MULTIDRUG RESISTANT URINARY TRACT INFECTIONS IN MOLDOVA, ROMANIA: FOCUSING ON UROPATHOGENS AND THEIR ANTIBIOTIC SUSCEPTIBILITY. CAN WE DO MORE?

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ABSTRACT

Objective: In the present report we were interested in to determine the community associated Urinary Tract Infections (UTI) causing uropathogen's prevalence, the antibiotic resistance patterns and the risk factors associated with it in the Parhon Hospital Iasi, the most important clinical facility of this type from Moldova region in Romania.

Material and Method: This was a retrospective chart review-study. We considered as multi-drug resistant, those germs that were resistant to more than five antibiotics. In addition, we were interested in better understanding the other variables associated with the positive urine culture and their value as main risk factors in UTI, as studied from the patients charts.

Results: Our data showed that mainly the most problematic germs were represented by Klebsiella pneumoniae/spp, Pseudomonas aeruginosa, Escherichia coli and Staphylococci (coagulase-negative/S. aureus/S. saprophiticus). Also, the bacteria responsible for UTI multidrug resistant (MDR) development presented a 100% resistance to the following 9 antibiotics: amoxicillin, ticarcillin, cefalexin, cefaclor, ceftibuten, penicillin, oxacillin, erythromycin and ceftaroline. In addition, for the first time in our country, a specific profile for the UTI MDR-risk patient was described in the present paper.

Conclusion: Thus, treatment for UTI should be done in accordance with the antibiogram results and for a sufficient period of time, in order to avoid the appearance of pan-resistant germs for which there are no reserve antibiotics available. Also, discarding certain commonly used antibiotics, to which the great majority of the strains are resistant, for a period of time, could perhaps lead to a possible shift in the spectrum of their sensitivity.

Keywords: Urinary tract infections, multidrug resistance, antibiotics. ***Nobel Med 2015; 11(3): 42-49***

MOLDOVA VE ROMANYA'DA İLACA DİRENÇLİ İDRAR YOLU ENFEKSİYONLARI: ÜROPATOJENLER VE ANTİBİYOTİK DUYARLILIĞINA ODAKLANMA. DAHA FAZLASINI YAPABİLİR MİYİZ?

ÖZET

Amaç: Bu yazımızda Romanya'nın Moldova bölgesindeki en önemli hastane olan İasi Parhon Hastanesi'nde toplumdan kazanılmış İdrar Yolu Enfeksiyonlarına (İYE) neden olan üropatojenlerin prevalansını, antibiyotik direnç tipleri ve ilgili riskleri bulmaya çalıştık.

Materyal ve Metot: Bu retrospektif bir özet grafik çalışması idi. Çoklu ilaç dirençli patojen olarak beşten fazla antibiyotiğe dirençli olan mikrop seçildi. Ayrıca, İYE'de pozitif idrar kültürü ve bunun ana risk faktörü olarak değerlendirilmesini, diğer değişkenleri de hasta çizelgelerine bakarak anlamaya çalıştık.

Bulgular: Çalışmalarımız sonunda en sorunlu organizmaların Klebsiella pneumoniae/spp, Pseudomonas aeruginosa, Escherichia coli ve stafilokoklar (koagulaz-negatif/S. aureus/S. saprophiticus) olduğu görüldü. Çoklu ilaç dirençli İYE gelişiminden sorumlu aşağıdaki bakterilerin aşağıdaki antibiyotiklere %100 dirençli olduğu bulundu: amoksisilin, tikarsilin, sefaleksin, sefaklor, seftibüten, penisilin, oksasilin, eritromisin ve ceftarolin. Ayrıca, ülkemizde ilk defa, İYE çoklu ilaç dirençli, riskli hastalar için özel bir profil, mevcut yazıda gösterilmiş oldu.

