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FULL PAPER

Differences between Community - and Hospital - acquired urinary tract infections in a tertiary care hospital

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SUMMARY

The aim of this retrospective study was to highlight the differences in antibiotic resistance between Hospital-acquired and Community-acquired urinary tract infections (UTIs).
Antimicrobial UTIs resistance data were collected from March 2011 to March 2018. Uropathogens were identified from 41,715 patients using routine laboratory methods. Differences in antibiotic resistance between Hospital and Community (non-hospitalized) patients were statistically validated. Odds ratio (OR) and p-values was used to determine whether a particular exposure (hospitalization) was a risk factor for a particular outcome (higher antibiotic resistance).
We reported a general increase of unnecessary urine cultures in both community and hospital patients. The most representative microorganism isolated from Community (58.2%) and Hospital (47.6%) was *E. coli*. UTIs causative bacteria in hospitalized patients was more than twice as resistant to Trimetoprim/sulphamethoxazole (OR 2.26) and Imipenem (OR 2.56), for Gram-positive and Gram-negative, respectively, than in Community patients.
Nitrofurantoin was the only agent without differences in resistance rate between community and hospital UTIs. Therefore, physicians could use it as a definitive therapy for uncomplicated cystitis and as a prophylactic agent for recurrent uncomplicated cystitis.
With this work we provided a general protocol applicable by physicians to select the most suitable, if necessary, UTIs empiric treatment.

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INTRODUCTION

Urinary tract infections (UTIs) are some of the most common bacterial infections with a significant financial burden on society. Approximately 15% of all community-prescribed antibiotics to non-hospitalized in the US are dispensed for UTI and data from some European countries suggest a similar rate (Naber *et al*., 2015). In Hospitals at least 40% of all infections are UTIs and bacteriuria develops in up to 25% of patients who require a urinary catheter for one week or more (Nicolle, 2014). Most of these infections involve the lower urinary tract, usually the bladder and the urethra. UTIs are more common in elderly than in young individuals and women are usually at three times greater risk for UTI than men. The common types of UTIs are cystitis, prostatitis, pyelonephritis and urethritis, and the symptoms are often non-specific (Kasper D, Braunwald E, Fauci AS, Hauser SL, Longo DL, 2012). The bacteria isolated from UTI patients are Gram-negative (Gram-) species like *E. coli, Klebsiella spp., Pseudomonas aeruginosa*, and *Proteus spp.* Other common bacteria are Gram-positive (Gram+) group B *Streptococcus*, *Enterococcus spp. and Staphylococcus aureus* (Naber *et al*., 2015).

Persistent recurrences and asymptomatic infections are usually responsible for difficulties in managing UTIs treatment. In Community, irrational drug use, such as low-dose antibiotics, long-term use and empiric therapy are usually reported (Ofori-Asenso and Agyeman, 2016). In Hospitals the selection of adequate treatment for the management of UTIs is increasingly challenging due to their etiology, the bacterial resistance profile and the evolving of adaptive strategies. Moreover, bacterial resistance has risen dramatically, with few therapeutic options, and one of the causes is the recurrent infection that leads to the development of multidrug resistance (MDR) (Almagor *et al.*, 2018).

Over the last few years, the issue of managing the unnecessary urine culture has become increasingly important in the health field. Although it aims to rationalize the healthcare expenditure, it is not limited to containing costs but is generally inspired to provide effective guidelines to physicians and to disseminate knowledge on the correct use of diagnostic prescriptions to citizens as well (Rosanne Sterry-Blunt *et al*., 2015). The costs associated with urine cultures vary according to the findings, and it is striking that 60% to 80% of all urine samples sent to the laboratory

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for culture are reported as negative for bacteria (Rosanne Sterry-Blunt *et al*., 2015).
The resistance rates to antimicrobials in UTIs can differ from region to region and patient to patient, so a deeper understanding of the Hospital and Community bacterial population is the first point to focus on (Mancini *et al*., 2016), after which an intervention in managing the urine cultures should be implemented, with a review of the prescriptive practices involving the collaboration of all operators, whether hospital or community physician. The aim of this study was to compare the nosocomial and community microorganisms isolated from patients with UTIs and determine their drug resistances, as well as to understand the unnecessary request rate and which antibiotic could be the most appropriate.

