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Diagnosis and Empirical Treatment of Urinary Tract Infections in Urologic Outpatients

Andreas Eisenhardt[a, b] Katharina Schneider[a, b] Herbert Hirche[c]
Hildegard Lax[c] Boris Hadaschik[b] Christian Rehme[b] Jan D. van Gool[c]

[a]Urologic Outpatient Clinic PURR, Mülheim an der Ruhr, Germany; [b]Department of Urology, University Hospital Essen, Essen, Germany; [c]Institute of Medical Informatics, Biometry, and Epidemiology, University Hospital Essen, Essen, Germany

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Antibiotic resistance · Antibiotic susceptibility · Bacteriuria · Co-trimoxazole · Fosfomycin

Abstract
Introduction: Due to a continuing increase of bacterial resistance in common uropathogens, we wanted to revisit our standards for the diagnosis and treatment of lower urinary tract infections, in the setting of urological outpatient care in a conurbation in Germany. ***Patients and Methods:*** All subjects presenting with significant bacteriuria at our urology clinics in Mülheim, Germany, in 2011 were included. Comorbidity, bacterial species, urinary tract symptoms, and empirically prescribed antibiotics were taken from the patients' records. ***Results:*** In 2011, a total of 1,324 patients were included (793 female, 531 male). Of the 771 patients with symptomatic bacteriuria, 647 received antibiotic treatment, as well as 116 of 409 patients with asymptomatic bacteriuria. *Escherichia coli* was identified in 60% of the included patients. In 427 *E. coli* infections, bacterial resistance was found in 14% of 316 cases treated with quinolone, in 21% of 53 cases treated with co-trimoxazole, and in only 3% of 58 cases treated with nitrofurantoin. ***Conclusions:*** We found a high use of fluoroquinolones for empirical first-line antibiotics in the treatment of lower urinary tract infections. In our regional setting, antibiotic stewardship needs to be promoted, along national and international guidelines, to avoid unnecessary prescription of fluoroquinolones for empirical treatment.

Introduction

Lower urinary tract infections (UTIs) have the highest prevalence in women. In Germany, in 2012, 7.3% of all women older than 12 years arranged for a medical consultation for signs and symptoms typical of UTI [1]. In our urology clinics (Praxiskliniken Urologie Rhein-Ruhr, Mülheim), in 2011, we counted 1,324 first referrals for the diagnosis and treatment of a possible UTI in patients older than 16 years (531 men, 793 women).

While non-pregnant women with signs or symptoms of a UTI usually will have an uncomplicated cystitis or overactive bladder, male patients with similar symptoms might have a UTI complicated by an infravesical obstruction [2]. On clinical grounds, antibiotic treatment is usu-

karger@karger.com
www.karger.com/uin

Andreas Eisenhardt
Praxiskliniken Urologie Rhein-Ruhr
Schulstrasse 11
DE–45468 Mülheim an der Ruhr (Germany)
a.eisenhardt@pur-r.de

ally started empirically, before colony count, species, and antibiogram of the causative microorganism (MO) are available, which will take 4–5 days.

Escherichia coli can be isolated from the urine in about 77% of patients with an uncomplicated UTI [3]. However, the choice of a first-line antibiotic is becoming more and more difficult, as the resistance rates of *E. coli* and other Enterobacteriaceae to quinolones and co-trimoxazole, often used for empirical treatment, clearly tend to increase year by year in North America as well as in Europe [4–7].

We wanted to investigate our current prescription patterns for empirical antibiotic treatment, when results of urine culture and antibiogram are not yet available, as well as the bacterial resistance rates for the 5 most widely prescribed antibiotics. We also wanted to analyze the steps in the diagnosis of UTIs in our urologic clinics, to see if the time could be shortened between the collection of the urine samples and assessment of both colony count and species of the causative MO. The results might help to decrease the risk of promoting bacterial resistance and increase the efficiency of our current treatment plans for lower UTI.

