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CLINICAL THERAPEUTICS

A Cohort Study of Risk Factors That Influence Empirical Treatment of Patients with Acute Pyelonephritis

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ABSTRACT The aim of the current study was to compare community-acquired acute pyelonephritis (CA-APN) with health care-associated acute pyelonephritis (HCA-APN), describe the outcomes, and identify variables that could predict antimicrobial susceptibility. We conducted an observational study that included all consecutive episodes of acute pyelonephritis (APN) in adults during 2014 at a Spanish university hospital. From each episode, demographic data, comorbidities, clinical presentation, microbiological data, antimicrobial therapy, and outcome were recorded. A multivariable logistic regression model was performed to define the variables associated with antimicrobial resistance. A total of 607 patients, 503 (82.9%) with CA-APN and 104 (17.1%) with HCA-APN, were included in the study. Patients with HCA-APN were older than patients with CA-APN (70.4 versus 50.6 years; $P < 0.001$) and had higher rates of previous urinary tract infections (UTIs) (56.5% versus 24.5%; $P < 0.001$) and previous antibiotic use (56.8% versus 22.8%; $P < 0.001$). *Escherichia coli* was more frequently isolated from patients with CA-APN than from patients with HCA-APN (79.9% versus 50.5%; $P < 0.001$). The rates of resistance of *Escherichia coli* strains from CA-APN patients versus HCA-APN patients were as follows: amoxicillin-clavulanic acid, 22.4% versus 53.2% ($P = 0.001$); cefuroxime, 7.7% versus 43.5% ($P = 0.001$); cefotaxime, 4.3% versus 32.6% ($P < 0.001$); ciprofloxacin, 22.8% versus 74.5% ($P < 0.001$); and co-trimoxazole, 34.5% versus 58.7% ($P = 0.003$). The site of acquisition, recurrent UTIs, and previous antibiotic use were independent risk factors for antimicrobial resistance. Relapse rates were significantly higher when definitive antimicrobial treatment was not adequate (37.1% versus 9.3% when definitive antimicrobial treatment was adequate; $P < 0.001$). Our study reflects the rise of resistance to commonly used antibiotics in acute pyelonephritis. In order to choose the adequate empirical antibiotic therapy, risk factors for resistance should be considered.

KEYWORDS antimicrobial resistance, epidemiology, urinary tract infection

Received 26 June 2017 **Returned for modification** 1 August 2017 **Accepted** 23 September 2017

Accepted manuscript posted online 2 October 2017

Citation Bosch-Nicolau P, Falcó V, Viñado B, Andreu A, Len O, Almirante B, Pigrau C. 2017. A cohort study of risk factors that influence empirical treatment of patients with acute pyelonephritis. Antimicrob Agents Chemother 61:e01317-17. https://doi.org/10.1128/AAC.01317-17.

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Urinary tract infections (UTIs) are a common reason for primary care consultation, hospital admission, and antimicrobial consumption. Although pyelonephritis is less common than cystitis, it causes important short-term morbidity and can lead to severe complications and even death (1). Prompt adequate antibiotic treatment constitutes the most important measure in terms of efficacy to decrease morbidity and mortality.

Most studies regarding the etiology of UTIs have been performed on female populations with uncomplicated lower UTIs. In the case of acute pyelonephritis (APN), despite its being a very common infection in hospital settings, the etiology has been less studied and is usually extrapolated from studies in patients with cystitis (2). The etiology of UTIs has changed little over time. In all studies, *Escherichia coli* remains the most frequently isolated microorganism (47.2% to 90%), followed by other Gram-negative bacilli (GNB), such as *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Pseudomonas*

aeruginosa. However, there is a wide range of variation, depending on the site of acquisition, age, and comorbid conditions (1, 3–7).

During the last few years, the antibiotic susceptibility of *E. coli* strains causing not only UTIs but also infections at other sites has been monitored in several studies (8, 9). In Europe, the rate of antimicrobial resistance among GNB, especially *E. coli*, is on the rise (10). In studies performed in Spain with samples obtained from patients with cystitis, rates of resistance to amoxicillin-clavulanic acid grew from 8.1% to 22.4% in only 5 years (3, 8).

