

# Factors associated with severe sepsis or septic shock in complicated pyelonephritis

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## Abstract

Severe sepsis or septic shock are the main factors influencing the prognosis of acute pyelonephritis (APN). Our aim was to analyze factors associated with the development of severe sepsis or septic shock in a large sample of patients with acute complicated pyelonephritis (ACPN).

This prospective observational study comprised 1507 consecutive patients aged 14 years or older who were admitted to a tertiary care hospital because of ACPN between 1997 and 2015. Covariates associated in univariate analysis with severe sepsis or septic shock were then analyzed by multivariate logistic regression.

Of the 1507 patients, 423 (28.1%) fulfilled the criteria for severe sepsis or septic shock at the time of admission. Crude and attributable mortality at 30 days were 17.7% and 11.7% in patients with severe sepsis or septic shock versus 1.7% and 0.6% in patients without severe sepsis or septic shock,  $P < .0001$  and  $P < .0005$ , respectively. An age  $> 65$  years, urinary instrumentation in the previous 2 weeks, the lack of mictional syndrome or costovertebral tenderness, an ectasia  $\geq$  grade II, and bacteremia were independent risk factors associated with severe sepsis or septic shock.

The prevalence of severe sepsis and septic shock in patients with ACPN is high. Some factors associated with severe sepsis are easy to identify in any emergency department. The information provided here could be useful when deciding which patients should be admitted to receive immediate treatment.

**Abbreviations:** ACPN = acute complicated pyelonephritis, APN = acute pyelonephritis, CI = confidence intervals, CPN = complicated pyelonephritis, CT = computed tomography, ESBL = extended-spectrum beta-lactamase, ICU = intensive care unit, IQR = interquartile range, OR = Odds, SD = standard deviation, SIRS = systemic inflammatory response syndrome.

**Keywords:** pyelonephritis, severe sepsis, urinary tract infection

## 1. Introduction

Acute pyelonephritis (APN) is a very common reason for attending emergency departments and leads to a significant number of hospital admissions. It has a high incidence (9–11 cases per 10,000 inhabitants).<sup>[1]</sup> The clinical spectrum of APN varies greatly, from mild costovertebral tenderness, mictional

syndrome, and fever to a life-threatening condition or even death.<sup>[2,3]</sup> Unlike uncomplicated pyelonephritis, the prognosis of which is usually good even in bacteremic patients,<sup>[4]</sup> the prognosis of acute complicated pyelonephritis (ACPN) is much worse, with mortality rates of 6% to 10%.

Factors associated with a poor prognosis in patients with ACPN include older age, immunosuppression, health care associated infection, obstructive uropathy, decreases in platelet count and serum albumin level, high C-reactive protein level, and bacteremia.<sup>[5–8]</sup> In addition, there is broad consensus that the development of severe sepsis or septic shock are the strongest independent risk factors for a poor prognosis and mortality in patients with ACPN.<sup>[9,10]</sup> However, studies about the factors associated with severe sepsis or septic shock in patients with ACPN are very scarce, contain few cases, or are limited to specific clinical scenarios.<sup>[6–8]</sup>

Accordingly, the aim of this longitudinal study was to assess the incidence and possible factors associated with severe sepsis or septic shock in a large cohort of patients with ACPN attending the emergency department.

## 2. Patients and methods

### 2.1. Study design, population, and setting

This observational study involved a prospective cohort of patients aged  $\geq 14$  years recruited consecutively in the emergency department of the Regional Hospital of Malaga between July 1,

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1997, and December 31, 2015, because they had a diagnosis of ACPN. The Regional Hospital of Malaga is a 1100-bed tertiary university hospital serving a population of approximately 350,000 people.

**2.1.1. Definitions.** APN and ACPN were both defined as previously described.<sup>[10]</sup> APN was considered to be present if the patient presented 2 or more of the following: chills or an axillary temperature  $\geq 38.3^{\circ}\text{C}$ ; flank pain or costovertebral angle tenderness or pain on bimanual palpation of the kidney; and mictional syndrome (involving at least 2 of dysuria, frequency, suprapubic pain, or urgency), in addition to pyuria or a positive urine culture. ACPN was considered if the patient had a urinary tract with structural or functional abnormalities, was immunosuppressed, had an anatomic or functional single kidney, a long-term indwelling catheter, a nephrostomy or double-J stent, or if the patient had undergone manipulation of the urinary tract during the 2 weeks before the onset of symptoms. In addition, any case of pyelonephritis in a man was considered complicated.

Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were all defined in accordance with the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.<sup>[11]</sup> All clinical and laboratory data defining SIRS, sepsis, and septic shock were collected at the time of admission.

## 2.2. Exclusion criteria

Patients with a kidney transplant, pregnant women, and patients who had recently undergone major urological surgery were excluded. Patients were also excluded from the study if, after diagnosis of ACPN, they were transferred to another hospital or managed on an outpatient basis.

All epidemiological, clinical, hematological, and biochemical data were collected prospectively following a specifically designed protocol, which provides for the admission of all patients diagnosed with ACPN. Blood and urine samples were taken on admission for later culture. An abdominal ultrasound was also done on arrival at the emergency department. An abdominal CT or other radiologic examinations were made at the discretion of the specialist (emergency medicine, internal medicine, or infectious diseases) responsible for the patient.

## 2.3. Microbiological studies

Blood and urine specimens were processed as previously described.<sup>[10]</sup> Blood cultures were incubated as per protocol for 5 days in a semiautomatic BACTEC 9240 device until 2011 and on a BACTEC FX (Becton Dickinson Diagnostic Instruments System Sparks, MD) from 2011 to the study end. Isolates were regarded as contaminants if they were isolated in just 1 blood culture bottle and were discrepant from urine cultures; these included *Bacillus* spp, *Corynebacterium* spp, *Micrococcus* spp, and coagulase-negative *staphylococci* except *Staphylococcus saprophyticus*. Urine specimens for culture were obtained using the midstream clean-catch urine technique or straight catheterization method. In patients with urinary catheters, the urine sample was collected from the catheter port. All urine cultures were inoculated on blood agar and McConkey agar. A positive urine culture was defined as the presence of 1 or 2 uropathogens at  $10^4$  cfu/mL or greater, or  $\geq 10^3$  cfu/mL in the presence of pyuria when the patient had a bladder or nephrostomy catheter. The identification and antimicrobial sensitivity tests were performed

in a VITEK 2 system (bioMerieux Inc, Durham, NC) or WIDER system (Soria Melguizo S.A., Madrid, Spain).

The presumptive antimicrobial resistances detected (presence of ESBL, carbapenemases, etc.) were confirmed routinely with the disk plate method (ROSCO Diagnostica A/S, Taastrup, Denmark) and with chromogenic ESBL media (BioMerieux Inc). All cultures and susceptibility tests were done in accordance with the procedures of the National Committee for Clinical Laboratory Standards.<sup>[12]</sup> In the event of discordant results between the urine culture and the blood culture, the ACPN was assumed to be caused by the microorganism producing the bacteremia.

## 2.4. Antimicrobial treatment and follow-up

Following the tentative diagnosis, the patients were admitted and treated, initially empirically in accordance with the hospital Guidelines for Antimicrobial Therapy until the causative microorganism was identified, after which they received targeted therapy for a minimum of 10 days. Briefly, the recommendations for the empirical treatment of ACPN in our center are based on the administration of ceftriaxone and gentamicin, meropenem for cases with risk factors for ESBL-producing enterobacterial infection, and meropenem and amikacin for patients with severe sepsis or septic shock. If the patient was allergic, the betalactam was replaced by ciprofloxacin or aztreonam and amikacin. In all cases, the dose of the antimicrobial agent used was adjusted according to renal function.

## 2.5. Statistical analysis

Data were analyzed using SPSS version 17.0 (SPSS Inc, Chicago, IL). We report continuous variables as the mean (SD) or median and interquartile range (IQR), as appropriate; categorical variables are reported as frequencies or percentages.

Normally and non-normally distributed quantitative variables were compared using *t* tests and Mann–Whitney *U* tests, respectively. Categorical variables were compared using the  $\chi^2$  test, or Fisher exact test when appropriate. All statistical tests were 2-tailed. Values of  $P \leq .05$  were considered statistically significant.

