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The Changing Epidemiology of Extended Spectrum Beta-Lactamases (ESBL) Infections of the Urinary Tract Focusing on Clinical Resistance and Therapeutic Options

Suresh J. Antony

*Texas Tech University Medical Center/Paul Foster School of Medicine
and The Center for Infectious Diseases and Travel Medicine
El Paso, Texas
USA*

1. Introduction

The first beta- lactamases were identified in a species of *E.coli* in 1940 (1). However, the ability of bacteria to produce enzymes that destroy the b-lactam ring was noted even before penicillin was developed. In fact, many of the gram-negative bacteria possess chromosomally mediated b- lactamases, which help the bacteria find a niche when faced with competition from other bacteria that naturally produce b-lactams.

In 1965, the first plasmid mediated beta- lactamases was discovered. This occurred in a strain of *E.coli* isolated from the blood culture of a patient from Greece whose name was Temoniera. The beta -lactamases was named TEM-1 after the patient's name from whom it was isolated. (2) This strain soon spread to other members of the Enterobacteriaceae species, *Hemophilus influenza*, *Neisseria gonorrhoeae* and *Pseudomonas aeruginosa* due to the plasmid mediated transfer.

Around the same time a second plasmid mediated beta-lactamases was found in *Klebsiella pneumoniae* and *E.coli*. This was called SHV-1 (sulfhydryl variable) (3). The advent of the b-lactam class of antibiotics was influenced largely by the discovery of these enzymes. An example of this was the development of oxyimino-cephalosporin, which showed good stability against the TEM-1 and SHV-1 b-lactamases (4). This class of antibiotics soon became the workhorse for these types of serious infections.

Unfortunately, resistance to this class soon became evident in 1985 with beta-lactamases showing the ability to hydrolyze these compounds in *K.pneumoniae* (5). Because this enzyme was noted to be active against expanded spectrum b-lactams these enzymes were labeled as "extended spectrum beta-lactamases" -ESBL.

Several b-lactamases have continued to be with over 130 TEMS types and over 50 SHV types known to date. These are mainly found in *E.coli*, *K.pneumoniae* and *P.mirabilis*, but have also been found in other species of the Enterobacteriaceae family and even in some nonenteric bacteria such as *Acinetobacter* species.

Shortly after the introduction of new broad-spectrum cephalosporins such as cefotaxime and ceftazidime, non-TEM and non SHV ESBL's were discovered. This new class of ESBL's

has been called CTX-M in reference to the potent hydrolytic activity of these enzymes against cefotaxime(6). There are over 40 of these enzymes reported. CTX-M producing ESBL pathogens usually have cefotaxime in the resistant range (MIC>64).

More recently, and of greater concern is the occurrence of carbapenemases which show activity against oxyimino-cephalosporins and cephamycins but also against carbapenems (7). There are two major groups in this class called metallo- β -lactamases (Verona integron encoded metallo β lactamases) (VIM) and carbapenemases. Structural studies of ESBL indicate that active site expansion and remodeling are responsible for the extended hydrolytic activity (8). These enzymes are globally present and appear to cause clinically significant disease such as urinary tract infections, abscesses and bacteremia.

With the advent of the ESBL pathogens, there has been a significant increase in the morbidity and mortality related to these infections. If the number of carbapenemase-producing organisms continues to increase, the treatment options will be seriously compromised.

In addition, ESBL producing pathogens are not only resistant to penicillin and cephalosporins but also to trimethoprim-sulphamethoxazole and fluoroquinolones which can compromise the treatment of both nosocomial and community acquired infections caused by *Enterobacteriaceae* and other species (9).

One of the major clinical problems has been the recognition of both nosocomial and community acquired urinary tract infections resulting from ESBL pathogens. The treatment options for these infections are limited, especially in the out patient setting.

This chapter will review the epidemiology, risk factors, clinical features and therapeutics options for ESBL-induced infections of the urinary tract.

2. Recent epidemiological data

ESBL producing organisms have been implicated in nosocomial infections. Over the last decade, there has been a steady increase of these infections in the community.

