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Antibiotic resistances of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in urine cultures: experience in a hospital of Southeast Spain

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The objectives of this study were to perform a systematic review of publications between 2010 and 2021 on the antibiotic resistance of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from urinary tract infections and to analyze changes over time in hospital urine cultures from 2016 through 2021. The literature was searched, and a retrospective cross-sectional descriptive study was performed in the hospital. Out of 21 838 positive urine cultures, 3.86% were due to *P. aeruginosa* and 0.44% were due to *A. baumannii*. For *P. aeruginosa*, lower resistance rates were observed to virtually all tested antibiotics than were obtained in the systematic review, and the present series of hospital samples showed an *in vitro* resistance rate <10% to ceftazidime, cefepime, meropenem, piperacillin-tazobactam, amikacin, tobramycin, and colistin. For *A. baumannii*, the resistance rates to almost all antibiotics were higher in the present series than in the systematic review, being lowest to colistin (10%). Both microorganisms show reduced *in vitro* susceptibility to some antibiotics during the years of the COVID-19 pandemic in comparison to previous years. In our setting, both piperacillin-tazobactam and meropenem can be recommended for the empirical treatment of UTIs by *P. aeruginosa*, whereas only colistin can be recommended for UTIs by *A. baumannii*.

Key words: *Pseudomonas aeruginosa*; *Acinetobacter baumannii*: urinary tract infections; multiresistance.

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The main causal agent of UTIs is *Escherichia coli* [1], although much less prevalent bacteria can be responsible for considerable morbidity. These include *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, which possess multiple antibiotic resistance mechanisms that hamper their effective treatment. UTIs are the most common infection in the hospital setting, and 80% of these are associated with devices (*e.g.*, vesical catheters) [1]. The development of new resistance mechanisms poses a major challenge, as more than 30% of hospitalized patients in Spain receive daily treatment with antibiotics, often beta lactams [2]. It is estimated that the lack of therapeutic alternatives against resistant microorganisms claims the lives of 25 000 people a year in the European Union (EU) [2].

Multiple mechanisms underlie the expected resistance phenotypes of these two microorganisms to different antibiotics, including the dysregulation of intrinsic resistance mechanisms, the acquisition of resistance factors from other bacteria, the alteration of membrane permeability, and the appearance of efflux pumps. *P. aeruginosa* possesses an inducible type AmpC chromosomal cephalosporinase that confers resistance to penicillins and to first, second, and third generation cephalosporins, with the exception of ceftazidime and cefepime, unless this β-lactamase is overexpressed, which may also confer

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resistance to these cephalosporins [3]. It can also acquire type A, B, or D carbapenemases and show alterations in OprD porin and active expulsion mechanisms such as MexAB-OprM, conferring resistance to carbapenems [4–6]. *A. baumannii* has been reported to show the presence of type AmpC chromosomal cephalosporinases, extended-spectrum β-lactamases, type D chromosomal (OXA-51), and plasmid (OXA-23, OXA-24, OXA-58, OXA 143, and OXA 134) carbapenemases, type A carbapenemases (KPC and GES), and type B carbapenemases (metallo-β-lactamases), with the alteration of porins and efflux pumps [7].

According to the 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections of the Infectious Diseases Society of America (IDSA) [8], traditional non-carbapenem β-lactam agents (piperacillin-tazobactam, ceftazidime, cefepime, aztreonam) are preferred to treat *P. aeruginosa* isolates, even when these prove susceptible to carbapenems. When patients are critically ill or there is poor source control with carbapenem-resistant *P. aeruginosa* isolates that are susceptible to traditional β-lactams, it is also appropriate to administer a novel β-lactam agent that tests susceptible (*e.g.*, ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam). In the 2022 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines [9], when severe infections caused by carbapenem-resistant *A. baumannii* (CRAB) are treated with polymyxins, aminoglycosides, or fosfomycin, the association of two drugs that test active *in vitro* is recommended. Both sets of guidelines suggest that CRAB infections are treated with high doses of ampicillin-sulbactam (total daily dose of 6–9 g of the sulbactam component) in combination with high doses of at least one other agent such as polymyxin B, minocycline, or tigecycline [8, 9]. IDSA guidelines state that cefiderocol should be reserved for CRAB infections refractory to these antibiotics and in cases of intolerance. However, prolonged high doses of meropenem are not recommended except with a MIC value of ≤8 mg/L and combined with at least one of the aforementioned agents [9].