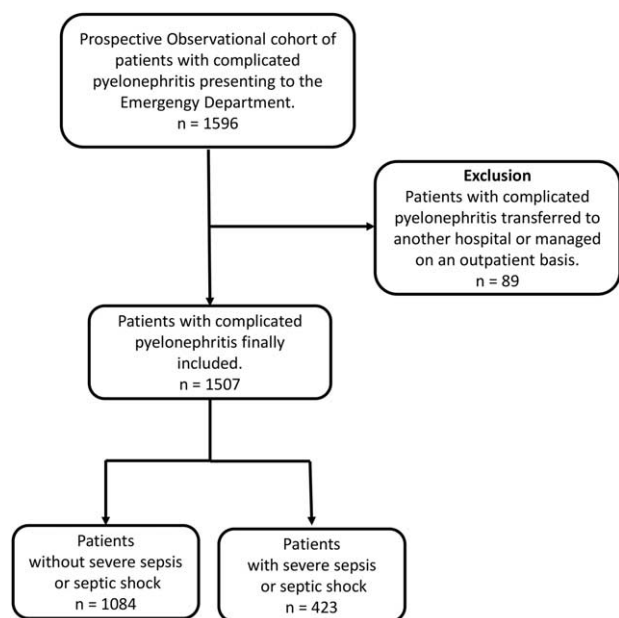
Measures of association were expressed as odds ratios (ORs) with their 95% confidence intervals (CIs) for dichotomous variables. Variables found to be associated with severe sepsis or septic shock on univariate analysis at a level of significance  $P < .1$  and those with an epidemiological rationale were considered for inclusion in a multivariate logistic regression analysis using a backward stepwise procedure.

The Ethics Committee of the Regional University Hospital of Malaga approved the study and authorized waiver of informed consent.

## 3. Results

The study involved 1507 patients (Fig. 1); 793 (52.6%) men and 714 (47.4%) women. The median age of the patients was 63 years (IQR 47–74) and the median duration of symptoms before admission was 3.0 days (IQR 2–6). For 904 (59.9%) patients, this was their first episode of ACPN, while the other 603 (40.1%) had had previous episodes. At the time of admission, 423 patients (28.1%) fulfilled the criteria for severe sepsis or septic shock.

Of the total, 1285 (85.3%) were admitted to the Infectious Diseases or Internal Medicine Departments, 207 (13.7%)



**Figure 1.** Flow chart illustrating the number of patients included and excluded in the study.

required ICU admission, and the remaining 15 (1%) were admitted to other medical or surgical departments.

On arrival at the hospital, a urine culture was performed for 1432 patients, of whom 941 (65.7%) were positive. Of the 1205 patients in whom blood cultures were performed, 436 (36.2%) had bacteremia. These data should be interpreted taking into account that during the week before admission, 588 patients (39.4%) had received at least 1 dose of antibiotics; 36.4% and 40.0% in patients with and without severe sepsis or septic shock, respectively ( $P > .05$ ).

The causative agent was identified in 1052 (69.8%) of the 1507 episodes of ACPN. No differences were found in the etiological spectrum between the patients with severe sepsis or septic shock and the other patients. Table 1 summarizes the microorganisms isolated in the cases in which the etiology was eventually confirmed. Of the isolates, 136 (12.9%) were ESBL producers; 12.3% in patients without severe sepsis and 14.2% in those with

severe sepsis or septic shock ( $P > .05$ ). Nine strains (0.8%) were carbapenemase-producing Gram-negative bacteria. All carbapenemase-producing enterobacteriaceae were of the OXA-48 type and 2 of them were also ESBL producers.

On arrival at the emergency department, an abdominal ultrasound was performed in 1239 (82.2%) cases as part of the initial study.

An age  $> 65$  years, male gender, the presence of prostate disease, urinary tract instrumentation in the previous 2 weeks, diabetes, nosocomial acquisition, and being the first episode of ACPN were associated with the presence of severe sepsis or septic shock (Table 2). Conversely, the presence of urinary symptoms and costovertebral tenderness were significantly less frequent in patients with severe sepsis or septic shock.

Overall, no differences were found in the duration of symptoms before the diagnosis between the patients with and without severe sepsis and/or septic shock;  $4.4 \pm 5.4$  versus  $4.9 \pm 5.6$  days, respectively;  $P > .05$ . Nevertheless, a duration of symptoms less than 3 days was significantly more frequent in the patients who had a history of ACPN; 60.1% versus 54.3%, respectively,  $P = .03$ . Likewise, more patients older than 65 years reported a duration of symptoms less than 3 days compared with those younger than 65 years; 61% versus 53.2%, respectively,  $P < .001$ . On the contrary, patients older than 65 years less often had fever and costovertebral tenderness; 85.1% versus 89.2% and 44.8% versus 66.6%,  $P < .05$  and  $P < .001$ , respectively. Table 3 summarizes the other main clinical, laboratory, and ultrasound data of the patients with and without severe sepsis or septic shock.

