Changing trends in antibiotic resistance for urinary *E. coli* infections over five years in a University Hospital

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ABSTRACT

Introduction: Empiric antimicrobial guidelines aim to target the most important causative organisms of an infection. They aim to optimise outcomes whilst minimising excess broad-spectrum antimicrobial use, which can drive resistance selection pressures and be associated with secondary problems such as *Clostridium difficile* infection. *Escherichia coli* remains the most common organism causing urinary tract infections in the UK.

Aim: We aimed to look at the antibiotic resistance patterns in our hospital for *E. coli* cultured from urine.

***Methods**:* Results were obtained of all positive urine cultures between January 2007 and December 2011 from both the hospital and urology department. Trends in susceptibility and resistance data for *E. coli* to trimethoprim, amoxicillin, ciprofloxacin, gentamicin and nitrofurantoin were examined.

Results: 40,722 hospital urine specimens were culture positive in the five year period, of which 15,311 (37.6%) grew *E. coli*. Of these *E.coli* positive urines, 161 (1.05%) were from the urology department. Across the hospital there was no evidence of change inresistance to trimethoprim over the five year period (38.1% in 2007 compared to 36.6% in 2011; P=0.313). The percentage resistance to amoxicillin rose slightly (52.6% to 54.4%), and this was statistically significant (P=0.011). Overall there was a statistically significant fall in resistance to ciprofloxacin but resistance has remained stable for the last 3 years (15.5% to 13.5%, P= 0.013). A trend of increasing resistance to gentamicin (P=0.002) resulted from the 2007 baseline of 3.4% to 4.9% in 2008, but resistance remained stably low thereafter. Resistance to nitrofurantoin fell significantly (from 10.4% to 1.6%; P=<0.0005). Similar patterns were seen in urology patients, with a significant decrease in resistance to nitrofurantoin (from 26% to 9%) although the small sample size does not permit accurate analysis of significance.

***Conclusions**:* The number of *E. coli* positive urine cultures from hospital in-patients remained broadly stable over this five year period. Resistance to trimethoprim and

amoxicillin remains high. Gentamicin resistance remains low, but the statistically significant rise over the 5 year period suggests resistance rates should continue to be carefully monitored. Nitrofurantoin resistance is very low and has significantly decreased. This narrow spectrum antibiotic should be considered the mainstay for treating uncomplicated urinary tract infections in females.

INTRODUCTION

Empiric antimicrobial guidelines aim to target the most important causative organisms of an infection and are based on local susceptibility patterns which can change over time. The purpose of these guidelines is to optimise outcomes whilst minimising excess broad-spectrum antimicrobial use, which can drive resistance selection pressures and be associated with secondary problems such as *Clostridium difficile* infection. It is important to continually monitor changes in antbiotic susceptibility in order to ensure that empiric treatment guidelines remain appropriate. *Escherichia coli* (*E. coli*) is the commonest cause of urinary tract infection (UTI) (1). The aim of our study was to examine the changes in trend of antibiotic resistance for urinary *E. coli* isolates over a 5 year period in our teaching hospital and urology department.

Patient and methods

The Department of Infection of University Hospital Southampton NHS Foundation Trust (UHSFT) collected results of organisms grown from urine cultures (data collated and provided by Public Health England). The data selected for use were all *E. coli* positive urine cultures from the whole hospital over a five year period (January 2007 to December 2011). Results of urine cultures from patients throughout the hospital and within the urology department were analysed. Information on *E.coli* susceptibility to five antibiotics (trimethoprim, amoxicillin, ciprofloxacin, gentamicin and nitrofurantoin) was collected.

The patterns of susceptibility and resistance were analysed with Statistical Package for Social Sciences (SPSS) using the Cochran-Armitage test for trend carried out at the 5% level. The degree of trend in resistance and its significance was calculated for each antibiotic. Analysis was performed on resistance of cultures from all patients in the hospital and repeated for cultures from urology department patients.

RESULTS

Across the hospital 40,722 urine specimens were culture positive in the five year period 2007-2011. The organism most commonly isolated was *E. coli* (15,311; 37.6%). Of these *E.coli* isolates,161 (1.05%) were from the Urology Department. Other common organisms identified in cultures from urine samples across the hospital were non-*E. coli* coliforms (14.39%) and enterococci (13.12%) (Table 1).

