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The Clinical Epidemiology and Antibiotic Resistance Patterns of Biliary Tract Infections Caused by Antimicrobial-Resistant *Escherichia coli*

Yun-Song Li and Xiang-Ling Meng

Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, 230022, PR China

Corresponding author: Xiang-Ling Meng

xianglingm@medmail.com.cn

Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, 230022, PR China.

Tel: +8655162922114

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Abstract

Objective: To investigate the risk factors and drug-resistance of *Escherichia coli* in patients with Biliary Tract Infections (BTIs). In addition, prognostic factors related to survival in patients with BTI were evaluated.

Methods: A retrospective observational study was performed to analyze the relationship between antimicrobial use and bacterial resistance.

Results: Biliary tract infection caused by *E. coli* was diagnosed in 0.81% of patients from general surgery (107 of 13163) admitted to the hospital between January 1, 2012 and December 31, 2014. Of the 107 isolates, 102 (95.3%) were resistant to at least one antimicrobial agent and 86.9% (93/107) to two or more antibiotics. 80.4% were resistant to piperacillin, 27.1% to piperacillin/tazobactam, 61.7% to cefuroxime, 57% to cefoxitin, 48.6% to cefotaxime, 43.9% to ceftazidime, 38.3% to cefepime, 44.8% to levofloxacin. However, all strains were susceptible to imipenem. The detection rates of ESBLs-producing *Escherichia coli* were 41.1%.

Conclusion: Prior receipt of antimicrobial therapy was significantly associated with infection caused by resistant organism and most strains were resistant to multiple antimicrobial agents.

Keywords: *Escherichia coli*; Epidemiology; Antimicrobial resistance; Risk factors; Biliary tract infection

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Introduction

Biliary tract infection is a common cause of *bacteraemia* and associated with high morbidity and mortality, particularly in older patients with co-morbid disease or when there is a delay in diagnosis and treatment [1,2]. The most common infecting organisms are *Enterobacteriaceae* ascending from the gastrointestinal tract [3,4]. The identification of causative organisms takes some time, and thus, the antibiotic treatment of biliary infections is directed towards suspected organisms. In addition to antibiotic treatment, biliary decompression is needed to control infections, and its timing depends on clinical course. Furthermore, despite the development of antibiotics and biliary decompression methods, mortality resulting from BTIs combined with bacteremia ranges from 10 to 20%. The prevalence of antibiotic-resistant pathogens continues to increase steadily. In the present study, we analyzed changing patterns of antibiotic resistance in patients with bacteremic BTI treated from 2012 to 2014. Furthermore, the risk factors predictive of resistance to empirically prescribed antimicrobials were identified to allow more effective management strategies to be devised for the treatment of BTIs.

Materials and Methods

Study population

This retrospective, observational cohort study was conducted at the First Affiliated Hospital of Anhui Medical University. Hospital records of patients treated from January 2012 through December 2014 were searched to identify all adult patients diagnosed with bacteremic BTI. The following patients were excluded: (i) patients with a positive culture for skin contaminants (i.e., coagulase-

negative *Staphylococci* or *Corynebacterium*, *Propionibacterium*, or Bacillus species) and (ii) patients with bacteremia due to a non-BTI.

Bacteria and antimicrobial susceptibility testing

Biliary tract infection caused by *E. coli* was diagnosed in 107 patients. The microbiologic data of *E. coli* organisms were collected through a daily review of the laboratory computer summary report from the clinical microbiology laboratory. Bacteria were identified by API20NE (BioMérieux Vitek Systems Inc.). Bacteria were maintained on Mueller-Hinton (MH) agar (Oxoid, Basingstoke, United Kingdom) or propagated in Luria-Bertani (LB) broth for liquid culture. All antibiotics were obtained from Sigma-Aldrich Ltd (St. Louis, MO, USA). Minimum Inhibitory Concentrations (MICs) were determined by Clinical and Laboratory Standards Institute (CLSI) reference broth micro dilution methods. Susceptibility was determined using CLSI breakpoints. The following antimicrobials were tested: piperacillin, tazobactam, cefuroxime, cefoxitin, cefotaxime, ceftazidime, cefepime, imipenem, levofloxacin.

Detection of ESBLs and AmpC β-lactamase

ESBL detection was based on a double-disk synergy test. The modified Hodge test was used to screen AmpC β-lactamase-producing strains. Quality control strains used in this study included *K. pneumoniae* ATCC 700603, *E. coli* ATCC 25922, and *E. coli* ATCC 35218. Isolates and control strains were stored at -70°C in Mueller-Hinton broth with 30% glycerol until the time of testing.

