

# Evidence-based prescription of antibiotics in urology: a 5-year review of microbiology

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## OBJECTIVE

To analyse the results of positive urine cultures over a 5-year period in a large hospital and urology department (amongst both inpatients and outpatients), assess the prevalence of different organisms and the resistance profiles of a range of antibiotics, and thus provide information on which organisms are likely to cause urosepsis.

## METHODS

The use of antibiotics should be based on knowledge of which pathogens are present and what resistance patterns are emerging, particularly relevant in surgical disciplines like urology, as antibiotics are now routinely

administered peri-operatively, whereby evidence-based prescription is preferable to generic guidelines. We therefore examined almost 25 000 positive urine cultures in our hospital over a 5-year period, and focused on the infections encountered amongst urology patients during this time.

## RESULTS

A significant proportion of inpatient urinary infection (40%) is caused by Gram-positive bacteria such as *Streptococcus faecalis*, underlining the need for including Gram-positive cover during urological prophylaxis. The commonest pathogen remains *Escherichia coli* among both inpatients and outpatients. The ineffectiveness of common

antibiotics such as ciprofloxacin and trimethoprim was identified, as was the increase in gentamicin resistance.

## CONCLUSION

We propose using an aminoglycoside with a penicillin for high-risk cases (e.g. endoscopic stone surgery) while low-risk cases (e.g. flexible cystoscopy with no risk factors) might be managed without such prophylaxis. Pathogenic patterns and resistance rates should be monitored regularly.

## KEYWORDS

antibiotics, urology, resistance

## INTRODUCTION

The prevention of infection in hospitals is now a significant public and political issue; newspaper articles related to the subject are very common. Numerous national initiatives have been introduced to minimize infection risks, with particular attention being given to the outbreaks of methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*. Rationalization of antibiotic usage plays a key role in the control of infection, but might be an underestimated aspect of sepsis prevention. The prophylactic use of antibiotics can reduce the risk of surgically related infection, and published guidelines have attempted to standardize their administration [1]. However, local practice should be based on local microbiological patterns and requirements, particularly as there have been steady increases in antibiotic resistance among particular common pathogens.

The ideal prophylactic antibiotic should offer broad coverage, have limited resistance,

produce few side-effects, overcome common virulence, be familiar and easy to administer, and be based on knowledge of local prevalence of organisms. Only with such local knowledge can patient safety be maximized, and informed decisions made when tackling major sepsis.

A pan-European study of over 200 urological units found that 9.7% of patients had a hospital-acquired UTI; of all hospital-acquired infections, urinary sepsis might account for >40%. We analysed the results of positive urine cultures over a 5-year period in our hospital and department (amongst both inpatients and outpatients). The prevalence of different organisms was determined, as was the resistance profiles of a range of antibiotics. This provides information on which organisms are likely to cause urosepsis in our hospital and which antibiotics we should be using to reduce morbidity.

This information is also valuable for limiting the advance of antibiotic resistance.

Hawkey's commentary [2] opens with the observation that bacteria 'are thought to have evolved 3500 million years ago ... antibacterial therapy has only emerged over the last 60 years', and therefore the emergence of antimicrobial resistance has been 'but a second in evolutionary time'. As we approach the bicentennial of Darwin's birth, it is fitting that we acknowledge the evolution of microbial virulence, and that we tailor our strategies based on scientific knowledge about patterns of infection and resistance.

## METHODS

We reviewed all positive urine cultures from January 2002 to December 2006 at Guy's and St Thomas' Trust, London, UK; this included all positive cultures among urology inpatients and outpatients. Urine samples were processed using an automated urine analyser; a bacterial count of >2000 would lead to formal culturing of the specimen.

FIG. 1. The range and prevalence of organisms among urology inpatients and outpatients.

