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# The relation between sale of antimicrobial drugs and antibiotic resistance in uropathogens in general practice

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***Background* – Overuse of antimicrobial drugs has resulted in an alarming increase in bacterial resistance in most countries. The relevance for general practice is unknown.**

***Objective* – To evaluate the impact of the sale of antimicrobial drugs on bacterial resistance as found in uropathogens from general practice.**

***Setting* – General practice in Belgium and Norway.**

***Methods* – Observational study.**

***Results* – The sale of antimicrobial drugs indicated for use in the treatment of urinary tract infection was four times higher in Belgium than in Norway (18.5 vs 4.4 DDD/1000 inhabitants/day). The antibiotic resistance reported by microbiological laboratories as valid for general practice was significant higher in Belgium than in Norway (ampicillins (44% vs 27%), co-trimoxazole (28% vs 17%), fluoroquinolones (12% vs 2%) and nitrofurantoin (16% vs 11%, $p < 0.0001$ for all). However, the antibiotic resistance found in urine samples from dysuric women in general practice was similar (trimethoprim 14% vs 12%, co-trimoxazole 14% vs 11%, nitrofurantoin 7% vs 3%), except in the case of ampicillins (30% vs 19%, $p < 0.05$).**

***Conclusion* – The impact of the antimicrobial sale on resistance in uropathogens seems less than expected at the general practice level, even though local microbiological reports mention fairly high antibiotic resistance data. Adapted methods for following-up bacterial resistance evolution in general practice are needed.**

***Key words:* general practice, urinary tract infection, antibiotic susceptibility.**

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Antimicrobial treatment for acute lower urinary tract infection (UTI) is well established. Results of standard treatment in general practice have until recently been satisfying (1), as cure rates for most antibiotics have varied between 85% and 95% (2). Multiresistant bacteria used to be regarded as a problem mainly for hospitals and other institutions where bacterial exposure to antibiotics was more constant; and the effect in general practice was thought to be small.

Increased use of antimicrobials, especially of new broad spectrum antibiotics, may have altered this picture, and increasing antibiotic resistance has been reported in general practice during recent years. The frequency of bacterial resistance to different antibiotics differs from country to country (3), and is related to the use of antibiotics within the country (4).

A recent study is the first to indicate a correlation between antibiotic resistance in coliform organisms in urine samples and the use of antibiotics in general practice (5). However, we have insufficient knowledge of resistance development in general practice, especially concerning uropathogens.

The aim of this study was to evaluate the impact of the sale of antimicrobial drugs on bacterial resistance as found in uropathogens from general practice.

## MATERIALS AND METHODS

The material of this study derives from three different sources in Belgium and Norway: (a) *Sales figures* for antimicrobial drugs in both countries; (b) *microbiological laboratory level*: bacteria found in urine samples spontaneously sent by general practitioners to the laboratory; (c) *general practice level*: bacteria found in urine samples from acute dysuric women recruited consecutively.

*Sales figures* for antimicrobial drugs in 1997 were provided by the Institute for Pharmaco-Epidemiology Belgium and the Norwegian Medicinal Depot (6,7). The figures cover the total consumption for human utilisation. Defined daily dose (DDD) was defined as the assumed average dose per adult patient per 24 h (8).

*At the microbiological laboratory level*, bacterial sensitivity was recorded during the study period for isolates found in all urine samples spontaneously received by the two regional microbiological laboratories from general practice. These samples represent the normal base for the bacterial sensitivity reports usually published as relevant for general practice by the laboratories.

*At the general practice level*, 279 acutely dysuric women, aged 15–54 (median 34) years, were recruited consecutively from 17 general practices in the Ghent region of Belgium from June 1995 to December 1996. Correspondingly, 172 acutely dysuric women aged 16–97 (median 41) years were recruited consecutively from 13 general practices in the Bergen area of Norway from August 1994 to February 1995.

Common criteria for inclusion were symptoms of acute lower UTI without fever. Pregnant women and women with known complicating illnesses, or complicating conditions of the urinary tract, were excluded. In the Belgian arm of the study, women reporting UTI in the previous 3 months, or reporting 3 or more episodes of UTI in the previous 12 months, were additionally excluded.