In fact, a recent study from Spain suggest there was been an increase in ESBL *E.coli* producers from 0.3% to 4.8% between 1995 and 2002. (10) Interestingly, during this same period there was a drop in the rate of ESBL producing *K.pneumoniae* following the control of nosocomial transmission of this pathogen. These *K. pneumoniae* were mostly clonally related and produced SHV and TEM.

In contrast, the ESBL *E.coli* strains were not clonally related and the predominant strain was a CTX-M. In addition, half of these strains were isolated from outpatients (10,11).

France was one of the first countries to report an outbreak of ESBL infections in 1986. In this study, 30% of *Enterobacter aerogenes* isolates in 2000 were ESBL producers (12). Since that time, virtually every country in Europe has reported ESBL producers with considerable geographical variability in the occurrence of ESBL's. Examples of this include a prevalence rate of ESBLs

K. pneumoniae in Sweden of 3% to 34% in Portugal (13). In one study done in France, it was noted that intestinal carriage prevalence of ESBL-*E.coli* was 8.0%, mainly the CTX-M type. At the same time, it was noted that there was an increase in antibiotic usage, especially the beta-lactams. This variability probably occurred because of the repeated introduction of new strains and plasmids and from inter-individual dissemination (14)

In Central and South America ESBL, rates in *Klebsiella* varied from 30 to 60% in countries such as Brazil, Columbia and Venezuela (15). The ESBL strains included SHV-2, 5, CTX-M and even non-TEM and non-SHV with no geographical predilection. (16, 17)

In Africa and the Middle East there has been a number of outbreaks of ESBL producing infections from South Africa to northern Africa. The rates of ESBL were variable depending on the country (18 19) .

In North America the first case of an ESBL producer was in 1988 and since then a variety of infections produced by TEM strains, SHV type and CTM-X have been reported. In fact, in a recent survey it was noted that non-susceptibility to third generation cephalosporin's may be as high as 13 %.(20,21). In the outpatient, setting 1.8% of *k.pneumoniae* and 0.4% were ceftazidime resistant (22)

In Asia, there seems to be a larger proportion of ESBL pathogens. Studies from several countries, including China, India, Japan, Korea, and Malaysia showed ranges from 30% to 40 % (23,24). Reports of a possible predominant CTM-X ESBL in countries like India, China Korea, Japan and Taiwan indicate that there may be a dominant ESBL type in Asia (25,26). More recently, there have been studies showing increasing numbers of carbapenemase producing pathogens, which is of increasing clinical importance due to the lack of effective antimicrobial therapy. (27-31).

Current data suggest that the incidence of ESBL producing infections is on the rise globally resulting in increasing difficulty in the diagnosis and treatment of these infections.

3. *In vitro* resistance studies for ESBL

In- vitro susceptibility testing of cephalosporins for ESBL producing enterobacteriaceae can be misleading. Testing may suggest that an isolated strain is susceptible to a given cephalosporin, but the drug may not be effective when used to treat a serious infection caused by the organism. Thus, CLSI guidelines recommend that laboratories report ESBL producing isolates as resistant to all penicillin's, cephalosporins and aztreonam irrespective of *in vitro* results. (32).

In vitro studies performed in Turkey found that *E.coli* isolated from CA-UTI infections had simultaneous resistance to trimethoprim-sulphamethaxazole, ciprofloxacin, and gentamicin in 4.6% of an ESBL negative group and 39.2% in the ESBL positive group. 90% of these ESBL isolates were found to have CTX-M 15. (33). This data is worrisome as therapeutic options are limited when oral antibiotics are used.

In Taiwan, Lau and colleagues looked at 201 patients with and without bacteremia in CA-ESBL UTI. They found that *e.coli* was the most common pathogen and was more frequent in the bacteremic than non-bacteremic group. Non-*E.coli* isolates such as *K.pneumoniae*, *Morganella morganii* etc were more common in the non-bacteremic group. *E.coli* isolates had a high rate of resistance to ampicillin (80%), gentamicin (29%) trimethoprim-sulphamethaxazole (56%). (34). Similar findings have been documented from other parts of the world such as Saudi Arabia (35).