Unfortunately, there has been an alarming increase in the resistance of *A. baumannii* to antibiotics, largely attributable to the widespread prescription of broad-spectrum antibiotics, including carbapenems and last-generation cephalosporins [10]. Hence, it is not uncommon to encounter multiresistant isolates of *A. baumannii* that can only be treated with colistin, although resistance has also been reported to this antibiotic [11]. Involvement of this pathogen in infections affecting fragile patients has drawn particular attention to this issue. Colistin prescriptions are restricted to infections by these multiresistant microorganisms due to the associated risk of nephrotoxicity. Initiation of the correct empirical treatment of UTIs can have a major impact on the acquisition of resistance by pathogens such as *A. baumannii* and *P. aeruginosa*. In addition, the SARS-CoV-2 virus pandemic increased the prescription of antibiotics, further compromising the fight against multiresistant microorganisms [12–16].

With this background, the objective of this study was to analyze changes in the antibiotic resistance of UTIs produced by *P. aeruginosa* and *A. baumannii* from 2010 through 2021 by conducting a systematic review of the literature, and an analysis of clinical isolates obtained in urine cultures in our hospital between 2016 and the first half of 2021, assessing the possible impact of the COVID-19 pandemic on resistance rates.

METHODS

Systematic review

The PRISMA guidelines (https://prisma-statement.org/) have been followed in the Medline database, through PubMed, using the search terms "*urinary tract infection*" and "*antibiotic resistance*" with the full scientific names of the different species. Inclusion criteria were publication date between January 1, 2010 and June 30, 2021; publication in Spanish, Portuguese, Italian, English, or French; inclusion of data on the resistance rates of microorganisms against antibiotics. Exclusion criteria were analysis of non-UTI samples, no separation of data between UTI-causing isolates and those responsible for other types of infections; information obtained outside the continent of Europe (including Russia and Turkey) except for studies on *A. baumannii*. After applying these selection criteria, 21 articles were retrieved for *P. aeruginosa* and 16 for *A. baumannii*.

Analysis of data from a regional hospital in southeastern Spain

Type of study and processing of urine culture samples

A retrospective cross-sectional descriptive study was undertaken of consecutive urine samples with a presumptive diagnosis of UTI received by the Microbiology Laboratory between January 1, 2016 and June 30, 2021, with no exclusion criteria.

Analyses were conducted of results obtained from the culture of isolates detected in these samples, which were processed according to the standard protocol of the laboratory [17]. In samples obtained by spontaneous micturition from permanent probe, collector bag, or nephrostomy catheter, a significant result was defined by a count $\geq 10^5$ CFU/mL or by a count of $>10^4$ CFU/mL for a single microorganism in the presence of >40 leukocytes/mL in uncentrifuged urine; urine cultures with a growth of >2

microorganisms were considered contaminated. In samples obtained by provisional transurethral catheterization, a significant result was defined by a count $\geq 10^4$ CFU/mL of one or two microorganisms. MALDI Biotyper (Bruker Daltonics, Billerica, MA) or MicroScan (Beckman Coulter, Barcelona, Spain) systems were used to identify the microorganisms grown in culture.

Tests of susceptibility to antimicrobials

MicroScan was also used for the study of their antibiotic susceptibility. The minimum inhibitory concentration was recorded for each antibiotic. Isolates were classified as susceptible, intermediate, or resistant to antibiotics according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) for each year up to 2019 and thereafter according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in the corresponding year. The Rapidec® Carba NP colorimetric test (BioMerieux, Marcy l'Etoile, France) and immunochromatography (NG5-Test Carba, NG Biotech, Guipry, France) were used for carbapenemase determination, selecting strains that showed resistance to imipenem or meropenem alongside no susceptibility to ceftazidime [18]. The carbapenemase-producing type was confirmed by the Andalusian Laboratory of Molecular Typification of the Spanish Program PIRASOA by massive sequencing (Illumina Inc, San Diego, CA, USA), using CLC Genomics Workbench v10 (Qiagen), ResFinder (Lyngby, Denmark) (https://cge.cbs.dtu.dk/services/ResFinder), and CARD databases (Hamilton, ON, Canada) (https://card.mcmaster.ca/).

Statistical analysis

Data were gathered on urine sample origin, microorganism, and patient age from the laboratory MODULAB® system, used by the Public Health System of Andalusia to support electronic clinical records. Data on UTI episodes were stratified by sex, age (≤14 years, 15–64 years, and ≥65 years), and origin (hospitalized vs community). No clinical information was obtained for the analysis of clinical factors associated with the presence of microorganisms.

Pearson's chi-squared test was applied to compare the percentage of resistance to the different antibiotics by sex, age, and origin; Fisher's exact test was performed when the chi-squared test conditions were not met (no more than 20% of expected frequencies <5). R 4.4.1 was used for data analyses, and $p < 0.05$ was considered significant.