Multiple logistic regression analysis showed that an age  $> 65$  years, urinary instrumentation in the previous 2 weeks, the lack of mictional syndrome or costovertebral tenderness, an ectasia  $\geq$  grade II, or a kidney abscess in the ultrasound study and bacteremia were independently associated with the development of severe sepsis or septic shock. On the contrary, a history of previous episodes of ACPN proved to be a protective factor in the development of severe sepsis or septic shock (Table 4).

The hospital stay was 13.6 days in the patients with severe sepsis or septic shock and 9.8 in the patients without severe sepsis,  $P < .001$ . The crude and attributable mortality in patients without and with severe sepsis or septic shock were 1.7% to 0.6%, and 17.7% to 11.7% ( $P < .0001$  and  $P < .0005$ , respectively).

**Table 1**  
Microorganisms responsible for the 1052 episodes of complicated pyelonephritis for which the etiology was confirmed.

Number (%)	Total patients Number = 1052	Patients with severe sepsis or septic shock Number = 329	Patients without severe sepsis or septic shock Number = 723	Significance
<i>Escherichia coli</i>	686 (65.2)	216 (65.7)	470 (65)	0.83
<i>Klebsiella/Enterobacter spp</i>	120 (11.4)	34 (10.3)	86 (11.9)	0.46
<i>Proteus spp</i>	73 (6.9)	23 (7.0)	50 (6.9)	0.96
Nonfermenting GNB*	61 (5.8)	15 (4.6)	46 (4.4)	0.24
<i>Enterococcus faecalis</i>	40 (3.8)	16 (4.9)	24 (3.3)	0.22
Other Gram-positive bacilli	10 (0.9)	3 (0.9)	7 (1.0)	0.79
Polymicrobial	34 (3.2)	11 (3.3)	23 (3.2)	0.89
<i>Candida spp</i>	9 (0.8)	3 (0.9)	6 (0.8)	0.82
Others	19 (1.8)	8 (2.4)	11 (1.5)	0.30
Infection caused by ESBL microorganism	136 (12.9)	47 (14.2)	89 (12.3)	0.37
Carbapenemase-producing GNB	9 (0.8)†	2 (0.6)	7 (0.9)	0.55

\* Gram negative bacilli.

† Two strains were also ESBL producers.

**Table 2****Baseline epidemiological and predisposing factors in patients with complicated pyelonephritis according to the presence of severe sepsis or septic shock.**

No. (%)	Patients with severe sepsis or septic shock Number = 423	Patients without severe sepsis or septic shock Number = 1084	Significance
Age > 65 y	250 (59.1)	430 (40)	0.0001
Gender			
Female	179 (42.3)	535 (49.4)	
Male	244 (57.7)	549 (50.6)	0.008
Underlying urologic condition	321 (75.9)	793 (73.2)	0.15
Nephrolithiasis	92 (21.7)	262 (24.2)	0.17
Structural bladder disorder	63 (14.9)	140 (12.9)	0.17
Functional bladder disorder	67 (15.8)	172 (15.9)	0.52
Prostatic disorder	82 (19.4)	148 (13.7)	0.004
Anatomic or functional single kidney	20 (6.6)	57 (8.3)	0.21
Permanent bladder catheter	50 (11.8)	101 (9.3)	0.08
Nephrostomy catheter	17 (5.6)	52 (7.6)	0.16
Urological instrumentation in the previous 2 wks	79 (18.7)	103 (9.5)	0.0001
Previous history of UTI	85 (28.1)	297 (43.3)	0.0001
Diabetes	146 (34.5)	295 (27.2)	0.003
Chronic renal failure	43 (22.5)	96 (17)	0.05
Immunosuppression	79 (18.7)	167 (15.4)	0.07
First episode of ACPN	227 (65.8)	627 (59.1)	0.01

ACPN=acute complicated pyelonephritis; UTI=urinary tract infection.