Detection of ESBL's is based on the fact that ESBL producers should be reported as resistant to all penicillin's, cephalosporins (except cephamycins) and aztreonam irrespective of routine antimicrobial susceptibility testing. (32)

Both broth dilution and disk diffusion can be used for the screening of ESBL producers. Specific phenotypic confirmatory tests should be done if the *E.coli*, *K.pneumoniae*, show MIC's >8ug/ml for cefpodoxime or MIC's >2 ug/ml against ceftazidime, cefotaxime or aztreonam. (36,37)

The E-test can also be used in the detection of ESBL. Automated methods for bacterial identification and susceptibility testing are also used in the detection of ESBL producing

organisms. These include the BD Phoenix system, Vitek 2 system and the Micoscan Walkway -96 system.

4. Risk factors for colonization /infection with ESBL

There have been several case controlled studies looking at the risk factors for colonization with or without infection due to ESBL producers. However, the results are conflicting due to study populations, geographical areas, selection of cases and controls and sample size. (38-48).

Despite these statistical differences, some generalizations can be made. (Table 1)

| |
|---|
| Diabetes mellitus |
| Previous antimicrobial exposure (quinolones, third generation cephalosporins, penicillin) |
| Previous hospital admissions |
| Older age |
| Male patients |

Table 1. Risk factors for the Development of Community ESBL Infections.

Some of these risk factors include seriously ill patients with prolonged hospital stays (11-67 days) who have usually had multiple invasive devices and co-morbidities such as urinary catheters, central lines, nasogastric tubes, jejunostomy tubes, arterial lines, total parental administration, recent surgery, decubitus ulcers, hemodialysis catheters and poor nutritional status.

The use of previous antibiotics such as third generation cephalosporins, quinolones, trimethoprim-sulphamethoxazole, aminoglycosides and metronidazole have also been implicated in several studies. (38,42,45,49,44,50,47, 48,51).

5. Community –acquired infections involving ESBL pathogens

In a large French study in 1993, looking at *E.coli*, *K.pneumoniae* and *P.mirabilis* (2500 isolates) from non-hospitalized patients, there was no evidence of community acquired ESBL infections (52). Since then, there have been several studies of true community acquired ESBL infections. These involved patients with diarrheal diseases such as *Shigella*, *Salmonella*, *Vibrio cholerae* and *E. coli*. (53-56)

The prevalence of colonization with enterobacteria is unknown. The percentage of ESBL producing *Enterobacteria* faecal carriers in Spain increased from 2.1% to 7.5% IN 2002. (57) . The most frequent types of ESBL were CTX-M, followed by SHV. In India, the rate of fecal carriage was 7% in a sample of healthy adults (60). In Canada, Pitout found 5.5 cases per 100,000 populations with 69% being community acquired. (59)

Three case controlled studies looking at risk factors for ESBL *E.coli* outpatient infections found that diabetes mellitus, previous use of antibiotics such as quinolones and cephalosporins, recurrent urinary tract infections, prior hospital admissions and older age were independent risk factors (59,60). However, infections due to ESBL producing *E.coli* in patients can occur without obvious risk factors. This may be related to the increase in healthy carriers colonized with this pathogen.

Colodoner et al evaluated 128 cases of UTI caused by ESBL *E.coli* and *K. pneumoniae* and found that age >60 years, male sex, previous use of quinolones or cephalosporins, previous

hospitalization, and previous infections caused by *K. pneumoniae* were independent risk factors.(61)

In community- acquired urinary tract infection (CA-UTI), the rate of ESBL associated UTI's varied from 1.4% in Spain up to 3.3% in the Gaza strip (60,62,63).

In the last 7 years, there have been an increasing number of publications from several countries showing and increase of community acquired ESBL infections, mainly in urinary tract. (64,65,61,57,30,59,60,31) Most of these patients had urinary tract infections (UTI's) with genes encoding for CTM-X type of ESBL's (60). Recently, there has been an increase in the diagnosis of infections caused by ESBL *E.coli* producers diagnosed in the outpatient's setting.(59,60,30)

Romero et al showed an increase from 0.3% in 1995 to 4.8% in 2002 in community acquired ESBL *E.coli* producers. (10). These ESBL *E.coli* producing strains were not clonally related with the majority belonging to the CTX-M family and more than 50% were isolated in the outpatient setting. (10, 11)

In one study in Spain up to 6.5% of community, acquired bacteremia was associated with ESBL *E.coli* UTI (60).