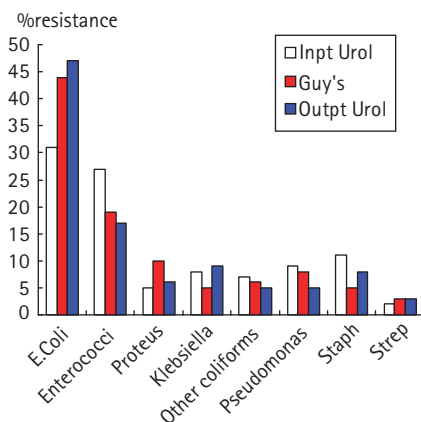
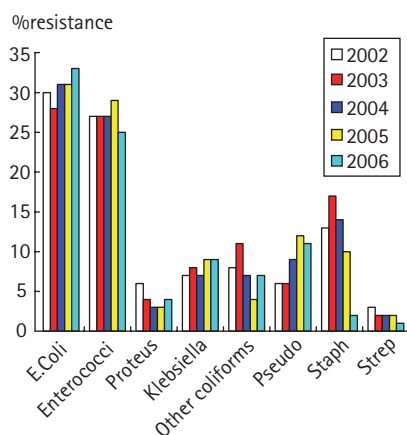


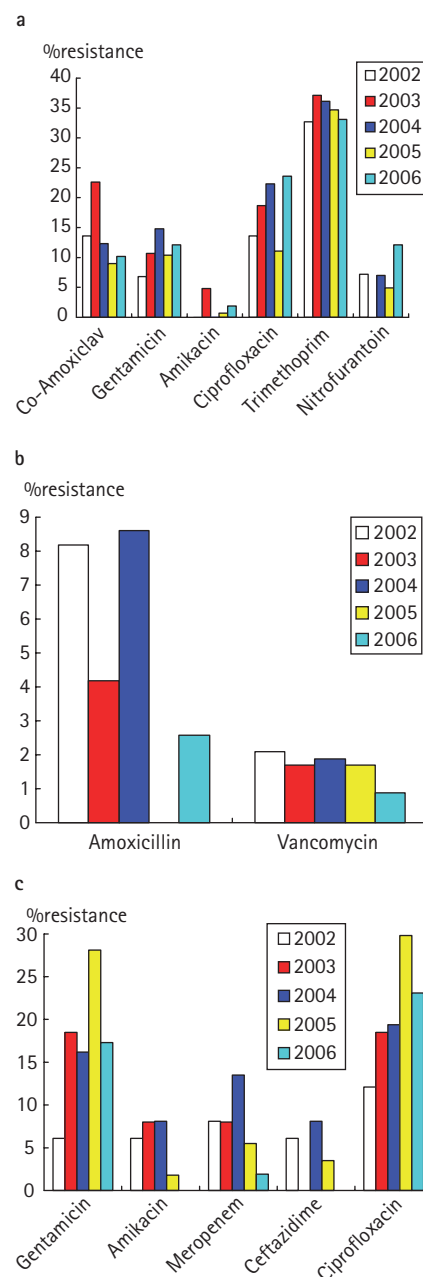
FIG. 2. The prevalence of respective organisms among inpatients during the study period.



## RESULTS

In all, 24 998 positive urine specimens from across the entire hospital were cultured during this period. Of these, 2305 were urology inpatients and 1571 urology outpatients. *E. coli* was the most prevalent cause of UTI (45% of all hospital UTIs, 47% of urology outpatient and 31% of urology inpatient UTIs). Figure 1 shows the broadly similar spectrum of organisms detected by positive urine samples among the three groups (urology inpatients/outpatients and total hospital results). However, the overall proportion of positive cultures caused by Gram-positive bacteria was strikingly high among urology inpatients, at 40% (vs 28% among outpatients, 27% overall in the hospital). Specifically, *Enterococci*

FIG. 3. The resistance rates of: a, *E. coli* to a range of antibiotics; b, *Enterococci* to amoxycillin and vancomycin; and c, *Pseudomonas* to a range of antibiotics, from 2002 to 2006.



(*Streptococcus faecalis*) accounted for 27% of urology inpatient cultures.