Looking at *E. coli* alone, results from both the hospital and urology demonstrated that the antibiotic with the highest frequency of resistance was amoxicillin (51.5%). The antibiotics with lowest frequency of resistance were gentamicin (4.8%) and nitrofurantoin (4.4%).

Over the five years, *E. coli* resistance to nitrofurantoin fell in the hospital and in the urology department. Within the hospital there was a statistically significant trend of decreasing resistance to nitrofurantoin (from 10.4% to 1.6%; P=<0.0005), (Figure 1). Resistance to nitrofurantoin was the least frequent of all selected antibiotics analysed in 2011. A similar trend was reflected in *E. coli* from urines taken from urology patients (Figure 2) however small sample size did not permit further valid statistical analysis.

There was increasing resistance to gentamicin over the period (from 3.4% to 5.1%; P=0.002) in the hospital, but after an initial rise occurred in 2008, the resistance rate remained stable. Resistance to gentamicin within urology patients fell (23.0% in 2007 to 9.0% in 2011) (Figure 2).

Resistance to trimethoprim and ciprofloxacin in the hospital was slightly lower in 2011 (36.6% and 13.5%) compared to 2007 (38.1% and 15.5% respectively); tests for trend over the period showed a lack of statistical significance for trimethoprim. Ciprofloxacin resistance rates remained stable for the last 3 years, (Table 2). The percentage resistance to amoxicillin was high and increased slightly (52.6% in 2007 to 54.4% in 2011 P=0.011). Similar patterns were seen in urology patients (Figure 2).

DISCUSSION

There are serious concerns that antibiotic efficacy will significantly diminish in future as increasing bacterial resistance is identified and fewer new antibiotics are developed. These risks have been highlighted by groups such as the British Society of Antimicrobial Chemotherapy Antibiotic Action forum. Prudent use of antimicrobials is important to minimise resistance selection pressures, side-effects to the patient and risks of secondary infections such as *Clostridium difficile*. Empiric antimicrobial therapy should be selected on the basis of organism susceptibility patterns and avoid the inappropriate use of broad spectrum antibiotics.

Similar to other studies, our study shows that *E. coli* is still the most common cause of UTIs (2,3). This means that attention to *E. coli* antibiotic susceptibility and resistance trends is particularly important in the preparation of empiric antibiotic guidelines for treatment of UTIs.

Our results demonstrated low resistance to nitrofurantoin. This has also been noted in a study in California which found 5% resistance of *E. coli* to nitrofurantoin in female patients (4). Similarly, the study also demonstrated higher rates of trimethoprim resistance (18%). With regard to gentamicin resistance, our results are comparable to Ababneh et al's study demonstrating an increase in rate and proportion of 166% and 124% of gentamicin-resistant *E. coli* in the United States over 7 years (5).

It is interesting to see that the trend in resistance for ciprofloxacin is plateauing and resistance remains under 14%. Ciprofloxacin continues to have a place in the treatment of UTIs in men, prophylaxis for trans-rectal prostate biopsies and upper renal tract infections in UHSFT due to excellent prostate and tissue penetration. In contrast, a study in The Netherlands of 17,486 E. coli isolates from 2008 to 2010 showed a trend of increasing resistance to ciprofloxacin from 12.4% to 15.5% (6).

A strength of our work is the large number of isolates analysed (15,289). We have assumed that the majority of urine cultures will be taken from hospitalised patients prior to commencement of empiric antibiotic therapy. Trimethoprim and amoxicillin are not appropriate empiric agents for treatment of UTI. It was not possible to validate historical data for co-amoxiclav hence its non-inclusion, but of note it is a relatively broad spectrum antibiotic with significant gastrointestinal side effects. The identification and use of an alternative narrow spectrum antibiotics would be preferable. Nitrofurantoin is a narrow spectrum antibiotic and resistance rates are reassuringly low, considering its local first line use in treatment of women with uncomplicated UTIs. It is both cost-effective and efficacious for empirical treatment of uncomplicated UTIs (7). The limitations of using nitrofurantoin are its poor penetration to the prostate and that it is ineffective in the treatment of systemic sepsis or upper renal tract infections. It is contraindicated in patients with poor renal function and infants less than 3 months old and should be used with caution in patients with hepatic impairment and close to time of delivery for pregnant women (8).

