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## **Simplified antibiotic guidelines in urology are associated with decreased multidrug-resistant Enterobacterales**

**Short title:** Antimicrobial stewardship in urology

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### **Statements and declaration**

**Funding source:** None; the study was done as part of routine work.

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**Data sharing:** The data used during the current study are available from the corresponding author on reasonable request

**Ethics approval:** The antibiotic audit was sponsored by the French National Health Agency.

**Informed consent:** The patients or their relatives provided written consent for computerization of their anonymized personal data for hospitalization and clinical research purposes according to the French national ethics recommendations. Our database was legally declared to the French National Commission on Informatics and Liberty (number 2224348v0).

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## Highlights

- We propose a simplified therapeutic guideline for UTI in urology
- No previous study has audited antibiotic prescriptions for bacteremia in urology
- Patients with bacteremia presented with nosocomial UTI due to multidrug-resistant (MDR) bacteria
- Adherence to simplified therapeutic guideline was significant and associated with decreased MDR bacteria in blood culture.

## Abstract

### Purpose

A simplified therapeutic guideline (STG) was established in our urology ward in 2019 for urinary infections. **Our aim was to describe the level of physician adherence to STG** and the impact of a limited number of antibiotic compounds on the rate of multidrug-resistant (MDR) bacteria. As guidelines should improve patient care, unfavorable outcomes were also reported.

### Methods

The STG for community-acquired and nosocomial urinary infections, including six antibiotics, was established in November 2019 and has been officially applied since January 2020. Treatment duration has to be  $\leq 14$  days. We conducted a before-after study to measure physician adherence to the STG for bacteremia treatment between January 2017 and December 2022. Adherence was defined as exclusive use of STG antibiotics. All isolated bacteria from blood cultures were recorded, including MDR Enterobacterales, defined as

AmpC  $\beta$ -lactamase- or ESBL-producing strains. Unfavorable outcomes were defined as uncontrolled infection, a second surgical procedure, ICU requirement, and/or death.

### Results

Seventy-six cases of bacteremia occurred between January 2017 and December 2019, and ninety between January 2020 and December 2022. The main comorbid condition was urological cancer (46%). The main reason for surgery was ureteral stent (32%). **Antibiotic management in accordance** with STG increased from 18% to 52%,  $p < 0.001$ , and treatments  $> 14$  days decreased from 53% to 28%,  $p < 0.001$ . MDR Enterobacterales bacteremia was reduced from 52% to 35%,  $p = 0.027$ . The rate of unfavorable outcomes was unchanged.

### Conclusion

STG adherence in urology was satisfactory and associated with reduced MDR Enterobacterales bacteremia.

### Introduction

Antimicrobial stewardship programs (ASPs) have been implemented for two decades, the primary target being the reduction of antibiotic misuse and an associated decrease of multidrug-resistant (MDR) bacteria [1,2]. Currently, ASPs include a wide range of complementary multidisciplinary approaches, in which antibiotic guidelines and audits with feedback are key [1,3]. We have found that real-time audits and immediate feedback information can lead to simplified therapeutic guidelines (STGs), allowing a reduction of antibiotic prescriptions at the institutional level, as well as improved quality of antimicrobial treatments at the patient level [4]. However, transforming national and/or international recommendations into STGs can be a complex task, since antibiotic choices are based on patient recruitment, clinical practices, and local bacterial resistance data [5].

The rise of MDR Enterobacterales has been acutely observed in the area of urinary tract infections (UTIs) [6]. Because most complicated UTIs are referred to urology departments, and because several urological procedures require JJ stent and/or bladder catheter, healthcare-associated infections are frequent, increasing the risk of successive antibiotic treatments, which may lead to Extended-Spectrum Beta-Lactamase-producing Enterobacterales (ESBL-E) [7-9]. That is why adapted ASM strategies in the urological community are mandatory [10]. Accordingly, in 2019 we introduced simplified therapeutic guidelines for UTI in our urology wards, making a distinction between community-acquired and healthcare-associated infections (HCAI). As ASPs were designed to combat the emergence of MDR bacteria, **our aim was to describe the level of physician adherence to STG, and to determine the impact of a limited number of antibiotic compounds on the rate of multidrug-resistant (MDR) bacteria in urology.**

### Methods

This was a single center, before-after study in the urology department of a university hospital auditing all antibiotic therapies for adult patients presenting with bacteremia during their stay in the ward. Our database was officially declared to the French National Commission on Informatics and Liberty (number 2224348v0).