Ethics approval and consent to participate

The study protocol was conducted in accordance with the Declaration of Helsinki [19] and the ethical considerations of epidemiological research. This was a non-interventional study, with no further investigation to routine procedures. The biological material was used only for the standard diagnosis of UTIs as ordered by attending physicians. No additional sampling or modification of the routine diagnostic protocol was performed. Data analyses were performed using a completely anonymous database, where subjects were replaced by different infectious episodes, occurring at least 6 weeks apart from the previous one, if any. Permission to access and use the data was granted by the Clinical Microbiology Management Unit of Virgen de las Nieves University Hospital (Granada, Spain). Ethics committee approval was considered unnecessary according to national guidelines (Law on Data Protection-Organic Law 15/1999 of 13 December on the protection of data of a personal nature, https://www.boe.es/eli/es/lo/1999/12/13/15).

RESULTS

Global prevalence

Between January 1, 2016 and June 30, 2021 the microbiology laboratory of the HUVN received 74 106 urine samples for suspicion of UTI, and 21 838 (29.5%) were found to be positive; 14% of these positive samples (3055 clinical isolates) corresponded to the microorganisms under study. Table 1 exhibits the number of clinical isolates and the percentage of positive urine cultures represented by each microorganism. Table 2 lists the number and percentage of clinical isolates for each microorganism according to the sex and age of the patients and the origin and type of the samples.

Pseudomonas aeruginosa was less frequently isolated than other microorganisms in samples from collector bag ($p = 0.022$) and midstream micturition ($p < 0.001$) and more frequently isolated in samples from provisional ($p = 0.046$) and permanent ($p < 0.001$) catheters. Both *P. aeruginosa* and *A. baumannii* were more frequently detected in males than in females ($p < 0.001$) and in samples of hospital vs community origin ($p < 0.001$).

Pseudomonas aeruginosa

Systematic review

Table 3 lists the 21 studies selected for review by year of publication. They report on a total of 11 706 clinical isolates of *P. aeruginosa* with antibiogram. The table describes the resistance rates of

Table 1. Number of clinical isolates and percentage of those positive for tested microorganisms each year

Microorganisms	Year (no. positive cultures)						
	2016 (n = 3811)	2017 (n = 4581)	2018 (n = 3851)	2019 (n = 4201)	2020 (n = 3654)	2021 (n = 1740)	Total (n = 21 838)
P. aeruginosa	138 (3.6)	167 (3.6)	134 (3.5)	154 (3.7)	170 (4.6)	79 (4.5)	842 (3.9)
A. baumannii	34 (0.9)	20 (0.4)	15 (0.4)	12 (0.3)	5 (0.1)	9 (0.5)	95 (0.4)

Data are expressed as number of clinical isolates (n) and percentages (%).

Table 2. Number and percentage of clinical isolates for each category

Variables	*P. aeruginosa* *n (%)*	*A. baumannii* *n (%)*
Gender		
Man	522 (62)	72 (75.8)
Woman	320 (38)	23 (24.2)
Age		
Children	48 (5.7)	3 (3.2)
Adults	308 (36.6)	38 (40)
Elderly	486 (57.7)	54 (56.8)
Health care		
Community	309 (36.7)	21 (22.1)
Hospital	533 (63.3)	74 (77.9)
Type of urine sample		
Clean catch midstream technique	385 (45.7)	25 (26.3)
Permanent catheterization	217 (25.8)	35 (36.8)
Urinary catheter	213 (25.3)	31 (32.6)
Nephrostomy catheter	19 (2.3)	4 (4.2)
Pediatric urine collection bag	8 (0.01)	–

antibiotics tested in at least six studies. Most reviewed studies do not gather demographic data on the patients providing samples, preventing comparisons between males and females or among age groups.

Calculation of the weighted mean resistance rate for each antibiotic revealed that the rate against *P. aeruginosa* was lowest for colistin (3.8%) and highest for aztreonam (50.6%). The resistance rate was 13.4% for ceftazidime and 13.1% for meropenem.

Pseudomonas aeruginosa in regional hospital

Among the total of 21 838 positive urine cultures analyzed during the study period, *P. aeruginosa* was detected in 842 clinical isolates (3.9%), and the susceptibility to ceftazidime, piperacillin-tazobactam, tobramycin, gentamicin, and ciprofloxacin was tested in all of them, analyzing the susceptibility to the other antibiotics in a slightly smaller number of isolates. The data obtained are displayed in Table 4 and Tables S1–S12.

Data on annualized general resistances show an increase over the study period in the resistance of *P. aeruginosa* against ticarcillin ($p < 0.001$), ceftazidime ($p < 0.001$), cefepime ($p < 0.001$), piperacillin-tazobactam ($p < 0.001$), amikacin ($p < 0.0001$), tobramycin ($p = 0.048$), gentamicin ($p < 0.001$), levofloxacin ($p < 0.001$), and colistin ($p < 0.001$). Resistance to ciprofloxacin ($p < 0.001$) and aztreonam ($p < 0.001$) decreased between 2018 and 2020 and then increased. Resistance to meropenem ($p < 0.001$) has decreased over the past few years, and this was the only antibiotic to which *P. aeruginosa* showed a virtually constant reduction in resistance up to 2020. The resistance rate of *P. aeruginosa* to imipenem increased year by year but then decreased in 2021. In general, the resistance rate of this microorganism to most of the antibiotics increased between 2016 and 2021.

