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Which antibiotics are used in urology worldwide

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Abstract

A literature search of meta-analyses and reviews on the use of antibiotics in urology was made, and papers included were reviewed. The use of antibiotics in certain urological conditions and the clinical results obtained are discussed in light of these meta-analyses and reviews. The results of the Global Prevalence of Infections in Urology studies on usage of antibiotics for nosocomially acquired urinary tract infections and for prophylaxis before urological interventions are also reviewed and compared with international guideline recommendations.

Although there are no precise data on the amount of consumption of antibiotics in urology, the papers reviewed shed light on the variety of antimicrobial agents used for urinary tract infections. The raising resistance to antibiotics and a relatively high non-compliance with guidelines recommendations emerge as important issues for consideration.

Summary of recommendations

General consumption of antibiotics is increasing worldwide (36% between 2000 and 2010). The highest increases are for cephalosporins, broad-spectrum penicillins and fluoroquinolones, which are the most frequently used antibiotics in urology. This rise is associated with an increase in resistance rates globally, although variations are observed between countries. Non-compliance with national and international guidelines, high rates of non-prescription antibiotic use in certain regions are main causes of this development. These facts underline a major threat to public health.

1 Introduction

Urinary tract infections are one of the most frequent infections resulting in the use of a remarkable amount and a broad variety of antibiotics worldwide. Although the prescription and consumption of antibiotics worldwide can be traced by various means, data documenting the amount of antibiotics used in urology only is unfortunately not available.

An overall estimation of the use of antibiotics in urological practice requires particular consideration of certain issues. Published studies and surveillance programmes have reported on the general consumption of antibiotics globally and regionally [1], [2], [3]. The use of a certain group of antibiotics for a given time interval, in a specific region or country can also be traced and documented [4], [5], [6]. Increased antibiotic use is reported to be associated with increased antibiotic resistance [7]. However, there is no direct evidence indicating that a specific antibiotic is used for the treatment of a specific urologic condition. The use of different methods to measure the amount of antibiotics prescribed (DDD vs. standard units) complicates estimations of antibiotic use, as well [8]. Of concern, there are areas where consumption is not limited with prescription [8], [9]. We aimed to find out which antibiotics are used more frequently in urology and which doses of these antibiotics were preferred. We also searched for a general trend in the amount of consumption of antibiotics in urology.

2 Methods

Given these two facts – i.e. lack of specific data on the amount of consumption of antibiotics in urology and the obvious relationship between use of antibiotics and development of resistance – there are several sources to retrieve information about the use of antibiotics in urology:

1. Studies analyzing the development of resistance to antibiotics

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2. Meta-analyses and review articles about antimicrobial treatment of various urological infections
3. Guidelines for the treatment/prophylaxis of urological infections
4. Prevalence and surveillance studies on infections in urology

Although these sources give indirect information, they are useful aids for estimating the use of antibiotics in urology, and they were reviewed to retrieve information about the use of antibiotics in urology.

Two separate systematic literature searches were performed to address the first two options mentioned above:

2.1 First systematic literature search

A systematic literature search was performed for publications between January 1990–January 2016 in MEDLINE with the following key words: “Anti-Bacterial Agents”[Mesh] AND “Prescriptions”[Mesh]) OR “Prescription Drug Overuse”[Mesh]) OR “Drug Prescriptions”[Mesh]) AND “Urology”[Mesh]) OR “Urology Department, Hospital”[Mesh])).

This search yielded 36 results. Fourteen of these publications were excluded because they were not in English; three more sources were excluded due to the lack of an abstract. After reviewing the 19 abstracts available, 14 were found to be non-relevant, i.e. not analyzing the usage or consumption of antibiotics. The remaining 5 were included in the evaluation [10], [11], [12], [13], [14].

None of these studies was a meta-analysis or systematic review.

2.2 Second systematic literature search

A second literature search was performed for publications between January 1990–January 2016 in MEDLINE with the following key words: ("Anti-Bacterial Agents"[Mesh]) AND "Urinary Tract Infections" [Mesh] with a filter to include only meta-analyses.