In daily clinical practice, urine samples for culture are not usually obtained from patients with uncomplicated UTIs. On the other hand, some studies of the etiology of UTIs and the antimicrobial resistance patterns of the organisms responsible for UTIs are based on samples that are collected for testing in microbiology laboratories but for which little information about the clinical characteristics of the patients or whether the infections were hospital acquired is obtained. Considering both of these facts, it may be possible that in some cases resistance rates could be magnified by recurrent infections or comorbidities (11, 12). Consequently, there is a need to review periodically both the etiology and antimicrobial susceptibility patterns recommended in guidelines (6, 8, 13, 14). It is also important to identify patient characteristics that act as risk factors for infections caused by resistant microorganisms in order to better design adequate empirical treatment (15).

In order to know the actual etiology and antimicrobial resistance patterns in adult patients with APN, we designed an observational study with the following objectives: (i) to compare community-acquired APN (CA-APN) with health care-associated APN (HCA-APN), (ii) to define baseline clinical variables that predict susceptibility to empirical treatments, and finally, (iii) to analyze clinical outcomes on the basis of the antimicrobial treatment administered.

RESULTS

Clinical characteristics. From January to December 2014, 607 episodes of APN in adults were diagnosed at the University Hospital Vall d'Hebron. There were 518 (85.3%) females and 89 (14.7%) males, with the mean age being 53.9 $\pm$ 23.5 years. On the basis of the location of acquisition of the episodes of infection, 503 (82.9%) episodes were CA-APN and 104 (17.1%) were HCA-APN, which are similar to the rates described elsewhere (16). The basal characteristics of both groups are shown in Table 1. Patients with HCA-APN were significantly older than patients with CA-APN (77 versus 47 years; $P < 0.001$), the proportion of men with HCA-APN was significantly higher than the proportion of men with CA-APN (33.7% versus 10.9%; $P < 0.001$), and patients with HCA-APN were more likely to have diabetes mellitus or chronic renal disease than patients with CA-APN. Among the patients with HCA-APN, 92% had either urological abnormalities or a chronic urinary catheter. A history of UTI (56.5% versus 24.5%; $P < 0.001$) and antibiotic use during the previous 3 months (56.8% versus 22.8%; $P < 0.001$) were also more frequently observed in the HCA-APN group than in the CA-APN group.

Microbiological diagnosis. Overall, a urine sample for culture was obtained from 585 patients (96.4%). For the remaining 22 patients, a urine sample for culture was not collected for several reasons. The urine culture was negative for 133 patients (22.7%), and 97 of these patients (72.9%) had previously received antibiotic therapy before admission to the emergency department. A microorganism was isolated from the cultures of urine and/or blood samples from 452 patients (74.5%). The causative agents of UTIs are shown in Table 2. We observed significant differences in the causative agents depending on the site of acquisition. Although *E. coli* was the most commonly isolated microorganism in both groups, it had a more predominant role in CA-APN than in HCA-APN (79.9% versus 50.5%; $P < 0.001$). In contrast, *P. mirabilis* was more frequent in patients with HCA-APN than patients with CA-APN (7.5% versus 1.9%; $P = 0.01$). *P. aeruginosa* was detected only in HCA-APN episodes. Gram-positive bacteria had a minor role, with *Enterococcus* spp. representing less than 5% of the causative organisms in both groups.

TABLE 1 Baseline characteristics of patients with acute pyelonephritis[d]

Characteristic	Value(s) for the following group:		*P* value
	CA-APN ($n = 503$)	HCA-APN ($n = 104$)	
No. (%) of patients by gender			
Male	55 (10.9)	34 (33.7)	<0.001
Female	448 (89.1)	70 (67.3)	<0.0001
Median (IQR) age (yr)	47 (31–71)	77 (56–77)	<0.0001
No. (%) of patients with the following comorbidity:			
Diabetes mellitus	69 (13.7)	23 (22.1)	0.035
Chronic renal disease	50 (9.9)	21 (20.2)	0.007
Solid organ transplantation	22 (4.4)	2 (1.9)	0.404
Solid cancer	11 (2.2)	5 (4.8)	0.169
Hematological cancer	5 (1)	0 (0)	0.594
No. (%) of patients with the following underlying urological abnormality:	175 (34.8)	96 (92.1)	<0.0001
Urinary incontinence	45 (8.9)	34 (32.7)	<0.0001
Renal lithiasis	52 (10.3)	4 (3.8)	0.04
Chronic urinary catheter	0	55 (52.9)	<0.0001
Cystocele	24 (4.8)	0	0.02
Renal transplantation	20 (4.0)	0	0.03
Prostatic hyperplasia	10 (2.0)	2 (1.9)	1
Other[a]	24	1	
No. of patients with recurrent UTIs[b]/total no. of patients with available information (%)	117/478 (24.5)	52/92 (56.5)	<0.0001
No. (%) of patients with previous antibiotic treatment[c]/total no. of patients with available information (%)	107/470 (22.8)	50/88 (56.8)	<0.0001