#### ***Simplified therapeutic guideline***

The STG for UTI in urology was discussed with our surgical team and infectious diseases (ID) specialists during the final months of 2019. It was based on epidemiological data regarding

bacterial resistance, which showed a high rate of MDR Enterobacterales in the facility, and included no more than six drugs. In empirical antibiotic therapy, cefotaxime was the drug of choice for community-acquired UTI, and in the event of healthcare-associated infection (HCAI), it was piperacillin-tazobactam. Amikacin could be added in the to types of infection for severe disease, and imipenem was recommended in cases of septic shock. Depending on *in vitro* susceptibilities, antibiotic reassessment proposed cotrimoxazole or ciprofloxacin. In case of resistance to these two drugs, ID advice was required. The duration of the antimicrobial treatments could not exceed 14 days.

### **Bacteriological study**

Blood cultures were collected directly during the venipuncture procedure in aerobic (Bact/AERT® FA Plus, bioMérieux, France) and anaerobic (Bact/AERT® FN Plus, bioMérieux, France) blood culture bottles and incubated in a BACT/ALERT® Virtuo® (bioMérieux, Marcy l'Étoile, France). Positive blood cultures were routinely subjected to Gram staining and sub-cultured on appropriate solid culture media. Pathogen identification was performed on overnight subcultures using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS, VITEK® MS system, bioMérieux, France) according to the manufacturer's recommendations. Susceptibility to antibiotics was tested by the disk diffusion method on Mueller–Hinton agar (bioMérieux, Marcy l'Étoile, France), and ESBL production was detected according to the 2019 guidelines of the CA-SFM/EUCAST [11]. Growth of *Bacillus*, *Corynebacterium*, and *Micrococcus* species and coagulase-negative staphylococci in single blood cultures was considered to be due to contaminants, and these cultures were consequently excluded.

Multidrug-resistant Enterobacterales were defined as those that were ESBL-positive and/or hyper-producing an Amp-C  $\beta$ -lactamase.

### **Antibiotic audit**

All data were extracted from electronic patient files, including patients' entire medical history and all laboratory results.

**Healthcare-associated infections were defined as a diagnosis established  $\geq 48$  h after hospital admission, and when observed fewer than 30 days after a urological procedure or after Day30 when observed in association with an underlying urinary catheterization. All other infections were classified as community-acquired [12].**

Co-morbidities were defined by prescription of a specific treatment prior to hospital care, or if the diagnosis was newly established during the hospital stay. Loss of autonomy, defined by ongoing neurological and/or psychiatric diseases limiting postoperative rehabilitation, was specifically reported as it could increase the duration of urinary catheterization and/or intravenous catheter, with the device becoming a source of bacteremia. Moreover, we specifically searched for risk factors of UTI such as known cancer of the urinary tract, previous UTI, a previous urological procedure of the urinary tract, endo-urinary catheterization, and asymptomatic bacteriuria prior to a surgical procedure, defined as the presence of bacteria ( $\geq 10^5$  CFU/mL) in urine culture without any symptom.

We recorded the details of the empirical antibiotic therapy and its reassessment, including the names of the drugs and the duration of the antimicrobial treatments. Accordingly, antibiotic reassessment was defined as any modification of the first-line treatment.

Our primary outcome was measurement of adherence to STGs, defined by the prescriptions of cited drugs only, during both empirical therapy and reassessment. As the historic goal of ASPs has been to reduce antibiotic consumption in order to decrease the frequency of MDR bacteria, our second outcome measured both. Antibiotic consumption was measured at the

institutional and (urology) departmental levels by means of the French search engine Consores<sup>®</sup>, through which all healthcare facilities are required to report their antibiotic consumption to the health authorities, defined as daily doses per 1000 days of hospitalization [13]. Relative variation of antibiotic consumption from 2018 to 2021 was calculated as follows:  $(Q_{2021}-Q_{2018})/Q_{2018}\times 100$ .