Sonuç: Bu nedenle, İYE tedavisinde hiçbir rezerv antibiyotik olmadığı, çoklu ilaç dirençli mikropların oluşumunu önlemek için, antibiyogram sonuçlarına göre ve yeterli bir süre tedavi yapılması gerekmektedir. Ayrıca, bir zamanlar suşlarının büyük bir çoğunluğuna, dirençli olan bazı yaygın olarak kullanılan antibiyotiklerin atılması, belki duyarlılık spektrumunda olası bir değişikliğe neden olabilir.

Anahtar kelimeler: İdrar yolu enfeksiyonları, çoklu ilaç direnci, antibiyotikler. **Nobel Med 2015; 11(3): 42-49**

INTRODUCTION

Generally, the infections are one of the most frequent medical pathologies, affecting people of all ages.[1] Meanwhile, the Urinary Tract Infections (UTI) are an important part of it and believed to cause serious health problems to millions of patients worldwide while displaying an overall incidence around of 18/1000 persons per year.[2-5] Moreover, 40% of women and 12% of men experience at least one symptomatic UTI during their lifetime.[6]

The associated costs are also estimated to be extremely high, only in regards to USA healthcare being accountable for 7 million clinical visits per year, which means an approximately 1.6 billion US dollars.[7] Since there are around 150 million cases annually worldwide, enormous costs are required in order to fight this condition.[6]

Considering the aforementioned reasons the prevalence of uropathogens antimicrobial-resistance is a source of increased interest among specialists around the world, which are mainly using the so-called empirical therapy to treat UTI.[8]

That is why, early diagnosis and individualized treatment are fundamental aspects required for the elimination of UTI. Moreover, according to our best of knowledge, this is the first study in Romania regarding UTI.

Also, the lack of studies regarding the UTI multidrug resistant (MDR) in Romania and the complicated process of applying the European guidelines onto the realities of practical medical care, led us to approach this problem at the only urological clinic in Moldova, which is addressed by the patients from this entire region with a population of about 6 millions inhabitants.

In this way, in the present report we were interested in determine the community associated UTI causing uropathogen's prevalence, the antibiotic resistance patterns and the risk factors associated with it in the Urological Clinic within Parhon Hospital Iasi, the most important clinical facility of this type from Moldova region in Romania.

MATERIAL AND METHOD

This was a retrospective chart review-study, mainly referring to the urocultures of the patients from the Urological Clinic within Parhon Hospital Iasi, Romania, from January 2013 – July 2014.

We considered as multi-drug resistant, those germs that were resistant to more than five antibiotics. Moreover, the solely selection criterion was represented by the adult patients aged more than 18 years old, which had a clinical diagnosis of UTI and complete urine culture results. UTI was diagnosed as the growth of more then 100,000 colony. Fresh midstream urine or urine obtained from catheter was collected aseptically

in a sterile plastic container, with increased efforts not to contaminate the probe and was submitted to the microbiology laboratory.

Also, all urine culture and susceptibility tests were performed by the central hospital's laboratory. Disc diffusion assay on agar was performed. In this way, the panel antimicrobials mainly include beta-lactam antibiotic (amoxicillin 30 µg), aminoglycosides (amikacin 30 µg, gentamicin 10 µg), cephalosporin antibiotics (gefixime 5 µg, cefotaxime 30 µg, cefpodoxime 10 µg), synthetic quinolone fluoroquinolones antibiotics (nalidixic acid 30 µg, ciprofloxacin 5 µg, ofloxacin 5 µg, norfloxacin 10 µg, levofloxacin 5 µg), macrolide (erythromycin 15 µg), semisynthetic penicillin (cloxacillin 5 µg, penicillin V 10 µg), glycopeptide antibiotic (vancomycin 30 µg), aminocoumarin (novobiocin 30 µg), nitrofuranes (nitrofurantoin 300 µg) and tetracycline 30 µg. Standard antibiotic discs available were used for this study, by respecting the EUCAST European protocol. In addition, we were interested in better understanding the other variables associated with the positive urine culture and their value as main risk factors in UTI, as studied from the patients charts.

Data Analysis

As mentioned before, data analysis was mainly performed by the chart reviewing, through descriptive analysis (such as absolute and relative frequencies for the variables within our study). In addition, we determined the independence between the nominal variables germ and urethral catheter, by using Pearson correlation test and also by measuring the association between these two, through the means of Cramer's V coefficient.

