Risk Factors for Urinary Tract Infection Caused by Enterobacteriaceae with Extended-Spectrum Beta-Lactamase Resistance in Patients Admitted to Internal Medicine Departments

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ABSTRACT: **Background:** Extended-spectrum beta-lactamase (ESBL) resistance is a growing concern in and outside hospitals. Physicians often face a true clinical dilemma when initiating empirical antibiotic treatment in patients admitted to internal medicine departments.

Objectives: To determine the prevalence of risk factors for ESBL resistance in patients with urinary tract infection (UTI) admitted to internal medicine departments.

Methods: We conducted a retrospective analysis of the medical records of patients with UTI admitted to an internal medicine division in a community-based academic hospital over a 1 year period. We collected clinical, laboratory and imaging data that were available to the treating physician at admission. Outcome measures included ESBL resistance and death.

Results: Of the 6754 admissions 366 patients were included in the study. Hospitalization during the previous 3 months (odds ratio 3.4, $P < 0.0001$), residency in a long-term-care facility (OR 2.4, $P = 0.004$), and the presence of a permanent urinary catheter (OR 2.2, $P = 0.015$) were correlated to ESBL resistance with statistical significance. These risk factors were extremely prevalent in our patient cohort.

Conclusions: ESBL resistance is becoming prevalent outside hospital settings, and patients admitted to an internal medicine department with UTI frequently carry risk factors for harboring resistant bacteria. In such patients a high index of suspicion and early targeted antibiotic treatment for ESBL-producing Enterobacteriaceae may be justified.

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Urinary tract infection is a common reason for admission to internal medicine departments [1]. Although guidelines for the empiric treatment of patients with UTI do exist [2], these reflect the current knowledge on the most frequent causative agents and their expected profile of antimicrobial sensitivity. In recent years, Gram-negative bacteria harboring extended beta-lactamase resistance have emerged, particularly but not exclusively *Escherichia coli* and *Klebsiella pneumoniae* [3]. The extended-spectrum beta-lactamases are resistant to many of the antibiotics currently available to treat patients with UTI, including penicillins, cephalosporins and monobactam. An infection with ESBL-producing bacteria is related to a worse clinical course, deferred clinical and microbiological response, longer hospitalizations, higher costs, and higher death toll [4,5].

Carriage of ESBL-producing Enterobacteriaceae is reported worldwide, particularly in hospital settings. The 2009 International Nosocomial Infection Control Consortium [6] reported rates of resistance to ceftriaxone and ceftazidime as high as 27.1% in infections related to *K. pneumoniae* and 8.1% in those related to *E. coli*. The rate is even higher in intensive care units. The prevalence of such resistant bacteria is still low in the community but is reported to be growing [7-9].

The local epidemiological profile is of considerable importance. In internal medicine departments most patients are elderly, with multiple underlying medical conditions and chronic medications [1]. Many of them live in nursing homes or long-term care facilities [10]. The prevalence of *E. coli* and *K. pneumonia*-producing ESBL in urine specimens in such facilities was reported to be as high as 22% and 40.5%, respectively [11]. In another report from a skilled care facility, the prevalence of ESBL carriage rates from *E. coli* and *K. pneumoniae* cultured from rectal, axillary, nasal and gastrostomy insertion sites, and from wounds was 15% and 18%, respectively [1]. Thus, one should suspect the existence of resistant bacteria even in patients arriving to the emergency department from their homes.

Deciding on empiric treatment for patients with UTI admitted to internal medicine departments is therefore challenging. Consideration of the general, local and personal epidemiology

OR = odds ratio
UTI = urinary tract infection

ESBL = extended-spectrum beta-lactamase

is warranted. The primary objective of this study was to determine the prevalence of risk factors associated with the existence of ESBL-producing Enterobacteriaceae as the causative pathogen in patients with UTI admitted to internal medicine departments. We also assessed which of the clinical, laboratory and imaging findings available to the treating physician during the first 24 hours of hospitalization are suggestive for UTI caused by ESBL-producing bacteria.

PATIENTS AND METHODS

This study was retrospective in design. The study population was derived from consecutive admissions to a 106-bed internal medicine division in a 450-bed community-based university-affiliated hospital in northern Israel. Patients were included in the study cohort if they were admitted to an internal medicine department with a working diagnosis of urinary tract infection according to clinical, laboratory and imaging findings. Exclusion criteria included an alternative source of infection or lack of bacteruria when urinary cultures were taken on the first day of hospitalization.

We evaluated only the data available within 24 hours of hospitalization. These included data on demographics, chronic diseases and medications, as well as clinical, laboratory and imaging data [Tables 1-3]. Outcome data included ESBL resistance (according to the Clinical Laboratory Standards Institute), length of hospital stay, in-hospital mortality and 28 day mortality.

Continuous data were analyzed using the *t*-test, and ordinary data by the Mann-Whitney test. Categorical data were analyzed by the chi-square test. $P < 0.05$ was considered significant. Parameters that were found to be significant in univariate analysis were analyzed in a multivariate analysis employing logistic regression. The study was approved by the local Institutional Review Board.