[a]Monorenal patients, nonlithiasic obstructive ureteropathy, renal cysts, and medullar lesion.
[b]Treated at least three times during the previous 12 months for cystitis or acute pyelonephritis.
[c]Use of antibiotics during the previous 3 months for any reason.
[d]Abbreviations: CA-APN, community-acquired acute pyelonephritis; HCA-APN, health care-associated acute pyelonephritis; IQR, interquartile range; UTI, urinary tract infection.

Susceptibility pattern and risk factors for antimicrobial resistance. The pattern of *E. coli* resistance to antibiotics is presented in Table 3. We observed significantly higher rates of resistance among the organisms from the patients in the HCA-APN group. Specifically, extended-spectrum β-lactamase (ESBL)-producing *E. coli* strains

TABLE 2 Microbiological agents responsible for APN[e]

Characteristic or microbiological agent	Value(s) for the following group:		*P* value
	CA-APN ($n = 503$)	HCA-APN ($n = 104$)	
No. (%) of patients with:			
Positive urine culture	359 (74.2)	93 (92.1)	<0.001
Positive blood culture	104 (31)	28 (37.2)	0.338
No. (%) of patients from whom the following agents were isolated:			
E. coli	287 (79.9)	47 (50.5)	<0.001
K. pneumoniae	34 (9.5)	7 (7.5)	0.687
P. mirabilis	7 (1.9)	7 (7.5)	0.012
P. aeruginosa	0 (0)	14 (15.1)	<0.001
Other GNB[a]	7 (1.9)	12 (12.9)	<0.001
S. saprophyticus	10 (2.8)	0 (0)	0.226
Enterococcus spp.	5 (1.4)	4 (4.3)	0.091
Other GPC[b]	1 (0.3)	1 (1.1)	0.061
No. of patients with polymicrobial infection[c]/total no. of positive urine cultures (%)	13/359 (3.6)	27/93 (29)	<0.001
No. of patients contaminated[d]/total no. of patients tested (%)	8/503 (2.2)	1/104 (1.1)	0.693

[a]Other GNB included *Enterobacter* spp., *Providencia stuartii*, *Morganella morganii*, *Serratia marcescens*, *Klebsiella oxytoca*, and *Salmonella* spp.
[b]GPC, Gram-positive cocci. Other Gram-positive cocci included *Corynebacterium accolens* and *Streptococcus agalactiae*.
[c]Polymicrobial infection was considered the isolation of 2 uropathogens from the urine culture.
[d]Contaminated was considered the isolation of 3 or more bacteria from the urine culture.
[e]Abbreviations: CA-APN, community-acquired acute pyelonephritis; HCA-APN, health care-associated acute pyelonephritis; GNB, Gram-negative bacilli.

TABLE 3 Percentage of *E. coli* isolates with antimicrobial resistance[a]

Antibiotic	% resistant *E. coli* isolates		*P* value
	CA-APN ($n = 287$)	HCA-APN ($n = 47$)	
Ampicillin	73.4	91.5	0.006
Amoxicillin-clavulanic acid	22.4	53.2	0.001
Piperacillin-tazobactam	18.4	53.8	0.001
Cefuroxime	7.7	43.5	<0.0001
Cefotaxime	4.3	32.6	<0.0001
Ertapenem	0	6.4	0.003
Imipenem	0	0	
Amikacin	2.7	4.2	0.547
Ciprofloxacin	22.8	74.5	<0.0001
Co-trimoxazole	34.5	58.7	0.003
Fosfomycin	1.2	10.8	0.006

[a]The percentages of extended-spectrum β-lactamase-producing *Enterobacteriaceae* isolates recovered from the patients in the community-acquired acute pyelonephritis and health care-associated acute pyelonephritis groups were 4.2 and 31.9%, respectively ($P < 0.001$). Abbreviations: CA-APN, community-acquired acute pyelonephritis; HCA-APN, health care-associated acute pyelonephritis.

were isolated from 12 CA-APN patients and from 15 HCA-APN patients, with the proportion being higher in the second group (4.2% versus 31.9%; $P < 0.001$).

