ABSTRACT

Aims: To determine the antimicrobial resistance of urinary tract infection isolates in a major metropolitan area for the purposes of tracking increases in resistance and to provide information that will help drive improved therapy.

Study Design: Antimicrobial resistance data on *Escherichia coli* isolated from urinary tract infections was collected and analyzed.

Place and Duration of Study: Data was collected from several large healthcare centers in the Detroit, Michigan area. Data collected was from January to July of 2008.

Methodology: Data on the antimicrobial susceptibility of 960 *Escherichia coli* isolated from urinary tract infections was collected and analyzed to determine resistance to typical drugs used in urinary tract infection susceptibility testing.

Results: The percentage of isolates that were resistant to one or more of the drugs tested was 47%. The most common drug resistance was to ampicillin (41%); with 11.6% of the isolates being only resistant to ampicillin. As to total resistance, 22.4% of the isolates were resistant to only one drug class, 14.4% were resistant to two classes, 7.2% to three classes, and 4.4% to more than three classes. Resistance as to antimicrobial effects were: 87.9% were resistant to drugs that
interfere with cell wall synthesis, 40.3% were resistant to drugs that inhibit protein synthesis, 38.3% to anti-metabolites, and 38.1% to drugs that inhibit nuclei acid synthesis.

**Conclusion:** The data indicate that *E. coli* isolated from urinary tract infections are manifesting disturbing resistance patterns. Not only is resistance to many drugs increasing, but the bacteria are becoming increasingly multi-drug resistant. This is not only true in this region, but seen worldwide as well.

**Keywords:** Antimicrobial resistance; urinary tract infections; *Escherichia coli*; resistance patterns.

1. **INTRODUCTION**

Urinary tract infections (UTIs) are the second most common type of infection found in any organ system, and the most common type of nosocomial infection [1]. These UTI infections are responsible for over eight million doctors visits per year [2], result in medical costs of over a billion dollars per year in the United States and over six billion dollars worldwide per year [3,4]. Most UTIs (at least 80%) are the result of infections with *Escherichia coli* [5].

Nonpathogenic strains of *E. coli* are an important part of the normal flora in the human intestinal tract. The strains of *E. coli* that infect the urinary tract are categorized as uropathogenic *E. coli* (UPEC) [6]. The UPEC strains are able to produce special surface proteins (adhesins) that allow them to attach to and invade the epithelial cells that line the urinary bladder [7-10]. If the infection is not eradicated while it is in the bladder (uncomplicated UTI), some strains of UPEC may then travel up the ureters to the kidneys and cause even more severe infections (complicated UTIs) which can lead to renal damage and possibly renal failure [6,11].

The antimicrobial agents that have traditionally been used to treat UTIs (β-lactams, fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, etc.) are becoming less effective [12,13]. Resistant strains of *E. coli* are being isolated frequently from urine cultures, and scientists are seeing a rise in the number of strains that are increasingly resistant to all the types of antimicrobial agents normally used to treat UTIs [14-18]. Even though scientists are constantly working to develop new and improved antimicrobials, almost as soon as a new drug is released, the bacteria show resistance to it. These isolates are also showing resistance to drug combinations [19,20,5].

We seem to be losing the race between drug development and resistance, and so we need to stay aware of the current levels of resistance and developing resistance patterns. The purpose of this study was to collect data on the antimicrobial resistance patterns of *E. coli* isolated from UTI cultures. The data was collected in the Southeastern Michigan urban area. The data was then analyzed to determine the frequencies of resistance to individual drugs, resistance patterns involving one or more drugs, resistance to drug classes, and frequency of resistance by drug effects. This data collection and analysis will help keep us aware of the resistance issues and hopefully this information will lead to improved development of more effective antimicrobial agents.

2. **MATERIALS AND METHODS**

2.1 **Data Collection**

Antimicrobial susceptibility data were collected on 960 isolates of *E. coli* from urine cultures. These cultures were analyzed at St. John Hospital & Medical Center in Detroit, Michigan between January and June of 2008. The susceptibility testing was performed on a Vitek 2 analyzer. Typical drug panels used on the analyzer contained 21 or 22 drugs each. All of the isolates were tested against at least the following antimicrobial agents: ampicillin (AMP), amoxicillin/clavulanic acid (AM/C), cefazolin (CZ), ciprofloxacin (CIP), gentamicin (GM), ticarcillin/clavulanic acid (T/C), and trimethoprim/sulfamethoxazole (TMP/SXT). In addition most of the isolates were tested with tetracycline (TET). Various other drugs were also tested depending on the panel used.