Finally, as ASPs could also help to improve clinical management, we monitored disease progression, defining an unfavorable outcome as one of the following: infection recurrence at most 30 days after the antibiotic prescription and/or need for a second surgical procedure, irrespective of the reason, during the same hospitalization and/or intensive care requirement and/or death.

### **Statistical analysis**

The data were analyzed with StatView software version 5.0, and statistical significance was established at  $\alpha=0.05$ . The continuous variables were compared with the Mann–Whitney test when appropriate. Proportions were compared with the  $\chi^2$  or Fisher's exact test when appropriate.

### **Results**

All in all, 166 cases of positive blood cultures were diagnosed in 141 patients between January 2017 and December 2022. Seventeen patients had two episodes of bacteremia, one patient had three and one patient had four. The successive episodes of bacteremia were not related. Of the 166 cases of positive blood cultures, 15 were polymicrobial, leading to the isolation of 182 pathogens.

Analysis of the patient charts showed that the port of entry of the bacteria was the urinary tract, or the anastomosis between the urinary and digestive tracts (in uretero-intestinal anastomosis), or the rectum flora (after trans-rectal prostate biopsy).

Seventy-six cases of bacteremia were observed between January 2017 and December 2019, and ninety between January 2020 and December 2022. Regarding the microbial results, 83 pathogens were isolated during the pre-STG period and 99 after STG implementation.

Table 1 lists the main patient characteristics, the microbial data, adherence to the STG for UTI, and the outcomes. The most frequent comorbid condition was urological cancer (76/166, 46%), which explains the high frequency of previous urological procedures (96/166, 58%), and endo-urinary catheterization (94/166, 57%). Previous UTI was noted in 58 cases (40%), and asymptomatic bacteriuria was diagnosed in 43 cases (26%) before surgery. In this context, the surgical procedure was performed in 50 cases during ongoing sepsis (30%). Of note, most patients presented with healthcare-associated infections (129/166, 78%), and the main reasons for surgery were a ureteral stent (32%) and nephrostomy (11%).

### **Bacteriological data**

Multidrug-resistant bacteria accounted for 72/166 (43%) patients, and due to polymicrobial bacteremia, 85 MDR strains were identified.

**Among risk factors for UTI, we found a relationship between previous urinary infection before urological procedure and MDR strains in blood cultures: 35/58 (60%) vs. 30/88 (34%),  $p = 0.001$ .**

*Enterococcus faecalis* was present in 11/166 patients (6.6%, all were susceptible to amoxicillin). A total of 12/15 *Staphylococcus sp.* bacteremia cases had the same strain with the same antibiotic pattern in the urine culture.

In 22 cases (13%), no urine culture had been performed, and there was a relationship between post-operative hematuria ( $n = 35$ ) and the absence of urine culture: 10/35 (29%) vs. 12/131 (9%),  $p = 0.002$ . Urine culture was sterile in 11/166 cases (7%). The same strain with the same

antibiotic pattern was isolated in both the blood and the urine cultures in 91/166 cases (55%). The second bacteria in urine associated with the strain isolated in blood was *E. faecalis* (n = 16).

#### **Adherence to simplified therapeutic guidelines**

**Management in accordance with current recommendations** improved between the two periods (*i.e.* STG adherence for the second period), increasing from 18% (14/76) to 52% (47/90),  $p < 0.001$ . Specifically, the empirical therapies were more in accordance with the STG than the documented therapies (see Table 1), and we observed significantly more antibiotic therapies without any third-generation cephalosporins (TGC) or fluoroquinolones (FQ) in the second period: 34% (26/76) vs. 53% (48/90),  $p = 0.013$ . Additionally, ceftriaxone prescriptions were significantly reduced: 37% (28/76) vs. 16% (14/90),  $p = 0.001$ .