To identify the variables associated with antimicrobial resistance, we carried out univariate and multivariate analyses of the basal characteristics, including age, gender, site of acquisition, comorbidities, presence of urinary tract abnormalities, a history of recurrent UTI, and previous antimicrobial use (Table 4). The most important factor associated with resistance to all antibiotics analyzed was health care-associated acquisition. A history of recurrent UTI was also an independent risk factor for resistance to cefuroxime, and antibiotic use during the previous 3 months was an independent risk factor for resistance to cefotaxime and ciprofloxacin. We also performed this analysis for co-trimoxazole and fosfomycin, with similar results (data not shown). The site of acquisition (odds ratio [OR], 1.81; 95% confidence interval [CI], 1.0 to 3.25) and the previous use of antibiotics (OR, 2.0; 95% CI, 1.24 to 3.24) were identified to be independent risk factors for co-trimoxazole resistance, and recurrent UTI was identified to be an independent risk factor for fosfomycin resistance (OR, 6.17; 95% CI, 1.55 to 24.49).

To better describe the rates of resistance to the most common antimicrobials used in empirical treatment, we also analyzed the global resistance pattern taking into account all microorganisms isolated. In Table 5 we show the resistance rates depending on the presence of risk factors for resistance. While organisms from CA-APN patients without risk factors showed the highest susceptibility rates, increasing resistance was observed among organisms from patients with risk factors (previous recurrent episodes and/or previous antibiotic use), especially in those with HCA-APN. More than 95% of the isolates from patients with CA-APN without risk factors remained susceptible to both cefuroxime and cefotaxime, while the rates of resistance to amoxicillin-clavulanic acid and ciprofloxacin were 17.1% and 17.5%, respectively.

Complications and outcomes. Table 6 shows the complications and outcomes for the patients. None of the 260 outpatients died, while 14 deaths were observed among the hospitalized patients (4%). There were only 5 deaths (1%) in the CA-APN group, whereas 9 patients (9.4%) in the HCA-APN group died ($P < 0.001$). Mortality was directly related to pyelonephritis in only 1 of the 5 patients with CA-APN who died and in 5 of the 9 patients with HCA-APN who died. In the CA-APN case, pyelonephritis was caused by *E. coli* isolates susceptible to all antibiotics. Among the patients who died, 44% had septic shock, whereas septic shock was observed in only 5.7% of the survivors.

Recurrence was detected in a total of 47 of the 497 (9.5%) patients for whom such data were recorded, with no significant differences on the basis of the need for hospitalization or the site of acquisition being detected.

Despite the high rates of resistance to common antibiotics, empirical treatment was considered adequate in 89% of the patients. Overall mortality was very low (2.3%) and

TABLE 4 Univariate and multivariate analysis of risk factors for resistance to most common antibiotics used in UTIs[c]

