

Extended-spectrum beta-lactamase-positive *Escherichia coli* causing complicated upper urinary tract infection: Urologist should act in time

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Abstract

Objective: Recently, many articles reported increased incidence of urinary tract infection (UTI) due to Extended-Spectrum Beta-Lactamase (ESBL)-producing *E. coli*. No data are available to date regarding patients presenting with complicated upper ESBL-positive *E. coli* UTI and sepsis. We report the clinical presentation, management, and outcomes in seven cases.

Materials and Methods: This prospective study was carried out between January 2008 and September 2011. Follow-ups varied in patients according to their disease presentation and clinical outcomes. All strains were cultured and identified by the Clinical Microbiology Laboratory and were recovered from blood and urine cultures. *In-vitro* presence of ESBL was confirmed with Clinical and Laboratory Standard Institute double disc method.

Results: In the study period, 49 patients needed hospitalization for upper UTI. Overall, in 25 patients (51%), cultures were negative. In the remaining, seven patients (14.3%) presented positive blood and urine-culture for ESBL + *E. coli*. Of these, four were female and three were male. Their median age was 73 years (range 66-84). The median hospital stay of these patients was 23 days (range 13 to 45 days).

Conclusions: The current situation of multiple bacterial antibiotic resistance has become a worrisome issue in UTI. Multi-drug-resistant *E. coli* can be readily encountered in hospital settings during daily clinical practice, and urologist should act timely. The management of such infections is extremely important for the future, with particular reference to prevention of new antibiotic resistance patterns.

Key Words: Extended-spectrum beta-lactamase positive, *Escherichia coli*, hydronephrosis, infection, pyonephrosis, sepsis

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INTRODUCTION

Urinary tract infections (UTIs) have been reported to affect up

to 150 million individuals annually worldwide.^[1] A complicated UTI is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that interferes with host defense mechanisms, which increases the risk of acquiring infection or of therapeutic failure.^[2] This could, for example, include the presence of an indwelling catheter or urinary stent, the presence of an obstructive uropathy of any etiology, or urinary tract modifications, such as an ileal loop or pouch.

The World Health Organization and the European

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Commission have recognized the importance of studying the emergence and determinants of acquired anti-microbial resistance and the need to devise appropriate strategies for their control.^[3-5] In particular, the Extended-Spectrum Beta-Lactamase (ESBL)-producing *Escherichia coli* are emerging worldwide.^[6-8] The ESBL-producing strains are particularly feared as they are resistant to all penicillins, to cephalosporins (including third and fourth generation agents), and to aztreonam. Furthermore, they are often cross-resistant to trimethoprim/sulfamethoxazole and quinolones. This combination of properties can significantly affect the course and outcomes of infections, both in the community and in the hospital setting.

Recently, many articles report the increased incidence of UTI due to ESBL-producing *E. coli*.^[6-8] Furthermore, different reports regarding the clinical presentation and management of sepsis to this resistant strain after trans-rectal prostatic biopsy have also appeared in recent literature.^[9-12] No data are available to date for patients presenting with complicated upper UTI and sepsis caused by ESBL-positive *E. coli*. We report the clinical presentation, the management, and the outcomes in seven cases.

MATERIALS AND METHODS

This prospective study was carried out between January 2008 and September 2011. All patients referred to the Department of Urology of IRCCS Policlinico di San Donato for complicated upper UTIs were followed up during the study period. Particular attention was given to the study of clinical presentation, management, and outcomes of infections due to ESBL-producing *E. coli*.

All the medical data were prospectively recorded after the admission of patients with the diagnosis of complicated upper UTI that was specifically followed by our department in collaboration with the Division of Internal Medicine and the Intensive Care Unit.

Patients were treated empirically according to the 2008 European Urological Association guidelines on the management of urinary and male genital tract infections.^[13] The knowledge of the spectrum of possible pathogens and local antibiotic resistance patterns, as well as assessment of the severity of the underlying urological abnormality (including the evaluation of renal function) were used to determine the antibiotic therapeutic regimens. Anti-bacterial spectrum of the antibiotic agent includes the most relevant pathogens. A Group 3a or b cephalosporin, an aminoglycoside or a carbapenem was prescribed.

Follow-ups varied between patients according to their disease and clinical outcomes.