RESULTS

In this way, there were recorded 2944 admissions, out of which 750 patients (25.47%) have developed urinary infections, while the number of MDR infections rose to 336, representing 11.41% of the total number of admissions and 44.80% of the total number of urinary infections.

As regarding the periodicity manifested by the UTI MDR, we have noticed that these occur mainly in following months: March, April, May (spring) and June, July, August (summer) + more or less the September month (Table 1). Very importantly, the prevailing germ that was present throughout the entire period was Klebsiella pneumoniae. Moreover, this had the same spectrum of resistance throughout the period: being resistant to ampicillin, amoxicilim + clavulanic acid, cephalosporins (cefuroxime, cefotaxime, ceftazidime, cefepime), gentamicin, fluoroquinolones (norfloxacin, ciprofloxacin).

Also, the second germ present for the duration of the experiment was Pseudomonas aeruginosa. In this case, the spectrum of resistance observed over the entire period included the following antibiotics: ceftazidime, cefepime, gentamicin and ciprofloxacin. The germ displayed high percentage resistance to the following antibiotics: cefoperazone-75% (particularly during the summer and autumn months- May- November), meropenem-66% (especially during the spring and summer, March-September), piperacillin-50% (especially during the summer months -June - September), imipenem-50% (especially during the summer months- June- September), levofloxacin-50% (especially during the summer months- June- September). In a lower percentage of resistance was also found to: cefotaxime-25%, norfloxacin-25%, tigecycline- 25%.

The third prevailing germ was Escherichia coli. It was present in >66% (68%) of the investigation period. The spectrum of resistance observed during the course of the study included the following antibiotics: ampicillin, cephalosporins (cefuroxime, cefotaxime, ceftazidime), fluoroquinolones (ciprofloxacin, norfloxacin). High-percent resistance was identified for the following antibiotics: amoxicilim +ac. clavulanic 65% (especially in the spring months of March - April and summer - June to August), cefepime -50% (especially during the summer months- April - August). Additionally, in a smaller percentage it was resistant to gentamicin-20%.Also, we have found high prevalence for other germs such as:

1. Enterococcus faecalis/spp. - present at a rate of ~ 75% (73.5%) during the period of study. The spectrum of resistance observed throughout the entire period included the following antibiotics: ampicillin, gentamicin, fluoroquinolones (levofloxacin, ciprofloxacin). A high percentage resistance was found for the following antibiotics: doxycycline - 85%, penicillin - 79% (especially in the spring months March -May and summer July - August).

2. Staphylococcus coagulase-negative - 75% / aureus 42% / saprophiticus 8.3% - present in 63% of the study period, for which we have found high-percent resistance to the following antibiotics: cefepim, imipenem, meropenem, penicillin, oxacillin - 83%, cefuroxime - 75%, fluoroquinolones (ciprofloxacin, levofloxacin) - 66% (especially during the spring and summer months, March - August), doxycycline- 50%, gentamicin, sulfamethoxazole - 42% (especially during the summer months - May -August). Also, a resistance lower percentage was found to clarithromycin - 16%.

Subsequently, we were particularly interested in finding whether long time urethral catheter represented a risk factor and the types of germs that would develop in these circumstances, especially since the patients had an increased risk of UTI MDR with most germs involved in their developing. In this way, analyzing the results from Table 2, the status of patient carrying an urethro-vesical catheter was UTI MDR associated with the following germs count:

-Klebsiella pneumoniae/spp - in 46.15% of the UTI MDR cases with this germ;
-Pseudomonas aeruginosa - in 41.67% of the UTI MDR cases with this germ;
-Escherichia coli - in 38.10% of the UTI MDR cases with this germ;
-Staphylococci (S. coagulase-negative/S. aureus/S. saprophiticus) - in 57.14% of the UTI MDR cases with these germs;
-Nonfermenting gram-negative bacilli - in 28.57% of the UTI MDR cases with these germs;
-Enterococcus faecalis/spp - in 40% of the UTI MDR cases with these germ;
-Corynebacterium urealyticum - in 50% of the UTIU MDR cases with these germ;
-Proteus vulgaris/mirabilis/spp – in 75% of the UTI MDR cases with these germ;
- Enterobacter cloacae – 66.67% of the UTI MDR cases with these germ.