**Table 3****Main clinical, hematologic, biochemical, and ultrasonography data of patients with complicated pyelonephritis according to severe sepsis/septic shock status.**

No. (%)	Patients with severe sepsis or septic shock Number = 423	Patients without severe sepsis or septic shock Number = 1084	Significance
Fever $\geq 38^{\circ}\text{C}$	363 (85.8)	950 (87.6)	0.19
Chills	302 (71.4)	810 (74.7)	0.10
Flank pain	192 (45.4)	663 (61.2)	0.0001
Costovertebral tenderness	185 (43.7)	636 (58.7)	0.0001
Mictional syndrome	206 (48.7)	725 (66.9)	0.0001
Leukocytosis $>20,000$ cells/mL	127 (30.0)	203 (18.7)	0.0001
C-reactive protein $>100$ mg/L	150 (69.4)	383 (62.5)	0.03
Bacteremia	215 (62.1)	221 (30.1)	0.0001
Ectasia $\geq$ grade II	97 (27.7)	130 (14.7)	0.0001
Kidney or ureteral stones	92 (21.7)	262 (24.2)	0.17
Complicated kidney cyst	20 (11.2)	77 (17.1)	0.04
Kidney or perinephric abscess	30 (7.1)	18 (1.7)	0.0001
Focal nephritis	21 (30)	38 (22.1)	0.12

**Table 4****Final logistic regression model with the factors associated with severe sepsis or septic shock in patients with complicated pyelonephritis.**

Risk factors	Odds ratio	95% CI	P
Age >65 y	1.795	1.195–2.695	.005
Previous episodes of ACPN	0.562	0.367–0.860	.008
Urinary instrumentation in previous 15 d	2.014	1.118–3.626	.02
Lack of mictional syndrome	1.830	1.227–2.729	.003
Absence of costovertebral tenderness	1.485	0.994–2.220	.05
Ectasia $\geq$ grade II	1.750	1.091–2.806	.02
Kidney or perinephric abscess	3.018	1.235–7.377	.01
Bacteremia	2.767	1.870–4.094	.0001

ACPN=acute complicated pyelonephritis; CI = confidence interval.

#### 4. Discussion

The urinary tract is the second or third most common source of infection in patients with sepsis and the source of infection is urinary in 6.2% to 38% of patients with severe sepsis or septic shock.<sup>[13–15]</sup> Except for a few cases due to acute bacterial prostatitis, virtually all cases of urinary sepsis are secondary to APN.

The prognosis for patients with ACPN is much worse than for those with uncomplicated pyelonephritis. However, the information about the incidence and factors associated with the development of severe sepsis and septic shock in patients with ACPN is very scarce and is practically limited to patients with obstructive uropathy.<sup>[7,16]</sup> As far as we are aware, this is the largest study dealing with severe sepsis or septic shock secondary to acute ACPN.<sup>[7,8,16]</sup>

Although previous studies have identified some risk factors related with the development of severe sepsis in patients with



ACPN, the lack of homogeneity in their design and the reduced number of patients included in some studies prevent drawing conclusions.

Our results show that an age >65 years, urinary instrumentation in the previous 2 weeks, the lack of mictional syndrome or costovertebral tenderness, ultrasound evidence of an ectasia  $\geq$  grade II, or renal abscess and bacteremia were independent risk factors for severe sepsis or septic shock.

Overall, our results are not surprising. Multiple studies have shown a greater risk for severe sepsis and a worse prognosis for patients >65 years, both for sepsis in general<sup>[13,17]</sup> and for sepsis of urinary origin in particular.<sup>[10,18,19]</sup> Nor was it surprising that absence of mictional syndrome or costovertebral angle tenderness were factors associated with severe sepsis in these patients. In a recent study from a cohort of 41,672 patients >65 years hospitalized for acute illnesses, 3487 (8.4%) of whom suffered some cognitive impairment, Shen et al<sup>[20]</sup> reported that cognitive impairment was associated with a 50% higher risk of severe sepsis after controlling for age, gender, surgical condition, comorbidity, and principal diagnosis. Older patients, particularly if they have cognitive impairment, have more difficulty describing their symptoms. This not only delays access to medical care, but it also makes diagnosis more difficult and thus delays the start of adequate therapy.