For a correct classification of the septic complications, the following definitions of bacteremia, septicemia, sepsis, septic shock, and multi-organ failure were adopted:^[14]

- Bacteremia: Presence of bacteria in blood based on blood cultures results
- Septicemia: Presence of any pathogenic micro-organism or its toxins in blood;
- Sepsis: Clinical condition of proven or suspected infection plus evidence of a systemic inflammatory response defined by the presence of at least two of the following: Fever (oral temperature > 38°C) or hypothermia (<36°C), tachypnea (>24 breaths/min), tachycardia (>90 beats/min), leukocytosis (>12,000/ μ L), leukopenia (<4,000/ μ L), or >10% bands
- Severe sepsis: Systemic inflammatory response plus one or more signs of organ dysfunction (cardiovascular: Arterial systolic blood pressure \leq 90 mmHg or mean arterial pressure \leq 70 mmHg, which responds to administration of intravenous fluid; renal: Urine output <0.5 mL/kg per hour for 1 hour, despite adequate fluid resuscitation; respiratory: Ratio of arterial partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FIO₂) \leq 250 or, if the lung is the only dysfunctional organ, \leq 200; hematologic: Platelet count <80,000/ μ L or 50% decrease in platelet count from highest value recorded over previous three days; unexplained metabolic acidosis: A pH \leq 7.30 or a base deficit \geq 5.0 mEq/L and a plasma lactate level >1.5 times the upper limit of normal for the reporting laboratory; adequate fluid resuscitation: Pulmonary artery wedge pressure \geq 12 mmHg or central venous pressure \geq 8 mmHg)
- Septic shock: Sepsis with hypotension (arterial blood pressure <90 mmHg systolic or 40 mmHg less than patient's normal blood pressure) for at least 1 hour despite adequate fluid resuscitation) or need for vasopressors to maintain systolic blood pressure \geq 90 mmHg or mean arterial pressure \geq 70 mmHg
- Multiple-organ dysfunction syndrome: Dysfunction of more than one organ or intervention required to maintain homeostasis.

Microbiological analysis

All strains were cultured and identified by the Clinical Microbiology Laboratory and were recovered from blood and urine cultures. Blood culture was conducted by Bact Alert and selective media (bioMérieux, Marcy l'Etoile, France). Urine culture was performed applying routine internal protocols and using selective media (bioMérieux, Marcy l'Etoile, France). Identification and anti-microbial susceptibility test were performed with ID 32 E and ATB 32 GN panels in the automated ATB Expression System (bioMérieux, Marcy l'Etoile, France). Antibiotics used for antibiotic susceptibility

testing were amikacin, amoxicillin/clavulanic acid, ampicillin, ceftazidime, cefepime, cefotaxime, ceftazidime, ciprofloxacin, gentamicin, imipenem, levofloxacin, nitrofurantoin, norfloxacin, meropenem, piperacillin/tazobactam, trimethoprim/ulfamethoxazole.

In-vitro presence of ESBL was confirmed with CLSI (Clinical and Laboratory Standard Institute) double disc method.

Microbiologist advised clinicians timely about the strain of bacteria isolated and also reported promptly the anti-microbial susceptibility test as soon as available.

RESULTS

In the study period, 49 patients needed hospitalization for complicated upper UTIs.

All blood and urine cultures were drawn prior to the institution of antibiotics whenever possible. If empiric treatment was deemed an emergency, blood cultures were drawn as soon as possible after institution of antibiotics. Overall, in 25 patients (51%), cultures resulted negative.

Isolated pathogens in blood and urine cultures are listed in Table 1.

Eleven patients (22.4%) presented positive blood and urine-culture for *E. coli*, of which seven were ESBL+ (14.3%). These were four women and three men. Their median age was 73 years (range 66-84). Their characteristics, their co-morbidities, underlying urological diseases, precipitating causes, clinical features, and management are reported in Table 2.

The underlying urological diseases were ureteral obstructing stone in two patients, monolateral staghorn calculus in two patients, uretero-pelvic junction stenosis in two patients, and a urinary tract modification (uretero-cutaneo-stomy following radical cystectomy for invasive bladder cancer concomitant nephrectomy for non-functioning kidney) in the remaining patient.

Table 1: Isolated pathogens in blood and urine cultures

Pathogens	Patients tot. (n°)	Positive blood cultures	Positive urine cultures
<i>Escherichia coli</i>	11	8	11
<i>Enterococcus faecalis</i>	4	3	4
<i>Candida albicans</i>	3	0	3
Bacterial contamination	2	1	1
<i>Staphylococcus spp</i>	1	1	1
<i>Staphylococcus aureus</i>	1	0	1
<i>Pseudomonas aeruginosa</i>	1	0	1
<i>Enterobacter cloacae</i>	1	1	1

All patients were septic at presentation in the Emergency Department. Three of them presented with septic shock (42.9%), one of which was associated to multiple-organ failure (14.3%). The initial manifestations were characterized by high fever and flank pain in all cases. Leukocytosis was present in five cases while leukopenia was present in two patients.