	Amoxicillin-clavulanate			Cefuroxime			Cefotaxime			Ciprofloxacin		
Risk factor	R (%)	*P* value by univariate analysis	OR (95% CI) by multivariate analysis	R (%)	*P* value by univariate analysis	OR (95% CI) by multivariate analysis	R (%)	*P* value by univariate analysis	OR (95% CI) by multivariate analysis	R (%)	*P* value by univariate analysis	OR (95% CI) by multivariate analysis
Age (yr)												
<65	24.3	0.220		11.1	0.035		6.1	0.14		22.6	<0.0001	
≥65	29.8			18.7			10.6			38.9		
Gender												
Male	35.9	0.091		24.6	0.029		10.9	0.454		45.2	0.003	
Female	25.2			12.9			7.7			26.9		
Mode of APN acquisition												
CA-APN	22.3	<0.0001	3.10 (1.74–5.54)	10	<0.0001	4.05 (2.02–8.13)	5.2	<0.0001	3.16 (1.34–7.44)	22	<0.0001	4.58 (2.62–8.03)
HCA-APN	47.9			36.1			22.2			61.4		
Diabetes mellitus												
No	28.0	0.312		13.9	0.361		7.6	0.349		28.5	<0.0135	
Yes	21.9			18.1			11			37.2		
Chronic renal disease												
No	26.8	1		14	0.408		7.8	0.423		29.1	0.359	
Yes	27.3			18.5			11.1			35.6		
Urinary incontinence												
No	24.5	0.013		13.5	0.117		7.1	0.071		27.4	0.008	
Yes	40.3			21.3			14.8			44.6		
Renal lithiasis												
No	26.2	0.346		14.5	0.81		8	0.547		29.6	0.592	
Yes	33.3			15.8			10.3			34.1		
Recurrent UTI[a]												
No	24.9	0.256		9.8	<0.0001	2.74 (1.41–5.31)	5.7	0.007		23.8	<0.0001	
Yes	30.7			26.5			14.5			43.2		
Previous antibiotic use[b]												
No	21.9	0.068		9.4	0.001		4.3	0.001	2.94 (1.27–6.80)	23.3	<0.0001	1.99 (1.22–3.27)
Yes	31			23			15.2			44.4		

[a]Treated at least three times for cystitis or acute pyelonephritis during the previous 12 months.
[b]Use of antibiotics during the previous 3 months for any reason.
[c]Abbreviations: APN, acute pyelonephritis; CA, community acquired; HCA, health care associated; R, resistance rate; OR, odds ratio; CI, confidence interval; UTI, urinary tract infection.

TABLE 5 Resistance rates considering all microorganisms isolated from all cases in relation to risk factors for resistance[c]

Antibiotic	Resistance rate (%)		
	CA-APN without RF (n = 300)	CA-APN with recurrent UTI[a] and/or previous antibiotic treatment[b] (n = 168)	HCA-APN (n = 104)
Ampicillin	69.7	78.3	84.6
Amoxicillin-clavulanic acid	17.1	27.8	44.3
Piperacillin-tazobactam	16.3	25	40.7
Cefuroxime	4.2	18.8	36.1
Cefotaxime	1.1	12.6	22.2
Ertapenem	0	0	4.3
Imipenem	0	0	8
Amikacin	2.6	2.3	2
Ciprofloxacin	17.5	30.8	61.4
Co-trimoxazole	26.8	40	50.7
Fosfomycin	0.6	6.7	11.9
ESBL-producing *Enterobacteriaceae*	0.7	8.3	15.4
AmpC-BL producing *Enterobacteriaceae*	0	0	2.1

[a]Treated at least three times for cystitis or acute pyelonephritis during the last 12 months.
[b]Use of antibiotics for any reason during the previous 3 months.
[c]For 35 patients, the presence or absence of risk factors could not be evaluated. Abbreviations: AmpC-BL, AmpC β-lactamase; CA-APN, community-acquired acute pyelonephritis; ESBL, extended-spectrum β-lactamase; HCA-APN, health care-associated acute pyelonephritis; RF, risk factor; UTI, urinary tract infection.

was not statistically significantly related to the adequacy of the empirical therapy received by each patient. However, the length of hospital stay was longer among patients in whom treatment was not adjusted according to susceptibility testing results than among those who received adequate antimicrobial treatment (6.6 days versus 156 days; $P = 0.013$). Even more importantly, the number of relapses was significantly higher among patients in whom treatment was not adjusted according to susceptibility testing results (37.1% versus 9.3%; $P < 0.001$).

DISCUSSION

The results of our study show high rates of resistance to the antibiotics most commonly used for the treatment of APN, particularly in patients with recurrent UTIs and in those with recent antibiotic exposure, with the highest resistance rates being in health care-associated cases.