MATERIALS AND METHODS

A retrospective study was carried out in 2018 based on the bacterial isolates reports of a hospital located in Central Italy with 288 beds and a mean of 31,000 inpatient days per year. All patients with clinical symptoms, from low to severe, admitted from March 2011 to March 2018 (14 half-year periods) were included in this study. Isolates collected from infections that occurred 48 hours after admission were identified as hospital infections, as defined by the Centers for Disease Control and Prevention (CDC and NHSN, 2014).
Outpatients not admitted in any hospital ward within 20 days and non-hospitalized were considered community infections. Moreover, the patient's medical records were reviewed for potential risk factors, such as indwelling catheter; age; sex; history of UTI; the presence of diabetes, cancer, or a chronic neurologic or urologic disorder; residence in a long-term care facility; hospitalization; antimicrobial use. These risk factors, when correctly entered in the local medical records, were used to assign the patient's infection to the community- or hospital-acquired category. Given that electronic health records were not available and thus not all variables were available over the 7-year period, only sex and age were considered in the statistical analysis.
Chemical and microscopy screening were done for every sample before culture (iq200, Iris Diagnostics, USA). Cultures were performed only if this screening test was positive and urine samples were inoculated at 37°C on selective media plates (BioMérieux, France). UTIs were confirmed by 10^4 colony-forming units/ml of one or two bacteria species in a urine sample (cases with >2 species were discussed with the physician). All antimicrobial susceptibility tests were performed with VITEK®2 (BioMérieux, France). Resistance to glycopeptides or others drugs were not confirmed by tests different from VITEK2 because confirmation tests are not routinely performed in our laboratory. A bacteria isolate was considered resistant to an antimicrobial agent when tested and interpreted as resistant (R) in accordance with the EUCAST breakpoints criteria adopted by our laboratory (EUCAST, 2018).
Duplicate data were discarded using the BioMérieux VIGIguard™ software if all the following conditions were true: isolate collected from the same patient, same specimen, same ward, same species and similar antibiotic pattern (S/R=1; I/R–S/I=2) within 20 days. After duplicate elimination, data were checked with Microsoft® Excel and verified.
According to the literature, eight main antibiotics were chosen: Cefotaxime (3rd-gen Cefalosporins), Fosfomycin (Epoxides), Trimetoprim-sulphamethoxazole (Sulfonamides), Nitrofurantoin (Nitrofurans), Amoxicillin/clavulanate (Aminopenicillins/BLI), Imipenem (Carbapenems), Ciprofloxacin (Quinolones) and Gentamicin (Aminoglycosides) (Stichting Werkgroep Antibioticabeleid, 2013). A multidrug-resistant microorganism was defined as being resistant to at least one agent in three or more antimicrobial categories (Magiorakos *et al.*, 2012). Differences in antibiotic resistance between groups and strength of association were checked by odds ratios, and results with p-value <0.05 were accepted. Odds ratio (OR) was used to determine whether a particular exposure (hospitalization) was a risk factor for a particular outcome (higher antibiotic resistance). An OR>1 means that the exposure is associated with higher odds of outcome while an OR<1 means lower odds of outcome (Szumilas, 2010).