This search yielded 38 results. Six of them were not in English and were excluded. Three papers were not about urological interventions, 9 were on pediatric patients and 6 studies evaluated the efficacy of single agents. Two other studies were found irrelevant to the search topic. After excluding these studies the remaining 12 meta-analyses and reviews were included and the data obtained from each study were discussed in the relevant sections of our review [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26].

Major guidelines for the treatment of urological infections were also reviewed to address the third option [27], [28]. Results obtained from the Global Prevalence study on Infections in Urology (2003–2014) were also reviewed. These studies were already retrieved during the first search [10], [12], [13]. A recently published report on adherence to the EAU Guidelines on the use of prophylactic antibiotics and a surveillance study which included patients from nine European countries and Brazil were also included [29], [30].

Data on the use of antibiotics could be extracted only for certain clinical conditions. These conditions and antibiotics used are listed and analysed below.

3 Results

Data on the use of antibiotics worldwide suggest a general trend towards an increase in time, favouring some groups of antibiotics over others. Van Boeckel et al. reviewed the consumption of antibiotics in 71 countries between 2000 and 2010 by analysing national sales data [8]. Their search of PubMed for articles up to 2014 using the search terms “antibiotic”, “utilization”, and “global” or “countries” revealed only one review published in 1987. However, their review on 16 groups of antibiotics revealed that utilisation of antibiotics increased by 36% between 2000 and 2010. The highest increases in this period were for cephalosporins, broad-spectrum penicillins and fluoroquinolones. They found out that India, China, and the USA were the three largest consumers of antibiotics. These authors noticed that antibiotic consumption was stable or moderately increasing in this period in high-income countries while the increase was substantial in developing countries. Rates of antibiotic use per person were higher in the USA compared to most European countries. Another finding was that there were different trends for different classes of antibiotics, across countries. The use of glycopeptides, carbapenems, polymixins, and monobactams increased in many countries while increases in the consumption of cephalosporins

and fluoroquinolones were observed mostly in middle-income countries (India and China). Unfortunately, the data van Boeckel et al. analysed covers only pharmaceutical sales distribution channels, which don't reflect the whole market activity in some countries. True consumption could only be estimated in this situation. Moreover, this type of data doesn't yield information about the indications for antibiotic use. Non-prescription use of antibiotics, which may amount to 19–100% of antimicrobial use outside of northern Europe and North America [9], further complicates these estimations.

3.1 Asymptomatic bacteriuria during pregnancy

Widmer et al. searched the Cochrane Pregnancy and Childbirth Group's Trials Register and reference lists of identified articles for randomized and quasi-randomized trials comparing antimicrobial therapeutic regimens that differed in duration [particularly comparing single dose with short course (three to seven days) regimens] in pregnant women diagnosed with asymptomatic bacteriuria [15]. Their review included 13 studies, involving 1,622 women. The antimicrobial agents used were fosfomycin trometamol, amoxicillin and nitrofurantoin.

3.2 Antibiotics for prophylaxis

Garcia-Perdomo et al. reviewed PubMed, CENTRAL and EMBASE to estimate the efficacy of antibiotic prophylaxis to prevent UTI in patients undergoing cystoscopy [16]. Their search ended up with seven randomized controlled trials with a total of 3,038 patients. The antibiotics used were ceftriaxone 1 g (2,284 pts), levofloxacin 500 mg (276 pts), cefoperazone 1 g (200 pts), gentamicin 120 mg (161 pts), norfloxacin 400 mg (126 pts), fosfomycin trometamol 3 g (60 pts) and sparfloxacin (47 pts). The authors concluded that prophylaxis couldn't be recommended for cystoscopy. However, GPIU Studies revealed that prophylactic antibiotics are used in 46.3% of patients undergoing cystoscopy; with ciprofloxacin, 2nd generation cephalosporins and cefotaxime in the order of preference [10].

Roberts et al. performed a meta-analysis of studies on the baseline prevalence of antimicrobial resistance among patients undergoing prostate biopsy by using Cochrane, MEDLINE, EMBASE and CINAHL databases [17]. In the nine studies which were included and where antibiotic prophylaxes were detailed, ciprofloxacin 1000 mg oral, ciprofloxacin 500 mg oral plus amoxicillin/clavulanate IV plus AMK, ceftriaxone, gentamicin, trimethoprim/sulfamethoxazole, meropenem, levofloxacin were the preferred antibiotics. Ciprofloxacin was found to be the most frequently used antibiotic (36%), followed by nitrofurantoin (31%) in the GPIU Study [10].