The rise in gentamicin resistance over the study period is not currently clinically important as overall gentamicin resistance remains low. Gentamicin still has a a place in our guidelines for the treatment of severe sepsis (including urosepsis) when it is frequently used as single dose prior to definitve culture results being available. Therefore, continued monitoring of resistance trends is called for given the importance placed on this agent in our guidelines.

Similar patterns in resistance were found in urine cultures from our urology department though numbers were small.

It is reassuring that a narrow spectrum agent remains highly effective in vitro even in this population. Promotion of nitrofurantoin use and avoidance of broad spectrum antibiotics such as co-amoxiclav is particularly valuable in a hospital setting where there is a a significant burden of antimicrobial use and potential for adverse consequences of broad spectrum therapy.

CONCLUSIONS

Nitrofurantoin resistance is low and has significantly decreased and therefore should now be considered the mainstay of empiric treatment of uncomplicated UTIs in females. This can be switched to targeted therapy on the basis of definitive subsequent culture results if required. Patient-specific factors such as renal function, presence of systemic sepsis, late pregnancy, age and the site of infection should also be considered. Gentamicin resistance remains low but susceptibility trends should be monitored considering the reliance placed on it as part of the empiric treatment of severe sepsis (including urosepsis) in our hospital.

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Conflict of interests:

None declared

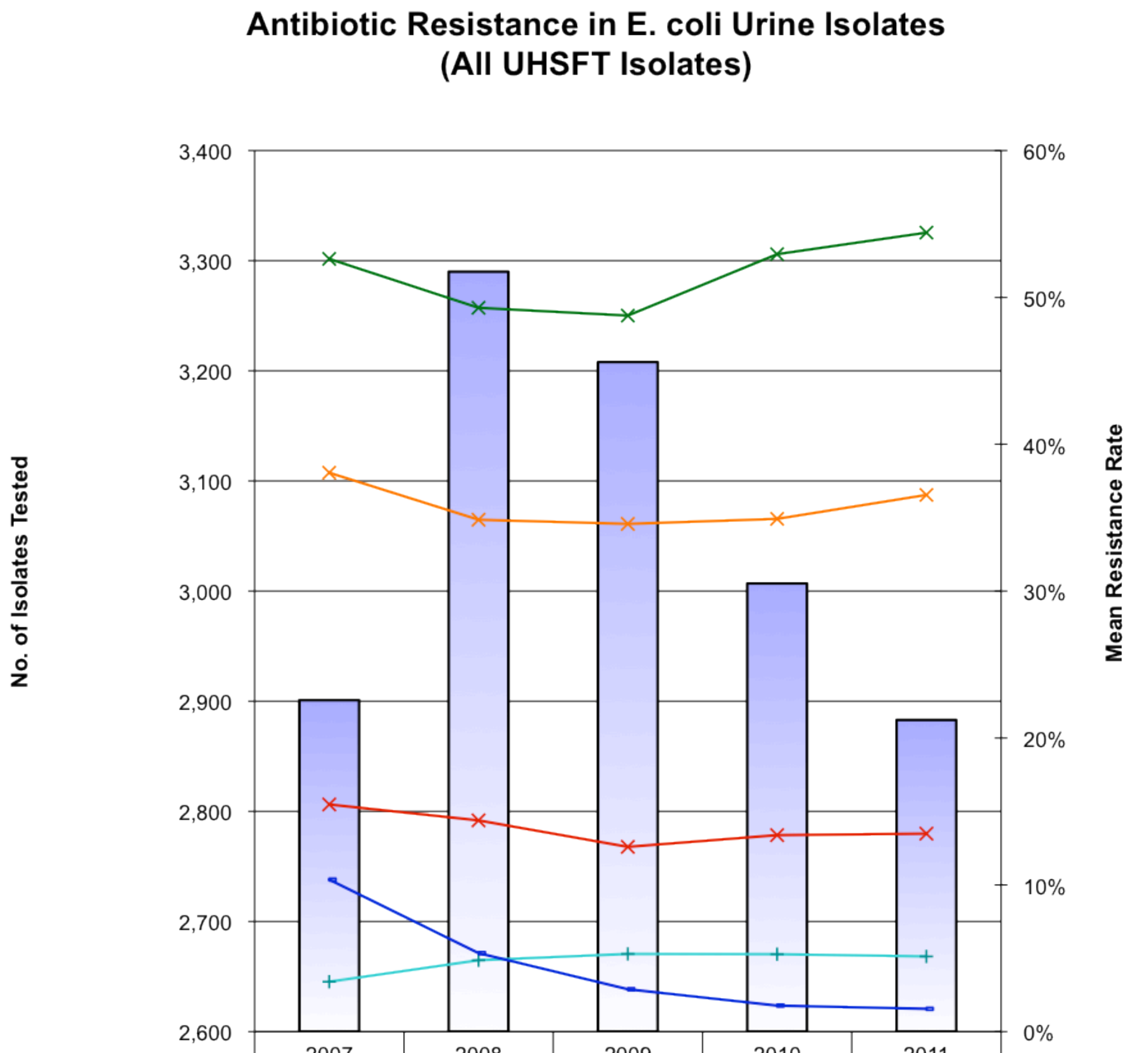
Table 1: Isolates from all UHSFT Urines 2007-2011

