelen E, Tazir Y, Rojas-Farreras S, Potter D, Rodriguez-Baño J. 26th European Congress of Clinical Microbiology and Infectious Diseases, 9-12 April 2016, Amsterdam, the Netherlands (poster P1477).
- Peeters P, Ryan K, Karve S, Potter D, Baelen E, Rojas-Farreras S, Pascual E, Rodriguez-Baño J. 26th European Congress of Clinical Microbiology and Infectious Diseases, 9-12 April 2016, Amsterdam, the Netherlands (poster EV0222).
- Karve S, Ryan K, Peeters P, Baelen E, Potter D, Rojas-Farreras S, Tazir Y, Pascual E, Rodriguez-Baño J. 26th European Congress of Clinical Microbiology and Infectious Diseases, 9-12 April 2016, Amsterdam, the Netherlands (poster EP0097).

Objectives and criteria for evaluation

The overall objective of this non-interventional cohort study was to describe the clinical management patterns of hospitalized patients with hospital-acquired or healthcare-associated complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI) and nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), across the five participating countries.

Table S1 Objectives and outcome variables

Objective		Outcome Variable
Priority	**Description**	**Description**
Primary	To describe and evaluate antibiotic management and document treatment outcome (i.e., treatment success, failure, indeterminate) associated with initial antibiotic treatment (IAT) among hospitalized patients with hospital-acquired or healthcare-associated cUTI, cIAI or NP (including VAP) in participating countries (France, Italy, Spain, Russia, and Brazil). IAT failure and success were assessed by patient, disease, pathogen and site characteristics, and type of IAT.	Proportion of patients with failure, success, or indeterminate IAT outcome, overall and by type of IAT (monotherapy, combination therapy).
Secondary	To identify potential risk factors related to outcomes (i.e., treatment success, failure, indeterminate) of IAT of hospitalized patients with hospital-acquired or healthcare-associated cUTI, cIAI or NP in participating countries, by assessment of the association between outcomes of IAT and the following: baseline patient, disease, pathogen and site characteristics and IAT patterns (i.e., monotherapy vs. combination therapy, first-line antibiotic regimens).	Association of predictors (including multi-drug resistant pathogen) with IAT failure (Odds ratios [ORs]).
Secondary	To describe healthcare utilization and costs associated with IAT outcome (i.e., treatment failure, success or indeterminate) in participating countries.	Length of stay (LOS) in hospital, surgical and other procedures, days on antibiotics, healthcare costs*.

*: Costs are not included in this synopsis.

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 cIAI patients).

A multi-drug resistant (MDR) pathogen infection was defined for the three conditions of interest as resistance to at least one drug in any three of the following drug classes - aminoglycosides, amphenicol, beta-lactams, carbapenems, cephalosporins, glycopeptides, glycylcicline, macrolides, mono bactam, nitroimidazole, oxalolidinones, penicillins, penicillins + beta-lactamase inhibitors, quinolones, streptogramins, tetracycline, and lipopeptides.

Study Design

This was a retrospective, multi-country, multi-center, non-interventional cohort study based on hospital medical records review of adult patients hospitalized for one of three conditions of interest (cUTI, cIAI, and NP, including VAP) in the period from July 01, 2013 through June 30, 2014. Patient selection was based on clinical definition of cases irrespective of pathogen identification. Enrolled patients were followed up through their medical records from index date (defined as the date of index diagnosis) until 30 days post-discharge from their index hospitalization, death while hospitalized or the end of study period (December 31, 2014), if not yet discharged alive from index hospitalization. Each site could accrue a maximum of 40 patients per type of infection.

Statistical methods

Descriptive statistics were provided for the IAT, including type of antibiotics, monotherapy or combination therapy, number of treatment days, reason for discontinuation, and treatment outcome. The relationships between MDR infection, IAT failure and mortality were explored through sub-group analyses. Logistic regression analyses were used separately for each of the three total cohorts (cUTI, cIAI, and NP) to explore the association of potential risk factors with IAT failure. Resource utilization was described and compared by IAT outcome using non-parametric statistics at 5% level of significance.

Subject population

Across the three conditions of interest and the five countries, 1,321 patients were included in the study, of which 1,244 (94.2%) patients had complete start and stop dates for IAT and comprised the Full Analysis Set (FAS). This included 408 patients with cUTI, 385 patients with cIAI, and 451 patients with NP. Of note, one site in Brazil included only patients (n=73) who were deceased at the time of data collection, with 100% IAT failure rate for the three conditions of interest.