Urine samples were collected at the surgery after careful instruction in the midstream technique. In the Belgian arm of the study, samples were immediately inoculated on a dipslide agar (Uricult) and taken to the bacteriology and virology laboratory at the University Hospital, State University Ghent, where they were examined using the Kirby-Bauer disk diffusion method, and following the criteria of the National Committee for Clinical Laboratory Standards (NCCLS) (9). In the Norwegian arm, within half an hour boric acid was added to 1.6%, and the samples were sent to the Department of Microbiology and Immunology, The Gade Institute, Haukeland Hospital, Bergen, Norway. The susceptibility to antibacterial agents was examined by an agar diffusion method (10) using paper discs from AB Biodisk, Solna, Sweden. The isolates were classified as resistant to the various agents according to criteria recommended by the Norwegian Working Group on Antibiotics (11). The two methods use the same break-points for ampicillins, trimethoprim and fluoroquinolones. For nitrofurantoin, the US break-point used in Belgium was higher than the Norwegian ones (80 vs 32 mg/l), and likewise for co-trimoxazole (128 vs 32 mg/l) (9,11). The susceptibility to cephalosporines was not compared, as testing for this group was based on cefuroxime in Belgium and cephalexin in Norway. Belgian laboratories did not routinely test for amoxy-clav and trimethoprim. Belgian data on trimethoprim are based on 104 samples in the GP group only, while amoxy-clav was only tested in the laboratory group. The Norwegian laboratory did not routinely test for quinolones, and data on this drug are based on 730 samples only.

Acute lower urinary symptoms were defined as acute dysuria, urinary frequency and/or suprapubic discomfort of a duration less than 7 days. Uropathogens were defined as *Escherichia coli* and other Gram-negative intestinal rods, *Staphylococcus saprophyticus* and enterococci. Significant bacteriuria was defined as $10^5$ colony-forming units (cfu)/ml or more uropathogens or any amount of *S. saprophyticus*. A lower UTI was defined as acute lower urinary symptoms and significant bacteriuria.

*Statistics*

Differences between fractions were tested using chi-squared tests.

## RESULTS

A total of 451 urine samples were obtained consecutively from acute dysuric women in general practice. Of these, 258 samples showed significant bacteriuria, 176 from the Gent region of Belgium and 82 in the Bergen region of Norway. The microbiological laboratories of the same regions received 10697 bacteriuric urine samples spontaneously sent from general practice surgeries during the same period, 1973 samples in the Ghent region and 8904 in the Bergen region.

As shown in Table I, sale of the antimicrobial drugs indicated for use in UTI was more than four times higher in Belgium than in Norway. The sale of just ampicillins/amoxycillins (J01C A + R) in Belgium was more than double the total sale of UTI-related antimicrobials in Norway.

The Belgian microbiological laboratory reported a substantially higher frequency of resistant bacteria than the Norwegian laboratory (Table II). This corresponds closely with the difference in sales figures between the two countries, and seems to be the case especially for ampicillins, co-trimoxazole and fluoroquinolones. As susceptibility to fluoroquinolones is not routinely tested for in the

Table I. The sale in 1997 of antimicrobial drugs (with ATC codes) indicated for use in the treatment of urinary tract infection in Belgium and Norway. Figures are given in defined daily doses (DDD) per 1000 inhabitants/day.

| Antimicrobial drug | ATC code | Belgium | Norway |
|---|---|---|---|
| Ampicillins[1] | J01C A | 4.2 | 1.86 |
| Amoxy-clav | J01C R | 6.8 | 0.02 |
| Cephalosporines | J01D A | 3.0 | 0.41 |
| Sulfa | J01E B/C/D | 0.06 | 0.003 |
| Trimethoprim | J01E A | 0.01 | 0.9 |
| Cotrimoxazole | J01E E | 0.7 | 0.55 |
| Fluoroquinolones | J01M A | 2.0 | 0.27 |
| Nitrofurans | G04A C | 1.7 | 0.38 |
| Fosfomycin | J01X X | 0.01 | Not marketed |
| Total | | 18.48 | 4.39 |

[1] Including pivmecillinam with a DDD/1000 inhabitants/day of 0.75 in Norway 1997. Pivmecillinam is almost not used in Belgium.