Of note, in the second period, out of the 105 antibiotic prescriptions exterior to the implemented STG, 34 (32%) were justified according to bacterial resistance of the bacteria. Finally, the rate of antibiotic therapy  $> 14$  days was significantly lower after STG implementation than before: 53% (40/76) vs. 28% (25/89),  $p = 0.001$ .

#### **MDR Enterobacterales bacteremia and antibiotic consumption.**

The frequency of MDR Enterobacterales in blood cultures decreased after STG implementation, from 57% to 38%,  $p = 0.014$ . While this reduction was obvious for AmpC-producing strains (whether ESBL+ or not): from 29% (24/83) to 13% (13/99),  $p = 0.003$ , for other bacterial strains it was not significant (see Table 1). These results need to be considered in our hospital context, which showed increased incidence density of ESBL-E in the latter (see Figure 1A).

We then compared the antibiotic prescriptions in the urology ward to those in the facility taken as a whole. Figure 1B shows the variations in the consumption of the drugs included in the STG or usual alternatives, in 2018 and in 2021. We did not find any quantitative difference in the consumption of these drugs between the two years ( $p = 0.939$ ). On the other hand, qualitative differences were suggested, with ciprofloxacin and amikacin consumptions increasing in the urology ward compared to all other wards, while ceftriaxone and imipenem consumption decreased.

#### **Finally, mean duration of hospital stay (11 days) was not altered by STG implementation.**

The rate of unfavorable outcomes remained unchanged: 20% vs. 21%,  $p = 0.827$ . Four patients died due to metastatic urological cancer not directly related to bacteremia.

#### **Discussion**

Our study shows that the level of adherence to the STG for UTI in urology was significant and associated with a reduced number of TGC and FQ prescriptions and with a lower duration of antibiotic treatments. In addition, STG implementation was associated with reduced AmpC  $\beta$ -lactamase-producing bacteria in blood cultures. Finally, to the best of our knowledge, our study is the first to focus on bacteremia in urology, underscoring the burden of HCAI.

Our study has some limitations. Firstly, **while we show a statistically significant relationship between STG implementation and a lower level of MDR Enterobacterales in blood culture, we have provided no proof of direct consequence.** Secondly, the available data on antibiotic resistance focused only on ESBL-positive strains at the institutional level, in accordance with national recommendations. Thirdly, we cannot rule out the possibility that an audit with feedback and STG implementation was associated with improved infection control in urology compared to a facility experiencing an outbreak of ESBL-positive strains (see Figure 1A). Of note, the high rate of dissimilar microbial results between blood and urine cultures (19%)

justified the limitation of our study to bacteremia, thereby avoiding uncertain interpretation of urine culture.

Simplified therapeutic guidelines were specifically proposed in urology because we previously observed unwarrantedly diversified antibiotic use during care for urolithiasis and JJ stent insertion [14]. Since our study shows substantial adherence to STGs including only six antibiotic compounds, it can be assumed STGs function as pre-prescription authorization, which is a tool in ASPs designed to control antibiotic overuse [15].

STGs have previously been associated with decreased antibiotic consumption at the institutional level and a higher rate of optimal antibiotic therapy at the patient level [4,16]. That said, monitoring the prevalence of MDR bacteria is of paramount importance, as STGs are associated with repeated use of a small number of antibiotics. This is particularly true in urology, where the high prevalence of bacterial resistance is well-documented [17]. Resistance to TGC and/or FQ among Enterobacterales has been regularly reported as exceeding 50% in urology departments [17-19]. For ESBL strains, incidence of up to 44% has been demonstrated [19].

The present study shows that the STG for UTI was associated with significantly reduced bacteremia due to Amp-C  $\beta$ -lactamase-producing Enterobacterales in a urological ward. A non-significant reduction in ESBL-producing bacteria was also observed, notwithstanding increasing incidence in our institution (see Figure 1A). This was probably linked to both reduced use of drugs known to promote MDR strains, (*i.e.* TGC and FQ, see Table 1) and the reduced duration of antibiotic therapies. **The decreased TGC and FQ use could be related to the high rate of HCAI, for which these drugs should be avoided.**