Table S2 Number of patients per country and condition of interest (FAS)

Number of patients in FAS	Brazil	France	Italy	Russia	Spain	Total
cUTI	82	63	65	85	113	408
cIAI	89	65	68	74	89	385
NP	100	91	64	76	120	451
Grand Totals	271	219	197	235	322	1244

FAS: full analysis set; cUTI: complicated urinary tract infection; cIAI: complicated intra-abdominal infection; NP: nosocomial pneumonia.

Baseline characteristics of the three total cohorts were the following:

- cUTI (n=408): mean age 68.7 years; 51.7% female; most common comorbidities: hypertension, diabetes, renal insufficiency, cerebrovascular disease, malignancy.
- cIAI (n=385): mean age 64.4 years; 56.4% male; most common comorbidities: hypertension, malignancy, diabetes.
- NP (n=451): mean age 66.0 years; 66.3% male; most common comorbidities: hypertension, diabetes, malignancy, chronic obstructive pulmonary disease.

Main results

cUTI

Except in Italy, the majority of patients had hospital-acquired cUTI (n=212/408, 52.0%; range across countries: 36.9% [Italy] to 61.9% [France]); 357 patients (87.5%) had microbiological documentation. Gram-negative pathogens were isolated in 308 patients (n=308/357, 86.3%; range across countries: 77.4% [Russia] to 91.3% [Spain]); the most frequent were *E. coli* (47.1% of patients with microbiological documentation), *Klebsiella* spp. (21.6%), *P. aeruginosa* (11.8%), *Enterobacter* spp. (6.4%), and *Proteus* spp. (6.2%). Gram-positive pathogens were identified in 82 patients (n=82/357, 23.0%; range across countries: 17.5% [Brazil] to 30.2% [Russia]), including *Enterococcus* spp. (15.7%) and *Staphylococcus* spp. (6.4%). *E. coli* was the most frequent isolate in all countries except in Russia, where it was surpassed by *Klebsiella* spp. An MDR pathogen was identified in 46.1% of patients with microbiological documentation (range across countries: 35.0% [France] to 56.6% [Russia]). The proportion of MDR pathogens resistant to carbapenems was 28.0% in the total cUTI cohort (range across countries: 14.3% [France] to 40.0% [Spain]).

IAT characteristics and outcomes (cUTI)

Total cUTI cohort (n=408): 72.5% of patients (n=296/408) were treated by monotherapy IAT, and 27.5% (n=112/408) by a combination of antibiotics. The most common antibiotics (all regimens) were ceftriaxone (n=109/408, 26.7%), ciprofloxacin (n=83/408, 20.3%), and piperacillin-tazobactam (n=52/408, 12.7%). The mean IAT duration was 7.8 days (median: 7.0, n=408) for all regimens, 7.4 days (median: 6.0, n=296) for monotherapy, and 8.9 days (median: 7.0, n=112) for combination therapy. The IAT failure rate was 54.4% (n=222/408) overall, 47.6% (n=141/296) for monotherapy and 72.3% (n=81/112) for combination therapy. Mortality rates were 35.0% (n=143/408) in-hospital and 37.3% (n=152/408) at 30-day post-discharge. Patients with an MDR infection (n=164) had numerically higher IAT failure rate (61.6% vs. 50.0%) and mortality rates (in-hospital: 39.6% vs. 29.7%; 30-day: 42.1% vs. 31.8%) compared to patients without an MDR infection (n=192). Mean LOS per IAT outcome was: success 23.2 days (n=155), failure 31.3 days (n=222), indeterminate 27.0 days (n=31) (success vs. failure/indeterminate: p=0.0053).

Brazil (n=82): 79.3% of patients on monotherapy IAT; most used antibiotics, ciprofloxacin (30.5%) and piperacillin-tazobactam (12.2%); mean IAT duration, overall 6.7 days (median: 5.5, n=82), monotherapy 6.0 days (median: 5.0, n=65), combination therapy 9.5 days (median: 7.0, n=17). IAT failure rate, overall 74.4%, monotherapy 67.7%, combination therapy 100%; in-hospital mortality rate 46.3%; 30-day mortality rate 47.6%. Patients with an MDR infection (n=30) had numerically higher IAT failure rate (86.7% vs. 66.0%) and mortality rates (in-

hospital: 70.0% vs. 32.0%; 30-day: 73.3% vs. 32.0%) than patients without an MDR infection (n=50). Mean LOS per IAT outcome: success 29.0 days (n=21), failure 43.5 days (n=61) (success vs. failure/indeterminate: p=0.0006).