A higher resistance rate was observed in hospital-origin vs community-origin clinical isolates against ceftazidime ($p < 0.001$), piperacillin-tazobactam ($p = 0.006$), amikacin ($p = 0.059$), and colistin ($p = 0.018$). No statistically significant difference was found between community and hospital isolates in the resistance rate to the remaining antibiotics.

A higher resistance rate was found in the elderly and adults than in the children against cefepime ($p = 0.014$), imipenem ($p = 0.008$), amikacin ($p = 0.039$), gentamicin ($p = 0.003$), ciprofloxacin ($p < 0.001$), and levofloxacin ($p < 0.001$). No significant difference was found between the sexes except for a higher resistance rate in males vs females against meropenem ($p = 0.014$) and levofloxacin ($p = 0.016$).

With respect to carbapenemase producers, two isolates with IMP-type carbapenemases were detected in 2018; two with IMP-type carbapenemases and one with NDM-type carbapenemases in 2019; two with VIM-type carbapenemases, one with IMP-type carbapenemases, and one with NDM-type carbapenemases in 2020; and one with VIM-type and one with IMP-type carbapenemases in 2021.

Acinetobacter baumannii

Systematic review

The review of worldwide studies retrieved 16 publications reporting on a total of 2471 clinical isolates of *A. baumannii* with antibiogram. Table 5 displays the data obtained for antibiotics analyzed in at least five of these studies. The lowest reported resistance rate was against colistin (4.6%), whereas one of the lowest rates among other tested antibiotics was against imipenem (68.6%).

Acinetobacter baumannii in regional hospital

Among the 21 838 positive urine cultures analyzed, *A. baumannii* was detected in 95 (0.4%). The susceptibility to ceftazidime, cefepime, tobramycin, gentamicin, ciprofloxacin, and trimethoprim-sulfamethoxazole was studied in all cases, testing the susceptibility to the other antibiotics in a slightly smaller number of isolates. Data obtained are reported in Table 6 and Tables S13–S24. A very high resistance rate was described for most antibiotics, notably 93.7% for ticarcillin, 93.7% for ciprofloxacin, and 94.3% for levofloxacin. The lowest

Table 3. Systematic review of the resistance rates (%) of *Pseudomonas aeruginosa* in urine cultures

Author (year of publication)	Year of study	Place	*N*	CAZ	FEP	ATM	IPM	MEM	TZP	AMK	TOB	GEN	CIP	LVX	CST
J. J. Koeijers (2010) [20]	2003–2004	Netherlands	13	–	–	–	–	–	–	–	–	–	100	–	–
F. Martins (2010) [21]	2008–2009	Portugal	32	21.9	43.7	–	15.5	–	3.2	15.7	–	43.7	5	–	–
M. Narten (2012) [38]	2006–2007	Germany	32	3	3	3	25	16	19	25	16	25	25	25	–
E. de Vecchi (2013) [22]	2010	Italy	18	22	17	–	–	18	18	18	–	22	29	29	0
R. K. Flamm (2014) [23]	2011	EU	47	21.3	44.7	–	–	29.8	25.5	–	–	–	29.8	–	–
D. Ironmonger (2014) [31]	2010–2013	England	6985	9.2	–	–	–	9.5	–	–	–	–	35.6	42.3	–
M. Pobiega (2014) [32]	2013	Poland	149	14.1	11.4	–	21.5	45	14.8	20.8	15.4	23.5	–	–	0
H. S. Sader (2014) [24]	2012	UE	109	24.8	25.7	–	–	26.6	31.2	–	–	25.6	–	31.2	–
E. Mantadakis (2015) [25]	2008–2014	Greece	9	0	0	–	0	0	0	11.1	0	11.1	–	–	–
Y. Yilmaz (2016) [26]	2012–2014	Turkey	21	33	17	15	7	7	0	0	25	24	6	8	–
M. Pobiega (2016) [33]	2013	Poland	26	11.5	7.7	–	19.2	38.5	11.5	15.4	7.7	7.7	19	23	–
F. Gravey (2017) [39]	2012–2015	France	613	15	13	73	21	–	21	8	11	18	33	–	1
G. J. Guerra (2018) [27]	2013–2016	Spain	651	7.8	10	83.6	8.7	11.7	12.6	32.8	–	–	37.4	–	8
F. Devrim (2018) [34]	2014–2017	Turkey	13	53.8	–	–	38.5	46.2	30.8	0	23	23	30.8	–	15.4
H. Ünsal (2019) [28]	2016–2017	Turkey	12	41.6	–	–	0	0	–	0	–	0	0	–	–
S. H. Lob (2019) [35]	2015–2017	Europe and Turkey	714	21.4	22.3	98	23.4	–	26	13.4	–	–	33.6	–	0.1
S. García-Fernández (2020) [29]	2017–2018	Portugal	90	35.6	–	–	–	22.2	35.6	18.9	–	–	38.9	–	27.8
V. Rafalskiy (2020) [40]	2017	Russia	714	21	–	0	24.5	26.7	21.2	25.6	–	38	51.1	–	10.7
T. Raupach (2020) [30]	2009–2018	Germany	30	0	–	0	0	0	5.3	–	–	0	3.3	–	–
Jan Hrbacek (2020) [36]	2011–2019	Czech Republic	503	18.7	31.5	–	15.6	31.8	30.6	9.3	–	31.4	38.1	–	0
R. Cantón (2021) [37]	2016–2018	Spain	925	28.2	27.7	20.3	2.4	11.3	33.2	5.4	22.6	–	36.5	44	0.7
Weighted averages[1]			11 706	13.4	21	50.6	20	13.1	24	15.6	17.6	26.8	36.4	42.1	3.8