The changes in the prevalence of specific organisms between 2002 and 2006 are shown in Fig. 2. The predominance of *E. coli* and *Enterococci* was sustained, with little change in prevalence for either organism. The prevalence of *Pseudomonas* appears to

have increased during the period, while *Staphylococci* conversely showed a decreasing trend.

Figure 3 shows typical antibiotic resistance patterns of *E. coli*, *Enterococci* and *Pseudomonas* as sample pathogens. *E. coli* had a resistance rate of 30–40% to trimethoprim, up to 25% to ciprofloxacin and 10% to gentamicin. Resistance of *Enterococci* to amoxycillin was low at 3%, having reached a peak of almost 9% in 2004 (Fig. 3b). The resistance to vancomycin was consistently low at 1–2%. *Pseudomonas* showed resistance rates of 20% to ciprofloxacin and 15% to gentamicin (Fig. 3c); similar values were reported for *Klebsiella*.

Antibiotic resistance patterns are also shown by year (Fig. 4) for gentamicin, amikacin, ciprofloxacin and amoxycillin. The overall increase in gentamicin resistance (Fig. 4a) was particularly striking among *Pseudomonas* and *Klebsiella* during this period, although the local cessation of gentamicin as the prophylaxis of choice in 2005 might explain the reversal of this trend in 2006. Nevertheless, overall resistance rates were 10–20% generally for the organisms listed. The introduction of prophylactic amikacin (replacing gentamicin) at the end of 2005 might explain the higher rates of amikacin resistance detected in 2006 (Fig. 4b), although all *Pseudomonas* was sensitive to this (Fig. 3c). The ineffectiveness of ciprofloxacin as a prophylactic antibiotic is shown in Fig. 4c, with resistance rates reaching 20% for *E. coli*, *Pseudomonas* and *Klebsiella* by 2006. The effectiveness of amoxycillin for Gram-positive coverage (as also seen with *Enterococci*, Fig. 3b) was maintained for the study period (Fig. 4d), while its ineffectiveness against *E. coli* is represented by a resistance rate consistently >50%.

## DISCUSSION

Hospital infections are a major clinical, managerial and political issue. In the UK, directives have led to the implementation of measures such as hand-washing, dress codes and procedures for isolation of ward areas. The widespread use of antibiotics calls for rationalization of their use; this is particularly relevant for surgery, where prophylactic use is commonplace. Knowledge about local microbiological patterns is essential for rationalizing both prophylaxis and treatment regimens.

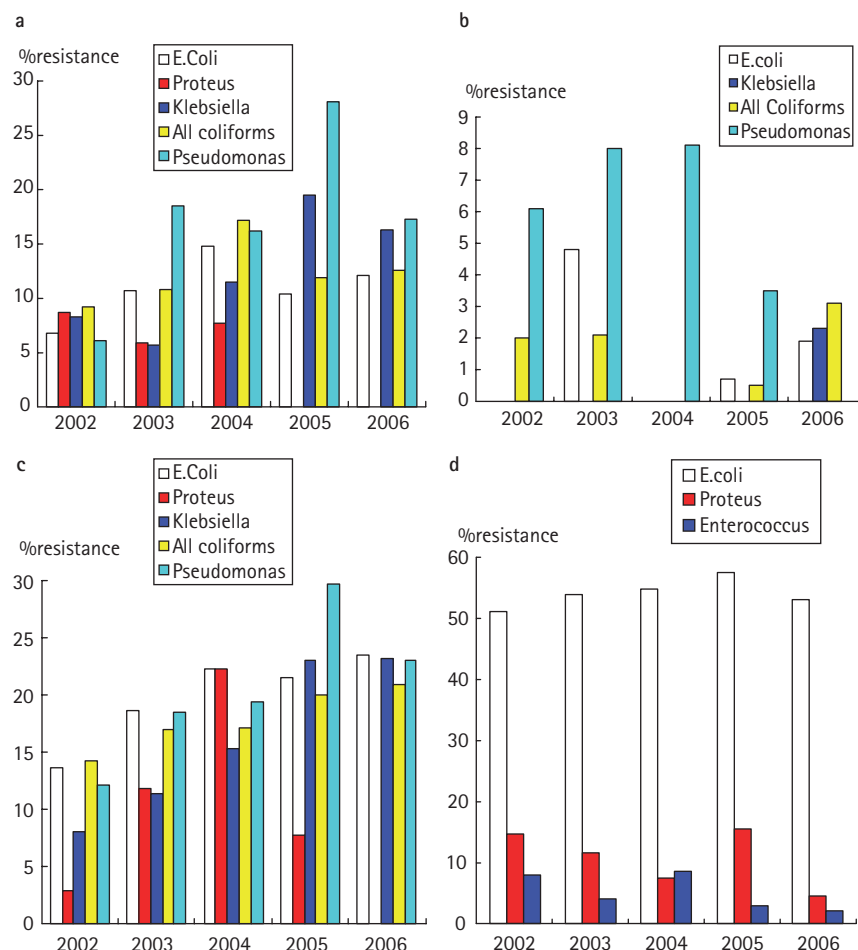
The findings of the present study show the need for dual coverage of Gram-positive and -negative bacteria in our practice, a difference between organisms among inpatients and outpatients, and the ineffectiveness of certain antibiotics (with high resistance rates). Finally, the findings support the need for longitudinal surveillance, regular review and liaison with the local microbiological department, which can be adopted by physicians across all clinical specialities.