Patients and Methods

Methods

The inclusion criteria for patients who had been referred to our urology clinics in 2011 were: positive results in a fresh urine sample with the Combur 10 Test® test-strips (Roche Diagnostics Deutschland GmbH, Mannheim, Germany) for the presence of nitrites and/or leukocyte esterase, in an automated photogrammetric procedure (Urisys® 1100, Roche Diagnostics Deutschland GmbH). Urine samples with a negative leukocyte esterase test (LET) in combination with a negative nitrite test were considered to have no significant bacteriuria and excluded from further tests.

In a second step, all urine samples with a positive LET and/or nitrite test were then plated with a 10-µL wire loop on a culture plate with 2 media: Columbia nalidixic acid agar (CAN; selective for Gram-positive bacteria), and MacConkey agar (selective for Gram-negative bacteria). The agar did not contain glucose-6-phosphate. After incubation at 36–40 °C for 24 h, these 2 media yield both a colony count and specific information about the MO that colonized one of the media – Gram-negative or Gram-positive. A third step consisted of a BioRAD® ID-Gram-test for assessment of the colony-forming MO as being purely Gram-positive or Gram-negative, to rule out possible mixed cultures.

The last step consisted of determination of the species of the cultured MO, followed by determination of the minimum inhibitory concentration for a wide range of antibiotics, in 2 sequential automated procedures (Vitek® 2 Compact; www.biomerieux-diagnostics.com).

The parameters collected per patient were: referring physician, fever at referral, UTI symptoms at referral, isolated MO and antibiogram, antibiotic treatment, number of UTIs diagnosed in 2011, and antibiotics used for UTIs in 2011. The following complicating urologic conditions were culled from our records: history of recurrent UTIs, overactive bladder, indwelling bladder catheter, urinary diversion, prostate hypertrophy, prostate carcinoma, urothelial carcinoma, urolithiasis, and renal insufficiency. Only 1 patient had diabetes mellitus type 1.

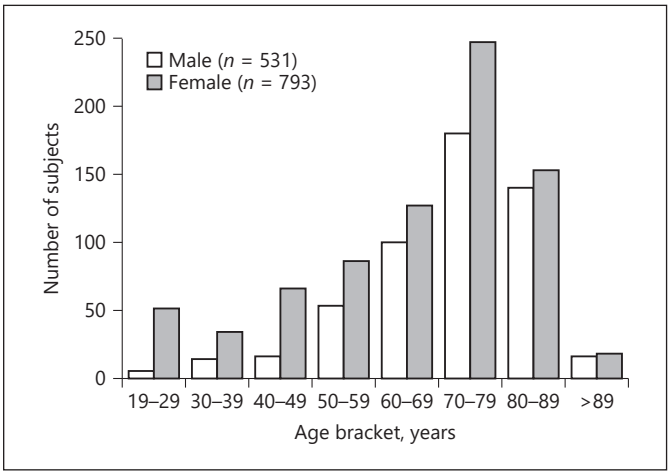

Fig. 1. Patients (n = 1,324) with significant bacteriuria at first referral, versus age and gender.

Data Assessment

All data were made accessible in an anonymized spreadsheet. Statistical analysis was performed with SAS© software (SAS Institute Inc., Cary, NC, USA). The ethics committee of the Medical Faculty, Essen-Duisburg University, approved both the protocol and data assessment for our study in writing, with a waiver for informed consent from individual patients.

Results

Patients and Parameters

Overall, 1,324 patients were included, 793 were female (60%) and 531 male (40%), with an average age of 71 ± 17 years (range 16–100). These 1,324 patients paid 2,484 visits to our urology clinics, 10% of the total number of outpatient visits in 2011 (n = 24,188). Figure 1 presents the numbers of included female and male patients versus age. The prevalences of specific and complicating parameters in the 1,324 included patients are listed in Table 1.