Our study shows differences in the etiology, antimicrobial susceptibility, and out-

TABLE 6 Complications and outcomes for patients with APN[b]

Characteristic	No. (%) of patients		P value
	CA-APN (n = 503)	HCA-APN (n = 104)	
No. (%) of patients admitted to hospital for <48 h	52.3	80.8	<0.0001
Median (IQR) hospital stay (days)	5 (4–7)	8 (6–12.75)	<0.0001
No. (%) of patients with the following septic complications:			
Focal pyelonephritis	52 (22.7)	3 (4.2)	0.006
Renal abscess	6 (2.7)	1 (2)	1
Septic shock	19 (7.4)	3 (4.2)	0.432
ICU admission	12 (4.7)	2 (2.9)	0.742
No. (%) of patients who died in hospital	5 (1)	9 (9.4)	<0.0001
No. (%) of patients with relapses[a]	36 (8.5)	11 (14.7)	<0.013

[a]A UTI caused by the same microorganism during the next 2 months of follow-up.
[b]Abbreviations: CA-APN, community-acquired acute pyelonephritis; HCA-APN, health care-associated acute pyelonephritis; ICU, intensive care unit; IQR, interquartile range.

come depending on the site of acquisition of the APN and shows that these factors have relevance in the selection of empirical therapy. According to previously provided definitions (16), we classified patients into the CA-APN and HCA-APN groups. In our experience, patients from long-term health care facilities, those with indwelling urinary catheters, and those with a recent manipulation of the urinary tract showed patterns of antimicrobial resistance, morbidity, and mortality different from those of the other patients.

As expected, HCA-APN patients were older and had more comorbidities. This group had more men than the CA-APN group, probably because of prostatic obstructive uropathy (17). Although a major rate of septic complications could be expected in HCA-APN patients, the frequencies of septic shock, admission to an intensive care unit (ICU), and renal abscesses were similar in both groups, as other studies have observed (12, 18).

An etiological agent was obtained in 75% of the cases. Most of the negative cultures could be explained by previous treatment before the consultation. This is a common situation in young females with recurrent cystitis, who often self-treat, and in older people admitted to long-term health care facilities (19). *E. coli* is the leading cause of APN, as it is found to be the etiological agent in almost all studies. However, its frequency varies depending on the site of acquisition. In our study, *E. coli* represented nearly 80% of the overall isolations from CA-APN patients, similar to the rates of 70 to 87% obtained in other series that included patients with uncomplicated APN or cystitis (1, 3, 7, 8). In the HCA-APN group, the proportion of cases caused by *E. coli* declined, while other GNB, such as *P. aeruginosa* (15.1%) or *P. mirabilis* (7.5%), gained a more prominent role, similar to what occurs in patients with complicated APN (12, 20). *Staphylococcus saprophyticus* is a well-known cause of acute cystitis in young sexually active females; however, its role in patients with APN is less well described (21, 22). In our series, this microorganism was the cause of 2.8% of all CA-APN cases, which may have therapeutic implications, since some commonly used antibiotics, such as third-generation cephalosporins and fosfomycin, are less active against this microorganism.

E. coli strains resistant to fluoroquinolones are a major concern, with global resistance rates being as high as 25 to 50% in southern European countries and 35%, on average, in the United States (10, 23). Epidemiological studies performed in patients with cystitis in Spain have shown that the rates of resistance of community-acquired *E. coli* strains to fluoroquinolones and amoxicillin-clavulanic acid are on the rise (3, 8). This situation is particularly relevant for amoxicillin-clavulanic acid, as it has been broadly used in our setting (24–26). In APN, international and local guidelines establish a threshold of rates of resistance to an antibiotic of 10% to allow its use as empirical treatment (11, 27). This recommendation is based on expert opinion, since there is no supporting evidence from controlled therapeutic trials. If it is assumed that this recommendation is correct, rates of resistance to fluoroquinolones and amoxicillin-clavulanic in all subgroups of greater than 17% invalidate them as empirical treatment, even for CA-APN.

An increase in the incidence of community ESBL-producing GNB has been observed in some countries, with these organisms being the cause of as many as 6.3% of cases of UTIs (28, 29). In our study, we found a similar proportion of such organisms of 4.2% in the CA-APN group. The high prevalence of ESBL-producing GNB, nearly 32% in the HCA-APN group, which was even higher than the 22% reported by Doi et al. (30), is relevant to guide empirical therapy for such patients.

The site of acquisition of pyelonephritis is the most important independent variable related to resistance to first-line antimicrobials. A similar risk was previously observed when nosocomially acquired APN was compared to community-onset APN, highlighting the importance of the site of acquisition when empirical treatment is selected (4, 31). In this way, organisms causing HCA-APN are closer to those causing nosocomial APN in terms of etiology and antimicrobial susceptibility. We did not find any relation between resistance and gender, age, or comorbidities, in contrast to the findings of previous studies in patients with cystitis and APN (16, 32).