AMK, amikacin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CST, colistin; FEP, cefepime; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; TOB, tobramycin; TZP, piperacillin-tazobactam.

[1]The weighted average is calculated by multiplying the resistance rate to each antibiotic by the *N* of each study and dividing the sum of these values by the total *N* of all studies of the antibiotic.

Table 4. General annualized resistances (%) of *Pseudomonas aeruginosa* during 2016–2021

Years	TIC	CAZ	FEP	ATM	IPM	MEM	TZP	AMK	TOB	GEN	CIP	LVX	CST
2016	28/128 (21.9)	10/138 (7.2)	7/138 (5.1)	29/128 (22.7)	17/138 (12.3)	14/130 (10.8)	4/138 (2.9)	6/130 (4.6)	6/138 (4.3)	9/138 (6.5)	41/138 (29.7)	37/128 (28.9)	1/126 (0.8)
2017	27/162 (16.7)	7/167 (4.2)	10/166 (6.0)	27/162 (16.7)	20/166 (12.0)	17/163 (10.4)	5/167 (3.0)	7/162 (4.3)	11/167 (6.6)	18/167 (10.8)	59/167 (35.3)	55/162 (33.9)	3/156 (1.9)
2018	21/127 (16.5)	8/134 (6.0)	5/134 (3.7)	12/126 (9.5)	21/134 (15.7)	10/127 (7.9)	3/134 (2.2)	2/127 (1.6)	4/134 (3.0)	4/134 (3.0)	30/134 (22.4)	30/127 (23.6)	2/121 (1.6)
2019	94/154 (61.0)	19/154 (12.3)	24/154 (15.6)	20/145 (13.8)	25/154 (16.2)	15/144 (10.4)	17/154 (11.0)	8/154 (5.2)	12/154 (7.8)	39/154 (25.3)	44/154 (28.6)	49/154 (31.8)	8/143 (5.6)
2020	88/169 (52.1)	15/170 (8.8)	25/168 (14.9)	20/166 (12.0)	27/149 (16.0)	12/166 (7.2)	15/170 (8.8)	7/170 (4.1)	11/170 (6.5)	47/170 (27.6)	50/170 (29.4)	58/170 (34.1)	33/164 (20.1)
2021	39/79 (49.4)	7/79 (8.9)	10/79 (12.7)	6/22 (27.3)	8/79 (10.1)	3/21 (15.0)	7/79 (8.9)	5/79 (6.3)	11/79 (13.9)	15/79 (19.0)	23/79 (29.1)	25/79 (31.6)	10/79 (12.7)
Total	297/819 (36.3)	66/842 (7.8)	81/839 (9.6)	114/749 (15.2)	118/820 (14.4)	71/751 (9.4)	51/842 (6.1)	35/822 (4.3)	55/842 (6.5)	132/842 (15.7)	247/842 (29.3)	254/820 (31.0)	57/789 (7.2)

AMK, amikacin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CST, colistin; FEP, cefepime; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; TIC, ticarcillin; TOB, tobramycin; TZP, piperacillin-tazobactam.