Treatment

On clinical grounds, 647 of 771 patients with symptomatic bacteriuria (84%) received empirical antibiotic treatment at referral, as well as 116 (39%) of 409 with as-

Table 1. Patients with significant bacteriuria, characteristics at first referral, with complicating urologic conditions

Referral characteristics	Male (*n* = 531), *n* (%)	Female (*n* = 793), *n* (%)	Total (*n* = 1,324), *n* (%)
Referral by general practitioner/gynecologist	473 (89)	744 (94)	1,217 (92)
Referral by hospital	27 (6)	32 (2)	59 (4)
Referral by nursing home	31 (5)	17 (4)	48 (4)
Asymptomatic bacteriuria	180 (34)	229 (29)	409 (31)
Symptomatic bacteriuria	260 (49)	511 (64)	771 (58)
No data on UTI symptoms	91 (17)	53 (7)	144 (11)
History of UTI	274 (52)	432 (55)	706 (53
Overactive bladder	26 (5)	106 (13)	132 (10)
Indwelling catheter	171 (33)	66 (28)	237 (18)
Urinary diversion	44 (9)	21 (3)	65 (5)
Prostate hypertrophy	279 (53)	–	279 (21)
Prostate carcinoma	111 (21)	–	111 (8)
Urothelial carcinoma	118 (22)	64 (8)	182 (14)
Urolithiasis	69 (13)	96 (2)	165 (12)
Renal insufficiency	50 (9)	83 (6)	83 (6)

Table 2. Significant bacteriuria at first referral in 2011, empirically treated with oral quinolones, nitrofurantoin, co-trimoxazole, cephalosporin, or fosfomycin (*n* = 792), with prevalences for bacterial resistance to each of 5 first-line choices

Genus and species, row totals (prevalence)	Quinolone	Nitro-furantoin	Co-trimoxazole	Cephalo-sporin	Fosfo-mycin
E. coli: *n* = 476 (60%)	316	58	53	30	19
Bacterial resistance, *n* (%)	45 (14)	2 (3)	11 (21)	7 (23)	4 (21)
K. pneumonia: *n* = 58 (7.3%)	28	12	5	10	3
Bacterial resistance, *n*	2	3	–	1	–
P. mirabilis: *n* = 39 (5.0%)	26	7	2	2	2
Bacterial resistance, *n*	5	6	1	1	1
E. faecalis: *n* = 24 (3.5%)	19	2	1	1	1
Bacterial resistance, *n*	1	1	1	1	–
E. cloacae: *n* = 18 (2.2%)	12	3	3	–	–
Bacterial resistance, *n*	–	–	–	–	–
S. saprophyticus: *n* = 15 (1.9%)	14	–	–	1	–
Bacterial resistance, *n*	–	–	–	–	–
M. morganii: *n* = 13 (1.6%)	11	1	1	–	–
Bacterial resistance, *n*	3	1	–	–	–
S. cohnii: *n* = 10 (1.3%)	6	2	2	–	–
Bacterial resistance, *n*	–	–	–	–	–
K. oxytoca: *n* = 9 (1.1%)	6	1	1	1	–
Bacterial resistance, *n*	–	–	–	1	–
S. Aureus: *n* = 8 (1.0%)	6	1	1	–	–
Bacterial resistance, *n*	2	–	–	–	–
P. aeruginosa: *n* = 7 (0.9%)	7	–	–	–	–
Bacterial resistance, *n*	–	–	–	–	–
S. fonticola/rubidaea: *n* = 7 (0.9%)	4	1	1	1	–
Bacterial resistance, *n*	–	–	–	–	–
Other genera/species: *n* = 108 (14%)	64	23	9	12	–
Bacterial resistance, *n* (%)	14 (22)	6 (26)	2 (22)	4 (33)	–

All treatment periods: 5–7 days. Not included are 16 patients who received ampicillin, tetracycline, or carbapenem.