In summary, ESBL infections can range from colonization to carriage to true infections involving sepsis syndromes and bacteremia.

6. Clinical features of CA-UTI infections caused by ESBL pathogens

Several studies have described the microbiological features of ESBL producing organisms in the outpatient setting. However, very few studies have correlated the microbiological findings with that of the clinical features and prognosis of these CA-UTI ESBL infections. Therefore, one may only draw some tentative conclusions from these studies.

In urinary tract infections, the majority of ESBL's isolated, not surprisingly, have been ESBL *E.coli*. This organism has also been isolated from other sources such as wounds, sputum, and occasionally blood. (59,60,11,)

In the United States, Chao Qi et al evaluated 193 single patient ESBL isolates in outpatient urine cultures during a 5-year period. 3% of *E.coli* had ESBL and this was noted to have increased 14 times from 2003 to 2008. This increase may have been in part due to the dissemination of CTX-M type of ESBL. (66) This was also noted in another study from nursing homes and out patient clinics. (67) . Resistance to ciprofloxacin and trimethoprim-sulphamethaxazole was much higher as well.

In another study of 49 patients with ESBL *E.coli* infections, ESBL *E.coli* was isolated from urine in 47 of the cases and from blood in 6 of the patients. Thirty-seven (76%) of these patients were considered to have symptomatic infections and 11 (22%) asymptomatic bacteriuria. 1 patient also had cholangitis and 6 (13.5%) of these patients were bacteremic. In this same study, 10 of the 28 patients who received antibiotics actually received an appropriate agent to which the organism was susceptible in vitro. 13% of these patients had a UTI relapse. There were no deaths in this study (60). It appears that the complication rate with CA-ESBL UTI's may not be higher than that associated with routine non-ESBL pathogens, although further studies are still needed. The main predictor of mortality caused by ESBL *E.coli* is probably inadequate initial antimicrobial therapy. In comparison, ESBL-EC associated mortality for hospitalized patients with serious infections such as bacteremia and sepsis was about 25%-31%. This was also associated with inadequate empiric antibiotic therapy. (68,69).

The most frequent cause of community-acquired bacteremia is *E.coli* (70,71) and currently available antibiotics such as quinolones, beta-lactams and third generation cephalosporins are commonly used to treat them. This may need to change with the advent of increasing antimicrobial resistance and increasing mortality associated with these CA-ESBL infections (44,59). Rodriguez-Bano examined CA-ESBL associated bacteremia and its features and found that in 95 patients with blood stream infections 7.3% were due to *E.coli*. The majority belonged to the CTX-M family of ESBL and was clonally unrelated. The risk factors associated with these patients included urinary foley catheter use and previous antimicrobial exposure (60). The sources of bacteremia were the urinary tract, intra-abdominal sites and respiratory tract. Interestingly, mortality associated with blood stream infections due to ESBL-*E.coli* was lower among patients who received empirical therapy with beta-lactam or its combinations or carbapenems than among those that received quinolones. In addition, higher mortality was associated with inappropriate empirical therapy in patients with bacteremia due to *E.coli*. (72)

In patients with solid organ transplants and renal transplants, the major site of infection was the urinary tract in 72% of the cases, with ESBL *K. pneumoniae* being more common in renal transplant patients (73).

Geriatric patients with ESBL UTI's pose an unusual clinical problem. These patients may be chronically colonized in either the gastrointestinal tract or the skin and reinfection is a possibility. In addition, many of these patients are asymptomatic and do not present with the classic symptoms of dysuria, frequency of urination, fever or leukocytosis. In general, one may not need to treat asymptomatic ESBL infections. If there is a change in the clinical status such as fever, leukocytosis or altered mental status then treatment options should be considered. Numerous outbreaks have been reported of patients with ESBL infections. Much of the spread is plasmid mediated and is therefore through direct and indirect transmission. Contact isolation should be instituted in patients with ESBL infections.

