Antibiotic Exposure in the Community and Resistance Patterns of *Escherichia coli* Community-Acquired Bloodstream Infection

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ABSTRACT: **Background:** Increasing antibiotic resistance in the community results in greater use of empiric broad spectrum antibiotics for patients at hospital admission. As a measure of antibiotic stewardship it is important to identify a patient population that can receive narrow spectrum antibiotics.

Objectives: To evaluate resistance patterns of *Escherichia coli* bloodstream infection (BSI) from strictly community-acquired infection and the impact of recent antibiotic use on this resistance.

Methods: This single center, historical cohort study of adult patients with *E. coli* BSI was conducted from January 2007 to December 2011. Patients had no exposure to any healthcare facility and no chronic catheters or chronic ulcers. Data on antibiotic use during the previous 90 days was collected and relation to resistance patterns was assessed.

Results: Of the total number of patients, 267 BSI cases met the entry criteria; 153 patients (57%) had bacteria sensitive to all antibiotics. Among 189 patients with no antibiotic exposure, 61% of isolates (116) were pan-sensitive. Resistance to any antibiotic appeared in 114 patients and 12 were extended-spectrum beta-lactamase (ESBL) producers. Quinolone use was the main driver of resistance to any antibiotic and to ESBL resistance patterns. In a multivariate analysis, older age (odds ratio 1.1) and quinolone use (odds ratio 7) were independently correlated to ESBL.

Conclusions: At admission, stratification by patient characteristics and recent antibiotic use can help personalize primary empirical therapy.

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KEY WORDS: community acquired bacteremia, *Escherichia coli*, quinolones, resistance

Mounting evidence shows the importance of appropriate empiric antibiotic selection in the first 48 hours of sepsis treatment [1-3]. This contention combined with increasing antibiotic resistance rates results in greater prescription of broad spectrum antibiotics to septic patients at hospital admission, further precipitating a vicious cycle of increasing antibiotic resistance.

Patients with community-acquired infection comprise a heterogeneous group. Stratification of community patients with low resistance probability can potentially allow differentiation of a subgroup that can receive narrow spectrum antibiotics [4-6]; thus, balancing between optimal patient outcome and judicial antibiotic use.

The aim of this study was to evaluate resistance patterns of *Escherichia coli* bloodstream infection (BSI) among patients with strictly community-acquired infection, and the effects of recent antibiotic use on this resistance.

PATIENTS AND METHODS

SETTING

The Meir Medical Center is a 740 bed, community-based hospital serving a population of approximately 600,000 individuals living in central Israel. This hospital is part of Clalit Health Services, which is a health maintenance organization that insures approximately 60% of the Israeli population.

PARTICIPANTS

Adult patients 18 years of age and older, who were insured by Clalit HMO and had been admitted to the hospital with community-acquired *E. coli* BSI from January 2007 to December 2011 were included in the study.

E. coli BSI was identified through the microbiology laboratory records. Bacterial sensitivity was determined according to Clinical & Laboratory Standards Institute guidelines [7]. Community-acquired BSI was defined as a positive blood culture obtained within 48 hours of hospital admission. Patients were excluded if they met one of the following criteria: hospitalized for 2 or more days in the previous 90 days; resided in a nursing home; underwent hemodialysis; received intravenous chemotherapy within the previous 30 days; received specialized nursing care; or had a central line, urinary catheter, nephrostomy, biliary tube, or any permanent drainage device; or if they had a pressure sore [8]. This information was retrospectively retrieved from hospital electronic medical records.

Information regarding antibiotics dispensed in the community 90 days prior to the BSI detection was retrospectively retrieved from the Clalit Health Service HMO pharmacy database.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). Categorical variables were compared using chi-square or Fisher's exact test, as appropriate. Continuous data were compared with *t*-tests. Multivariate logistic regression analysis was conducted including variables significantly associated with the dependent variable on univariate analysis ($P < 0.1$).

RESULTS

During the study period 604 patients were admitted to our facility with *E. coli* BSI. Of these, 267 infection episodes in 267 (44%) patients met study criteria for strictly community-acquired BSI and were included in the final analysis. The mean age of the patients was 65.9 ± 18.1 years (range 19–97); 66% were female.

Antibiotic sensitivity was 80% to quinolones, 73% to cefazolin, 94% to cefuroxime, 95.5% to ceftriaxone, 95.5% ceftazidime, 80% to amoxicillin/clavulanate, and 92% to gentamicin. Extended-spectrum beta-lactamases (ESBL) producing organisms were found in 12 patients (4.5%). Of the 267 *E. coli* isolates, 153 (57%) were susceptible to all of these antibiotics. All 267 isolates were sensitive to piperacillin/tazobactam and carbapenems.

Seventy-eight patients (29%) were exposed to antibiotics within the 90 days period prior to the BSI episode. The most prevalent antibiotic exposure was to quinolones, detected in 23 patients [Table 1].

Overall, antibiotic exposure correlated with the presence of antibiotic resistance. Among the patients who did not receive any antibiotic treatment in the 90 days prior to admission, 61% (116/189) had bacteria sensitive to all tested antibiotics, whereas among patients who received prior antibiotic treatment, only 47% (37/78) had sensitive bacteria ($P = 0.036$).

When we investigated the effect of specific antibiotic use on resistance by univariate analysis, quinolone use was the only predictor for any antibiotic resistance ($P < 0.001$). Moreover, exposure to quinolones correlated with resistance not only to quinolones ($P < 0.001$), but also to cefazolin ($P = 0.021$), cefuroxime ($P = 0.005$), ceftriaxone or ceftazidime ($P = 0.002$), and gentamicin ($P = 0.001$).