Table 3. Significant bacteriuria with lower urinary tract symptoms at first referral in 2 subgroups, one with documented historical UTIs (index patients) and one without control patients

Patient groups index/control	Quinolone	Nitrofurantoin	Co-trimoxazole	Cephalosporin	Fosfomycin	Row totals
Index: UTIs in history						
E. coli UTIs, *n*	131	36	37	20	12	236
Resistance, *n* (%)	30 (23)	2 (6)	11 (30)	4 (20)	3 (25)	50 (21)
Resistance, 95% CI	16–30	0.7–19	16–47	6–44	6–57	16–27
Controls: no UTIs in history						
E. coli UTIs, *n*	185	22	16	10	7	240
Resistance, *n* (%)	15 (8)	0 (0)	0 (0)	3 (30)	1 (14)	19 (8)
Resistance, 95% CI	5–13	0–15	0–21	6–65	0.3–58	5–12

Both groups were treated empirically with quinolones, nitrofurantoin, co-trimoxazole, cephalosporin, or fosfomycin, orally, for 5–7 days.

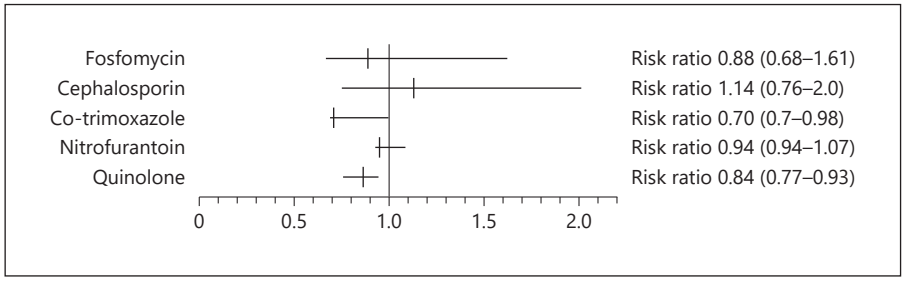

Fig. 2. *E. coli* susceptibility rates in 236 index patients with historical UTI divided by the susceptibility rates in 240 control patients without historical UTI, with 95% CIs, for each of the 5 empirically chosen antibiotic treatments: quinolone, nitrofurantoin, co-trimoxazole, cephalosporin, fosfomycin (Table 3).

ymptomatic bacteriuria (ASB). From the 144 patients without data on UTI symptoms, 29 (20%) received antibiotics empirically. Table 2 lists the isolated MOs, the first-line choices for empirical antibiotic treatment, and the prevalences for bacterial resistance to these antibiotics.

Distribution of Causative MOs

E. coli was isolated in 60% of all patients who received empirical antibiotic treatment, followed by *Klebsiella pneumoniae* (7.4%) and *Proteus mirabilis* (5%). The high prevalence of UTIs with *E. coli* is a key finding in most studies on lower UTIs, and this prevalence varies slightly with the gender ratio in the populations studied [3, 8].

Risk Factors for Bacterial Resistance to Antibiotics

Quinolones were the preferred choice for empirical antibiotic treatment of UTIs in our urology clinics. The largest number of treated UTIs (n = 476, 60%) were caused by *E. coli*. Of the 316 *E. coli* infections empirically treated with quinolones, 45 (14%) turned out to be resistant to quinolones, and in the 53 *E. coli* infections empirically treated with co-trimoxazole, bacterial resistance was demonstrated in 21%. Bacterial resistance was found in only 3% of the 58 *E. coli* infections treated with nitrofurantoin, and in 21% of the 19 *E. coli* infections treated with fosfomycin. The numbers of UTIs caused by *K. pneumoniae* and *P. mirabilis* were too small to render statistically relevant resistance rates for comparing the 5 first-line choices for antibiotic treatment (Table 3).