Although *E. coli* remains the single most common organism to cause urinary infection, the proportion of Gram-positive organisms is very high at 40% among urology inpatients, with *Enterococci* accounting for 27%. To reduce the risk of *Enterococci* sepsis it would seem prudent to use ampicillin/amoxicillin in addition to an aminoglycoside for prophylaxis, especially in high-risk cases. Given the almost universal resistance of *Enterococci* to cephalosporins, it is surprising that they continue to be recommended in guidelines [1].

It might be that rational prophylaxis should be based around combinations of antibiotics, with specific agents being reserved for treating established sepsis. A single agent would seem to be highly unlikely to provide the breadth of cover that adequate prophylaxis demands.

A recent systematic review has focused on the published evidence for antibiotic prophylaxis in urology [3]. The authors indicate that only TURP and prostate biopsy have a high level evidence favouring the use of antibiotics before the procedure. Surprisingly there were only four evaluable randomized controlled trials for cystoscopy, of which two concluded there was no benefit from prophylaxis, while the other two showed a decrease in symptomatic infections and bacteriuria; the overall conclusion was that there was no need for antibiotic prophylaxis in the absence of risk factors for UTI (such as a history of symptomatic UTI, or other procedures during cystoscopy). Given the risk of sepsis associated with percutaneous nephrolithotomy (PCNL), it is disappointing that only one randomized controlled trial was identified for this procedure. It compared placebo to antibiotic prophylaxis, and the sample size was judged too small to reach a statistically significant difference. Case studies addressing prophylaxis for PCNL suggest no difference between single-dose

FIG. 4. Resistance to: a, gentamicin; b, amikacin; c, ciprofloxacin; and d, amoxicillin, shown by a range of organisms during the study period.



prophylaxis and multiple doses of quinolones or cephalosporins before surgery. Our experience of single-dose prophylaxis is at odds with the Edinburgh experience, which reported a benefit from 1 week of preoperative ciprofloxacin [4]. The frequent isolation of *Enterococcus* has led us to add ampicillin/amoxicillin to an aminoglycoside before surgery.

It is questionable whether prophylaxis has much of a role in low-risk diagnostic procedures such as cystoscopy, and it might be better to give clear instructions to patients and primary-care physicians about the treatment of the occasional infection.

Although the media and policy-makers have focused on methicillin-resistant *S. aureus* [5] and *C. difficile*, the increase in antimicrobial resistance is more widespread. Resistance to

commonly prescribed antibiotics, including trimethoprim, quinolones and cephalosporins, is significant, and even seen in aminoglycosides such as gentamicin.