To confirm the dependence between these two factors (status of urethra-vesical catheter carrier and the type of germ), we used Pearson χ^2 test (Pearson Chi-Square), as mentioned before. Thus, by using the data from Table 2, we obtained a value of 49.39 for the χ^2 statistical test. This value has to be confronted with the theoretical value of χ^2, for a risk α of 0.05 and 10 degrees of freedom, for which we obtained χ^2 0,05;10=18,30. Therefore, by comparing the calculated value of this test with the theoretical one (χ^2 =49,39 > χ^2 0,05;10=18,30), we can conclude that there is a statistical significant association between the status of urethra-vesical catheter carrier and the type of germs.

Further on, in order to measure the level of association between our variables, the Cramer's V coefficient was calculated. Based on our data, for this coefficient it was obtained a value of 0,5624, suggesting that between the factors represented by the bacteria type and status of urethra-vesical catheter there is a statistical significance dependence, with a high level of association. In addition, the most problematic germs were represented by:

-Klebsiella pneumoniae/spp - UTI MDR with Klebsiella pneumoniae/spp. was associated with the insertion and replacement of "JJ" stents (33.33%), with endourological interventions (transurethral resection of prostate- TUR-P 14.10%, transurethral resection of a bladder tumor-TUR-BT 23.08%), with clinical records of diabetes mellitus (19.23%), of bladder tumors (17.95%) or prostatic neoplasm (14.10%), with the status of urethro-vesical probe carrier (46.15%) and with the insertion of probes for percutaneous nephrostomy (15.38%).
-Pseudomonas aeruginosa-UTI MDR with Pseudomonas aeruginosa was associated with: the insertion and replacement of "JJ" stents (58.33%), with endourological interventions (TUR-BT –25%), with clinical records of bladder tumors (12.5%) and with the status of urethro-vesical probe carrier (41.67%).
-Escherichia coli-in this way, UTI MDR with Escherichia coli was associated with the insertion and replacement of "JJ" stents (100%), with the insertion of probes for percutaneous nephrostomy (38.10%), with endourological interventions (uretheroscopy + UPGR -14.29%), with history of urothelial tumors (19.05%) and with the status of urethro-vesical probe carrier (38.10%).
-Staphylococci (coagulase-negative/S. aureus/S. saprophiticus) - UTI MDR with staphylococci was associated with: history of diabetes mellitus (28.57%), penian tumors (28.57%) and with the status of urethro-vesical probe carrier (57.14%).
-Nonfermenting gram-negative bacilli - UTI MDR with nonfermenting gram-negative bacilli was associated with the insertion and replacement of double J stents (57.14%), with endourological interventions (TUR-BT - 28.57%), with case history of bladder tumor (28.57%) and with the status of chronic urethro-vesical probe carrier (28.57%).

Table 1. The periodicity of the cases during the 19 months of experiment.

No.	Month	No. of cases
1	January 2013	10
2	February 2013	16
3	March 2013	33
4	April 2013	53
5	May 2013	19
6	June 2013	29
7	July 2013	48
8	August 2013	68
9	September 2013	23
10	October 2013	17
11	November 2013	10
12	December 2013	10
13	January 2014	15
14	February 2014	16
15	March 2014	20
16	April 2014	31
17	May 2014	36
18	June 2014	24
19	July 2014	27

Table 2. The relationship between long time urethral-vesical catheter and the type of germ.