In patients with documented historical UTIs, usually treated with antibiotics, resistance rates in *E. coli* UTIs were more than twice as high as in patients without historical UTIs, for all antibiotic treatments together (row totals in Table 3). In patients without historical UTIs, quinolones had a resistance rate of 8% (95% CI 5–13), versus 23% (95% CI 16–31) in patients with historical UTIs; for co-trimoxazole these rates were 0% (95% CI 0–21) and 30% (95% CI 16–47), respectively. However, the resistance rate of *E. coli* to nitrofurantoin hardly changed between "no UTIs in history" (rate 0%, 95% CI 0–15) and "UTIs in history" (rate 6%, 95% CI 0.7–19).

We expressed the relative risk (risk ratio) for *E. coli* susceptibility as the ratio of the susceptibility rate among index cases divided by this rate in control cases. A graphical representation of these relative risks for each of the 5 empirically prescribed antibiotics is given

in Figure 2: in the index patients, susceptibility of *E. coli* for co-trimoxazole and quinolone shows a significant decrease compared with control patients (ratio's with 95% CIs <1.00), while the susceptibility for nitrofurantoin remains unchanged. The low number of patients treated with cephalosporin or fosfomycin (Table 3) preclude a meaningful evaluation of differences in these rates between the subgroups without and with historical UTIs.

In our study, the prevalence of historical UTIs, as well as historical antimicrobial use for infections outside the urinary tract, were the most important specific risk factors of multidrug resistance, followed by the prevalences of prostate hypertrophy and indwelling catheters. It is important to note that this study presents evidence on the local resistance rates of *E. coli* to antibiotics – these rates are an important tool for making the right choice for empirical treatment in patients referred with a UTI, while waiting for urine culture results [9], but they will vary between different geographical regions, depending on local patterns in the use of antibiotics, and regional differences in the prevalence of specific uropathogens. Our rates were obtained specifically in outpatients: it follows that rates obtained from hospitalized patients cannot be used for outpatients, and vice versa [10].

Discussion

Empirical Choice of First-Line Antibiotic

Over many years, the susceptibility of *E. coli* to nitrofurantoin (as well as to fosfomycin) has been preserved very well, in association with minimal effects on the human gut microbiome [10–13]. The guidelines for uncomplicated lower UTIs, jointly published by the Infectious Diseases Society of America and the European Society for Microbiology, stipulate that co-trimoxazole cannot be recommended for empirical treatment where local resistance rates exceed 20%. The same caveat applies to quinolones where local resistance rates are above 10% [10]. According to these guidelines, the resistance rates of *E. coli* for the antibiotics in Table 2 (quinolones, nitrofurantoin, co-trimoxazole, cephalosporin, fosfomycin) direct the empirical choice of an antibiotic in patients referred with a lower UTI. In patients with a history of recurrent UTIs, available prior urine cultures and resistance rates should also be used when choosing the appropriate antibiotic for a new UTI [9].

Antibiotics and Bacterial Resistance

In our urologic clinics, the empirically chosen first-line antibiotics had substantial resistance rates, except nitrofurantoin – the rational use of antibiotics always has to account for bacterial resistance rates in the local population of patients. Prescriptions for antibiotics in clinical medicine use about 20% of the annual global antibiotic production. The remaining 80% is applied in pig farms, poultry farms, calves and cattle feedlots, and fish farms. The classes of antibiotics prescribed in these (mega-) farms are similar to those prescribed in human medicine: tetracyclines, aminoglycosides, β-lactams, macrolides, sulfonamides, lincosamides [14, 15].

Environments known for heavy use of antibiotics constitute an increasing risk for exposure to antimicrobial-resistant bacteria [16–19]. Despite bans on the use of antibiotics for growth promotion in animals (European Medicines Agency, 2006; US Food and Drug Administration, 2017), antibiotics are still prescribed for prophylaxis, as well as for metaphylaxis of herds of animals in mega-farms, to be added to feed and water in subtherapeutic doses and for longer periods of time. Antibiotic-resistant bacteria associated with farm animals are easily transmitted to humans via food chains, and in the form of animal waste they are widely disseminated as environmental pollutants [14, 15].