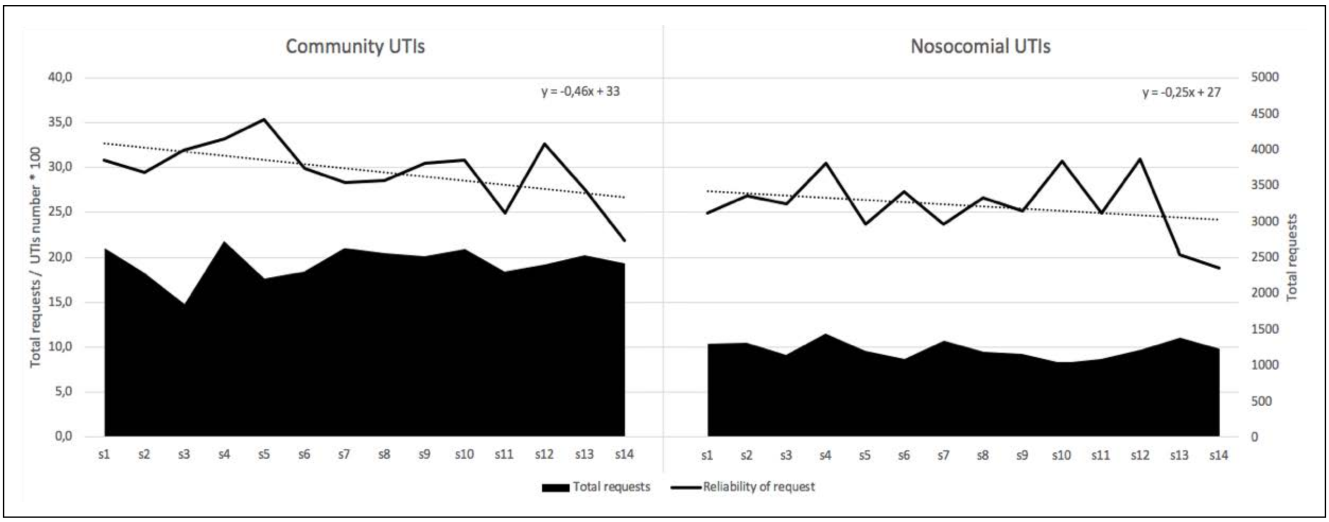

Figure 1 - *Total urine culture requests on the bottom area-graph (no. of requests) and total positive requests on the upper broken-line-graph (% of positive requests).*

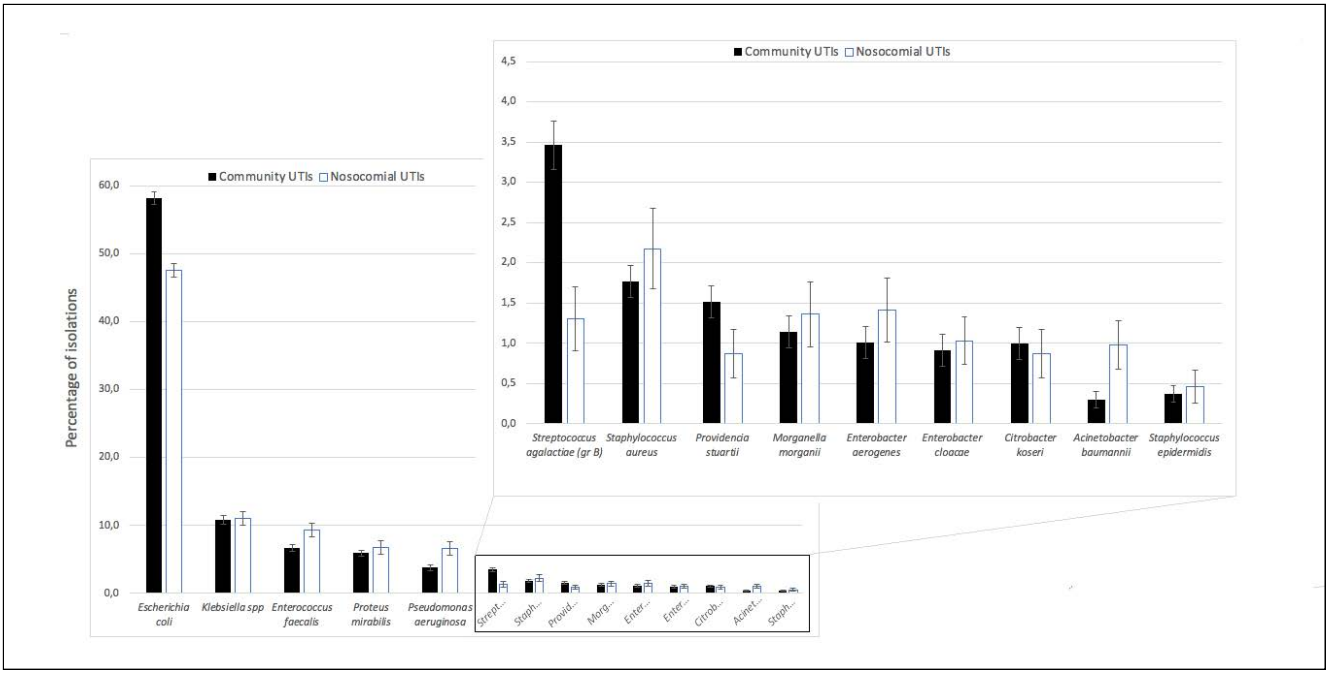

Figure 2 - *Differences between the most prevalent Uropathogens isolated from the Central Laboratory Analysis.*