Germ	Urethral catheter (observed frequencies)		Total	Urethral catheter (theoretic frequencies)	
	Yes	No		Yes	No
Klebsiella pneumoniae/spp.	36	42	78	16.50	43.50
Pseudomonas aeruginosa	10	14	24	5.08	13.38
Escherichia coli	8	13	21	4.44	11.71
Staphylococcus. coagulase-negative/S. aureus/S. saprophiticus	4	3	7	1.48	3.90
Nonfermenting gram-negative bacilli	2	5	7	1.48	3.90
Enterococcus faecalis/spp.	2	3	5	1.06	2.79
Corynebacterium urealyticum	2	2	4	0.85	2.23
Proteus vulgaris/mirabilis/spp.	3	1	4	0.85	2.23
Enterobacter cloacae	2	1	3	0.63	1.67
Citrobacter freundii/spp.	0	2	2	0.42	1.12
Serratia marcescens	0	1	1	0.21	0.56
Total	69	87	156	-	-

-Enterococcus faecalis-/spp - UTI MDR with Enterococcus faecalis/spp. was associated with: clinical records of diabetes mellitus (40%), bladder tumors (28.57%) and with the status of chronic urethro-vesical probe carrier (40%). On the other hand, the antibiotics that did not deliver any results in these infections were mostly represented by:

-Amoxicillin, ampicillin, amoxicilim + clavulanic acid, ampicillin + sulbactam;
-Cephalosporins: ceftazidime, cefuroxime, cefotaxime, cefepime, cefoperazone, cefalexin, cefaclor, cefixime, ceftibuten, cefpirome, ceftaroline;
-Gentamicin;
-Fluoroquinolones:levofloxacin,ciprofloxacin, norfloxacin;
-Penicillin, oxacillin;
-Clarithromycin, erythromycin;
-Doxycycline;
-Sulfamethoxazole (as seen in Table 3).

Also, for the Table 3 which included antibiotics and uroculture results, we decided to use a relative frequencies statistical interpretation. As conformed, to these results we could observe that the bacteria responsible for UTI development presented a 100% resistance to the following 9 antibiotics: amoxicillin (2 cases), ticarcillin (2 cases), cefalexin (3 cases), cefaclor (3 cases), ceftibuten (5 cases), penicillin (52 cases), oxacillin (19 cases), erythromycin (1 case) and ceftaroline (1 case).

In addition, an increased resistance was also noticed for the following antibiotics: 98.54% for cefuroxime (337 out of 334 cases); 97.74% for ampicillin (346 out of 354 cases); 95.69 for cefotaxime (333 out of 348 cases); 94.12% for cefixime (16 out of 17 cases); 93.64% for ceftazidime (412 out of 440 cases), 93.20% for levofloxacin (137 out of 147 cases); 90.43% ciprofloxacin (397 out of 439 cases); 89.94% for norfloxacin (313 out of 348 cases); 86.36% for ampiplus (19 out of 20 cases).

On the other side, UTI presents 0% resistance on the treatment with linezolid (0 out of 63 cases) and rifampicin (0 out of 1 case). Also, a very low resistance can be also observed in the treatment with: 13.3% for teicoplanin (2 out of 64 cases); 3.17% vancomycin (2 out of 63 cases) and 8.15% for colistin (11 out of 135 cases). We also managed to identify a so-called profile of the patient with UTI MDR, which would be represented by the following factors:

-Male: 71.57% of cases during the period of study;
-Predominantly aged over 60, the peak incidence is between 60 and 80 years old;
-Diabetic - 16.88% of cases during the period of study;
-With a history of neoplastic incidents - 43.51% cases during the study;
-Chronic beneficiary of urethral catheter or DOUBLE J stent;
-With clinical records of transurethral resections (prostate, bladder tumors)

DISCUSSION

The presented data are highly relevant for the distribution and antibiotic susceptibility patterns of the bacterial species which were isolated in cultures from our UTI MDR patients.In this way, we have to mention even from the beginning that we consider our study very useful for the monitoring of the antibiotic susceptibility patterns at different uropathogens identified in Moldavia region, since this is extremely important not only because of the emerging problems of antibiotic resistance, but also in helping the aforementioned empirical therapy by developing a future antibiotic resistance database prescription.