The rate of mortality from APN is usually below 10% (12, 33). In our study, none of the outpatients died, while the rate of mortality was only 4% among inpatients. The rate of mortality was significantly higher in patients with HCA-APN than in those with CA-APN (9.4% versus 1%). We observed no differences in mortality according to whether treatment was adequate or not (2.4% versus 2.8%). Despite the fact that fluoroquinolone resistance may negatively impact patients with bacteremic pyelonephritis, recent studies showed similar mortality rates in patients with CA-APN treated with fluoroquinolones and even in those with CA-APN caused by fluoroquinolone-resistant isolates (34–36). Other authors have also described the same clinical and microbiological outcomes, despite discordant empirical treatment, even in patients with infections caused by ESBL-producing GNB (31).

However, it is important to remark that those patients treated with inadequate antibiotic treatment had significantly higher relapse rates (37.1% versus 9.3%) in the follow-up. Thus, efforts should be made to adjust the antibiotic therapy when susceptibility data are available, particularly in outpatients.

Taking into account all these observations, when we determine the empirical treatment to be used for patients with APN, we have to consider susceptibility data, risk factors for resistance, and the need to avoid the extensive use of broad-spectrum antibiotics. Because the initial treatment does not seem to have a determinant role in mortality, mainly in nonbacteremic clinically stable patients with CA-APN, we advocate the use of narrow-spectrum antibiotics, even though a longer hospital stay may be observed. Therefore, second- and third-generation cephalosporins may be a reasonable option for patients with CA-APN without risk factors for resistance. Organisms from all subgroups of patients with APN had low rates of resistance to fosfomycin. Clinical and safety data indicate that the use of intravenous fosfomycin for this indication should be reevaluated (37). As the rate of mortality is very low in patients without septic shock, the use of carbapenems should probably be restricted only to severely ill patients. It is mandatory to ensure close follow-up to tailor the treatment once the antimicrobial susceptibility of the causative agent is known to avoid the emergence of multidrug-resistant microorganisms (38).

Our study has some limitations. First, this is a single-hospital-based study. Second, because we used *International Classification of Diseases*, ninth revision, *Clinical Modification* (ICD-9-CM) codes, some cases could have been dismissed because of incorrect codification in the emergency department. Finally, because this study had a retrospective design, information on the gentamicin susceptibility of the causative organism, certain patient basal characteristics, the patient's previous antibiotic therapy, or follow-up for outpatients, which was obtained from the primary care database, could have been missed. Despite these limitations, the major strength of our study is that we present a large series of adult patients with APN for whom a correlation between microbiological and clinical data could be made. Our population represents patients seen in everyday clinical practice in different departments and a broad population of interest, including men and patients with all kinds of comorbidities.

In conclusion, our study reflects the rise in the rates of resistance to antibiotics commonly used to treat CA-APN and especially HCA-APN. In order to choose adequate empirical antibiotic therapy, risk factors for resistance should be considered.

MATERIALS AND METHODS

Study design and inclusion criteria. We conducted a retrospective observational study, collecting data from all adult patients (age, ≥16 years) diagnosed with APN or urinary sepsis at the emergency department or during the first 48 h of the hospital stay. Data were collected from January to December 2014 in the Vall d'Hebron University Hospital, a 1,100-bed teaching hospital in Barcelona (Spain).

We included subjects with *International Classification of Diseases*, ninth revision, *Clinical Modification* (ICD-9-CM) codes 590.10, 590.11, 590.2, and 590.8 in our computerized database. We excluded infections that occurred during pregnancy or peripartum and hospital-acquired infections, defined as those that presented after 48 h of hospital admission or 1 month after a previous hospital discharge.

Definitions and data collection. APN was defined when the patient had (i) a temperature of >38°C and/or a history of fever and chills within 48 h before presentation and (ii) at least one of the following symptoms: a lower UTI (dysuria, urgency, increased frequency, and pelvic pain), costovertebral angle

tenderness, or leukocyturia (>30 cells/ml). Every episode could have or could not have been microbiologically confirmed by culture of urine and/or blood specimens. Cases suggestive of prostatitis (prostatic tenderness on rectal examination) were excluded.