Five patients (71.4%) had undergone urological surgery in the preceding six months. All patients received multiple quinolone (ciprofloxacin or levofloxacin) or third-generation cephalosporins antibiotic therapies in the months previous to emergency ward acceptance.

All patients underwent urgent surgical stenting procedures (single-J, double-J, or nephrostomy tubes) procedures in order to “drain” an obstructed tract or facilitate drainage in non-obstructed urinary tracts. Urine drained from the upper urinary tract was always purulent.

The isolation of *E. coli* occurred in the urine cultures of all patients and in blood cultures in five. All *E. coli* isolates were ESBL-positive and were classified as MRDO (multi-drug-resistant micro-organism) being sensitivity only to amikacin and carbapenems.

All patients after an initial broad-spectrum antibiotic therapy were treated in accordance with anti-biogram sensibility with carbapenems.

One patient died of acute respiratory distress syndrome 10 days after nephrectomy for severe infected non-functioning kidney. All other patients presented negative urine cultures.

The median hospital stay of these patients was 23 days (range 13 to 45 days). Patient three presented a high rate of new hospital re-admissions related to persistence of ESBL-producing *E. coli* recurrent urinary infection.

It was not possible to perform any comparison because of the small size of this sample.

Moreover, even if statistically significant, an adequate statistical power could not be guaranteed.

DISCUSSION

Enterobacteriaceae have become one of the most important causes of nosocomial and community-acquired infections. Their acquired resistance to beta-lactams is mainly mediated by ESBLs that confer bacterial resistance to all beta-lactams except carbapenems and cephamycins, which are inhibited by other beta-lactamase inhibitors such as clavulanic acid. The

Table 2: Patients' characteristics, co-morbidities, underlying urological diseases, precipitating causes, clinical features, and their clinical management

Patient	Age (years)	Sex	Urological disease	Co-morbidities	Risk factors	Precipitating cause	Fever	Positive blood culture	Positive urine culture	Sepsis/ septic shock	Multi-organ failure
1	73	Female	Hydronephrosis due to impacted urethral stone	Hypertension	Multiple antibiotic therapies	Upper-UTI and pyonephrosis	Yes	Yes	Yes	No	No
2	64	Female	Staghorn lithiasis	None	Multiple antibiotic therapies	Upper-UTI, peri-renal abscess and pyonephrosis	Yes	Yes	Yes	Yes	Yes
3	66	Female	Stag horn stone treated with PCNL and ESWL for residual lithiasis	Hypertension	Urological surgery, multiple antibiotic therapies	Hydronephrosis due to impacted ureteral stone and pyonephrosis	Yes	Yes	Yes	Yes	No
4	79	Female	Right uretero-cutaneo-stomy	Hypertension and hypothyroidism	Urological surgery, multiple antibiotic therapies	Accidental stent removal and pyonephrosis	Yes	Yes	Yes	No	No
5	84	Male	Uretero-pelvic junction stenosis and pyelic lithiasis	Hypertension and chronic renal insufficiency	Urological surgery, multiple antibiotic therapies	Displacement of ureteral stent and pyonephrosis	Yes	Yes	Yes	No	No
6	69	Male	Uretero-pelvic junction stenosis and anastomotic stenosis in continent neo-bladder	Hypertension, ischemic heart disease and atrial fibrillation	Urological surgery, multiple antibiotic therapies	Malfunctioning ureteral stent and pyonephrosis	Yes	Yes	Yes	Yes	No
7	74	Male	Uretero-pelvic junction stenosis and ureteral stone	Hypertension	Urological surgery, multiple antibiotic therapies	Hydronephrosis due to impacted ureteral stone and pyonephrosis	Yes	Yes	Yes	Yes	No

earliest ESBLs, first identified in the 1980s, were mutants of the plasmid-borne TEM and SHV penicillinases that had disseminated in *E. coli* and other Enterobacteriaceae in the 1960s and 1970s. The prevalence of ESBLs differs among patient groups and clinical and geographic settings.

We report the clinical presentation, the management, and the clinical outcome in seven patients affected by upper UTI due to ESBL-positive *E. coli*. All patients presented with pyonephrosis and sepsis, three of which were related to septic shock. The urinary tract obstruction in conjunction to infections and the accompanying “infected urine under pressure” causes a rapid deterioration of the patient’s clinical conditions. Thus, an early recognition and treatment of acute infections of the kidney, especially in patients with suspected urinary tract obstruction, are of paramount importance. Some of the new approaches to management of severe sepsis and septic shock appear to be time-dependent, suggesting a “golden hour” and “silver day” perspective to the management of this disorder, giving the early recognition and treatment of the disease a more important

role in the care of these patients. All patients presenting with pyonephrosis and urosepsis should be diagnosed at an early stage in order to decrease overall mortality rate.^[9] All patients underwent an urgent antegrade or retrograde decompression of the upper urinary tract. Drainage of the obstruction in conjunction with the antibiotic therapy leads to resolution of symptoms.