When it comes to the other results from the literature, we firstly have to mention that these other data are relevant to a certain point, since the spectrum of resistance may vary temporally, between different countries, but also within countries and between regions and even different institutions.[9-12] In this way, a North American trial conducted by Zhanel et al., from 2005 called the North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study determined the antibiotic susceptibility to commonly used agents for urinary tract infections of outpatient Escherichia coli urinary isolates obtained from various geographic regions in the USA and Canada, from more than 40

medical centers.[13] There are also studies that took place in specific areas such as the one of Santo et al. from 2007 in Brazil, which was focused on the multidrug-resistant urinary tract isolates of Escherichia coli from a specific area of Sao Paulo, Brazil or the similar ones from India, Lebanon or Turkey.[14-19]

Thus, while the findings of the aforementioned studies varied in some specific details, which we are not going to insist now, they all agreed that the main cause of this resistance could be either the self increased and unnecessary usage of antibiotics, the prescription of modern antibiotics with newer combinations in order to get a faster effect in different infections, continuous antibiotic pressure, lower dosage or shorter duration that may have resulted in a selection of mutant resistant strains.[8,15]

In fact, in our study we reported that almost a quarter of the germs detected in UTI were MDR. As compared to the other studies described above, this is a very increased percentage. That is why we consider our study quite important, since it is, according to our best of knowledge, the first study in Romania testing these aspects in an important clinical center that is also representative for the entire Moldova area. These specific aspects for our country are very important considering the well-known problems regarding a somehow equivocal control on the drug prescription practices, and some problems as well with inadequate access to antibiotics (e.g. increased or misuse of them). We do believe also that the increased prevalence of uropathogens described in our present results is an important alarm signal.

Even more, besides the connection between environmental parameters and UTI occurrences, in the present study we characterized, also for the first time in our country, aspecific profile for the UTI-risk patient and, as we mentioned before, seems to be male, predominantly aged over 60, diabetic, with a history of neoplastic incidents, carrier of urethro-vesical catheter or "JJ" stent and also with clinical records of transurethral resections (prostate, bladder tumors).

This is of course very important, judging from the fact that a patient like that could be mentioned as a risky one, that needs to have his uroculture monitorized and is also resistant or is specifically responding to a certain type of antibiotic. In addition, in accordance with international literature, we also noticed some seasonal modification in UTI manifestations that contribute furthermore to the already mentioned aspects.[15]

Another related problem described in the literature is represented by the recurrent UTI, since it was recently stated that a repeated course of antibiotics is often prescribed for the treatment and prevention of recurrent UTI, which could for example select for resistant strains of uropathogenic Escherichia coli.[20,21]

Unfortunately we are facing the situation in which patients depending on chronic urethral catheters are receiving - unjustifiably! - antibiotic medication for an illusory prevention of the infection. This still widespread attitude in our medical world (as it is not only the urologist that regularly changes the catheter!) does not bring any benefit to the patient, because the urinary infection - asymptomatic bacteriuria - will develop anyway, and in addition it will also decisively help the pathogens acquire antibiotic resistance, which will lead to complications if possible antibiotherapy is necessary at some point. In this way, the latest EAU guides clearly recommends that only the infectious complications that occur in the patients with urethral catheters should be treated strictly targeted, as based on the antibiogram.

We do believe that one possible solution that could be considered is represented by stopping the administration of some classical drugs such as the norfloxacin, ciprofloxacin or levofloxacin for an amount of time. This could perhaps result in a "reactivation" of the sensitivity for the germs, of course after these drugs are hypothetically not prescribed in the hospital or at home for a fair amount of time, like the possible case of nitrofurantoin. In fact, if we look at the previous literature for the nitrofurantoin, it was found to be active against most of uropathogens and to have a low resistance and in this way it remains an important option that should be considered for the treatment of UTI.[22,23] One possible explication for this will be represented by the fact that it is not closely related to other antimicrobials and therefore cross-resistance is unlikely to develop, as well as the aforementioned fact that we could talk about a possible reactivation of the germs sensitivity after a time of non-administration.[8,16]