France (n=63): 61.9% of patients on monotherapy IAT; most used antibiotics, ceftriaxone (49.2%) and piperacillin-tazobactam (20.6%); mean IAT duration, overall 8.7 days (median: 8.0, n=63), monotherapy 8.3 days (median: 8.0, n=39), combination therapy 9.4 days (median: 8.5, n=24). IAT failure rate, overall 50.8%, monotherapy 33.3%, combination therapy 79.2%; in-hospital mortality rate 36.5%; 30-day mortality rate 41.3%. Patients with an MDR infection (n=21) had numerically comparable IAT failure rate (47.6% vs. 51.3%) and lower mortality rates (in-hospital: 23.8% vs. 43.6%; 30-day: 33.3% vs. 46.2%) than patients without an MDR infection (n=39). Mean LOS per IAT outcome: success 32.9 days (n=27), failure 37.9 days (n=32), indeterminate 30.3 days (n=4) (success vs. failure/indeterminate: p=0.4559).

Italy (n=65): 87.7% of patients on monotherapy IAT; most used antibiotics, piperacillin-tazobactam (18.5%) and ciprofloxacin (12.3%); mean IAT duration, overall 9.6 days (median: 9.0, n=65), monotherapy 9.6 days (median: 9.0, n=57), combination therapy 9.5 days (median: 6.0, n=8). IAT failure rate, overall 40.0%, monotherapy 35.1%, combination therapy 75.0%; in-hospital mortality rate 20.0%; 30-day mortality rate 21.5%. Patients with an MDR infection (n=33) had numerically higher IAT failure rate (48.5% vs. 33.3%) and similar mortality rates (in-hospital and 30-day: 18.2% vs. 22.2%) as patients without an MDR infection (n=27). Mean LOS per IAT outcome: success 24.3 days (n=36), failure 30.2 days (n=26), indeterminate 13.0 days (n=3) (success vs. failure/indeterminate: p=0.4906).

Russia (n=85): 61.2% of patients on monotherapy IAT; most used antibiotics, ceftriaxone (42.4%), ciprofloxacin (35.3%), and metronidazole (18.8%); mean IAT duration, overall 8.1 days (median: 7.0, n=85), monotherapy 7.8 days (median: 7.0, n=52), combination therapy 8.6 days (median: 8.0, n=33). IAT failure rate, overall 67.1%, monotherapy 69.2%, combination therapy 63.6%; in-hospital and 30-day mortality rates 61.2%. Patients with an MDR infection (n=30) had numerically comparable IAT failure rate (76.7% vs. 73.9%) and higher mortality rates (in-hospital and 30-day: 70.0% vs. 60.9%) than patients without an MDR infection (n=23). Mean LOS per IAT outcome: success 16.2 days (n=24), failure 16.9 days (n=57), indeterminate 35.3 days (n=4) (success vs. failure/indeterminate: p=0.8492).

Spain (n=113): 73.5% of patients on monotherapy IAT; most used antibiotics, ceftriaxone (25.7%), amoxicillin-clavulanic acid (21.2%), and ciprofloxacin (15.9%); mean IAT duration, overall 6.9 days (median: 5.0, n=113), monotherapy 6.4 days (median: 5.0, n=83), combination therapy 8.3 days (median: 6.0, n=30). IAT failure rate, overall 40.7%, monotherapy 33.7%, combination therapy 60.0%; in-hospital mortality rate 15.0%; 30-day mortality rate 18.6%. Patients with an MDR infection (n=50) had numerically higher IAT failure rate (52.0% vs. 32.1%) and mortality rates (in-hospital: 24.0% vs. 7.5%; 30-day: 26.0% vs. 13.2%) than patients without an MDR infection (n=53). Mean LOS per IAT outcome: success 17.9 days (n=47), failure 29.3 days (n=46), indeterminate 26.8 days (n=20) (success vs. failure/indeterminate: p=0.0022).