In summary, ESBL infections can present from simple colonization to active UTI's and to serious bacteremia associated with sepsis syndrome.

7. Treatment options for ESBL UTI infections

Treatment options for ESBL infections are the same for both nosocomial and community acquired infections. The major problem at this time is the lack of effective oral antibiotics for the treatment of outpatient ESBL infections.

7.1 Overview of available antibiotics

ESBL's hydrolyze aztreonam, penicillin and cephalosporins (with the exception of cephamycins) with varying degrees of hydrolytic activity. Usually the TEM and SHV type ESBL's have greater hydrolytic activity for ceftazidime than for cefotaxime (74). Therefore, ESBL producing organisms may appear susceptible to some of the above-mentioned antibiotics in vitro. In addition, there is frequent co-expression of resistance by these organisms to classes of antimicrobial agents other than those hydrolyzed by the ESBL's. This has been documented for quinolones, aminoglycosides, tetracycline's (excluding glycylicline) and trimethoprim-sulphamethoxazole (59)

Some of the other antibiotic classes used to treat ESBL infections include beta lactam/beta-lactamases inhibitors. The level of activity for these agents varies by the type of inhibitor

and by the class of ESBL. For example, tazobactam appears to be more effective than clavulanic acid against certain types of CTX-M type ESBL's and both of these agents are more effective than sulbactam in inhibiting TEM and SHV type ESBL. (75,76). This data is mainly from in-vitro studies. Clinical information is sparse in regards to beta-lactam and inhibitor combinations, but some favorable outcomes have been reported with piperacillin/tazobactam. However, it is important to note that favorable results have not been consistently reported (74,77). One possible oral option may be amoxicillin/clavulanate, which has shown some activity in CA-ESBL Enterobacteriaceae UTI infections (60,78)

Few studies have evaluated cephalosporins in the treatment of both bacteremic and non-bacteremic ESBL infections. The results have been equivocal when ceftazidime or cefepime were compared to Imipenem in *e. coli* bacteremia and in ICU patients with Enterobacteriaceae infections. (79,80). In vitro data also suggests suboptimal outcomes when the cephalosporins were used to treat ESBL infections. Thus, most experts' advise against using cephalosporins in the treatment of ESBL associated infections.(79,80)

Cephamycins have not been well studied in the treatment of ESBL associated infections. In one small retrospective study, there was no obvious difference in the mortality rates between the cephamycins and carbapenems. Recent studies have documented resistance to the cephamycins (49,74).

The glycolcycline class of antibiotics, specifically tigecycline, thus far evaded the common mechanisms of resistance in both gram positive and gram-negative pathogens. It has excellent in vitro activity against ESBL-*E.coli* and *K. pneumoniae*. However, clinical data is sparse in the treatment of ESBL UTI's and bacteremia. In addition, only a fraction of the drug is excreted in the urine as unchanged drug. In addition, tigecycline does not achieve high concentrations in the blood, casting doubts on its potential effectiveness in the treatment of bacteremia.(81)

Fosfomycin has been used in Europe but is not available in most parts of the world. It is a phosphor derivative of streptomycin and inhibits cell wall synthesis and impairs adherence to urogenital mucosa. A study in Spain found that the resistance rate to fosfomycin of ESBL-EC was 0.3%. (82). It has been used in cystitis and asymptomatic UTI in pregnancy. (82,83). In the United States 90% of the isolates in one study were susceptible to fosfomycin and to a combination of cefdinir plus amoxicillin-clavulanate. (84,85)

Pivmecillinam is a beta lactam antibiotic, which binds penicillin-binding protein 2 (PBP-2) and inhibits cell wall synthesis. This drug has been used in the treatment of cystitis due to Enterobacteriaceae. (86).

Nitrofurantoin is a bactericidal drug, which acts by altering bacterial ribosome's proteins and can be used for UTI as well.

Finally, carbapenems are considered the drug of choice for ESBL infections. All the drugs in the class appear to have the same efficiency in the treatment of ESBL. Ertapenem, is the only drug in this class that can be administered once a day. It can be used in the outpatient setting as long as the in vitro activity is similar to imipenem, doripenem or meropenem.(87,88). However, recent reports of carbapenem resistance have emerged and the spread of resistance is of concern. One possible option might be to add amikacin to the empiric regimen in community-acquired sepsis originating in the urinary tract since amikacin resistance among CTX-M isolates is relatively low.