Several studies have shown that antibiotic restriction was associated with improved susceptibilities to antibiotics. In a before-and-after study, prior authorization for prescription of most parenteral antibiotics was associated with significantly reduced MDR-strains among Gram-negative bacilli and did not alter the prognosis of patients with bacteremia [20]. Additionally, the favoring of cefotaxime as opposed to ceftriaxone led to a decrease in AmpC  $\beta$ -lactamase-producing Enterobacterales at the institutional level [21]. Moreover, the prescription of piperacillin/tazobactam to avoid TGC was associated with decreased ESBL-positive *K. pneumoniae* and *E. coli* in a pediatric facility [22]. Recently, a German study conducted in a urological ward showed that an antimicrobial stewardship program with new guidelines and multidisciplinary weekly rounds to discuss the antibiotic therapies with the bedside physicians led to a reduction in antibiotic prescriptions and to a decrease in bacteria resistant to fluoroquinolones [23]. In contrast, our results were obtained with limited human resources and no financial support, suggesting improved efficiency by non-specialized prescribers.

The second main result of our study was the substantial portion of HCAs (78%) among the patients with bacteremia in a urological ward. The high rate of care-related infections can be explained by the presence of risk factors for UTI, including urinary tract catheterization, endo-urological transurethral surgery, and previous urinary tract infection [17-19,24]. Up to 75% of the patients admitted to a urology ward presented at least one of these risk factors for infection [24]. To the best of our knowledge, no study has been published on bacteremia in urology, a lack making any comparison difficult. Another study focusing on radical cystectomy showed that 69/147 patients (47%) had a post-operative infection, 18% of which were with bacteremia [25]. Our study and others suggest that long-term follow-up of elderly patients with urological cancer receiving successive endo-urinary catheterizations may reveal



significantly increased incidence of UTI due to MDR bacteria. Further studies are required for better assessment of these patients.

In conclusion, simplified therapeutic guidelines for UTIs, which were limited to six antibiotic compounds, was well-accepted in urology, and demonstrably associated with a decline in AmpC  $\beta$ -lactamase-producing Enterobacterales in blood cultures.