2.2 **Data Analysis**

The data collected was analyzed as to: percentage of isolates resistant to each drug, number of drugs that each isolate was resistant to, most common resistance patterns of drugs, frequency of resistance for different drug classes, and frequency of resistance patterns by antimicrobial effects of the drugs.
3. RESULTS AND DISCUSSION

3.1 Frequency of Antimicrobial Resistance to One or More Drugs

Of the 960 isolates characterized, 53% were susceptible to all of the tested drugs, and 47% were resistant to at least one drug. Fig. 1 shows the percentages of the isolates that were resistant to one or more drugs, up to ten or more drugs. Over 40% of the isolates were resistant to 2 or more drugs, 30% were resistant to 3 or more drugs, nearly 25% were resistant to 4 or more drugs, nearly 20% were resistant to 5 or more drugs, 15% were resistant to 6 or more drugs, 10% were resistant to 7 or more drugs, 8% were resistant to 9 or more drugs, and 4% were resistant to 10 or more drugs.

3.2 Frequency of Resistance to Various Drugs

The isolates were characterized as to the frequency of resistance to any of the eight drugs common to all of the panels tested, both as a percentage of just resistant isolates and as a percentage of all isolates (Table 1). The isolates showed the highest frequency of resistance to ampicillin (86% of resistant isolates, 41% of all isolates). The combination of ticarcillin/clavulanic acid showed the lowest frequency of resistance (10% of resistant isolates, 5% of all isolates). All of the drugs used had at least one isolate that was resistant to each one.

3.3 Frequency of Most Common Resistance Patterns

The isolates were also analyzed for patterns of resistance. Table 2 shows the most common patterns and the frequency among resistant isolates and the frequency among all isolates. Since the most frequent resistance was to ampicillin, it follows that the most common resistance pattern was to ampicillin alone (24.5% of resistant isolates, 11.6% of all isolates). Ampicillin is included in nine of the twelve most common patterns. Tetracycline alone (3.3% of resistant isolates, 1.6% of all isolates) and ciprofloxacin alone (2.9% of resistant isolates, 1.4% of all isolates) were the only other single drugs included in the common patterns. The patterns range from one drug (AMP, TET, CIP) to five drugs (AMP, CIP, GM, TMP/SXT, TET).

3.4 Frequency of Resistance to Different Drug Classes

Isolates were characterized according to the frequency of resistance to the various antimicrobial classes (Table 3). The frequency ranged from highest for one drug class (47.4% of resistant isolates, 22.4% of all isolates), to lowest for more than three classes (9.3% of resistant isolates, 4.4% of all isolates). The β-lactam drug class had the highest frequency of isolates resistant to just that class, 73.0%.

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**Table 1. Frequency of resistance to various antimicrobial agents**

| Antimicrobial                | Percent resistant of resistant isolates | Percent resistant of all isolates |
|-----------------------------|----------------------------------------|---------------------------------|
| Ampicillin                  | 86%                                    | 41%                             |
| Trimethoprim/sulfamethoxazole | 38%                                    | 18%                             |
| Ciprofloxacin               | 34%                                    | 16%                             |
| Tetracycline                | 28%                                    | 13%                             |
| Amoxicillin/clavulanic acid | 17%                                    | 8%                              |
| Cefazolin                   | 14%                                    | 7%                              |
| Gentamicin                  | 12%                                    | 5%                              |
| Ticarcillin/clavulanic acid | 10%                                    | 5%                              |

**Table 2. Frequency of most common resistance patterns**

| Resistance pattern | Percentage of resistant isolates | Percentage of all isolates |
|--------------------|---------------------------------|-----------------------------|
| AMP                | 24.5%                           | 11.6%                       |
| AMP, TMP/SXT       | 10.1%                           | 4.8%                        |
| AMP, CIP           | 9.5%                            | 4.5%                        |
| TMP/SXT            | 4.4%                            | 2.1%                        |
| AMP, CIP, TET, TMP/SXT | 4.0%                        | 1.9%                        |
| AMP, AMC           | 3.5%                            | 1.7%                        |
| TET                | 3.3%                            | 1.6%                        |
| AMP, TET           | 2.9%                            | 1.4%                        |
| CIP                | 2.9%                            | 1.4%                        |
| AMP, CIP, GM, TET, TMP/SXT | 2.9%                        | 1.4%                        |
| AMP, CIP, GM, TET, TMP/SXT | 2.6%                        | 1.3%                        |
| TMP/SXT            |                                 |                             |
| AMP, AM/C, CZ      | 2.6%                            | 1.3%                        |