Any invasive diagnostic or surgical procedure involving the urinary tract can result in infection.<sup>[21]</sup> In a population-based study including 75,190 men who underwent a transrectal prostate ultrasound-guided biopsy in Ontario, Canada, between 1996 and 2005, the 30-day hospital admission rate for complications increased from 1.0% in 1996 to 4.1% in 2005, with 72% of the admissions for infection-related reasons.<sup>[22]</sup>

Much evidence points to the progressive increase in quinolone-resistant uropathogens. Even so, because of their broad spectrum and excellent bioavailability, this class of antibiotics is widely used in prophylaxis for urinary tract instrumentation.<sup>[23]</sup> In the present study, 40% of those patients who had undergone urinary tract instrumentation during the previous 2 weeks had received prophylaxis with quinolones, even though the resistance rate of *Escherichia coli* to quinolone is >20% in our area (data not shown). As 18.7% of our patients who developed severe sepsis or septic shock had undergone urinary tract instrumentation, we feel it is important to remember that the choice of specific agent for prophylaxis should take into consideration the local epidemiology of drug resistance in potential uropathogens.

Despite intensive management and emergency drainage, obstructive uropathy associated urinary tract infection leads to a high rate of morbidity and mortality.<sup>[7]</sup> In the present study, 27.7% of the patients with ultrasound evidence of an ectasia  $\geq$  grade II had severe sepsis or septic shock. Similar results have been reported by others.<sup>[5,7]</sup>

Although the presence of bacteremia does not influence the prognosis in uncomplicated pyelonephritis,<sup>[4]</sup> this is not the case in ACPN. The results of this study show a clear relation between bacteremia and severe sepsis. Similar findings were reported by Hsu et al<sup>[8]</sup> in a study of 128 patients with ACPN, 42% of whom had bacteraemia.

Infections due to ESBL-producing microorganisms have become an emerging cause of community and nosocomial infections worldwide, a high proportion of which concern urinary tract infections. In our study, 12.9% of the patients had infections caused by ESBL-producing microorganisms, though this finding was not associated with the development of severe sepsis or septic shock. Similar findings were reported by

Rodríguez-Baño et al<sup>[24]</sup> in a large sample of patients with community-onset bacteremia due to ESBL-producing *E. coli*. The explanation for this could be related to the fact that the guidelines at our center contemplate the use of carbapenems in the empirical treatment of patients with ACPN who also have any risk factor for infection with ESBL-producing Enterobacteriaceae.

Interestingly, a prior episode of ACPN seemed to be a protective factor against the development of severe sepsis or septic shock. This association, which has not been reported before, may be related to the fact that patients who have already had this condition probably seek medical attention sooner than patients with a de novo infection, thus leading to them being treated sooner.

Our study has several limitations. The first is inherent to any study with a very long recruitment period. In these situations, changes in epidemiology, methods of diagnosis, and treatment can affect the results from one period to another. This does not appear to be the case here, as the diagnostic and therapeutic protocol was homogenous throughout the study period. In addition, except for the percentage of patients with ACPN caused by ESBL-producing microorganisms, there were no relevant differences over the study years regarding age, percentage of patients with obstructive uropathy, or bacteremia, all of which are basic variables related with the presence of severe sepsis or septic shock (data not shown).

Second, patients were not included if they had recently undergone major urological surgery or kidney transplantation, even if these patients met the criteria for ACPN.<sup>[10]</sup> The principal reason for excluding these patients was because these 2 special situations involve a particular epidemiology that is unlikely to be representative of most patients, who generally present with a community-acquired infection and are initially seen by primary care physicians. Third, only patients admitted to the hospital were included. Thus, studying patients discharged home from the emergency department could have influenced the results. This though is also unlikely because in our center, all patients diagnosed with ACPN are admitted to hospital and receive parenteral treatment until the clinical evolution is clearly favorable. Finally, our definitions of severe sepsis and septic shock, although appropriate at the time of the study, have been recently reformulated.<sup>[25]</sup>

In contrast, our study possesses important strengths. First, to our knowledge, this is the largest cohort of ACPN patients to date. Second, this study was undertaken in patients with ACPN presenting to the emergency department, thus reflecting our daily clinical practice. Third, the patients were recruited prospectively in accordance with well-defined criteria. Fourth, all the patients were managed in the same way throughout the whole study period.

In conclusion, our results clearly indicate that the prevalence of severe sepsis and/or septic shock in patients diagnosed with ACPN is high. Epidemiological, laboratory, and imaging data exist that are easily recognizable at the bedside or available shortly after arrival of the patient at the hospital, which can aid in deciding which patients should be admitted to receive immediate treatment. It would be interesting to see whether the findings of the present study are reproduced using the recently updated criteria regarding severe sepsis and septic shock.

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