Polymerase Chain Reaction (PCR)

For the ESBL screen-positive isolates, a search for the blaTEM, blaSHV, blaCTX-M, and blaOXA genes was performed by PCR amplification as previously described. For the isolates with cefoxitin MICs of 16 mg/liter, plasmid DNA was extracted using a Qiagen plasmid purification kit (Qiagen, Hilden, Germany), and ampC amplification was carried out using multiplex PCR, which can detect various types (MOX, CMY, LAT, DHA, ACC, MIR-1, ACT-1, and FOX) of pAmpCs. Conjugation experiments were carried out for all ESBL gene- and/or pAmpC gene-positive isolates with sodium azide-resistant *Escherichia coli* J53 as the recipient, as previously described. Transconjugants were selected on Luria-Bertani (LB) agar plates supplemented with sodium azide (100 mg/liter) (Sigma Chemical Co., St. Louis, MO) and FOX (16 mg/liter) or CAZ (2 mg/liter). Plasmid DNA was extracted from donors and trans conjugants by using a Qiagen plasmid purification kit. The trans conjugants were examined for the presence of β-lactamase genes by PCR using plasmid DNA as the template and tested for susceptibility as described above for the wild strains. For all 146 *S. marcescens* isolates, a search for the presence of qnrA, qnrB, qnrS, qnrC, qnrD, aac (6')-Ib-cr, and qepA was performed by PCR using the methods described previously. All the purified PCR products were sequenced on an ABI Prism 3730 sequence analyzer (Applied Biosystems, Foster City, CA). Sequence alignment was compared with the GenBank nucleotide database using the nucleotide BLAST program.

Collection of clinical data

A retrospective study was performed and the following data were abstracted from the medical records: age, sex, service rendering treatment, underlying illness, medical history, recent surgery, antimicrobial therapy, and immunosuppressive therapy. Patients from whom *E. coli* organism was isolated <48 hours after admission were assumed to have a community-acquired infection. All other infections were considered to be nosocomial infection. Patients whose medical records were not available were not included in the epidemiological analysis.

Statistical analyses

The data of clinical, epidemiological and laboratory findings were analyzed by SPSS 17.0 software. Two-sides were checked to all P values. The significance was considered as P value <0.05. Risk factors associated with infection caused by a strain resistant to at least one antimicrobial agent and assessment of resistance to piperacillin, piperacillin/ tazobactam, cefuroxime, cefoxitin, cefotaxime, levofloxacin in patients who received prior antimicrobial treatment were analyzed by logistic regression model.

Results

Characteristics of patients

From January 1, 2012 to December 31, 2014, *E. coli* was isolated from 107 clinical specimens (bile) from 13163 inpatients of general surgery, representing an infection rate of 0.81%. The patients mainly suffered from gallstone with acute cholecystitis (75.7%), follow by acute suppurative cholangitis (16.9%), cholangiocarcinoma (5.6%), biliary drainage in patients with pancreatic cancer (1.8%). The 107 case-patients ranged from 30 to 88 years (57 ± 26.3 years), 50 (46.7%) were male, 57 (53.3%) were female. 93 (86.9%) came from their home and 14 (13.1%) had hospital acquired infection. 66 (61.7%) had invasive operation history and/or underlying illness (24.3% diabetes, 13.1% cancer, 19.6% with indwelling urinary catheter, 4.7% with deep venous catheter).

Antimicrobial therapy received before *E. coli* infection

Of the 107 patients in this study; all patients had received empirical anti-infective therapy before surgery. 77.6% of those patients received two or more antimicrobials agents. The most common antimicrobial agents administered were as following: ampicillin/sulbactam (20.6%), second generation cephalosporins (61.7%), third generation cephalosporins (54.2%), fluoroquinolines (78.5%), metronidazole (71%).

Antimicrobial resistance

Of the 107 isolates, 102 (95.3%) were resistant to at least one antimicrobial agents and 86.9% (93/107) to two or more antibiotics. 80.4% were resistant to piperacillin, 27.1% to piperacillin/tazobactam, 61.7% to cefuroxime, 57% to cefoxitin, 48.6% to cefotaxime, 43.9% to ceftazidime, 38.3% to cefepime, 44.8% to levofloxacin. However, all strains were tested

susceptible to imipenem. The detection rates of ESBLs-producing *E. coli* were 41.1%.