Table II. Bacterial resistance pattern (in %) among uropathogen isolates in urine samples consecutively collected from women with lower UTI in general practice (GP) in the Ghent region of Belgium and the Bergen region of Norway compared to bacterial resistance reported during the research period as valid for general practice by the microbiological laboratories (Lab) in the same regions. Comparisons between groups were done using chi-squared tests.

| | | % Resistance | | | |
|---|---|---|---|---|---|
| | | Lab | | GP | |
| | | B | N | B | N |
| Antimicrobial drug | n = | 1793 | 8904 | 176 | 82 |
| Ampicillins | | 44 | 27[1] | 30[2] | 19[3] |
| Amoxy-clav | | 10 | | 6 | |
| Pivmecillinam | | | 3 | | 1 |
| Trimetoprim | | | 20 | 14 | 12 |
| Co-trimoxazole | | 28 | 17[1] | 14[2] | 11 |
| Fluoroquinolones | | 12 | 2[1] | 1[2] | |
| Nitrofurantoin | | 16 | 11[1] | 7[4] | 3[5] |

[1] Lab Belgium vs Lab Norway, $p < 0.0001$.
[2] GP Belgium vs Lab Belgium, $p < 0.0001$.
[3] GP Belgium vs GP Norway, $p < 0.05$.
[4] GP Belgium vs Lab Belgium, $p < 0.01$.
[5] GP Norway vs Lab Norway, $p < 0.05$.

Norwegian microbiological laboratory, the Norwegian figures for fluoroquinolones represent a subgroup of 730 cases in whom testing was specifically required by the patient's doctor. Even in this highly selected group of isolates the fraction of uropathogens resistant to fluoroquinolones was significantly lower than in the Belgian material.

These differences between the two countries were not replicated on the general practice level, as the resistance patterns in uropathogens at this level were fairly similar for both countries with regard to most antimicrobial drugs except ampicillin (Table II).

In both countries there were both statistically significant and clinically relevant differences between the resistance levels reported by regional microbiological laboratories and those found in general practice (Table II). The laboratory data give an overestimation of the resistance problem in general practice.

The Norwegian material was analysed for differences between subjects with less than 3 episodes of UTI in the preceding 12 months versus 3 or more episodes in the same period. No differences were found in bacterial resistance pattern. Bacteria found in urine from women aged 60 years or more showed basically the same resistance pattern as bacteria in urine samples from younger women.

The distribution of uropathogens is given in Table III. There were no differences of statistical or clinical importance between samples from the general practice level in the two countries. The bacterial distributions in samples from the local laboratories were also similar for the two countries, but were significantly different from those in general practice. They were characterised by three times more samples with non-*E. coli* Gram-negative rods, and far fewer samples with *S. saprophyticus*. Non-uropathogenic cocci were not included in the report from the Norwegian laboratory.

## DISCUSSION

As expected, we found a close relation between the substantially higher sales of antibiotics in Belgium than in Norway and the correspondingly higher bacterial resistance reported by the Belgian microbiological laboratory than by the Norwegian one. However, quite unexpectedly, we found that these differences were not reflected at the general practice level.

The antibiotic resistance reported by the microbiological laboratories is dependent on the method used. As shown, the two laboratories used comparable methods, except for a few antibiotics where the NCLLS break-points used in the Ghent region were slightly higher than the Norwegian ones. This will result in a lower threshold for classifying an isolate as

Table III. Bacterial findings in samples consecutively collected from women with lower UTI in general practice in the Ghent region of Belgium and the Bergen region of Norway, compared with urine bacterial findings reported during the research period as valid for general practice by the microbiological laboratories in the same regions. Only statistically significant differences are marked.

| | General practice | | Microbiological laboratories | |
|---|---|---|---|---|
| | Belgium n = 176 | Norway n = 82 | Belgium n = 1793 | Norway n = 8904 |
| *E. coli* | 79% | 73% | 79% | 73% |
| Non *E. coli* Gram – rods | 7% | 5% | 17% | 16% *** |
| *S. saprophyticus* | 9% | 13% | 1% | 2% *** |
| Enterococci | 2% | 0% | 2% | 9% |
| Other Gram+cocci | 2% | 9% | 2% | |

*** $p < 0.001$, the combined laboratory materials versus the combined materials from general practice.

resistant by the Norwegian laboratory, or, in other words, had the NCCLS criteria been applied to the Norwegian isolates, the reported antibiotic resistance would have been even lower.