Isolate Name	No. of Isolates	Percentage of Total
Escherichia coli	15,311	37.60%
Non- *E.coli* coliforms	5861	14.39%
Enterococci	5,343	13.12%
Pseudomonas species	2,065	5.07%
Proteus species	1,795	4.41%
Other	10,347	25.4%
Total	**40,722**	**100.00%**

Table 2: Number(%) resistance of *E.coli* in urine from UHSFT to selected antibiotics 2007-2011

	2007	2008	2009	2010	2011	*Total*	Cochran Armitage test for trend P value
Number of isolates Hospital (Urology)	2901 (35)	3290 (33)	3208 (31)	3007 (40)	2883 (22)	***15289 (161)***	
Trimethoprim	1004 (38.1%)	1147 (34.9%)	1109 (34.6%)	1050 (34.9%)	1054 (36.6%)	***5464 (35.7%)***	**0.313**
Amoxicillin	1527 (52.6%)	1622 (49.3%)	1564 (48.8%)	1592 (52.9%)	1569 (54.4%)	***7873 (51.5%)***	**0.011 (significant)**
Ciprofloxacin	449 (15.5%)	473 (14.4%)	404 (12.6%)	402 (13.4%)	389 (13.5%)	***2117 (13.8%)***	**0.013 (significant)**
Gentamicin	99 (3.4%)	160 (4.9%)	170 (5.3%)	159 (5.3%)	148 (5.1%)	***735 (4.8%)***	**0.002 (significant)**
Nitrofurantoin	300 (10.4%)	176 (5.4%)	93 (2.9%)	53 (1.8%)	45 (1.6%)	***668 (4.4%)***	**<0.0005 (significant)**