Statistical Predictors of IAT Failure (cUTI)

In the total cUTI cohort, two predictive factors showed a statistically significant association with IAT failure: age class (p=0.003) with highest odds of IAT failure in patients aged ≥ 65 years (OR=8.73, 95% CI [1.89; 40.38]; reference group: 18-44 age class); and country (other countries combined vs. Spain used as reference, p<0.001), with highest odds of IAT failure in Brazil (OR=22.29, 95% CI [5.13; 96.89]) and Russia (OR=8.52, 95% CI [3.17; 22.92]) than in the reference country (Spain).

cIAI

The majority of patients had hospital-acquired cIAI (n=239/385, 62.1%; range across countries: 53.9% [Brazil] to 74.3% [Russia]); 270 patients (70.1%) had microbiological documentation. Gram-negative pathogens were isolated in 221 patients (n=221/270, 81.9%; range across countries: 72.9% [France] to 90.7% [Russia]); the most frequent were *E. coli* (47.0% of patients with microbiological documentation), *Klebsiella* spp. (17.0%), *P. aeruginosa* (11.1%), *Enterobacter* spp. (8.5%), and *Acinetobacter* spp. (5.2%). Gram-positive pathogens were identified in 92 patients (n=92/270, 34.1%; range across countries: 14.0% [Russia] to 40.9% [Italy]), including *Enterococcus* spp. (20.0%), *Staphylococcus* spp. (10.7%), and *Streptococcus* spp. (5.9%). *E. coli* was the most frequent isolate in all countries except in Russia, where it was matched by *Klebsiella* spp. An MDR pathogen was identified in 41.5% of patients with microbiological documentation (range across countries: 31.3% [Brazil] to 51.2% [Russia]). The proportion of MDR pathogens resistant to carbapenems was 31.3% in the total cIAI cohort (range across countries: 13.0% [France] to 40.0% [Brazil].

IAT characteristics and outcomes (cIAI)

Total cIAI cohort (n=385): 48.6% of patients (n=187/385) were treated by a monotherapy IAT, and 51.4% (n=198/385) by a combination of antibiotics. The most common antibiotics (all regimens) were metronidazole and piperacillin-tazobactam (n=110/385, 26.8% each), and ceftriaxone (15.8%). The mean IAT duration was 11.1 days (median: 9.0, n=385) for all regimens, 9.2 days (median: 8.0, n=187) for monotherapy, and 12.8 days (median: 10.0, n=198) for combination therapy. The IAT failure rate was 68.3% (n=263/385) overall, 70.6% (n=132/187) for monotherapy and 66.2% (n=131/198) for combination therapy. Mortality rates were 40.8% (n=157/385) in-hospital and 41.0% (n=158/385) at 30-day post-discharge. Patients with an MDR infection (n=112) had numerically higher IAT failure rate (81.3% vs. 62.7%) and mortality rates (in-hospital: 44.6% vs. 36.1%; 30-day: 45.5% vs. 36.1%), compared to patients without an MDR infection (n=158). Mean LOS per IAT outcome was: success 27.5 days (n=99), failure 29.3 days (n=263), indeterminate 29.7 days (n=23) (success vs. failure/indeterminate: p=0.0059).

Brazil (n=89): 53.9% of patients on monotherapy IAT; most used antibiotics, metronidazole and ciprofloxacin (25.8% each), and ampicillin-sulbactam (24.7%); mean IAT duration, overall 8.6 days (median: 7.0, n=89), monotherapy 8.5 days (median: 7.0, n=48), combination therapy 8.6 days (median: 7.0, n=41). IAT failure rate, overall 78.7%, monotherapy 83.3%, combination therapy 73.2%; in-hospital mortality rate 56.2%; 30-day mortality rate 56.2%. Patients with an MDR infection (n=20) had numerically higher IAT failure rate (95.0 vs. 75.0%) and mortality rates (in-hospital and 30-day: 75.0% vs. 45.5%) than patients without an

MDR infection (n=44). Mean LOS per IAT outcome: success 9.1 days (n=18), failure 25.5 days (n=70), indeterminate 22.0 days (n=1) (success vs. failure/indeterminate: p<0.0001).