Table 5. Systematic review of the resistance rates (%) of *Acinetobacter baumannii* in urine cultures

Author (year of publication)	Year of study	Place	*N*	FEP	IPM	MEM	TZP	AMK	GEN	CIP	LVX	SXT	CST
Taneja. N. (2011) [46]	2007–2008	India	205	–	25.4	–	31.7	73.2	79.5	72.8	–	83	–
Lu P. (2012) [47]	2009–2010	Asia	56	76.8	64.3	–	75	64.3	–	82.1	80.4	–	–
Mishra M. (2013) [48]	2011–2012	India	72	42.6	–	–	60.7	52.9	60.7	–	31.1	61.8	–
Hayajneh W. (2015) [49]	2011–2013	Jordan and Lebanon	11	82	–	–	82	82	–	82	82	–	–
Mohammed M. (2016) [50]		Libya	2	0	0	0	0	0	0	0	0	50	–
Jean S. (2016) [51]	2010–2013	Pacific Asia	218	75.2	59.2		69.7	61.5	–	73.4	70.2	–	–
Karlowsky J. (2017) [52]	2013–2015	Latin America	43	79.1	81.4	–	79.1	58.1	–	–	81.4	–	–
Karlowsky J. (2017) [53]	2013–2015	Pacific Asia	65	84.6	83.1	–	84.6	67.7	–	–	67.7	–	–
Yang Q. (2017) [54]	2010–2014	China	143	–	53.1	–	–	53.8	–	–	63.6	–	–
Jiménez-Guerra G. (2018) [27]	2013–2016	Spain	90	88.9	53.3	74.1	31.4	77.8	–	94.4	–	–	4.7
Kuntaman K. (2018) [55]	2012	Indonesia and Japan	6	100	100	100	83.3	83.3	50	83.3	83.3	–	0
Al-Naqshbandi. Ahmed A. (2019) [56]	2014–2016	Iraq	5	80	80	100	80	100	80	80	80	60	100
Zhang H. (2020) [57]	2015–2017	China	1356	–	78.2	78	79.2	66.3	–	81	–	–	4.4
Arbianti N. (2020) [58]	2013	Indonesia	4	–	–	25	–	–	–	50	–	75	–
Alrahmany D. (2021) [59]	2016–2017	Oman	42	–	–	59	76	66.7	73	88	–	44	0
Alamri A. (2021) [60]	2013–2016	Saudi Arabia	153	–	–	–	–	–	–	90.9	85.7	38.8	–
Weighted averages[1]			2471	74.9	68.5	77.1	71.1	65.7	73.6	78.2	69.7	62	4.6

AMK, amikacin; CIP, ciprofloxacin; CST, colistin; FEP, cefepime; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; SXT, trimethoprim-sulfamethoxazole; TZP, piperacillin-tazobactam.

[1]The weighted average is calculated by multiplying the resistance rate to each antibiotic by the *N* of each study and dividing they sum of these values by the total *N* of all studies of the antibiotic.

Table 6. General annualized resistances (%) of *Acinetobacter baumannii* during 2016–2021

Years	SAM	TIC	CAZ	FEP	IPM	MEM	AMK	TOB	GEN	CIP	LVX	MIN	STX	CST
2016	23/29 (79.3)	26/28 (92.9)	28/34 (82.3)	28/34 (82.3)	22/26 (84.6)	22/32 (68.7)	22/30 (73.3)	21/34 (61.8)	25/34 (73.5)	31/34 (91.2)	27/28 (96.4)	2/28 (7.1)	30/34 (88.2)	1/32 (3.1)
2017	11/20 (55.0)	19/20 (95.0)	17/20 (85.0)	17/20 (85.0)	16/20 (80.0)	16/20 (80.0)	12/20 (60.0)	14/20 (70.0)	14/20 (70.0)	20/20 (100.0)	20/20 (100.0)	3/18 (16.7)	17/20 (85.0)	1/20 (5.0)
2018	10/14 (71.4)	13/14 (92.9)	13/15 (86.7)	15/15 (100.0)	14/15 (93.3)	13/14 (92.9)	9/14 (64.3)	10/15 (66.7)	12/15 (80.0)	15/15 (100.0)	14/14 (100.0)	3/14 (21.4)	14/15 (93.3)	4/15 (26.7)
2019	12/12 (100.0)	2/2 (100.0)	9/12 (75.0)	11/12 (91.7)	9/12 (75.0)	9/12 (75.0)	9/12 (75.0)	7/12 (58.3)	8/12 (66.7)	10/12 (83.3)	9/12 (75.0)	2/12 (16.7)	8/12 (66.7)	2/11 (18.2)
2020	5/5 (100.0)	–	5/5 (100.0)	5/5 (100.0)	4/5 (80.0)	4/5 (80.0)	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)	5/5 (100.0)	1/4 (25.0)	5/5 (100.0)	0/5 (0.0)
2021	9/9 (100.0)	–	8/9 (88.9)	6/9 (66.7)	7/9 (77.8)	7/9 (77.8)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)	8/9 (88.9)	5/9 (55.6)	8/9 (88.9)	1/7 (14.3)
Total	70/89 (78.6)	60/64 (93.7)	80/95 (84.2)	82/95 (86.3)	72/87 (82.8)	71/92 (77.2)	65/90 (72.2)	65/95 (68.4)	72/95 (75.8)	89/95 (93.7)	83/88 (94.3)	16/85 (18.8)	82/95 (86.3)	9/90 (10.0)

AMK, amikacin; CAZ, ceftazidime; CIP, ciprofloxacin; CST, colistin; FEP, cefepime; GEN, gentamycin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; SAM, sulbactam-ampicillin; STX, trimethoprim-sulfamethoxazole; TIC, ticarcillin; TOB, tobramycin.

global resistance rates throughout the study period were for minocycline (18.8%) and colistin (10%).