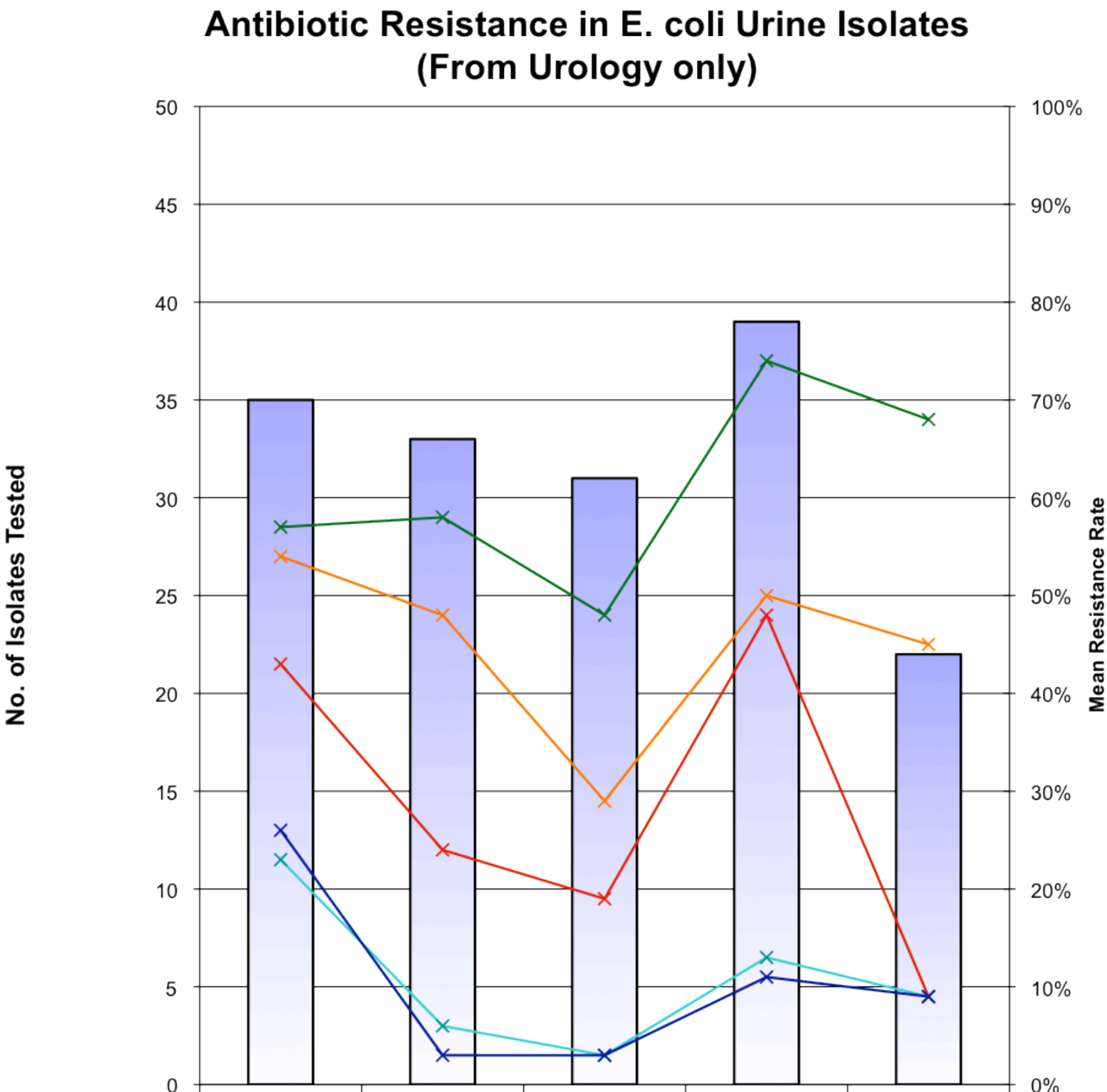
Figure 1: Antibiotic resistance in *E. coli* Urine Isolates across the Hospital



	2007	2008	2009	2010	2011
Total Tested	2901	3290	3208	3007	2883
% Resistant to Trimethoprim	38.1%	34.9%	34.6%	34.9%	36.6%
% Resistant to Amoxycillin	52.6%	49.3%	48.8%	52.9%	54.4%
% Resitant to Ciprofloxacin	15.5%	14.4%	12.6%	13.4%	13.5%
% Resistant to Gentamicin	3.4%	4.9%	5.3%	5.3%	5.1%
% Resistant to Nitrofurantoin	10.4%	5.4%	2.9%	1.8%	1.6%

Figure 2: Antibiotic resistance in *E. coli* Urine Isolates from the Urology Department

Data shown for information only – statistical interpretation not possible due to low sample numbers



	2007	2008	2009	2010	2011
Total Tested	35	33	31	39	22
% Resistant to Trimethoprim	54.0%	48.0%	29.0%	50.0%	45.0%
% Resistant to Amoxycillin	57.0%	58.0%	48.0%	74.0%	68.0%
% Resitant to Ciprofloxacin	43.0%	24.0%	19.0%	48.0%	9.0%
% Resistant to Gentamicin	23.0%	6.0%	3.0%	13.0%	9.0%
% Resistant to Nitrofurantoin	26.0%	3.0%	3.0%	11.0%	9.0%

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