France (n=65): 38.5% of patients on monotherapy IAT; most used antibiotics, piperacillin-tazobactam (49.2%), metronidazole and amikacin (23.1% each), and ceftriaxone (16.9%); mean IAT duration, overall 14.0 days (median: 7.0, n=65), monotherapy 5.7 days (median: 5.0, n=25), combination therapy 19.2 days (median: 10.0, n=40). IAT failure rate, overall 64.6%, monotherapy 68.0%, combination therapy 62.5%; in-hospital and 30-day mortality rates 46.2%. Patients with an MDR infection (n=23) had numerically comparable IAT failure rate (60.9% vs. 64.0%) and lower mortality rates (in-hospital and 30-day: 34.8% vs. 48.0%) than patients without an MDR infection (n=25). Mean LOS per IAT outcome: success 28.7 days (n=20), failure 29.6 days (n=42), indeterminate 13.0 days (n=3) (success vs. failure/indeterminate: p=0.2998).

Italy (n=68): 50.0% of patients on monotherapy IAT; most used antibiotics, piperacillin-tazobactam (36.8%), metronidazole (27.9%) and meropenem (16.2%); mean IAT duration, overall 11.0 days (median: 9.0, n=68), monotherapy 10.7 days (median: 9.0, n=34), combination therapy 11.3 days (median: 9.0, n=34). IAT failure rate, overall 61.8%, monotherapy 64.7%, combination therapy 58.8%; in-hospital and 30-day mortality rates 26.5%. Patients with an MDR infection (n=14) had numerically higher IAT failure rate (92.9% vs. 50.0%) and mortality rates (in-hospital and 30-day: 35.7% vs. 23.3%) than patients without an MDR infection (n=30). Mean LOS per IAT outcome: success 51.5 days (n=22), failure 25.2 days (n=42), indeterminate 34.3 days (n=4) (success vs. failure/indeterminate: p=0.3862).

Russia (n=74): 35.1% of patients on monotherapy IAT; most used antibiotic, metronidazole (55.4%), ceftriaxone (51.4%), amikacin (21.6%) and cefotaxime (18.9%); mean IAT duration, overall 10.8 days (median: 9.0, n=74), monotherapy 6.9 days (median: 6.0, n=26), combination therapy 13.0 days (median: 11.0, n=48). IAT failure rate, overall 71.6%, monotherapy 76.9%, combination therapy 68.8%; in-hospital and 30-day mortality rates 54.1%. Patients with an MDR infection (n=22) had numerically higher IAT failure rate (100% vs. 61.9%) and higher mortality rates (in-hospital and 30-day: 72.7% vs. 42.9%) than patients without an MDR infection (n=21). Mean LOS per IAT outcome: success 15.2 days (n=19), failure 21.6 days (n=53), indeterminate 8.0 days (n=2) (success vs. failure/indeterminate: p=0.2583).

Spain (n=89): 60.7% of patients on monotherapy IAT; most used antibiotics, piperacillin-tazobactam (47.2%), metronidazole and ampicillin-sulbactam (13.5% each); mean IAT duration, overall 11.8 days (median: 10.0, n=89), monotherapy 11.6 days (median: 9.0, n=54), combination therapy 12.0 days (median: 10.0, n=35). IAT failure rate, overall 62.9%, monotherapy 61.1%, combination therapy 65.7%; in-hospital mortality rate 21.3%; 30-day mortality rate 22.5%. Patients with an MDR infection (n=33) had numerically higher IAT failure rate (69.7% vs. 57.9%) and comparable mortality rates (in-hospital: 18.2% vs. 23.7%; 30-day: 21.2% vs. 23.7%) than patients without an MDR infection (n=38). Mean LOS per

IAT outcome: success 27.9 days (n=20), failure 43.9 days (n=56), indeterminate 36.2 days (n=13) (success vs. failure/indeterminate: p=0.0106).

Statistical Predictors of IAT Failure (cIAI)

In the total cIAI cohort, three predictive factors showed a statistically significant association with IAT failure: admission/transfer to an ICU setting (OR=2.49, 95% CI [1.13; 5.51], p=0.024); patient-level isolation of an MDR pathogen (OR=5.45, 95% CI [2.05; 14.52], p<0.001), and treatment with beta-lactam antibiotics in the prior three months (OR=3.20, 95% CI [1.15; 8.87], p=0.025).