RESULTS

A total of 41,715 patients were tested, 27,677 (66.3%) for community-acquired UTIs (C) and 14,038 (33.7%) for hospital-acquired UTIs (H). 24,908 (59.7%) of urine samples were from women and 16,709 (40.0%) were from men (98 from sex unknown).

The total positive requests (32.2%) were calculated as the ratio between the total number of requests and the positive samples (13,417). The hospital positive requests in every period (six months) ranged from 18.9% to 30.8% while the community requests ranged from 21.9% to 33.2%. As shown in (*Figure 1*), over the 7 years there was a general increase in unnecessary urine cultures both in community and hospital requests, with a regression line of y=-0.46x+33 (R^2 0.3) and y=-0.25x+27 (R^2 0.08), respectively. The most representative microorganisms isolated from community samples were *E. coli* 58.2% (CI95% 57.3-59.1), *Klebsiella spp.* 10.8% (CI95% 10.2-11.4), *Enterococcus faecalis* 6.7% (CI95% 6.2-7.2), *Proteus mirabilis* 5.9% (CI95% 5.5-6.3) *and Pseudomonas aeruginosa* 3.8% (CI95% 3.4-4.2). Hospital isolations were similar, but *E. coli* 47.6% (CI95% 46.0-49.2) was less frequent in hospital than community, and *Enterococcus faecalis* 9.4% (CI95% 8.5-10.3) and *Pseudomonas aeruginosa* 6.6% (CI95% 5.8-7.4) were more frequent in hospital isolations than community. Other differences were in *Streptococcus agalactiae* and *Providencia stuartii*, more prevalent in community infections, and *Acinetobacter baumanii*, more common in hospital UTIs (*Figure 2*). The most active antimicrobial agents to Gram+ bacteria, with the lowest percentage of resistance, both in community and hospital isolations, were Amoxicillin/clavulanate (C 1.3% - H 1.0%), Imipenem (C 1.5% - H 1.5%) and Nitrofurantoin (C 8.4% - H 0.9%). The drugs of election against Gram- bacteria were Imipenem (C 3.2% - H 7.8%) and Nitrofurantoin (C 8.4% - H 9.4%). Descriptive statistics are provided in supplementary *table 1* and *2*. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. In our case the question was whether a hospitalized patient had a higher risk of contracting a pathogen more or less resistant to a particular antimicrobial agent.

The only agent without differences in resistance rate between community and hospital UTIs were Nitrofuran-

Table 1 - *Differences in resistance rate between community – and hospital – acquired isolates from UTIs. Odds ratios were calculated separately for GRAM+ and GRAM- groups. Statistically significant differences (P<0.05) are indicated in bold.*

	Odds Ratio	
	GRAM+ (CI 95%)	*GRAM- (CI 95%)*
	P-value	*P-value*
Cefotaxime	4.24 (1.24-14.8)	**1.54 (1.40-1.69)**
	P>0.05	P<0.0001
Fosfomycin	**1.00 (0.90-1.10)**	**1.11 (0.99-1.25)**
	n/a	P>0.05
Trimetoprim/ sulphamethoxazole	2.26 (1.74-2.93)	1.19 (1.09-1.30)
	P<0.0001	P=0.0001
Nitrofurantoin	0.50 (0.17-1.47)	1.13 (0.94-1.36)
	P>0.05	P>0.05
Amoxicillin/ clavulanate	0.77 (0.23-2.51)	**1.37 (1.25-1.50)**
	P>0.05	P<0.0001
Imipenem	1.00 (0.37-2.72)	**2.56 (2.13-3.08)**
	P>0.05	P<0.0001
Ciprofloxacin	**1.87 (1.45-2.42)**	1.02 (0.94-1.11)
	P<0.0001	P>0.05
Gentamicin	**1.43 (1.11-1.84)**	1.10 (0.99-1.23)
	P=0.005	P>0.05
MDR	1.05 (0.77-1.44)	**1.32 (1.15-1.52)**
	P>0.05	P=0.0001