Table 1. Demographic data

Age (yrs) (average, SD)	81.62 (11.37)
Gender	
Male	124 (33.8)
Female	242 (66.2)
Mental status	
Dementia	172 (46.9)
Normal	138 (37.7)
Unknown	55 (15.4)
Functional status	
Debilitated	263 (71.8)
Normal	91 (24.8)
Unknown	12 (3.4)
Residency	
Home	234 (63.9)
Long-term care facility	127 (34.6)
Unknown	5 (1.5)

Values are presented as number (%)

SD = standard deviation

RESULTS

Of 6754 admissions over a 1 year period (starting date November 2006), 366 patients met the study's inclusion criteria. Demographic data are detailed in Table 1 and clinical and medication related data in Table 2. The average age of our study population was 81.62 years (range 22–101). The male to female ratio was 1:1.95. Seventy-two percent of the patients in our study cohort were defined as debilitated to a certain extent, and 34.6% were residents of long-term care facilities; 62% suffered from medical conditions related to the urinary system, some with co-existing urinary-related pathologies. In particular, 25.9% had a permanent urinary catheter, and 14.7% had benign prostate hyperplasia [Table 3]. Interestingly, 164 patients (44.8%) had previous urinary tract infections, while 73% (19.9%) and 37 (10.1%) had UTI within 3 and 1 month prior to their hospitalization, respectively.

Table 2. Chronic medical conditions and medications

Chronic medical diseases		Chronic medication use	
Ischemic heart disease	142 (38.7)	ACE-inhibitors/ARB	150 (40.9)
Congestive heart failure	74 (20.2)	Diuretics	166 (45.3)
Cerebrovascular disease	116 (31.6)	Beta-blockers	130 (35.5)
COPD	30 (8.1)	Calcium channel blockers	101 (27.5)
Chronic renal disease	88 (24.0)	Alpha-blockers	23 (6.2)
Diabetes mellitus	118 (32.2)	Oral hypoglycemic	64 (17.4)
Hypertension	252 (68.8)	Insulin	29 (7.9)
Hypothyroidism	55 (15.0)	Glucocorticoids	27 (7.3)
Chronic liver disease	20 (5.46)	NSAIDs	5 (1.3)
Malignancy	69 (18.8)	Opiates	8 (2.1)
Obesity	15 (4.0)	Anti-coagulants	43 (11.7)
Smoker/past smoker	47 (12.8)		
Ethylism	0 (0)		
Drug abuse	0 (0)		
Parkinson's disease	20 (5.4)		
Pressure sores	70 (19.1)		
Urinary tract-related disorder	228 (62.2)		

Values are presented as number (%)

COPD = chronic obstructive pulmonary disease, ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, NSAIDs = non-steroidal anti-inflammatory drugs

Table 3. Urinary tract-related disorders

Neurogenic bladder	2 (0.5)
Benign prostatic hyperplasia	54 (14.7)
Hydronephrosis	27 (7.3)
Nephrolithiasis	27 (7.3)
Previous urinary tract intervention	18 (4.9)
Urinary tract-related tumor	28 (7.6)
Pelvic prolapse	2 (0.5)
Permanent urinary catheter	95 (25.9)
Cystostomy	2 (0.5)
Nephrostomy	4 (1.0)

Values are presented as number (%)

Bacteria harboring ESBL resistance were detected in urinary cultures in 61 (16.6%) of the patients. The average length of hospital stay in our cohort was 9.19 ± 12.38 days (median 6 days, range 1–142). The total mortality rate was 32.3%. Of these, 83 patients died during their hospitalization (22.6%), and 34 additional patients died outside the hospital within 28 days of their admission (9.7%). The parameters that were significantly correlated to ESBL resistance in a multivariable analysis were UTI in the previous 3 months (odds ratio 3.4, $P < 0.0001$), residency in a long-term care facility (OR 2.4, $P = 0.004$), and the presence of a permanent urinary catheter (OR 2.2, $P = 0.015$). These were detected in 19%, 34.6%, and 25.9% of our patient cohort, respectively.

Predictors of in-hospital mortality were dehydration (OR 7.21, $P < 0.0001$), desaturation at admission (OR 4.43, $P < 0.0001$), hypoalbuminemia (OR 5.89, $P < 0.008$), chronic liver disease (OR 11.34, $P < 0.0001$), and a concurrent infiltrate in a chest X-ray (OR 8.06, $P < 0.0001$).

DISCUSSION

The decision on empiric treatment in hospitalized patients is never easy. In internal medicine departments many elderly patients present with sepsis and vague clinical symptoms. The diagnosis and hence the choice of treatment is thus challenging. This is exacerbated when accounting for the rise in prevalence of resistant bacteria in and outside the hospital setting [13-16]. On the one hand, a cautious approach to the use of broad-spectrum antibiotics is strongly advocated, while deferring the correct treatment may lead to dire consequences on the other [17].