Green et al. searched CENTRAL, PUBMED, LILACS and relevant conference abstracts for randomized controlled trials on prophylaxis in renal transplant patients and performed a meta-analysis [18]. Their meta-analysis included 545 patients from six trials. While they concluded that prophylaxis reduced bacteriuria and sepsis in this specific patient group, the antibiotics used were TMP/SMX 160/800 mg (X1 or X2), ciprofloxacin 250 mg (X1), ampicillin 250 mg (X1), cephalexin 250 mg. (X1). The duration of the antibiotic regimen varied between one month and 8.5 months (average; maximum period not mentioned).

Latthe and co-workers searched Cochrane Central Register of Controlled Trials, MEDLINE, CINAHL, TRIP LILACS, and the National Library for Health for randomized controlled trials on prophylactic antibiotic in patients undergoing urodynamics [19]. They identified eight randomized controlled trials with 995 patients. Although the studies were reportedly of low quality and methods were poorly described, they concluded that prophylaxis reduced the risk of significant bacteriuria after urodynamic studies. The antibiotics preferred in the reviewed trials were: trimethoprim, nitrofurantoin, augmentin, ciprofloxacin, norfloxacin, and cinoxacin. All were used as a single dose per day for periods varying between one and five days.

3.3 Uncomplicated UTI

Knottnerus et al. performed a network meta-analysis of randomized trials on the effectiveness of antibiotics for uncomplicated UTI [20]. They identified twelve studies comparing different antibiotics with different treatment regimes. The antibiotics and the regimens included in these studies are summarized in Table 1. The authors reported a higher efficacy for ciprofloxacin and gatifloxacin treatment in patients with uncomplicated UTI.

Table 1: Studies on antibiotics for uncomplicated UTI (adapted from Knottnerus et al.[20])

Randomized trials	First author (year)	(N) patients
Ciprofloxacin 250 mg b.i.d. or TMX 160/800 mg or Norfloxacin 400 mg b.i.d. (285 pts)	Arredondo-Garcia (2004)	285 pts
Pivmecillinam 400 mg t.i.d. or Sulfamethiazole 1 g b.i.d.	Bjerrum (2009)	175 pts
Prulifloxacin 600 mg s.d. or Pefloxacin 2X 400 mg s.d.	Cervigni (2003)	231 pts
Nitrofurantoin 100 mg q.i.d. or placebo	Christiaens (2002)	78 pts
Pivmecillinam 200 mg b.d. or Pivmecillinam 200 mg t.i.d. or Pivmecillinam 400 mg b.d. or placebo	Ferry (2007)	1,143 pts
TMX 160/800 mg or nitrofurantoin 100 mg b.d.	Gupta (2007)	308 pts
Amoxicillin/Clavulanate 500/125 mg b.d. or Ciprofloxacin 250 mg b.d.	Hooton (2005)	322 pts
Gatifloxacin 400 mg s.d. or Gatifloxacin 200 mg s.d. or Ciprofloxacin 250 mg b.d.	Naber (2004)	1,102 pts
Pivmecillinam 400 mg b.d. or Norfloxacin 400 mg b.i.d.	Nicolle (2002)	901 pts
Ciprofloxacin 500 mg qid or Trimethoprim/Sulfamethoxazole 160/800 mg	Park (2007)	65 pts
Gatifloxacin 400 mg s.d. or Gatifloxacin 200 mg s.d. or Ciprofloxacin 10 mg b.d.	Richard (2002)	673 pts
Fosfomycin 3 g s.d. or Nitrofurantoin 50 mg q.i.d.	Van Pienbroek (1993)	231 pts

Katchman et al. performed a meta-analysis to compare the efficacy and safety of short-term (3 days) antibiotic treatment of uncomplicated cystitis in adult non-pregnant women with longer (5 days or longer) treatment [21]. They searched The Cochrane Library, the Cochrane Renal Group's Register of trials, EMBASE, and MEDLINE for randomized controlled trials comparing two different regimes. Thirty-two trials and 9,605 patients met the inclusion criteria. They concluded that antibiotic therapy for 3 days is similar to prolonged therapy in achieving symptomatic cure for cystitis, while the prolonged treatment is more effective in obtaining bacteriological cure.