Suggestively, nitrofurantoin, a drug involuntarily "abandoned" when the promising new 2nd and 3rd generations of quinolones were introduced, is often the only efficient "weapon" with oral administration to which the multidrug resistant germs, especially the E. coli, are exhibiting sensitivity, according to the antibiogram. We believe that this observation could be the starting point for a courageous strategy to proceed to the exclusion of certain antibiotics or chemotherapy drugs which statistically demonstrated their ineffectiveness in vitro against most bacterial species causing urinary infections. In this way, two apparent advantages could derive from this strategy: the dismissal of unnecessary use of an antibiotic that does not treat, but cause side

Table 3. The results of the uroculture for most of the used antibiotics.

Antibiotic	The results of the uroculture			Total (%)
	Resistent (%)	Sensitive (%)	Intermediary (%)	
Ampicillin	346 (97.74)	8 (2.26)	0 (0)	354 (100)
Amoxicillin	2 (100)	0 (0)	0 (0)	2 (100)
Amoxicilim + ac. clavulanic	275 (81.36)	33 (9.76)	30 (8.88)	338 (100)
Ampicillin + sulbactam	19 (86.36)	2 (9.09)	1 (4.55)	22 (100)
Piperacillin	99 (25.78)	267 (69.53)	18 (4.69)	384 (100)
Ticarcillin	2 (100)	0 (0)	0 (0)	2 (100)
Ceftazidime	412 (93.64)	27 (6.14)	1 (0.23)	440 (100)
Cefuroxime	337 (98.54)	4 (1.17)	1 (0.29)	342 (100)
Cefotaxime	333 (95.69)	15 (4.31)	0 (0)	348 (100)
Cefepime	354 (80.45)	67 (15.23)	19 (4.32)	440 (100)
Imipenem	84 (23.26)	272 (75.35)	5 (1.39)	361 (100)
Meropenem	111 (26.30)	305 (72.27)	6 (1.43)	422 (100)
Gentamicin	326 (64.69)	162 (32.14)	16 (3.17)	504 (100)
Norfloxacin	313 (89.94)	27 (7.76)	8 (2.30)	348 (100)
Ciprofloxacin	397 (90.43)	34 (7.75)	8 (1.82)	439 (100)
Cefoperazone	112 (81.75)	21 (15.33)	4 (2.92)	137 (100)
Colistin	11 (8.15)	121 (89.63)	3 (2.22)	135 (100)
Tigecycline	33 (42.86)	40 (51.95)	4 (5.19)	77 (100)
Ertapenem	13 (17.34)	58 (77.33)	4 (5.33)	75 (100)
Cefalexin	3 (100)	0 (0)	0 (0)	3 (100)
Cefaclor	3 (100)	0 (0)	0 (0)	3 (100)
Cefixime	16 (94.12)	1 (5.88)	0 (0)	17 (100)
Ceftibuten	5 (100)	0 (0)	0 (0)	5 (100)
Cefpirome	30 (78.95)	6 (15.79)	2 (5.26)	38 (100)
Levofloxacin	137 (93.20)	7 (4.76)	3 (2.04)	147 (100)
Penicillin	52 (100)	0 (0)	0 (0)	52 (100)
Oxacillin	19 (100)	0 (0)	0 (0)	19 (100)
Vancomycin	2 (3.17)	61 (96.83)	0 (0)	63 (100)
Clarithromycin	4 (80)	1 (20)	0 (0)	5 (100)
Erythromycin	1 (100)	0 (0)	0 (0)	1 (100)
Rifampicin	0 (0)	1 (100)	0 (0)	1 (100)
Linezolid	0 (0)	63 (100)	0 (0)	63 (100)
Teicoplanin	2 (3.13)	62 (96.87)	0 (0)	64 (100)
Doxycycline	48 (77.42)	13 (20.97)	1 (1.61)	62 (100)
Sulfamethoxazole	13 (68.42)	6 (31.58)	0 (0)	19 (100)
Ceftaroline	1 (100)	0 (0)	0 (0)	1 (100)
Fosfomycin	2 (16.67)	9 (75)	1 (8.33)	12 (100)