**Note:** AMP – ampicillin, AM/C – amoxicillin/clavulanic acid, CIP – ciprofloxacin, CZ – cefazolin, GM – gentamicin, TET – tetracycline, TMP/SXT – trimethoprim/sulfamethoxazole
Table 3. Frequency of resistance to different antimicrobial classes

| Drug class | Drugs in that class | Percentage of resistant isolates | Percentage of all isolates |
|------------|---------------------|----------------------------------|---------------------------|
| β-lactams  | Ampicillin          | 47.4%                            | 22.4%                     |
|            | Amoxicillin/clavulanic acid |                    |                           |
|            | Cefazolin           |                                  |                           |
|            | Ticarcillin/clavulanic acid |                    |                           |
| Aminoglycosides | Gentamicin           | 30.4%                            | 14.4%                     |
| Fluoroquinolones | Ciprofloxacin       | 15.2%                            | 7.2%                      |
| Others     | Tetracycline        | 9.3%                             | 4.4%                      |
|            | Trimethoprim/sulfamethoxazole |                |                           |

3.5 Frequency of Resistance Based on Antimicrobial Effect

Then the isolates were characterized as to the frequency of resistance based on the antimicrobial effects of the drug (Table 4). The frequency ranged from the highest for inhibition of cell wall synthesis (87.9% of resistant isolates, 41.6% of all isolates) to the lowest for inhibition of nucleic acid synthesis (38.1% of resistant isolates, 18.0% of all isolates). The β-lactam drugs, such as ampicillin, are the main drugs involved in inhibition of cell wall synthesis.

3.6 Discussion

Not surprisingly, nearly 50% of the *E. coli* isolates were resistant to at least one of the antimicrobial agents tested. Even though ampicillin is not considered a drug of choice for *E. coli* UTI isolates, it is still tested and the resistance tracked. What is concerning is the fact that so many isolates were resistant to 2 or more drugs, and resistance was often across multiple drug classes.

Table 4. Frequency of resistance based on antimicrobial effects

| Drug effect                      | Percentage of resistant isolates | Percentage of all isolates |
|----------------------------------|----------------------------------|---------------------------|
| Inhibition of cell wall synthesis| 87.9%                            | 41.6%                     |
| Inhibition of protein synthesis  | 40.3%                            | 19.1%                     |
| Anti-metabolites                 | 38.3%                            | 18.1%                     |
| Inhibition of nucleic acid synthesis | 38.1%                          | 18.0%                     |

The drugs of choice for acute, uncomplicated UTIs as recommended by the Infectious Diseases Society of America (IDSA) and the
European Society for Microbiology and Infectious Diseases are nitrofurantoin, trimethoprim/sulfamethoxazole, fosfomycin, fluoroquinolones, and certain β-lactams (2nd or 3rd generation cephalosporins, amoxicillin/clavulanic acid) [13]. As shown in Table 1, resistance to these recommended drugs is present in many isolates (TMP/SXT – 18%, CIP – 16%, AMC – 8%). In addition, Table 2 shows that many isolates are also showing resistance to combinations including these recommended drugs. Similar patterns of resistance have been seen in several other countries, as well [18].

An important issue to address is that of multiple-drug resistant organisms (MDROs). The CDC defines an MDRO as a microorganism that is resistant to at least three of the antimicrobial drug classes (Roberta B. Carey, Ph.D., personal communication, 10/07/2008). Others consider a bacteria to be an MDRO if they are resistant to just more than one drug class. Because E. coli is a gram-negative bacteria, in urine cultures it is routinely tested against drugs from four or five different drug classes. Table 3 shows that, of the resistant organisms, 15.2% were resistant to at least three drug classes, and 9.3% were resistant to all four classes (as defined in this study). If we consider those isolates that were resistant to two classes (30.4%), that could potentially represent a lot of MDROs. We are left pondering just how long it will be before even more organisms acquire resistance to another class, and join the MDROs.