Leibovici et al. reviewed 25 trials with 2,397 patients, comparing single dose treatment with conventional treatment of UTI [22]. Amoxicillin, TMP/SMX, and various oral cephalosporins were used in these trials. The authors concluded that single dose treatment of UTI is less effective than conventional treatment.

The ARESC Study evaluated the resistance rates of microorganisms to antimicrobials in 4,264 female patients with cystitis [30]. The authors reported that fosfomycin, mecillinam, and nitrofurantoin have preserved their in vitro activity in all countries investigated. However, the prescription rates of these antibiotics were not reported in this study.

3.4 Complicated UTI

Bai et al. searched the PubMed, EMBASE, and the Cochrane Library for published randomized controlled trials (RCTs) that compared the efficacy and safety of ertapenem with ceftriaxone for the treatment of complicated infections including complicated urinary tract infections (cUTIs) [23]. Eight RCTs, involving 2,883 patients, were included in this meta-analysis which concluded that Ertapenem is as efficient and safe as Ceftriaxone for the treatment of complicated UTI.

Singh et al. selected three antimicrobial drugs (doripenem, levofloxacin, and imipenem-cilastatin) for their meta-analysis on antimicrobial treatment in complicated UTI [24]. The estimated eradication rates were

comparable (81%, 79%, and 80.5% consecutively).

Eliakim-Raz et al. reviewed all randomized controlled trials comparing treatment periods of ≤7 days and >7 days in acute pyelonephritis and septic UTI [25]. In the eight trials they included in their meta-analysis, the antibiotics used were ciprofloxacin (626 pts), levofloxacin (1,420 pts), ceftriaxone + cefixime (304 pts), fleroxacin (54 pts), pivampicillin/pivmecillinam (77 pts) and ampicillin (42 pts).

Pohl searched the Cochrane Renal Group's specialized register, the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE to assess whether the mode of administration of antibiotic therapy for severe UTI has an effect on cure rate, re-infection rate and kidney scarring [26]. No restriction of age and sex was applied in this search. Fifteen RCTs (1,743 pts) were included. Pohl concluded that there is no evidence suggesting that oral antibiotic therapy is less effective for treatment of severe UTI than parenteral or initial parenteral therapy.

3.5 Management of Chlamydia Trachomatis infections

Dale et al. conducted a survey for their audit on the management of Chlamydia infections in 31 Genitourinary Medicine Clinics in the UK [14]. They reported that antibiotic prescription for these infections were largely in accordance with the UK National Guidelines, the guidelines, which are Doxycycline 100 mg b.d. for 7 days or Azithromycin 1 g orally in a single dose.

3.6 Global Prevalence studies in Infections in Urology (GPIU) and the EAU Guidelines

Probably the best available data on antibiotic use in urology clinics can be retrieved from Global Prevalence studies on Infections in Urology (GPIU), reported by Bjerklund-Johansen et al. The first two publications reported the prevalence, microorganisms and resistance of microorganisms in nosocomially acquired urinary tract infections (NAUTI) [5], [6], [12], [13]. The first two years of this study (PEP and PEAP) included 4,706 of the 6,033 hospitalized patients on study days; 2,617 were receiving antibiotics (56%); 26% of the antibiotic use was for a microbiologically proven UTI, 21% for a clinically suspected, but not microbiologically proven UTI, 7% for other infections, and 46% for prophylaxis [12], [13]. Among 686 of the 727 patients with NAUTI the largest group was asymptomatic bacteriuria (29%) followed by cystitis (26%), pyelonephritis (21%), and urosepsis (12%). The most commonly used antibiotics for the treatment of these infections were fluoroquinolones (in 35% of cases), cephalosporins (in 27% of cases). Sixteen percent of the patients received penicillins, mostly aminopenicillins with beta-lactamase inhibitor. Aminoglycosides (in 15% of patients) and co-trimoxazol in 8% followed these antibiotics. Trimethoprim alone was given in less than 1% of cases. Other antibiotics given were imipenem (6%), vancomycin (2%), antifungal drugs (2%), and tetracyclines (2%). Important findings of these studies are regional differences in terms of pathogen spectrum, susceptibility patterns, as well as the differences in prophylactic regimens.