Balance between Condition and Treatment

Patterson coined the term "collateral damage" for the ecological adverse effects of antimicrobial therapy: selection of drug-resistant MOs or infection with multidrug-resistant bacteria [10, 20]. The use of cephalosporin has been associated with the advent of vancomycin-resistant enterococci, extended-spectrum β-lactamase-producing *K. pneumoniae*, and β-lactam-resistant *Clostridium difficile*. Using quinolones has been linked to infections with methicillin-resistant *Staphylococcus aureus* and quinolone-resistant *Pseudomonas aeruginosa* [20].

The Case for Nitrofurantoin

From 1953, nitrofurantoin was prescribed widely, until co-trimoxazole (trimethoprim-sulfamethoxazole) became available. After 2000, when resistance to co-trimoxazole started to increase, several guidelines repositioned nitrofurantoin as first-line choice for treatment of lower UTIs.

Nitrofurantoin is basically bacteriostatic, but at high concentrations it also has a bactericidal effect [21], for Gram-positive as well as Gram-negative bacteria, with the exception of some *Klebsiella* spp, *P. aeruginosa*, and most

Proteus spp. Although pharmacokinetic studies are old, we have solid evidence for a bioavailability of 80%, with very low serum levels, and active concentrations confined to the lower urinary tract. Nitrofurantoin is not recommended for treatment of upper UTIs, and also not for UTIs in men, because of possible concomitant prostatitis.

Gastrointestinal side effects were reduced by roughly 50% with the advent of the macrocrystalline formulation. A recent meta-analysis [11] found no difference between nitrofurantoin 100 mg 2 dd for 5–7 days and comparators (co-trimoxazole, ciprofloxacin, amoxycillin) for side effects or for clinical cure [11].

Severe adverse effects, pulmonary fibrosis, and hepatotoxicity, have been documented almost exclusively in patients who received low-dose nitrofurantoin prophylaxis over 6–12 months or longer. These adverse effects, presumed to be autoimmune reactions, proved reversible when and if detected early [11]. Dosage adjustment for patients with moderately impaired kidney function is not necessary.

The Case for Fosfomycin

Fosfomycin tromethamine, approved in Europe and the USA for uncomplicated UTIs, is a bactericidal antibiotic interfering with cell wall synthesis in both Gram-positive and Gram-negative bacteria. After oral administration, fosfomycin tromethamine is converted to fosfomycin (40% bioavailability) and eliminated by glomerular filtration, with a half-life of 4–8 h. Fosfomycin reaches clinically relevant serum and tissue concentrations, bactericidal against Gram-positive cocci and many Gram-negative bacteria; fosfomycin also has antimicrobial activity against bacteria in biofilms. Bactericidal activity in cerebrospinal fluid is reduced. [13].

Randomized controlled trials in female subjects with lower UTIs showed no differences in clinical and microbiological cure rates, nor in side effects, between oral fosfomycin and comparators. In a few studies in pregnant women, fosfomycin had significantly fewer side effects than comparators.

The usual oral dose of fosfomycin is 3 g, as a single dose for the treatment of uncomplicated UTI. This dose rapidly results in high concentrations in the bladder and urine for 72–84 h, and is clinically as effective as a 7- to 10-day treatment with nitrofurantoin, co-trimoxazole, or norfloxacin. Dosage adjustment for patients with moderately impaired kidney function is not necessary [12, 13].

The resistance rate for fosfomycin in *E. coli* UTI reported in this paper (Table 2) does not fit the published data on fosfomycin susceptibility, probably because glucose-6-phosphate was not added to the agar culture plates in our study. The small number of patients treated with fosfomycin might also play a role.

