



Recognition and Management of Extended Spectrum Beta Lactamase Producing Organisms (ESBL)

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Urinary tract infections (UTI) are one of the most commonly diagnosed infections, and typically among the most easily treated infections in the young and healthy. Emerging over the last twenty five years is the growing problem of **extended spectrum beta-lactamase (ESBL)**-producing organisms which cause UTI. ESBL organisms produce enzymes that hydrolyze the beta-lactam ring of beta lactam antibiotics like penicillins and cephalosporins, rendering them ineffective. Beta lactamase producers are typically gram negative organisms, namely *E. coli*, *K. pneumoniae* and *Klebsiella oxytoca*. However, ESBL production has also been observed in *Proteus*, *Pseudomonas*, *Serratia*, *Enterobacter*, *Salmonella*, *Acinetobacter* and *Citrobacter* species, among others. The gene for beta-lactamase production appears to be carried on plasmids which can be easily transferred from bacteria to bacteria. ESBL-producing bacteria inactivate the following antibiotics: beta lactams, extended spectrum cephalosporins, monobactams, and cephamycins. In addition to, or as a by product of their evasiveness to antibiotic therapy, ESBL organisms are more likely to produce invasive disease and yield higher mortality. The only proven therapeutic option for severe infections caused by ESBL-producing organisms is the carbapenem family of antibiotics: imipenem, meropenem, and ertapenem.

While ESBL infections may present with typical UTI symptoms, in the elderly population it is important to consider asymptomatic or atypical presentations. Dysuria, urinary frequency and fever may not be evident, or may be confused with symptoms of other disease processes; i.e., benign prostatic hypertrophy, bladder dysfunction, etc. Common findings in the geriatric population associated with UTI include a change in energy level, or lethargy, mental status changes, confusion, new or increased combativeness, or, in patients with dementia, a rapid change in baseline cognitive or behavioral state. Since many of these symptoms are non-specific, diagnosis in older adults can be challenging. Several clinical criteria can assist in determining diagnosis:

- The McGeer criteria for nursing home residents are often used and cited. These criteria propose that 3 of the following must be met to diagnose a UTI: (1) a temperature of 38 C (100.4 F) or higher; (2) new or increased burning sensation on urination, frequency of urination, or urgency of urination; (3) new flank or suprapubic pain/tenderness; (4) change in character of urine; and (5) worsening of mental or functional status.

- Other guidelines for UTIs were proposed by Loeb et al. and can also be useful to determine necessity for empirical antibiotic therapy. For nursing home residents, the Loeb criteria suggest empirical coverage in the setting of: acute dysuria alone or fever (a temperature of greater than 37.9 C (100F), plus at least 1 of the following: new or worsening urgency or frequency of urination, suprapubic pain, gross hematuria, costovertebral angle tenderness, or urinary incontinence.

These criteria are used in conjunction with **urinalysis (UA)** results. Typically a patient, to be diagnosed with UTI, should have findings on UA that raise concern for UTI such as pyuria, bacteriuria or evidence of leukocyte esterase, blood or other abnormal cells. These findings in conjunction with the above diagnose UTI. In some patients there is pyuria, bacteriuria or both without the clinical findings above; these patients are considered asymptomatic and do not require treatment. These criteria, while useful in the geriatric population, are not recommended in patients with additional risk factors like indwelling devices like urinary catheters.

A note about asymptomatic bacteriuria – this is a common condition where urine gram stain and/or culture are positive, but there are no symptoms, typical or atypical, of infection. This clinical situation is found in up to 50% of women and 30% of men over the age of 65. It is not associated with any of the adverse outcomes typically seen in urinary tract infections, and does not necessitate treatment.

RISK FACTORS

UTIs are more common in individuals with a history of UTI, incontinence, neurologic or cognitive impairment, poor nutrition, immunosuppression, or other comorbid disease states. Multidrug resistant organisms can be found more commonly in individuals who are frequently hospitalized, live in a nursing home or other institutionalized long term care facilities. UTIs in the elderly patient are more likely to be due to more complicated bacterial origins than simple gram negative infection. Gram positive infections as well as mixed infections with multiple flora are seen more frequently, necessitating broader spectrum antibiotic coverage than simple gram negative coverage alone. In addition, multidrug resistant organisms are seen more frequently in this population, necessitating more complicated therapy.

These organisms, like most **multi drug resistant organisms (MDROs)**, are associated with certain risk factors; i.e., Institutionalization, previous use of any antibiotic, previous hospitalization, ICU stay, age, chronic underlying disease, G-tubes, abdominal surgery, urinary catheters, and gut colonization. Gender plays very little, if any, role in risk.

TREATMENT

First-line therapies are drugs in the carbapenem family of antibiotics. Meropenem 500 mg intravenously three times a day is a standard antibiotic regimen for ESBL. Carbapenems are effective, but evidence is based mainly on observational studies. In addition, they have a number of treatment considerations. They must be administered parenterally and are costly. Meropenem can cost up to \$150/day, at \$50/dose. The carbapenems do have a wide spectrum of activity; however, this very asset can become problematic. The widespread activity can promote infections with other organisms such as yeast and other bacterium. In addition, there has been recent evidence of selection for carbapenem resistant organisms. Carbapenem resistance is a growing problem, and there are few agents with limited activity that can be used to treat these organisms. Fosfomycin, and tigecycline have shown some activity against ESBL organisms, but other options are limited. The emergence of carbapenem resistant gram negative rods is a major clinical concern. Always striving for the narrowest spectrum antibiotic possible for treatment of an infection is critical to stem the tide of MDROs.

Acute infections can be resolved with antibiotic treatment. However, colonization is an issue for patients who have a history of an ESBL infection. There is no agreed upon way to screen for continued GI colonization. Even if urine cultures are negative after treatment, there is evidence to suggest gastrointestinal colonization and skin colonization persists indefinitely. Numerous institutional outbreaks have been reported with ESBLs. Transmission occurs through direct and indirect contact. There is ample epidemiological evidence that MDROs are carried from one person to another via hands of healthcare workers. Hands are easily contaminated during the care giving process or from contact from the environmental surfaces in close proximity to the infected or colonized patient. Patients

with a history or known infection with and ESBL gram negative bacteria should be placed on contact precautions in acute care hospitals. Strict adherence to hand hygiene compliance and environmental cleaning is imperative. Attention to the patient's personal hygiene and containment of urine and feces is also imperative with these patients.

SUMMARY

ESBL organisms provide a continuing challenge in the geriatric community. They are increasingly prevalent, and pose unique challenges in treatment. Carbapenems are the mainstay of therapy; however they are expensive medications that require prolonged intravenous administration. Carbapenem resistance is a growing concern among frequently hospitalized patients and nursing home residents, and options for treatment of MDROs are limited. Attempts at minimizing the spread of beta-lactamase producers through hygiene and contact precautions are imperative, as is ongoing research into more effective antimicrobial agents.

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