Antibiotics used for prophylaxis in urology departments were analyzed by Çek et al. [10]. The authors reported data on 13,723 patients enrolled in the GPIU studies between 2005 and 2010. Of these patients, 8,178 received antibiotics on the study days; 3,898 (47.7%) for prophylaxis. The three most frequently used prophylactic antibiotics for various specific conditions are listed in table 2 together with major guideline recommendations for these conditions. Non-adherence with EAU guidelines in the application of prophylaxis in procedures like cystoscopy, URS, TUR-BT, and clean operations are evident in this table. Variation in antimicrobial prophylaxis in urological practice is recently reported by Mossanen et al. [31]. The authors reported a wide variance of compliance rates with AUA Best Practice Statement, between 0.6% for radical cystectomy and 97% for shock wave lithotripsy. Cai et al. compared the data for 3,529 urologic procedures performed after implementation of a protocol for antibiotic prophylaxis according to the EAU Guidelines, with data for 2,619 procedures performed before the implementation of this protocol. They showed that adherence to EAU guidelines on antibiotic prophylaxis reduced antibiotic usage without increasing post-operative infection rate and lowered the prevalence of resistant uropathogens [29].

Extracted Table: Table 2

As Bell et al. pointed out 90% of antibiotics in Europe are used for non-hospitalized patients; however, data on the use of antimicrobials and resistance patterns are overwhelmingly about hospitalized patients [7]. This gap will hopefully be filled by future studies in this area.

4 Further research

There are various reasons for the overuse of antimicrobials. One of the reasons is non-compliance with guidelines. Hulscher and co-workers reviewed antibiotic prescribing in hospitals from a social and behavioral point of view [32]. They discussed the determinants that influence the use of antibiotics in hospitals, in an attempt to improve strategies for better prescription policies. Further research should definitely concentrate on factors influencing prescription habits and aim to increase compliance with guidelines for the use of antimicrobials in urology.

5 Conclusions

Antibiotic consumption is increasing globally. Although there is no direct evidence for the share of prescriptions in urology, increasing resistance rates confirm that more antibiotics are used in urology, too.

Reports on the use of antibiotics in urology are generally from secondary and tertiary centers. This may be regarded as a bias while assessing the amount and variety of antibiotics used in urological infections. The influence of non-prescription use of antibiotics in certain geographical areas cannot be assessed.

Compliance with guidelines is rather low, although adherence with guidelines has been shown to result in lower prevalence of resistant microorganisms, as well as diminishing treatment costs.

5.1 Treatment of asymptomatic bacteriuria

The most preferred antibiotics are fosfomycin, amoxycilin, and nitrofurantoin.

5.2 Prophylaxis

Various investigations have evaluated the value of prophylaxis in cystoscopy using fluoroquinolones, cephalosporins, Fosfomycin, etc. However, prophylaxis for diagnostic cystoscopy is not recommended by EAU and AUA.

Ciprofloxacin is the most frequently used antibiotic for prophylaxis before TRUS-Bx of the prostate. This finding is supported by the data of GPIU studies (ciprofloxacin in 36% of patients, followed by nitrofurantoin in 31%) [3].

Renal transplantation is probably the single procedure, which is associated with the longest application of antibiotic prophylaxis (TMP/SMX, Ciprofloxacin and Ampicillin), extending up to 8.5 months [11].

5.3 Uncomplicated UTI

Various antibiotics and various regimens have been evaluated (see table 1). Single dose treatment with amoxicillin and trimethoprim-sulfamethoxazol seems to be inferior to longer regimens of 3–7 days.

5.4 Complicated UTI

Carbapenems (ertapenem) are shown to be as efficient and as safe as ceftriaxone. No route of administration (oral vs. parenteral) has been shown to be superior.

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