The bacterial resistance reported also depends on which urines the laboratories receive. It is likely that general practitioners most often culture urine samples from patients suspected to have complicated UTI (12), and these patients more often have resistant bacteria. Data from the microbiological laboratories will consequently reflect this selection process.

This is illustrated by the fact that the data from microbiological laboratories usually show a very low frequency (1–4%) of *S. saprophyticus* (13). These bacteria are responsible for 10–20% of all cases of UTI in general practice (14), and are a typical uropathogen in healthy young women in whom complicated infections are rare.

So, are the indications for culturing urine the same in the two countries? That is, could cultural differences in clinical decision-making between the two countries be responsible for the differences observed in our data? We have found no studies that directly elucidate this problem. However, there are studies indicating that Belgian doctors may be more defensive, and do more clinical tests than doctors in neighbouring countries, such as in The Netherlands and the UK (15). Data comparing Norwegian and Belgian diagnostic strategies in general practice are missing, but the available information does not indicate a greater tendency of Norwegian general practitioners to send urine samples to the laboratory than their Belgian colleagues do. If Belgian general practitioners had a wider indication for culturing urine, this would result in a lower proportion in reported resistant bacteria.

At the general practice level, the similarity of the resistance patterns found in the two countries is striking. It is fairly well established that the level of antibiotic resistance in a country is related to the amount of antibiotic use (3,4). We found that the Belgian sales figures of antimicrobial drugs were more than four times as high as the Norwegian ones, and we found parallel differences in antibiotic resistance reported by the regional microbiological laboratories. Nevertheless, with the exception of ampicillins, there were no differences of clinical importance in the frequency of resistance strains observed in the Belgian and Norwegian general practice material.

We have no unequivocal explanation for this, but one reason could be that the majority of dysuric female patients in general practice are healthy women who through the year receive little antimicrobial therapy and whose bacteria therefore develop little antibiotic resistance.

Even so, it would be imprudent to conclude that antimicrobial therapy can be used freely in general practice without any unwanted consequences. As can be seen from our data, ampicillins have the highest sales figures of all antimicrobial drugs in both countries, and (when including amoxi-clav) they also have over five times higher sales figures in Belgium than in Norway. Ampicillins show the highest bacterial resistance in general practice in the two countries. Further, there was a close parallel between the sales of ampicillins and the proportion of ampicillin resistance at the general practice level in the two countries.

Only pivmecillinam seems to escape on the emergence of resistance that has affected the aminopenicillins. Our data show that it is one of the main drugs in Norway for treating UTI, and has been so for years. Still, very few uropathogens in Norway are found to be resistant to pivmecillinam. A main reason may be that pivmecillinam is used only in the treatment of UTI, and mainly lower UTI, while the broad-spectrum penicillins are used also in respiratory infections.

Our material at the general practice level also indicates that the other ''simple'' drugs, such as trimethoprim and nitrofurantoin, are still suited as first drug of choice for acute, uncomplicated lower UTI in adult, non-pregnant women. These considerations indicate that local laboratory reports on resistance patterns in uropathogens may not be valid for general practice (16,17). Further, general practitioners who base their empirical treatment on data from local laboratories will overestimate the resistance problem and will tend to use unnecessary broad-spectrum antibiotics.

This persistently high bacterial susceptibility to these drugs may result from the fact that they are used almost exclusively in the treatment of uncomplicated lower UTI in general practice. Their effectiveness is further augmented by the fact that antibiotics used in the treatment of UTI reach very high concentrations in the urine. Consequently, they may still be effective even if the bacteria are classified as resistant, as the definition of resistance by the laboratories is based mainly on the attainable serum levels (18).

We conclude that the impact of the sale of antimicrobial drugs on resistance in uropathogens seems less than expected at the general practice level, even though local microbiological reports mention fairly high antibiotic resistance data. General practitioners must be conscious that resistance data from bacteriological laboratories must be considered critically. Changes in empirical treatment strategies should be based only on data from surveys done in a general practice setting. Better adapted methods to follow-up

bacterial resistance evolution in general practice are needed.

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