Assessment of risk factors associated with infections caused by resistant strains

By using univariate analysis, no significant differences were found between patients with resistant isolates and patients with susceptible isolates with regard to sex, urinary catheterization, venous peripheral catheterization, or underlying illness and invasive operation history.

The data were also analyzed for determining whether the use of an antimicrobial leads to the emergence of resistance to the antimicrobial agents. No significant association was found between prior receipt of fluoroquinolines and a subsequent infection caused by a strain resistant to levofloxacin (P=0.627), prior receipt of metronidazole and a subsequent infection caused by a strain resistant to metronidazole (P=0.461). In contrast, a significant association was observed between prior receipt of β-lactams and a subsequent infection caused by a strain resistant to piperacillin/tazobactam (P<0.001), prior receipt of any second/third generation cephalosporin and a subsequent infection caused by a strain resistant to cefotaxime (P=0.025).

Discussion

The emergence of multidrug-resistant organisms restricts the therapy choices for hospital-acquired infections. Actually, multidrug-resistant organisms are mainly confined to hospitals. Because *E. coli* is an important pathogen frequently involved in nosocomial infections, nosocomial infection of *E. coli* producing ESBLs has become more prevalent, and is difficult to eradicate because these organisms develop resistance to multiple antimicrobial agents. Our study showed that 96.3% *E. coli* strains were resistant to at least one antimicrobial agent and 77.6% to two or more antimicrobial agents. Prior receipt of any antimicrobial, whatever the number of different antimicrobials administered, was a risk factor associated with infections caused by resistant strains. This indicates the emergence of multidrug-resistant *E. coli* strains is associated with massive antimicrobial use at the teaching hospital in Anhui Province.

As previously described, the prior use of β-lactams was significantly associated with infection caused by *E. coli* strains resistant to piperacillin/tazobactam. The prior use of third generation cephalosporins was also significantly associated with infection caused by *E. coli* strains resistant to third generation cephalosporins. However, no association was observed between prior use of fluoroquinolines and a subsequent infection caused by a strain resistant to fluoroquinolines. This finding is difficult to interpret due to the small sample size and the role played by other potential risk factors, such as duration of the antimicrobial therapy and mode of administration of the drugs, should be assessed. Our study did not show that invasive operation was a risk factor. But some researchers reported that after invasive operation, the ecological balance of the body surface flora would be destroyed by a series of therapeutic measures such as the use of antibiotics to prevent infection and invasive operation, as a result, normal microbial flora were inhibited and resistant Gram-negative bacilli were selected and colonized on the body surface to form a stable reservoir, and these pathogens may cause nosocomial infection easily [5].

In this study, except that the rate of resistance to piperacillin was similar to those published and all strains tested were susceptible to imipenem, the rates of resistance to other antimicrobials were much higher than those published. The problem was perhaps that the integron that acted as a transposon mediated multiple-resistant determinants (cassettes) and mediated multiple-resistance patterns to nonrelated antibiotics. Probably because of the widespread use of β-lactams, particularly third generation cephalosporins, *E. coli* strains produced ESBLs or the chromosomally encoded AmpC-lactamase. In addition, *E. coli* strains that hyperproduce SHV-5 type ESBLs become resistant to β-lactamase inhibitor combinations. ESBL-producing strains often make SHV-1 or TEM-1 type β-lactamases as well, and if enough of these enzymes are made, resistance to β-lactamase inhibitor combination therapy results. Finally, ESBL-producing *E. coli* can develop resistance *in vitro* or *in vivo* by loss or decreased expression of outer membrane proteins that provide porin channels for inhibitor entry [6,7].

This emergence of resistance can occur either at the site of infection or in the flora of the gastrointestinal tract. There seems to be no simple solution to these developments: the problem is that over prescription of antibiotics remains rampant. In addition to infection control measures, such as antimicrobial discontinuation, shortening the duration of therapy, manipulation of the dose of antibiotics, antimicrobial rotation (cycling) strategies and antimicrobial combinations, new and innovative approaches to limiting empirical usage of antimicrobial agents may be the answer. Effective control can be achieved only through more understanding of the transmission process [8-10].

Conclusion

Prior receipt of antimicrobial therapy was significantly associated with infection caused by a resistant organism and most strains were resistant to multiple antimicrobial agents.

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