No statistically significant difference in resistance rate was observed among age groups, sample types, or years studied or between the sexes; the only significant difference observed was a higher resistance rate to gentamicin in isolates of hospital vs community origin (81.1 vs 57.1%, p = 0.018). Four OXA-23-type carbapenemase producing isolates were detected in 2019, 5 in 2020, and 6 in 2021.

DISCUSSION

Pseudomonas aeruginosa

All studies in the systematic review followed CLSI [20–30] and EUCAST [31–37] guidelines except for three, which used those published by the Deutches Institut für Normung [38] or Antibiogram Committee of the French Microbiology Society [39] or did not specify the criteria used to define the infection [40].

As shown in Table 4, resistance rates for *P. aeruginosa* were lower in our hospital than in the systematic review (Table 3) against all antibiotics except for colistin, which showed a slightly higher rate (7.2%) than described in the systematic review (3.8%).

Resistance rates against cefepime, imipenem, amikacin, gentamicin, ciprofloxacin, and levofloxacin were significantly higher in the elderly and adults than in children. Older age, as well as worse nutritional status and greater morbidity, is known to be associated with a greater susceptibility to microorganism colonization and higher antibiotic resistance rates [41].

Comparison with data obtained from the same hospital between 2013 and 2016 [27] revealed a major decrease in the resistance to aztreonam (from 83.6 to 15.2%) and amikacin (from 32.8 to 4.3%) and a smaller decrease in the resistance to piperacillin-tazobactam (from 12.6 to 6.1%), ciprofloxacin (from 37.7 to 29.3%), and meropenem (from 11.7 to 9.4%). These reductions can be attributed to the lesser administration of these antibiotics during the 2016–2021 period, recovering the *in vitro* susceptibility of *P. aeruginosa* to piperacillin-tazobactam, meropenem, and amikacin, which can again be recommended as empirical treatments in our setting. In contrast, the resistance rate to imipenem was higher (8.7%) than reported in previous years (14.1%). No carbapenemase-producing isolates had been detected in the previous series [27], and their presence in UTIs by *P. aeruginosa* was recorded for the first time in 2018, with the emergence of two IMP-type carbapenemase-producing isolates, and this trend continued in the following years, especially during the COVID-19 pandemic.

According to the present resistance data, UTIs due to *P. aeruginosa* can be treated with ceftazidime, cefepime, meropenem, piperacillin-tazobactam, amikacin, tobramycin, and colistin, given that <10% of *P. aeruginosa* isolates were resistant to these drugs. Most of these antibiotics are recommended for the empirical treatment of these patients [42], with aminoglycosides being indicated in monotherapy, unlike in other infections.

Acinetobacter baumannii

All studies in the systematic review adopted CLSI criteria except for two that followed the guidelines of the manufacturer of VITEK 2 (BioMérieux, Paris, France) [39, 40].

In contrast to the findings for *P. aeruginosa*, *A. baumannii* isolates obtained in our hospital (Table 6) showed higher resistance rates to all the antibiotics tested than described in the systematic review (Table 5). This difference may be explained by the inclusion of worldwide data in the review due to the scant number of European studies, with geographic variability impeding observation of a clear pattern.

The resistance rates recorded in our hospital laboratory during the study period did not differ from those reported between 2013 and 2016 [27] except for an increased resistance to imipenem (from 53.3 to 82.8%), meropenem (74.1 to 77.2%), and colistin (4.7 to 10%). No OXA-23-type carbapenemase-producing isolates were detected in the previous series [27], with the first four cases being observed in 2019, followed by five in 2020 and six in 2021).

Three main mechanisms can underlie the resistance of *A. baumannii* to antibiotics: control of their transport through membranes (reduced porin permeability or increased efflux); modification of their target(s), and their enzymatic inactivation [43]. Data on *A. baumannii* obtained in our laboratory evidence high resistance rates for all tested antibiotics except for minocycline and colistin, which remain among the few options for the empirical treatment of UTIs produced by *A. baumannii* in our setting. However, given the low renal excretion of minocycline, it might be advisable to consider other tetracyclines such as doxycycline, which has higher renal excretion and has yielded good outcomes in acute complicated cystitis produced by extended spectrum beta-lactamase-producing Enterobacteriaceae [44]. These findings are in line with recommendations for the treatment of multiresistant strains of *A. baumannii* with sulbactam or colistin and for the treatment of isolates resistant to both carbapenems and sulbactam with minocycline or doxycycline [43].