Journal Pre-proofs

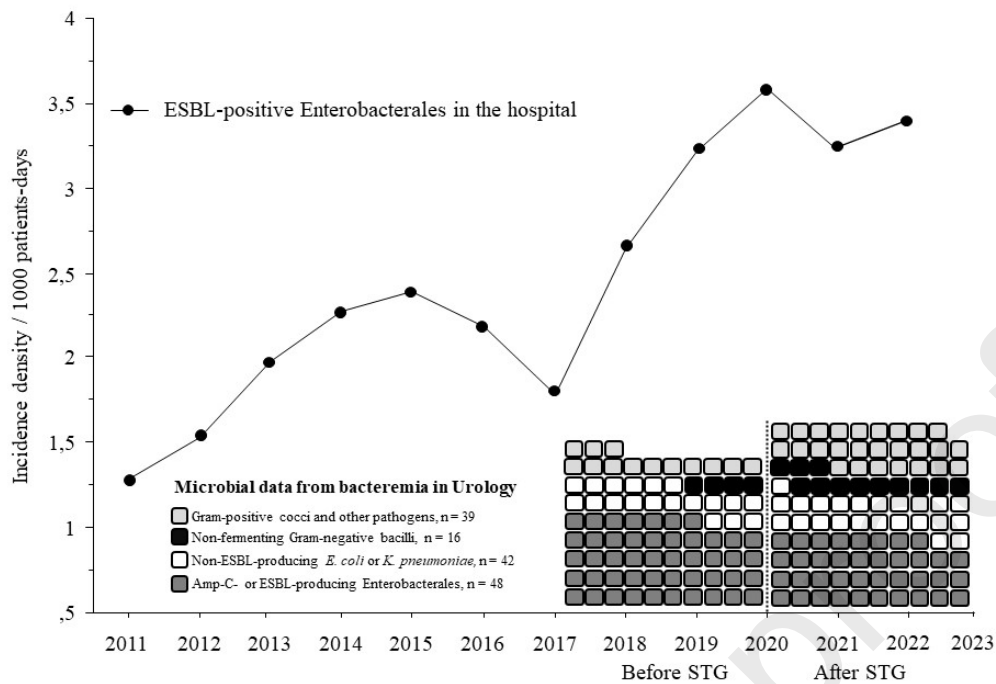
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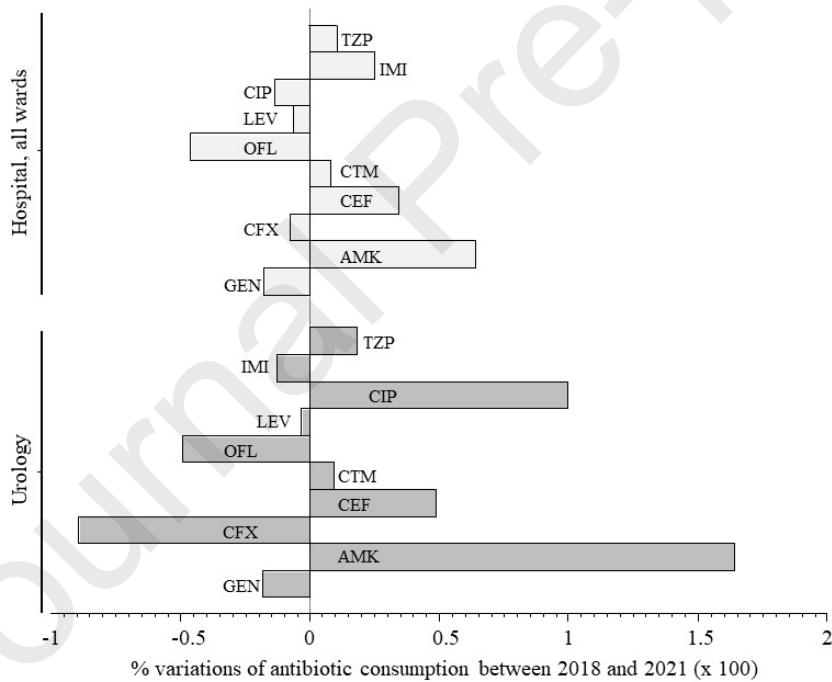
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**Figure 1. Antimicrobial resistances are to be analyzed together with antibiotic consumption at the institutional level. 1.A.** Incidence of ESBL-positive Enterobacteriales in the hospital over ten years. An increase in ESBL-positive strains (excluding intestinal carriage) was observed during the study period in the institution, contrasting with reduction in the proportion of AmpC  $\beta$ -lactamase- and ESBL-producing strains in bacteremia in urology (considering all isolates). Each box represents a bacterial isolate **1.B.** Variation in antibiotic consumption between 2018 and 2021; no quantitative difference was observed from one year to another.

## 1.A.



## 1.B.



**Table 1: Main characteristics of the patients, microbial data, and antibiotic therapies before and after STG implementation.** Considering polymicrobial bacteremia, bacteriological results included all isolates. Reassessment was defined as any modification of the empirical therapy.