NP

In the total NP cohort, the main source of infection was hospital-acquired pneumonia (HAP, n=196/451, 43.5%), followed by VAP (n=142/451, 31.5%) and healthcare-associated pneumonia (HCAP, n=113/451, 25.1%), with strong variations between countries: majority of hospital-acquired infections in France (HAP: 35.2%; VAP: 57.5%), Brazil (HAP: 52.0%; VAP: 31.0%) and Russia (HAP: 65.8%; VAP: 28.9%), majority of HCAP (51.6%) in Italy, and share between HCAP (43.3%) and HAP (37.5%) in Spain. Microbiological documentation was available for 297 patients (65.9%). Gram-negative pathogens were isolated in 240 patients (n=240/297, 80.8%; range across countries: 74.2% [Brazil] to 93.3% [Russia]); the most frequent were *P. aeruginosa* (24.9% of patients with microbiological documentation), *Klebsiella* spp. (24.6%), *E. coli* (14.5%), *Acinetobacter* spp. (12.8%), *Enterobacter* spp. and *Haemophilus* spp. (6.1% each). *P. aeruginosa* was the most common Gram-negative isolate in France, and Italy, *Klebsiella* spp. in Russia and Brazil, and *E. coli* in Spain. *Acinetobacter* spp. was isolated in 18.1, 19.7 and 22.2% of patients with microbiological documentation in Spain, Brazil and Russia, respectively. Gram-positive pathogens were identified in 95 patients (n=95/297, 32.0%; range across countries: 11.1% [Russia] to 47.2% [Spain]), mainly *Staphylococcus* spp. (22.2%). An MDR pathogen was identified in 52.4% of patients with microbiological documentation (range across countries: 31.6% [France] to 80.0% [Russia]). The proportion of MDR pathogens resistant to carbapenems was 41.6% in the total NP cohort (range across countries: 24.0% [France] to 60.5% [Spain]).

IAT characteristics and outcomes (NP)

Total cIAI cohort (n=451): 62.5% of patients (n=282/451) were treated by a monotherapy IAT, and 37.5% (n=169/451) by a combination therapy. The most common antibiotics (all regimens) were piperacillin-tazobactam (n=114/451, 25.3%), ceftriaxone (n=105/451, 23.3%), and amoxicillin-clavulanic acid (n=58/451, 12.9%). The mean IAT duration was 8.8 days (median: 7.0, n=451) for all regimens, 7.7 days (median: 6.0, n=282) for monotherapy, and 10.6 days (median: 9.0, n=169) for combination therapy. The IAT failure rate was 72.5% (n=327/451) overall, 70.9% (n=200/282) for monotherapy and 75.1% (n=127/169) for combination therapy. Mortality rates were 59.0% (n=266/451) in-hospital and 61.2% (n=276/451) at 30-day post-discharge. Patients with an MDR infection (n=154) had numerically higher IAT failure rate (82.5% vs. 71.4%) and in-hospital mortality rates (in-hospital: 68.2% vs. 56.4%; 30-day: 68.2% vs. 60.0%), compared to patients without an MDR

infection (n=140). Mean LOS per IAT outcome was: success 30.4 days (n=100), failure 29.5 days (n=327), indeterminate 37.3 days (n=24) (success vs. failure/indeterminate: p=0.4024).

Brazil (n=100): 68.0% of patients on monotherapy IAT; most used antibiotics, piperacillin-tazobactam (33.0%), and cefepime (16.0%); mean IAT duration, overall 7.5 days (median: 6.0, n=100), monotherapy 6.6 days (median: 5.0, n=68), combination therapy 9.2 days (median: 7.5, n=32). IAT failure rate, overall 90.0%, monotherapy 86.8%, combination therapy 96.9%; in-hospital mortality rate 72.0%; 30-day mortality rate 76.0%. Patients with an MDR infection (n=27) had numerically higher IAT failure rate (100% vs. 83.3%) and mortality rates (in-hospital: 85.2% vs. 61.1%; 30-day: 85.2% vs. 69.4%) than patients without an MDR infection (n=36). Mean LOS per IAT outcome: success 37.1 days (n=7), failure 32.2 days (n=90), indeterminate 40.0 days (n=3) (success vs. failure/indeterminate: p=0.8398).