Diagnostic Steps

When dealing with a presumptive diagnosis of UTI, it is important to know that the LET can be false negative, compared to a classical white blood cell count in a urine sediment, in the presence of, for example, glucosuria, proteinuria, antibiotics, and high specific gravity. Under these conditions, the photogrammetric procedure of the LET used in this study will lose sensitivity. Adding a negative nitrite test to the conditional first step does not increase the sensitivity of the combination: with both tests negative, significant bacteriuria can be ruled out with a sensitivity of 68–88% [22]. For a faster service, without losing diagnostic performance, the LET and nitrite tests could both be omitted.

After 24 h of incubation at 36–40 °C, the CFU of the CNA medium inoculated with a patient's urine will read positive or negative for significant bacteriuria with a Gram-positive MO, and the MacConkey agar for a Gram-negative MO. This offers a more specific choice of a first-line antibiotic than just empiricism. Adding a third medium, specific for *E. coli*, would reveal the species of the offending MO in about 60–70% of all cases, within 24 h.

Conclusions

Collateral damage should be avoided when treating uncomplicated lower UTIs, which have a very small risk of progression to upper tract UTI or sepsis. Moreover, in placebo-controlled studies for treatment of uncomplicated UTIs, clinical cure (spontaneous resolution) occurred for placebo in about 50% of female participants, although symptoms did persist in a number of cases [3, 23, 24]. This is not a plea to withhold antibiotic treatment of lower UTIs, but to aim for the best balance between the severity of the condition and the choice of empirical antibiotic treatment. There is evidence that symptomatic treatment with ibuprofen can be used, within a strategy of delaying the empirical prescription of antibiotics until the sensitivity tests for the causative MOs are available [25, 26].

More than 10 years after the surveillance study by Naber et al. [3], in a German survey among urologists concerning guideline adherence for antibiotic treatment of lower UTIs, 80% of the participants declared that they

follow the guidelines, which contrasts markedly with the high rate of prescription for fluoroquinolones and co-trimoxazole in our data (Table 2), as well as with other publications about German guideline adherence in treating UTIs [2, 27]. In this context, antibiotic stewardship remains a common issue in the treatment of UTIs, and it needs more than just a smartphone app to be implemented successfully [28, 29].

Limitations of this Study

Our retrospective study has insufficient data on comorbidity for the group with ASB (n = 409), although 39% of this subgroup did receive empirical antibiotic treatment at referral. A 2019 update of the 2005 IDSA guideline [10], published specifically for the management of ASB [30], gives new recommendations on screening for and treatment of ASB, for the most important categories of comorbidity, including those that were not addressed in the 2005 guideline.

Statement of Ethics

The Ethics Committee of the Medical Faculty, Essen-Duisburg University, approved both the protocol and data assessment for our study in writing, with a waiver for informed consent from individual patients.

Disclosure Statement

Dr. Andreas Eisenhardt is lecturer/consultant for Janssen Cilag, Ipsen Pharma, Apogepha and Medac. Dr. Boris Hadaschik is consultant/lecturer for Lightpoint medical, Astra, Astellas, Bayer, Janssen-Cilag, and received a research grant of the German Cancer Aid. Dr. Katharina Schneider, Dr. Herbert Hirche, Dr. Hildegard Lax, Dr. Christian Rehme, and Dr. Jan D. van Gool do not have any financial disclosures to declare.

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Author Contributions

Dr. Andreas Eisenhardt took part in study design, data acquisition, statistical analysis, interpretation of the data and writing of the manuscript. Katharina Schneider contributed to study design, data acquisition, statistical analysis, and interpretation of the data. Dr. Herbert Hirche took part in statistical analysis, interpretation of the data, and writing of the manuscript. Hildegard Lax contributed to study design, statistical analysis, interpretation of the data, and writing of the manuscript. Dr. Boris Hadaschik contributed to study design, interpretation of the data, and writing of the manuscript. Dr. Christian Rehme contributed to statistical analysis, data interpretation, and writing of the manuscript. Dr. Jan D. van Gool took part in study design, statistical analysis, interpretation of the data, and writing of the manuscript.

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