4. CONCLUSION

All things considered, the fact that antibiotic resistance in general is continuing to increase, and that the incidence of MDROs is also increasing, should cause sufficient alarm, and lead to more consideration of how we treat UTI infections. Since β-lactam drugs have so little effect on gram-negative bacteria in general, and UPEC more specifically (as indicated in this and other studies), these drugs are not likely to be useful for treatment in the future. We need to carefully consider the treatment options and be vigilant as to resistance levels. Hopefully we can stop the increasing resistance rates by being good stewards of the antimicrobial agents that we now have. If we continue to misuse these drugs, it may not be very long before we have few or no options for drug treatment. We are already losing the race to discover and market new, effective antimicrobial drugs.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Carson C, Naber KG. Role of fluoroquinolones in the treatment of serious bacterial urinary tract infections. Drugs. 2004;64(12):1359-1373.
2. National Institute of Diabetes and Digestive and Kidney Diseases. Urinary tract infection in adults. National Kidney and Urologic Diseases Information Clearinghouse, National Institutes of Health. 2011-2097.
3. Anderson GG, Martin SM, Hultgren SJ. Host subversion by formation of intracellular bacterial communities in the urinary tract. Microbes Infect. 2004;6:1094-1101.
4. Kucheria R, Dasgupta P, Sacks SH, Khan MS, Sheerin NS. Urinary tract infections: new insights into a common problem. Postgrad Med J. 2005;81:83-86.
5. Karger J, Nataro JP, Mobley HLT. Pathogenic Escherichia coli. Nat Rev Microbiol. 2004;2:123-140.
6. Billips BK, Schaeffer AJ, Klumpp DJ. Molecular basis of uropathogenic Escherichia coli evasion of the innate immune response in the bladder. Infect Immun. 2008;76:3891-3900.
7. Hung C, Zhou Y, Pinkney JS, Dodson KW, Crowley JR, Heuser J, Chapman MR, Hadjifrangiskou JP, Hultgren SJ. Escherichia coli biofilms have an organized and complex extracellular matrix structure. Mbio. 2013;4(5):e00645-13.
9. Wright KJ, Seed PC, Hultgren SJ. Development of intracellular bacterial communities of uropathogenic Escherichia coli depends on type 1 pili. Cell Microbiol. 2007;9(9):2230-2241.

10. Marrs CF, Zhang L, Foxman B. Escherichia coli mediated urinary tract infections: are there distinct uropathogenic E. coli (UPEC) pathotypes? FEMS Microbiol Lett. 2005;252(2):183-190.

11. Pichon C, Héchard C, Du Merle L, Chaudray C, Bonne I, Guadagnini S, Vandewalle A, Le Bouguénec C. Uropathogenic Escherichia coli AL511 requires flagellum to enter renal collecting duct cells. Cell Microbiol. 2009;11(4):616-628.

12. Tandogdu Z, Cek M, Wagenlehner F, Naber K, Tenke P, Van Ostrum E, Johansen TB. Resistance patterns of nosocomial urinary tract infections in urology departments: 8-year results of the global prevalence of infections in urology study. World J Urol. 2014;32:791-801.

13. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Nicolle LE, Raz R, Schaeffer AJ, Soper DE. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious diseases society of America and the European Society for microbiology and infectious diseases. Clin Infect Dis. 2011;52(5):e103-120.

14. Landgren M, Oden H, Kuhn Osterlund A, Kahlmeter G. Diversity among 2481 Escherichia coli from women with community-acquired lower urinary tract infections in 17 countries. J of Antimicrob Chemother. 2005;55:928-937.

15. Matsumoto T, Hamasuna R, Ishikawa K, Takahashi S, Yasuda M, Hayami H, Tanaka K, Kiyota H, Muratani T, Monden K, Arakawa S, Yamamoto S. Nationwide survey of antibacterial activity against clinical isolates from urinary tract infections in Japan (2008). Int J Antimicrob Agents. 2011;37(3):210-218.

16. Sahm DF, Thornsberry C, Mayfield DC, Jones ME, Karlowsky JA. Multidrug-resistant urinary tract isolates of Escherichia coli: prevalence and patient demographics in the United States in 2000. Antimicrob Agents Chemother. 2001;45(5):1402-1406.

17. Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Weshnoweski B, Johnson J, Noreddin A, Low DE, Karlowsky JA, Hoban DJ. Antibiotic resistance in Escherichia coli outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents. 2006;27:468-475.

18. Kahlmeter G, Poulsen HO. Antimicrobial susceptibility of Escherichia coli from community-acquired urinary tract infections in Europe: the ECO.SENS study revisited. Int J Antimicrob Agents. 2012;39(1):45-51.

19. Miller K, O’Neill AJ, Chopra I. Escherichia coli mutators present an enhanced risk for emergence of antibiotic resistance during urinary tract infections. Antimicrob Agents Chemother. 2004;48(1):23-29.

20. Miller LG, Tang AW. Treatment of uncomplicated urinary tract infections in an era of increasing antimicrobial resistance. Mayo Clin Proc. 2004;79(8):1048-1054.