The rise in resistance of urinary pathogens towards quinolones has been reported worldwide [6], partly due to overuse based on their efficacy in treating respiratory infections and uncomplicated UTIs. Resistance rates in our hospital have steadily increased, and now stand at 20–25%; this level is similar to reports from other studies [7,8].

Resistance of *P. aeruginosa* to ciprofloxacin is now very common (20%). A multiresistant *P. aeruginosa* caused the death of a patient in our endourology unit, and presented a worrying potential glimpse of the future [9]. Kashanian *et al.* [6] recently reported a retrospective analysis of the antibiotic

susceptibilities of 10 417 *E. coli* urine cultures collected from 2003 to 2007, showing a mean resistance rate of 24% to ciprofloxacin. In a review of single-dose prophylactic ciprofloxacin, resistance of *E. coli* to ciprofloxacin has risen from 3% to 12% [10].

A large prospective double-blind randomized trial showed a reduction in bacteriuria by administering one dose of ciprofloxacin before flexible cystoscopy [11]. Whether a reduction in bacteriuria justifies the risk of triggering general ciprofloxacin resistance is open to question. It will be interesting to observe the effect of this policy on the resistance rates in the authors' centre over a longer period.

*E. coli* cultured from both inpatients and outpatients currently shows a 35–40% resistance rate to trimethoprim in our unit. This level of resistance is not unusual [6,8], and might provide evidence against the routine use of trimethoprim prophylactically or for empirical therapeutic use in a urology unit. It might be that trimethoprim will be more effective in community-acquired UTIs, but the fact that sensitivities for *E. coli* are similar for both inpatients and outpatients is worrying.

Gentamicin is the most commonly prescribed prophylactic antibiotic in urology. Of concern is that resistance rates have been steadily increasing (Fig. 4a), with *E. coli* resistance now >10% in our department. In 2005, following an outbreak of ciprofloxacin- and gentamicin-resistant *P. aeruginosa*, a switch to amikacin prophylaxis was instituted in our department [9]. It is still too early to evaluate any changes in rates of resistance towards gentamicin and amikacin as a consequence of this change.

The appropriate response to the development of resistance is difficult to judge; options would include an overall reduction and modification of antibiotic usage, increased surveillance mechanisms, and greater non-antibiotic infection control measures. Our unit is not the first to introduce amikacin in response to increasing gentamicin resistance. Gerding *et al.* [12] reported twice over a 10-year period when the introduction of high-level amikacin usage reduced resistance to gentamicin and tobramycin; when gentamicin was reintroduced quickly after the first period, gentamicin resistance recurred rapidly, whereas a more gradual reintroduction of

gentamicin, after the second period, did not cause such a rise in resistance. There was no change in amikacin resistance throughout. Pooled data from 14 hospitals that introduced high-level amikacin usage (85% of aminoglycoside use) revealed a small but statistically significant increase in amikacin resistance (from 1.4% to 1.7%), not detectable in individual units [13]. The one organism which showed a significant increase in resistance was *P. aeruginosa*.

The second study showed a reduction in gentamicin resistance from 17.4% to 7.4% after exclusive use of amikacin, analysing sensitivities in >9000 Gram-negative strains [14]. The initial resistance of *P. aeruginosa* resistance to gentamicin decreased from 63% to 28% over the 3-year study period. The overall amikacin resistance was unchanged.

A lack of increase in amikacin resistance, which would seem counterintuitive after unrestricted use, was also shown by Acar *et al.* [15]. Our findings (Fig. 4b) allude to a slight increase in amikacin-resistance in *E. coli*, *Klebsiella* and coliforms between 2005 and 2006. Acar *et al.* also suggested that the combination of aminoglycoside with a  $\beta$ -lactam antibiotic was logical, as mutations affecting both types of antimicrobial are very rarely reported. This would appear to substantiate our view that high-risk cases (e.g. PCNL) should be prescribed prophylaxis covering both Gram-positive and -negative organisms.