Possible impact of the COVID-19 pandemic on antibiotic resistances

The Spanish Agency of Medicines and Medical Devices issued recommendations for the optimal use of antibiotics during the COVID-19 pandemic in 2020 and 2021, highlighting that their excessive or inappropriate prescription could facilitate the development of resistant bacteria and reduce the effectiveness of future treatments [45]. In the present series, increased resistance to colistin was observed in UTIs produced by *P. aeruginosa* during 2020 and 2021 in comparison to previous years, resistance to aztreonam and tobramycin increased in 2021, and the emergence of carbapenemase-producing isolates increased from 2018 onward. No changes were observed in resistance rates of *A. baumannii* to any tested antibiotic during the pandemic (2020 and 2021) except for a reduction in the resistance to cefepime from 100% in 2019 to 88.7% in 2020, while the resistance rate to colistin (0% in 2020 and 14.3% in 2021) was also lower than recorded in previous years. Detection of OXA-23-type carbapenemase-producing isolates commenced and gradually increased during the years of the pandemic.

It can be speculated that the clinical impact of the COVID-19 pandemic was responsible for an increase in the resistance to some antibiotics used against UTIs produced by *P. aeruginosa* or *A. baumannii*. However, antibiotic resistance is not exclusive to a specific type of infection, and further research is needed on the behavior of these microorganisms in other types of infection to analyze a larger number of cases.

LIMITATIONS

Although data were gathered during 2020 and the first half of 2021, coinciding with the COVID-19 pandemic, the whole of 2021 needs to be studied to assess the full impact of the pandemic on antibiotic resistance development. The study of UTIs produced by *A. baumannii* was limited by the small sample size of only 95 isolates, preventing the detection of any statistically significant differences as a function of the age and sex of patients and the origin and type of samples.

CONCLUSIONS

UTIs due to *P. aeruginosa* analyzed in our hospital laboratory between 2016 and 2021 showed resistance rates that were lower than reported in other European studies and were higher in older than

younger patients. Resistance rates <10% were found for piperacillin-tazobactam, meropenem, antipseudomonal cephalosporins, tobramycin, and colistin, which can continue to be recommended for the empirical treatment of UTI caused by *P. aeruginosa*. However, the high resistance of UTI by *A. baumannii* to most antibiotics limits the options for its empirical therapy to colistin in our setting. The resistance of UTIs produced by *P. aeruginosa* and *A. baumanni* to some antibiotics appeared to increase during the COVID-19 pandemic, which also coincided with the gradual emergence of carbapenemase producers. Studies with a larger number of clinical isolates are needed to verify these observations.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

FUNDING INFORMATION

Universidad de Granada / CBUA

DATA AVAILABILITY STATEMENT

The data presented in this study are available in the main text.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Resistances to beta-lactams (%) of *Pseudomonas aeruginosa* in 2016.
Table S2. Resistances to beta-lactams (%) of *Pseudomonas aeruginosa* in 2017.
Table S3. Resistances to beta-lactams (%) of *Pseudomonas aeruginosa* in 2018.
Table S4. Resistances to beta-lactams (%) of *Pseudomonas aeruginosa* in 2019.
Table S5. Resistances to beta-lactams (%) of *Pseudomonas aeruginosa* in 2020.
Table S6. Resistances to beta-lactams (%) of *Pseudomonas aeruginosa* in 2021.
Table S7. Resistances to non-beta-lactams (%) of *Pseudomonas aeruginosa* in 2016.
Table S8. Resistances to non-beta-lactams (%) of *Pseudomonas aeruginosa* in 2017.
Table S9. Resistances to non-beta-lactams (%) of *Pseudomonas aeruginosa* in 2018.
Table S10. Resistances to non-beta-lactams (%) of *Pseudomonas aeruginosa* in 2019.
Table S11. Resistances to non-beta-lactams (%) of *Pseudomonas aeruginosa* in 2020.
Table S12. Resistances to non-beta-lactams (%) of *Pseudomonas aeruginosa* in 2021.
Table S13. Resistance to beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2016.
Table S14. Resistance to beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2017.
Table S15. Resistance to beta-lactam antibiotics (%) of *Acinetobacter baumannii* in Resistance to beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2018.
Table S16. Resistance to beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2019.

Table S17. Resistance to beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2020.
Table S18. Resistance to beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2021.
Table S19. Resistance to non-beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2016.
Table S20. Resistance to non-beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2017.
Table S21. Resistance to non-beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2018.
Table S22. Resistance to non-beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2019.
Table S23. Resistance to non-beta-lactam antibiotics (%) of Acinetobacter baumannii in 2020.
Table S24. Resistance to non-beta-lactam antibiotics (%) of *Acinetobacter baumannii* in 2021.