Known risk factors that increase the risk of harboring ESBL-producing bacteria are mostly related to nosocomial infections [3]. For community-acquired infections, the most commonly reported risk factors for ESBL-producing *E. coli* infections are contact with health care centers (recent hospitalization, residence in a long-term care facility, bladder catheterization), recent use of antimicrobial agents, and presence of comorbidities [14]. Particularly, for urinary tract infection acquired in the community, a recent study found that more than three UTI episodes in the last year, the use of a beta-lactam antibiotic in the preceding 3 months, and prostate disease were associated with ESBL-producing *E. coli* [18].

In this "real life" analysis, we looked at data that were readily available to physicians at or close to admission. We have shown that an episode of UTI in the preceding 3 months, residency in a long-term care facility, and the presence of a permanent urinary catheter were all strong predictors of ESBL resistance in patients with UTI admitted to internal medicine departments. These risk factors are in concordance with those known to date. We have also shown a very high percentage of urinary tract-related conditions (> 60%) and of residencies in long-care facilities (> 30%) in our study population, and a high prevalence of risk factors for UTI caused by ESBL-producing bacteria. These findings reflect the case mix of today's internal medicine admissions [1], with a high prevalence of elderly, debilitated and poly-morbid patients. In view of the relation between prostatic disease, permanent urinary catheterization, out-of-home residencies, and the rise in prevalence of ESBL-producing bacteria in the community, it is evident that treatment directed against these bacteria should be considered early in the course of the disease. Such coverage should therefore not be restricted only to hospital-acquired infections.

The factors found to be predictive of death in the hospital were related to severe clinical states at admission (dehydration, desaturation, concomitant infiltrate in a chest X-ray) and an overall poor status (hypoalbuminemia, chronic liver disease). Although the severity of the clinical presentation is not necessarily suggestive of the type of bacteria, clearly these patients are prone to the adverse outcome of wrong treatment choices; thus in these situations one should suspect the existence of resistant bacteria as the causative agents. To conclude, we found that in our cohort of patients admitted to a general internal medicine department, the risk factors associated with ESBL resistance comply with known risk factors reported in previous studies. Specifically, this study illustrates a very high prevalence of these factors in patients admitted to internal medicine departments from the community. These data were all available to treating physicians during the first 24 hours of hospitalization. A careful use of these data, combined with an understanding of the patient's clinical status and risk for morbidity and mortality, can be used by internists to guide empiric treatment until bacteriological data are available.

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Capsule

Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis

All homeotherms use thermogenesis to maintain their core body temperature, ensuring that cellular functions and physiological processes can continue in cold environments. In the prevailing model of thermogenesis, when the hypothalamus senses cold temperatures it triggers sympathetic discharge, resulting in the release of noradrenaline in brown adipose tissue and white adipose tissue. Acting via the β3-adrenergic receptors, noradrenaline induces lipolysis in white adipocytes, whereas it stimulates the expression of thermogenic genes, such as PPAR-γ co-activator 1a (Ppargc1a), uncoupling protein 1 (Ucp1) and acyl-CoA synthetase long-chain family member 1 (Acsl1), in brown adipocytes. However, the precise nature of all the cell types involved in this efferent loop is not well established. Nguyen et al. report an unexpected requirement in mice for the interleukin-4 (IL-4)-stimulated program of alternative macrophage activation in adaptive thermogenesis. Exposure to cold temperature rapidly promoted alternative activation of adipose tissue macrophages, which secrete catecholamines to induce thermogenic gene expression in brown adipose tissue and lipolysis in white adipose tissue. Absence of alternatively activated macrophages impaired metabolic adaptations to cold, whereas administration of IL-4 increased thermogenic gene expression, fatty acid mobilization and energy expenditure, all in a macrophage-dependent manner. Thus, the researchers have discovered a role for alternatively activated macrophages in the orchestration of an important mammalian stress response, the response to cold.

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Capsule

Rebuilding muscle after injury

Skeletal muscle injury can be debilitating and potentially lethal. Factors released by the damaged muscle can stimulate local skeletal muscle stem cells (satellite cells) to become motile, proliferate, and differentiate into replenishing myofibers. Stark et al. (*Development* 2011; 138: 5279) suggest that even satellite cells distant from a site of injury could be recruited to help. The authors found that satellite cell motility was controlled by cell surface proteins called ephrins that are expressed by healthy and regenerating muscle cells. Ephrins and their Eph receptors function as a guidance system in a variety of developmental processes. Ephrins elicited a repulsive signal that caused satellite cells to alter their migratory course. Mouse satellite cells grafted into either the developing hindbrain or limb bud of quail embryos respected ephrin-defined boundaries as they migrated in vivo. The authors propose that Eph-ephrin interactions may modulate satellite cell migration and patterning during muscle fiber development. In another study Page et al. (*Tissue Eng* 2011; Part A 17: 2629) used microthreads of fibrin to restore muscle function in mice with substantial leg muscle injury. When placed into the damaged area, the microthread scaffolds, seeded with adult human muscle cells that were coaxed into a stem cell-like state, restored healthy muscle fibers. Surprisingly, most of the new muscle was generated from recruited mouse satellite cells. Together, these studies point to potential therapies for treating major muscle injuries.

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