France (n=91): 63.7% of patients on monotherapy IAT; most used antibiotics, piperacillin-tazobactam (25.3%), amoxicillin-clavulanic acid (24.2%) and ceftriaxone (16.5%); mean IAT duration, overall 7.7 days (median: 7.0, n=91), monotherapy 6.9 days (median: 7.0, n=58), combination therapy 9.2 days (median: 8.0, n=33). IAT failure rate, overall 72.5%, monotherapy 69.0%, combination therapy 78.8%; in-hospital and 30-day mortality rates 67.0%. Patients with an MDR infection (n=25) had similar IAT failure rate (72.0% vs. 70.4%) and mortality rates (in-hospital and 30-day: 68.0% vs. 63.0%) as patients without an MDR infection (n=54). Mean LOS per IAT outcome: success 43.2 days (n=22), failure 28.5 days (n=66), indeterminate 62.7 days (n=3) (success vs. failure/indeterminate: p=0.0090).

Italy (n=64): 68.8% of patients on monotherapy IAT; most used antibiotics, piperacillin-tazobactam (42.2%) and ceftriaxone (21.9%); mean IAT duration, overall 11.7 days (median: 10.0, n=64), monotherapy 10.3 days (median: 8.5, n=44), combination therapy 14.8 days (median: 14.5, n=20). IAT failure rate, overall 43.8%, monotherapy 40.9%, combination therapy 50.0%; in-hospital and 30-day mortality rates 18.8%. Patients with an MDR infection (n=23) had numerically higher IAT failure rate (56.5% vs. 41.7%) and comparable mortality rates (in-hospital and 30-day: 26.1% vs. 33.3%) than patients without an MDR infection (n=12). Mean LOS per IAT outcome: success 23.0 days (n=31), failure 30.5 days (n=28), indeterminate 29.6 days (n=5) (success vs. failure/indeterminate: p=0.1161).

Russia (n=76): 55.3% of patients on monotherapy IAT; most used antibiotics, ceftriaxone (50.0%), amikacin and metronidazole (26.3% each), and cefotaxime (19.7%); mean IAT duration, overall 11.0 days (median: 9.0, n=76), monotherapy 9.2 days (median: 7.5, n=42), combination therapy 13.3 days (median: 11.5, n=34). IAT failure rate, overall 78.9%, monotherapy 85.7%, combination therapy 70.6%; in-hospital and 30-day mortality rates 75.0%. Patients with an MDR infection (n=36) had numerically higher IAT failure rate (91.7% vs. 55.6%) and mortality rates (in-hospital and 30-day: 88.9% vs. 44.4%) than patients without an MDR infection (n=9). Mean LOS per IAT outcome: success 59.1 days (n=9), failure 22.5 days (n=60), indeterminate 32.7 days (n=7) (success vs. failure/indeterminate: p=0.2954).

Spain (n=120): 58.3% of patients on monotherapy IAT; most used antibiotics, piperacillin-tazobactam (25.8%), levofloxacin (23.3%), ceftriaxone (20.8%) and amoxicillin-clavulanic

acid (20.0%); mean IAT duration, overall 7.7 days (median: 5.50, n=120), monotherapy 6.8 days (median: 5.0, n=70), combination therapy 8.9 days (median: 7.0, n=50). IAT failure rate, overall 69.2%, monotherapy 67.1%, combination therapy 72.0%; in-hospital mortality rate 53.3%; 30-day mortality rate 58.3%. Patients with an MDR infection (n=43) had slightly higher IAT failure rate (83.7% vs. 75.9%) and in-hospital mortality rate (in-hospital: 62.8% vs. 51.7%; 30-day: 62.8% vs. 58.6%) than patients without an MDR infection (n=29). Mean LOS per IAT outcome: success 18.9 days (n=31), failure 32.3 days (n=83), indeterminate 35.2 days (n=6) (success vs. failure/indeterminate: p=0.0184).

Statistical Predictors of IAT Failure (NP)

In the total NP cohort, two predictive factors showed a statistically significant association with IAT failure: patient-level isolation of an MDR pathogen (OR=3.39, 95% CI [1.41; 8.16], p=0.007), and country (other countries combined vs. Spain used as reference, p=0.010). However, no significant increase was seen for any country compared individually to the reference country (Spain).

Healthcare Resource Utilization

IAT failure and indeterminate IAT outcome were associated with a prolongation of the total antibiotic treatment duration, compared to patients with IAT success. In the cUTI and cIAI total cohorts (but not in the NP total cohort), IAT success was associated with shorter hospital stay and lower ICU attendance.