We classified patients into the CA-APN and HCA-APN groups. Patients with HCA-APN were defined as those who resided at long-term-care facilities, had had a urinary manipulation during the 2 weeks before admission, and/or had an indwelling urinary catheter. We used the definition of recurrent UTI for patients who were treated at least three times during the previous 12 months for cystitis or APN (39, 40).

For the patients included in the study, we accessed their medical and nursing records from the hospital and primary health care centers. Demographic data, comorbidities, clinical presentation, health care-associated factors, antibiotic exposure for any reason during the previous 3 months, outcome, microbiological data, and antimicrobial therapy were recorded for each episode.

We recorded the following comorbidities: renal impairment, defined as a basal creatinine concentration of >1.2 mg/dl; diabetes mellitus, defined as treatment with insulin or oral hypoglycemic agents; cancer, defined as the receipt of antineoplastic chemotherapy; actively treated hematological diseases; receipt of any solid organ transplant; and urinary abnormalities, including structural and functional abnormalities.

For all patients, we recorded the adequacy of treatment, defined as the use of an agent active against the isolated microorganism(s); relapses when the patient had another UTI (cystitis or pyelonephritis) caused by the same microorganism during the next 2 months of follow-up; and the use of antibiotics during the previous 3 months for any reason. For inpatients, we recorded the length of hospital stay, the presence of focal pyelonephritis or a renal abscess detected by echography and/or a computed tomography scan, septic shock (defined as the use of vasopressor drugs), admission to an intensive care unit (ICU), urinary obstruction, and mortality.

Microbiology and antimicrobial susceptibility data. A positive urine culture was defined as the isolation of a uropathogen at $\geq 10^4$ CFU/ml or $\geq 10^3$ CFU/ml if an indwelling catheter was present. Urine cultures positive for 2 microorganisms were taken into account when both organisms were suggestive of uropathogens and pyuria and/or clinical symptoms were present. Antimicrobial susceptibility was performed by microdilution (Vitek bioMérieux, France). The MIC values of ampicillin, amoxicillin-clavulanic acid, piperacillin-tazobactam, cefuroxime, ceftazidime, cefotaxime, ertapenem, imipenem, amikacin, ciprofloxacin, trimethoprim-sulfamethoxazole, and fosfomycin were interpreted according to criteria established by European Committee for Antimicrobial Susceptibility Testing (EUCAST) 2012 (version 2.0) guidelines (www.eucast.org). Isolates with intermediate resistance were considered resistant.

Statistical analysis. Categorical variables are expressed as percentages, and numerical data are expressed as the mean ± standard deviation (SD) for variables with a normal distribution or the median and interquartile range (IQR) for those with a skewed distribution. Categorical variables were compared by the chi-square test or Fisher exact test, and continuous variables were compared by the Student *t* test or the Mann-Whitney U test, depending on the distribution.

Crude and adjusted odd ratios (ORs) were calculated using logistic regression analysis to identify risk factors for the development of antibiotic resistance. Variables showing statistically significant differences between microorganisms with or without antibiotic resistance in the univariate analysis were then tested in multivariate models. Models were performed in a sequential fashion beginning with the variable most strongly associated with the development of resistance and continuing until no other variable reached significance or changed the ORs of variables already in the model. In addition, clinically relevant factors with *P* values of <0.1 that were considered potential confounders on the basis of experience and data in the literature were forced into the multivariate model to investigate their effect. Colinearity was ruled out if the variance inflation factor was <20, the tolerance value was >0.1, and the conditional index was small. The Hosmer and Lemeshow chi-square statistic test was used to measure the accuracy and the goodness of fit of the prediction models. All statistical tests were two-tailed, and the threshold of statistical significance was a *P* value of <0.05.

Statistical analyses were performed using SPSS (version 20.0) software (SPSS, Inc., Chicago, IL, USA).

Ethics statement. The study was approved by the Ethics Committee of the Vall d'Hebron Research Institute under registration code FAL-ATB-2015-01. The Ethics Committee assessed our study and waived the need for informed consent, as all data and samples were analyzed retrospectively and collected as part of normal care in daily clinical practice, according to current guidelines.

ACKNOWLEDGMENT

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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