The development of antibiotics has contributed greatly to reduce patient mortality caused by infection. Nonetheless, as the use of antibiotics becomes generalized, the vicious circle of the development of the emergence of resistant bacteria and the use of new more efficacious antibacterial molecules cannot be severed. We have recently observed that our patient population presents an elevated prevalence of *E. coli* resistance to commonly used antibiotics.^[15] This was already documented by the impressive rising of ESBL-positive *E. coli* sepsis after prostatic biopsy and the growth in hospitalizations for the cure of symptomatic infections to the urinary tract secondary to multi-resistant bacterial strains. ESBL-producing strains are

particularly important as they are resistant to all penicillins, to the majority cephalosporins (including third and fourth generation agents) and to aztreonam; furthermore, they are often cross-resistant to trimethoprim/sulfamethoxazole and quinolones.

Early identification of ESBL production is becoming increasingly important in terms of appropriate treatment and effective infection control in hospitals. Patients with infections caused by ESBL producers may experience delay in the initiation of appropriate therapy compared with patients with non-ESBL infections.^[16] In addition, infection with ESBL-producing bacteria raises mortality, and it prolongs hospital along with an increase of treatment costs. This finding is of importance in as far as the therapeutic options for ESBL-producing bacteria might be limited. In our study, similarly, excluding amikacin and carbapenems, antibiotics with sensitivity higher than 50% to ESBL-producing *E. coli* were absent.

It is, therefore, very important to assess the risk factors for the emergence of ESBL-producing bacteria in order to prevent such resistance. ESBL-producing bacteria is more frequent in patients with contact to the health care system (recent hospitalization, residence in a long-term care facility, recent surgery, and bladder catheterization), recent use of antibacterial agents (in particular third- and fourth-generation cephalosporins and fluoroquinolones), poor functional performance, greater disease severity, and co-morbidities.^[17-22] Recently, Ben-Ami et al. identified five risk factors, which are independently predictive of ESBL positivity by multivariate analysis: Male sex, age > 65 years, recent antibiotic use, recent hospitalization, and residence in a long-term care facility.^[18] All patients with ESBL-positive *E. coli* infections had been hospitalized in the previous six months. Five patients had a history of recent uro-genital surgery. Furthermore, all patients were exposed to quinolones or third-generation cephalosporins in the last year.

These data suggest two possible points of intervention: Limiting infection within hospitals could reduce the prevalence of ESBL-producing bacteria and lower the spread to communities while the policy of restricted indications for administering antibiotics could reduce the incidence of resistance.

The outcomes of our patients were favorable in six especially considering that three cases presented severe sepsis. The only case of multi-organ failure occurred in a patient who received untimely medical care. In this patient, the delay in draining the upper urinary tract was complicated by a large peri-nephric abscess. This underlines the importance of the early recognition of the clinical picture and immediate treatment of the pyonephrotic kidney. Hospitalization is protracted in these patients, particularly due

to the time taken for the antibiotic therapy to achieve remission of the infection. Furthermore, hospitalization time results longer due to the fact that in Italy, carbapenems are prescribed only in the hospital setting and in order to prevent the persistence of the pluri-resistant *E. coli* in the urinary tract, and to avoid the comparison of resistance to carbapenems, prior to the discharge all patients' cultures need to be negative.

In only one patient, the antibiotic therapy resulted in profuse diarrhea due to *Clostridium difficile* infection. The definitive management of stones and obstruction with ureteroscopy, lithotripsy, or PCNL was performed after the resolution of infection, generally during the same recovery, and it is essential in reducing hospital re-admission, by resolving a clinical condition, which increases the risks of failed therapy.

CONCLUSIONS

As recently reported in international literature, a rise in urinary tract infection due to ESBL-positive *E. coli* exists. For the first time, we report the clinical outcome in septic patients affected by complicated upper urinary tract infection that will become an urgent treatment in our clinical practice. The current incidence of resistance to antibiotics has reached a serious point when contemplating appropriate therapy for urinary tract infection. We underline the importance of early recognition of the clinical picture, and urologist should implement timely therapy. Hospitalization is protracted in these patients, particularly due to the time taken for the antibiotic therapy to achieve remission of the severe infection picture. The correct management of such infections is extremely important for the future, in particular in term of reducing the incidence of new antibiotic resistance patterns.

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