Table 2 - *Differences in multi-drug resistance between community and h. Odds ratios were calculated separately between Hospital and Community groups by sex and Hospital and Community groups by age. Statistically significant differences (P<0.05) are indicated in bold.*

	MDR Odds Ratio	
MDR by Sex	*OR (CI95%)*	*P-value*
Female	**1.35 (1.13-1.61)**	P=0.0007
Male	1.10 (0.91-1.32)	P>0.05
MDR by Age (years)	*OR (CI95%)*	*P-value*
<5	1.21 (0.55-2.68)	P>0.05
5-15	n/a	n/a
16-35	1.87 (0.92-3.82)	P>0.05
36-50	**2.64 (1.43-4.87)**	P=0.0018
>=51	**1.23 (1.07-1.40)**	P=0.0026

toin. Gram+ in hospitalized patients were 1.5 times more resistant than in community patients to Trimetoprim-sulphamethoxazole (OR 2.26), Ciprofloxacin (1.87) and Gentamicin (OR 1.43). Gram from hospital patients were more resistant to Cefotaxime (OR 1.54), Trimetoprim-sulphamethoxazole (OR 1.19), Amoxicillin/clavulanate (OR 1.37) and more than 2.5 times more resistant to Imipenem (OR 2.56). There were no differences in multi-drug resistance among Gram+, but Gram- MDR were slightly prevalent in hospital-acquired UTIs (OR 1.32) (*Table 1*).

MDR UTIs were more prevalent in hospital than in community female patients (OR 1.35), with no differences in male patients. The highest difference was in the 36-50y range (OR 2.64), while among older patients >=51y we reported a lower difference (OR 1.23). However, both community and hospital male patients showed a higher rate (C 15.0% - H 16.2%) of MDR microorganisms than female patients (C 5.9% - H 7.8%) (*Table 2*).

DISCUSSION

As shown in *Figure 1*, the ratio between the total number of requests and the positive samples is gradually decreasing in both hospital and community requests. This is the first goal of a long-term intervention to decrease expenditures and increase service quality. Continuous personnel training and updating to the latest guidelines has led us to reduce false positives. The next step should be to implement and sustain a new antimicrobial management campaign, particularly in long-term care units, aimed at reducing the total number of requests by physicians. A recent study (Leis *et al.*, 2014), requiring health care professionals to call the central laboratory to obtain the urine culture results, led to a 36% reduction in treatment of asymptomatic bacteriuria (ASB). Other implementation programs have decreased antibiotic overuse for ASB by using education, pocket cards, audit and feedback, and computer-based reminders (Kelley *et al.*, 2014). These programs could be relatively easy to integrate in the hospital routine but very difficult to integrate in the community due to phenomena such as negligent antibiotic use, the dismissal of warnings against antibiotic overuse, self-medication and self-prescription (Rather *et al.*, 2017).

In agreement with previous studies, the Enterobacteriaceae family was predominant in UTIs and the main isolated pathogens were *E. coli*, *Klebsiella spp.*, *Enterococcus faecalis, Proteus mirabilis* and *Pseudomonas aeruginosa* (Flores-Mireles *et al., 2015)* (Foxman, 2010).

Our data showed a higher prevalence of *E. coli*, Group B *streptococcus,* and *Providencia stuartii* in community than in hospital UTIs. *E. coli* is the most common causative pathogen in uncomp*licated urinary tract infections, and these are by more prevalent in the community (Linhares et al., 2013)*. This can explain its higher prevalence in community UTIs. Group B *streptococcus* is the leading cause of infection in newborns and pregnant women (Edwards and Baker, 2005), more prevalent in community than in hospital.

The genus Providencia is a urease-producing GRAM- bacillus of the family *Enterobacteriaceae* and is the most common cause of catheter-associated urinary tract infections, especially in the elderly with long-term indwelling urinary catheters. In contrast, our results showed a greater incidence of *P. stuartii* in community than in hospital. This may be because it is commonly found in community water, soil, and animal reservoirs (Wie, 2015).