In conclusion, Gram-positive organisms are a common cause of urosepsis in hospital. Antibiotic prophylaxis for high-risk urological procedures should include cover for *Enterococcus*, in addition to the standard Gram-negative cover. A combination of ampicillin and gentamicin seems to be pragmatic. Resistance of urinary pathogens to ciprofloxacin and trimethoprim is worrying. Hospital departments should review infection patterns and antibiotic sensitivities regularly.

## CONFLICT OF INTEREST

None declared.

## REFERENCES

- 1 Naber KG, Bishop MC, Bjerklund-Johansen TE *et al.* Perioperative antibacterial prophylaxis in urology.

EAU Guidelines on the Management of Urinary and Male Genital Tract Infections, EAU, 2006, pp. 100–9

- 2 Hawkey PM. The growing burden of antimicrobial resistance. *J Antimicrob Chemother* 2008; **153** (Suppl. 1): 1–9
- 3 Bootsma AM, Laguna MP, Geerlings SE, Goossens A. Antibiotic prophylaxis in urologic procedures: a systematic review. *Eur Urol* 2008; **54**: 1270–86
- 4 Mariappan P, Smith G, Moussa SA, Tolley DA. One week of ciprofloxacin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. *BJU Int* 2006; **98**: 1075–9
- 5 Thiruchelvam N, Yeoh SL, Keoghane SR. MRSA in urology: a UK hospital experience. *Eur Urol* 2006; **49**: 896–9
- 6 Kashanian J, Hakimian P, Blute M *et al.* Nitrofurantoin: the return of an old friend in the wake of growing resistance. *BJU Int* 2008; **102**: 1634–7
- 7 Vromen M, van der Ven A, Knols A, Stobberingh EE. Antimicrobial resistance patterns in urinary isolates from nursing home residents. Fifteen years of data reviewed. *J Antimicrob Chemother* 1999; **44**: 113–6
- 8 Kurutepe S, Surucuoglu S, Sezgin C, Gazi G, Gulay M, Ozbakkaloglu B. Increasing antimicrobial resistance in *Escherichia coli* isolates from community-acquired urinary tract infections during 1998–2003 in Manisa, Turkey. *Jap J Inf Dis* 2005; **58**: 159–61
- 9 DasGupta R, French G, Glass JM. Multi-resistant *Pseudomonas aeruginosa* outbreak in an endourology unit. *Eur Urol* 2008; **53**: 1009
- 10 Wagenlehner F, Stower-Hoffmann J, Schneider-Brachert W, Naber KG, Lehn N. Influence of a prophylactic dose of ciprofloxacin on the level of resistance of *Escherichia coli* to fluoroquinolones in urology. *Int J Antimicrob Agents* 2000; **15**: 207–11
- 11 Johnson MI, Merrilees D, Robson WA *et al.* Oral ciprofloxacin or trimethoprim reduces bacteriuria after flexible cystoscopy. *BJU Int* 2007; **100**: 826–9
- 12 Gerding DN, Larson TA, Hughes RA, Weiler M, Shanholtzer C, Peterson LR. Aminoglycoside resistance and aminoglycoside usage: ten years of experience in one hospital. *Antimicrob Agents Chemother* 1991; **35**: 1284–90
- 13 Cross AS, Opal S, Kopecko D. Progressive increase in antibiotic

resistance of gram negative bacterial isolates. Walter Reed Hospital, 1976 to 80: specific analysis of gentamicin, tobramycin and amikacin resistance. *Arch Int Med* 1983; **143**: 2075–80

- 14 Ruiz-Palacios GM, Ponce de Leon S, Sifuentes J *et al.* Control of emergence of

multi-resistant Gram-negative bacilli by exclusive use of amikacin. *Am J Med* 1986; **80**: 71–5

- 15 Acar JA, Goldstein FW, Menard R, Bleriot JP. Strategies in aminoglycoside use and impact on resistance. *Am J Med* 1986; **80**: 82–7

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**Abbreviations:** PCNL, percutaneous nephrolithotomy.