Exposure to cefuroxime correlated with gentamicin resistance. Exposure to amoxicillin/clavulanate or to penicillin did not correlate with any resistance.

In univariate analysis, predictors of ESBL included male gender, older age, and quinolone use. ESBL prevalence was only 3% in those with no quinolone treatment and up to 22% in patients with recent exposure to quinolones ($P < 0.001$) [Table 1]. In multivariate analysis, quinolone use (odds ratio [OR] 7, 95% confidence interval [95%CI] 1.7–29.4), and older age (OR 1.097, 95%CI 1.024–1.176) remained independent factors correlated with *E. coli* ESBL.

Table 1. Characteristics of 267 patients with community-acquired *Escherichia coli* bacteremia over a 5 year period: antibiotic exposure and susceptibility

Variable	All isolates (N=267)	Sensitive to all (N=153)	*P*	ESBL 12	*P*
Age, years, mean ± standard deviation	66 ± 18	66 ± 19	0.46	77.7 ± 8	‹ 0.001
Gender, male	91 (34%)	49 (32%)	0.42	8 (66%)	0.02
Any antibiotic	78 (29%)	37 (24%)	0.04	7 (58%)	0.05
Quinolones	23 (34%)	4 (3%)	‹ 0.001	5	0.002
Cefuroxime	21 (8%)	11 (7%)	0.64	3	0.06
Amoxicillin or penicillin v	22 (8%)	12 (8%)	0.79	0	0.6
Amoxicillin/clavulanate	14 (5%)	9 (6%)	0.59	2	0.13
Other*	21 (8%)	12 (8%)	0.99	1	1.0

*Less than 10 exposures to each one: macrolide, tetracycline, trimethoprim/sulphamethoxazole, macrodantin, cefazolin

ESBL = extended-spectrum beta-lactamase

DISCUSSION

Limiting unnecessary antibiotic use is of paramount importance for reducing resistance. One of the tools used to achieve this goal is personalizing patient treatment. Local antibiograms are used to guide physicians regarding the appropriate empirical antibiotic use. The disadvantage of this tool is the crude dichotomy of nosocomial vs. community-acquired infections. Information on previous healthcare exposure and antibiotic use can further refine the appropriate therapy [9].

In this study we demonstrate that broad spectrum antibiotic use can be substantially reduced in community-acquired BSI based on these clinical criteria because infections in such low-risk patients are by and large antibiotic sensitive.

The current study population was relatively healthy, resided at home, and had no healthcare exposure in the 90 days prior to infection. Thus, our patients apparently had none of the traditional risk factors for a resistant organism, except for antibiotic consumption. This factor indeed proved to be of major importance.

We observed a strong correlation between antibiotic use and any antibiotic resistance, as previously shown [10]. Our findings emphasize the effects of antibiotic exposure and enable evaluation of the contribution of each antibiotic to resistance separately. We observed that quinolone consumption was the main driver of resistance. This finding of collateral damage of quinolone exposure corresponds with prior studies [11-13]. In another report from Israel, Bishara and colleagues [14] reported higher ESBL prevalence of up to 10% of *E. coli* isolates, with no distinction between nosocomial and community-acquired infection. However, in the current

study, which focused strictly on community-acquired infections, ESBL prevalence was uncommon (4.5%). Moreover ESBL prevalence was only 3% among those not exposed to quinolone treatment, and less than 2% in patients not exposed to any antibiotic. Similar to our results, Zahar and co-authors [15] found ESBL prevalence of 8% among patients admitted with community-onset bacteremia. However, two-thirds of episodes actually qualified as healthcare associated infections, and true community-acquired ESBL-producing *Enterobacteriaceae* bacteremia was identified in only 22 patients (3.2%) [15].

This significant effect of quinolone on resistance in the community is even more of a concern considering their widespread use for treatment of urinary tract infections and pneumonia in the community [16-18]. In an effort to reduce their extensive use, the Infectious Diseases Society of America treatment guideline recently discouraged quinolone use [16]. Notably, in a previous study, we showed that minimizing quinolone use in the community can indeed decrease quinolone resistance [19].

Our findings indicate that antibiotic exposure other than quinolones did not have a similarly significant impact on antimicrobial resistance. A possible explanation for the minor impact of cephalosporins is that third generation cephalosporins were not used in our cohort.

In our current study, only 44% of the BSIs that occurred within 48 hours of admission were included in the final analysis, stressing the heterogeneity of the definition of community-acquired BSI and emphasizing the need to further stratify patients with this diagnosis.

The main limitation of this study was the local nature of the data. The resistance profile depicted here is specific to our geographic area. Another limitation is the small absolute number of antibiotic courses. Thus, a less robust effect on resistance of other antibiotic classes cannot be ruled out as was described by Sun et al [20] who observed a correlation between quinolones and aminopenicillins use and resistant E. coli, which was noted 1 month later.

A second limitation is that antibiotic use was derived from purchase pharmacy data rather than actual use. Another limitation is that, although we looked at antibiotic use in the 90 days prior to admission, we cannot rule out possible long-term effects of antibiotic treatment before that period. Yet, we believe that this study provides valuable practical clinical information.

CONCLUSIONS

The information presented here highlights the detrimental effects of unselected use of quinolones in the community and may imply that when appropriate clinical background information is obtained, a selected group of patients can receive narrow spectrum empirical antibiotics on admission.

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