Enterococcus faecalis, Pseudomonas aeruginosa and Acinetobacter baumanii were most commonly isolated in hospital patients. *Enterococci* are among the most frequent causes of nosocomial infection, especially of the bloodstream, urinary tract and surgical sites (Medscape and News, 2009). *P. aeruginosa*, a typical nosocomial pathogen, is the third most common organism after *Escherichia coli* and *enterococci* isolated from UTI patients in the hospital setting (Medscape and News, 2009). It also causes biofilm-mediated infections, including catheter-associated urinary tract infection, and is therefore more common in hospital-acquired than in community-acquired infections. *Acinetobacter baumanii* is usually related to hospital UTIs and linked to catheter-associated infection or colonization (Villar *et al.,* 2014). It is unusual for *A. baumanii* to cause complicated UTIs in outpatients, and the higher rate of complicated UTIs among hospitalized patients explain this greater prevalence (Almasaudi, 2018).

Hospital origin was associated to higher resistance rates to all drugs except to Nitrofurantoin. In patients suspected of having a complicated UTI, a urine culture and susceptibility test should always be performed before starting a therapy. In the IDSA guidelines for the treatment of uncomplicated UTIs (Gupta *et al.*, 2011), it is recommended that the resistance percentages of causative micro-organisms must be below 20% to consider an agent suitable for empirical treatment of a lower UTI and must be below 10% for treatment of an upper UTI (Stichting Werkgroep Antibioticabeleid, 2013). Our data showed that Nitrofurantoin could be used as a definitive therapy for uncomplicated cystitis and as a prophylactic agent for recurrent uncomplicated cystitis (Stichting Werkgroep Antibioticabeleid, 2013). Numerous studies have demonstrated its effectiveness in eliminating both Gram- and Gram+ pathogens (Huttner *et al.*, 2018) (Bader *et al.*, 2016). Our results agreed with these studies and today nitrofurantoin may still be reasonably considered a first-line therapy for acute uncomplicated cystitis in adults, in children, and in catheterized patients in our hospital and community. Another very effective antibiotic both in community and hospital, but more expensive than Nitrofurans, could be Imipenem (Zhanel *et al.*, 2007), with a very low rate of resistance (even lower than Nitrofurantoin). However, in the hospital setting, physicians should be careful to start an empiric treatment with this class of drugs. As confirmed by results, Gram- bacteria in hospital samples are more resistant than in community and more prone to develop a greater resistance (carbapenem-resistant *Enterobacteriaceae*) after a wrong therapy management (Bader *et al.*, 2016).

Several risk factors are associated with UTIs, including gender. The shorter distance to the bladder in women makes it easier for bacterial colonizers to reach it (Foxman, 2010). Male patients, conversely, have a lower risk of contracting uncomplicated UTIs but are more prone to contracting complicated or MDR infections. Our data reflect the severe nature of UTI in men, in which infections are caused by more dangerous and infectious MDR microorganisms than in female patients (*Table 2*) (Schaeffer and Nicolle, 2016). Even if females had a lower incidence of MDRs than males, female patients in hospital wards had a higher MDR incidence compared with their community counterpart. This is probably an artefact reflecting the higher incidence of uncomplicated UTIs in females in community than in hospital (Naber *et al.*, 2015), which had lowered the MDRs rate. We reported a higher rate of MDRs in nosocomial patients >36 years than in community, with the greatest increase between 36 and 50 years. This difference is notably due to the higher percentage of MDRs in older (>=51y 9.7% MDRs) than in younger (36-50y 3.1% MDRs) community patients, in which the variable "age" as a risk factor for UTIs MDRs infections plays an important role (Cars *et al.*, 2008).

Our data provide precise information about the role of different microorganisms as etiologic agents of UTIs and highlight their differences in prevalence and antibiotic resistance between hospital and community UTIs. We also provide a general description of multi-drug resistant microorganisms that will guide physicians to selecting the most suitable, if strictly necessary, empiric treatment for UTIs.

Conflicts of interest

The authors declare no financial or competing interests.

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