The treatment for upper UTI's may have to be limited to the intravenous antibiotics mentioned above especially as the patients tend to be sicker and may present with systemic

inflammatory response syndrome and occasionally bacteremia. These should include carbapenems. Occasionally, ampicillin-sulbactam and tigecycline may be alternate therapies although data on these drugs in the treatment of ESBL UTI infections is sparse.

In lower UTI's, some of the oral antibiotics such as nitrofurantoin, fosfomycin, amoxicillin-clavulanate and trimethoprim-sulphamethaxazole may be used if the pathogen is susceptible to them.

8. Conclusion

Antimicrobial resistance has become a global problem of increasing importance. It is now essential that laboratories be able to rapidly identify and characterize resistant organisms. This is, of even more importance, in ESBL producing organisms that clearly have a higher morbidity and mortality associated with their infections. There is also increasing evidence, that ESBL organisms frequently possess resistance factors to other classes of other antimicrobials, like the aminoglycosides and quinolones. ESBL producing bacteria are being found both in the hospital and in the community, especially the CTX-M beta -lactamases.

The increasing number of community isolates, especially *E. coli* producing CTX-M-15 have become global and now are being seen in the hospital as well. It is thought that the CTX-M -15 producing *E. coli* is mostly due to a single clone named ST131, which appears to have originated in the Indian sub-continent. In addition, the increasing number of carbapenemases could also seriously compromise our treatment options. Therefore, empiric antimicrobial coverage may need to be modified in patients who present with serious sepsis syndromes, especially, after travel to countries that are high risk for this clone.

Treatment of ESBL infections requires the use of carbapenems in seriously ill patients. Imipenem, meropenem, doripenem are all viable alternatives. Ertapenem can be used in the out patient setting, in the absence of *Pseudomonas aeruginosa*. Agents such as fosfomycin, nitrofurantoin, amoxicillin/clavulanic acid, pivmecillinam, temocillin can be alternate drugs in uncomplicated UTI's and in patients with drug allergies to the carbapenems. Salvage therapy using tigecycline and colistin can be used in seriously ill patients who are CTX-M producers and Amp-C producing isolates.

In addition to understanding the complex mechanisms involved in ESBL infections, strict antimicrobial stewardship, appropriate infection control measures and aggressive treatment of seriously ill patients is necessary in reducing the mortality and morbidity associated with these infections.

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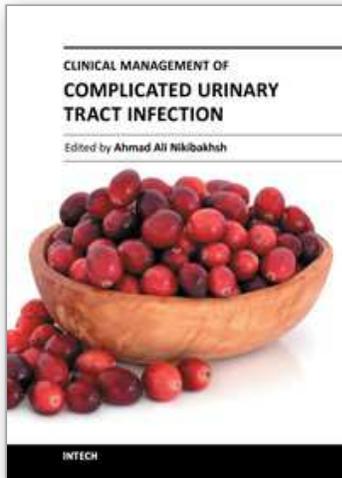
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Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are associated with significant morbidity and health care costs. Knowledge of baseline risk of urinary tract infection can help clinicians make informed diagnostic and therapeutic decisions. Prevalence rates of UTI vary by age, gender, race, and other predisposing risk factors. In this regard, this book provides comprehensive information on etiology, epidemiology, immunology, pathology, pathogenic mechanisms, symptomatology, investigation and management of urinary tract infection. Chapters cover common problems in urinary tract infection and put emphasis on the importance of making a correct clinical decision and choosing the appropriate therapeutic approach. Topics are organized to address all of the major complicated conditions frequently seen in urinary tract infection. The authors have paid particular attention to urological problems like the outcome of patients with vesicoureteric reflux, the factors affecting renal scarring, obstructive uropathy, voiding dysfunction and catheter associated problems. This book will be indispensable for all professionals involved in the medical care of patients with urinary tract infection.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Phone: +86-21-62489820
Fax: +86-21-62489821

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