effects ranging from simple allergies to anaphylactic shocks and also the eventually reintroduction of the previously "fallen in disgrace" antibiotics after years of avoidance, during which the bacterial populations may have become sensitive again to that drug. In addition, another important antibiotic that should be mentioned in this context is represented by fosfomycin, which in fact is recommended, in the same way as in the case of nitrofurantoin, for treating adults with uncomplicated urinary tract infections (no fever or flank pain).[24] In fact, there are some recent observational studies which reported that a clinical success of 94.2% or 92.2% occurs when treating urinary tract infections caused by MDR organisms by fosfomycin.[25-27]

As Giamarellou et al. highlighted in 2010, in the last years, drug companies mainly focused in developing new antimicrobial agents against Gram-positive bacteria, neglecting the problem of multidrug resistance induced by Gram-positive microorganisms.[11]

Also, in a report published in 2013 by Bennadi et al. it was suggestively showed that in developed countries self-medication is between 8-13%, while in others poorly developed can reach up to 73%, due to the self-medication correlated to bad local regulations (e.g. no prescription required etc). That is one of the reasons why our study is so important, since it brings increased levels of knowledge on the antimicrobial resistance patterns for most of the uropathogens. This could be essential in order to improve the actual guidelines on the empirical antibiotic therapy and also to finally result in appropriate use of antibiotics.[9,16,28]

Regarding the limitations of our current study, we could mention of course the fact that our study was only retrospective, from just one single clinical center, with no clear inclusion criteria selected other then clinical diagnosis of UTI and complete urine culture results, as well as the fact that previous antibiotic usage in the study population was not investigated. In this way, further studies in this area of research seems warranted, with the final goal of developing new antimicrobials for multi-drug resistant UTI, as well as for rapid diagnosis of UTI, and also accurate presumptive identification of patients with resistant pathogens.[15] Regarding some final take home messages we could say that the results we are presenting here are strongly suggesting that there is an urgent need to implement much more strict regulations regarding the use of antibiotics.

Moreover, antibiotics must be also used with prudence to treat recurrent UTI effectively. Also, in regards to the morbidity and treatment costs, the MDR urinary tract infections are a very important problem of public health. Therefore, treatment should be done in accordance with the antibiogram results and for a sufficient period of time, in order to avoid the appearance of pan-resistant germs for which there are no reserve antibiotics available. Additionally, discarding certain commonly used antibiotics, to which the great majority of the strains are resistant, for a period of time, could perhaps lead to a possible shift in the spectrum

of their sensitivity. In this way, considering all the aforementioned features, it seems that some regional surveillance studies, like we did in our present study are more than welcomed.

CONCLUSION

In the present report we were interested in determine the community associated UTI causing uropathogen's prevalence, the antibiotic resistance patterns and the risk factors associated with it in the most important clinical facility of this type from Moldova region in Romania. Our data showed that mainly the most problematic germs were represented by Klebsiella pneumoniae/spp, Pseudomonas aeruginosa, Escherichia coli and Staphylococci (coagulase-negative/S. aureus/S. saprophiticus). Also, the bacteria responsible for UTI MDR development presented a 100% resistance to the following nine antibiotics: amoxicillin, ticarcillin, cefalexin, cefaclor, ceftibuten, penicillin, oxacillin, erythromycin and ceftaroline. Moreover, an incresed resistance was also observed for the following antibiotics, in the following order: cefuroxime, ampicillin, cefotaxime, cefixime, ceftazidime, levofloxacin, ciprofloxacin, norfloxacin and ampicillin + sulbactam. In addition, for the first time in our country, a specific profile for the UTI MDR-risk patient was described in the present paper, being represented by male gender, predominantly aged over 60, diabetic, with a history of neoplastic incidents, carrier of urethro-vesical catheter or double J stent and also with clinical records of transurethral resections (prostate, bladder tumors).

* The authors declare that there are no conflicts of interest.

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