	Before STG, n = 76 (46%)	After STG, n = 90 (54%)	p	All cases n = 166 (100%)
Age (years, mean ± std dev)	67±12	69±13	0.187	68±12
Male	64 (84)	73 (81)	0.600	137 (83)
Female	12 (16)	17 (19)	“	29 (17)
<b>Main comorbid conditions</b>				
Loss of autonomy <sup>1</sup>	60 (78)	63 (70)	0.189	123 (74)
Urological cancer	37 (49)	39 (43)	0.490	76 (46)
Cardio-vascular diseases	29 (38)	48 (53)	0.050	77 (46)
Diabetes	10 (13)	21 (23)	0.093	31 (19)
Chronic renal insufficiency	9 (12)	7 (8)	0.376	16 (10)
<b>Context</b>				
Community-acquired infections	20 (26)	17 (19)	0.252	37 (22)
Healthcare-associated infections	56 (74)	73 (81)	“	129 (78)
<b>Reasons for surgery</b>				
JJ stent insertion	20 (26)	33 (37)	0.154	53 (32)
Nephrostomy	9 (12)	10 (11)	0.882	19 (11)
Acute urinary retention with hematuria	12 (16)	23 (26)	0.124	35 (21)
Transurethral resection, prostate or bladder	11 (14)	4 (4)	0.024	15 (9)
Uretero-intestinal anastomosis	5 (7)	7 (8)	0.766	12 (7)
Radical prostatectomy	7 (9)	5 (6)	0.365	12 (7)
Others	18 (24)	15 (17)	0.259	33 (20)
<b>Surgical procedure with urinary infection</b>	21 (28)	29 (32)	0.520	50 (30)
<b>Risk factors for post-operative infections</b>				
Previous urinary infections	33 (43)	25 (36)	0.341	58 (40)
Previous urological surgery	44 (58)	52 (58)	0.987	96 (58)
Endo-urinary catheter	41 (54)	53 (59)	0.663	94 (57)
Asymptomatic bacteriuria before surgery	23 (30)	20 (22)	0.238	43 (26)
<b>Bacterial species in blood culture (all isolates)</b>				
	<b>n = 83</b>	<b>n = 99</b>		<b>n = 182</b>
Non-ESBL <i>E. coli</i> or <i>K. pneumoniae</i>	19 (23)	23 (23)	0.956	42 (23)

Amp-C-positive ESBL-negative Enterobacterales	24 (29)	13 (13)	0.008	37 (20)
ESBL-producing Enterobacterales	23 (28)	25 (25)	0.707	48 (26)
Non-fermenting Gram-negative bacilli	4 (5)	12 (12)	0.083	16 (9)
Cocci Gram-positive strains and others	13 (16)	26 (26)	0.082	39 (21)
<b>Urines cultures</b>	<b>n = 66</b>	<b>n = 78</b>		<b>n = 144</b>
Results similar to blood cultures	41 (62)	50 (64)	0.806	91 (63)
Results dissimilar to blood cultures	4 (6)	5 (6)	> 0.999	9 (6)
Urine culture: sterile or polymicrobial	21 (28)	23 (26)	0.762	44 (27)
<b>Antibiotic therapies</b>				
No treatment	0	1	-	1
No empirical therapy	4 (5)	14 (14)	0.064	18 (10)
Empirical therapy in accordance with STG	30 (42)	50 (62)	0.013	80 (52)
Reassessment in accordance with STG	41 (54)	58 (64)	0.169	99 (60)
<b>All steps in accordance with STG</b>	14 (18)	47 (52)	< 0.001	61 (37)
Antibiotic therapies without TGC or FQ <sup>2</sup>	26 (34)	48 (53)	0.013	74 (45)
Antibiotic combinations	8 (11)	22 (24)	0.020	30 (18)
-using an aminoglycoside	7 (87)	20 (91)	> 0.999	27 (90)
Fluoroquinolone prescriptions	11 (14)	22 (24)	0.108	33 (20)
-among ciprofloxacin / levofloxacin / ofloxacin	7/2/2	20/2/0	0.075	27/4/2
Efficient empirical therapy <sup>3</sup>	52 (63)	66 (67)	0.543	118 (65)
Duration of treatment (days, mean $\pm$ std dev) <sup>4</sup>	14.2 $\pm$ 3.7	12.8 $\pm$ 4.4	0.001	13.5 $\pm$ 4.1
Duration of treatment > 14 days	40 (53)	25 (28)	< 0.001	65 (39)
<b>Duration of hospital stay (days)</b>	10.3 $\pm$ 7.3	11.3 $\pm$ 9.7	0.546	10.9 $\pm$ 8.7
<b>Adverse clinical outcome</b>	15 (20)	19 (21)	0.827	34 (20)
Relapse of UI	8	7		15
Novel surgical procedure required	6	9		15
Intensive care unit requirement and/or death	1	3		4

1. Loss of autonomy = ongoing neurological and/or psychiatric diseases limiting post-operative rehabilitation; 2. TGC or FQ = third generation cephalosporins or fluoroquinolones; 3. Efficient empirical therapy considering the *in vitro* susceptibilities of the identified bacteria; 4 Including duration of the antibiotic therapy after discharge.

Journal Pre-proofs