Urinary tract infections due to multi-drug-resistant bacteria at Mohammed VI University Hospital Center of Oujda-Morocco

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ABSTRACT

Aims: Multidrug-resistant bacteria urinary tract infections (MDR-UTI) are a global concern, leading to increased morbidity, mortality and financial costs. The aim of this study was to determine the prevalence of MDR-UTI and establish the epidemiological profile of UTI due to different phenotypes of MDR-UTI.

Methodology and results: This is a retrospective study of MDR-UTI assessed at the microbiology laboratory of Mohammed VI University Hospital Center of Oujda over 37 months from March 2016 to April 2019. The study included all requests for cytobacteriological examination of urine (CBEU) according to the instructions of the medical microbiology guidelines. An agar medium was utilized for bacterial culture experimentation. Antibiotic susceptibility testing was performed according to the European Committee on Antimicrobial Susceptibility Testing guidelines. CBEU in UTIs allowed the isolation of 1078 isolates. They were dominated by Gram-negative bacteria (87.65%; n=945), followed by Gram-positive bacteria for 12.34% (n=133). This included 181 (16.80%) multidrug-resistant strains, which were dominated by extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E) (n=144; 79.55%). Young male adults exhibited a higher occurrence of isolated ESBL-E and carbapenem-resistant Acinetobacter baumannii (CRAB). As for the distribution by department, there was a near equality between the MDR isolates isolated from outpatients (n=88; 49%) versus the inpatients (n=95; 51%). Exactly 152 (84%) isolated MDR cases were observed in patients who did not have a urinary catheter, 157 (87%) and 141 (78%) cases of MDR of UTI were not associated with care and occurred in non-immunocompromised patients, respectively. Prior antibiotic exposure was observed in only 58 (32%) cases.

Conclusion, significance and impact of study: This study confirmed the increasing prevalence of multidrug-resistant urinary tract infections in the community and hospitals. The fight against this problem will require all stakeholders’ involvement to achieve the goals from one health perspective in line with international agenda.

Keywords: Epidemiology, Morocco, multidrug-resistant bacteria, urinary tract infection

INTRODUCTION

According to the Infectious Diseases Society of America (IDSA), urinary tract infections (UTIs) are defined as the association of significant bacteriuria, leukocyturia and suggestive clinical symptoms (Nicolle et al., 2019). UTIs are common reasons for consultation in general practice and emergency departments (Amawi et al., 2021). Approximately 150 million UTI episodes are registered yearly worldwide (Stamm and Norrby, 2001). UTIs are curable diseases whose prognosis depends on the clinical context (simple, complicated, community and healthcare-associated urinary tract infection) and risk factors (age, history of urinary tract infection, sexual activity and diabetes) (López and Cortés, 2012; Flores-Mireles et al., 2015). However, the emergence of multidrug-resistant bacteria (MDR) leads to therapeutic failures and increased mortality and morbidity rates, forming a significant threat to public health worldwide (WHO, 2001; Tacconelli et al., 2018). The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have established a list of...
critical MDR for which there is an urgent need to research/develop new treatments (Tacconelli et al., 2018; CDC, 2019). These include extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E) (serious threats according to CDC, critique priority according to WHO), carbapenem-resistant Enterobacteriaceae (CRE) (urgent threats according to CDC, critique priority according to WHO), carbapenem-resistant Acinetobacter baumannii (CRAB) (urgent threats according to CDC, critique priority according to WHO), cefazidime-resistant Pseudomonas aeruginosa (CRPA) (serious threats according to CDC, critique priority according to WHO), methicillin-resistant Staphylococcus aureus (MRSA) (serious threats according to CDC, high priority according to WHO) and vancomycin-resistant Enterococcus faecium (VRE) (serious threats according to CDC, high priority according to WHO) (Tacconelli et al., 2018; CDC, 2019).

Antibiotic resistance increases morbidity, mortality and medical costs (Ventola, 2015). The CDC estimated that antibiotic resistance in the United States caused more than 2.8 million infections and 35,000 deaths by the year of 2017 (CDC, 2019). The European CDC estimated that nearly 672,000 infections were due to antibiotic-resistant bacteria in 2015, responsible for 33,000 deaths and 1 billion Euros in costs per year (OMS, 2021). National studies of MDR UTIs have focused on β-lactamase and/or carbapenemase-producing Enterobacteriaceae.

No study has specified the prevalence of UTIs due to the other resistance phenotypes (Lahliou Amine et al., 2009; El Bouamri et al., 2014).

This study was aimed to determine the prevalence of MDR-UTI and establish the epidemiological profile of UTIs due to different phenotypes of MDR at Mohammed VI University Hospital Center of Oujda.

MATERIALS AND METHODS

This is a retrospective study of the UTIs-MDR at the Mohammed VI University Hospital Center of Oujda Microbiology Laboratory. The study period was from March 2016 to April 2019 (37 months). Our study included all requests for cytobacteriological urine examination (CBEU). It was performed in accordance with the instructions of the medical microbiology guidelines (Rémic, Société française de microbiologie, 2015; 2018). A culture of bacteria was performed on UTI Brilliance Agar® (Oxoid ™). Cytology was determined by UF1000i Sysmex®. Identification of bacterial strains was performed by the PHOENIX 100 automaton (BD ™). Antibiotic susceptibility testing was performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (EUCAST, 2016; 2017; 2018). Results analysis was performed using MS Office Excel 2016. The definition of multi-drug-resistant adopted in our work corresponds to the list approved by the World Health Organization and the Centers for Disease Control (Tacconelli et al., 2018; CDC, 2019).

RESULTS AND DISCUSSION

We have collected 23217 requests for CBEU. Sterile cultures were reported in 13780 (59%) cases, polymorphic culture in 7265 (31%) cases, UTIs were reported in 1013 (5%) cases and urinary colonization in 1159 (5%) cases. The sex ratio in UTIs was 0.6 (62% occurred in female patients and 38% in male patients). The CBEU in UTIs allowed the isolation of 1078 bacteria. They were dominated by Gram-negative bacteria (87.65%; n=945), followed by Gram-positive bacteria (12.34%; n=133). Exactly 181 (16.80%) strains were MDR. They were dominated by ESBL-E (79.55%; n=144), EBLS-E and CRAB were isolated more in young male adults. VRE was more isolated in elderly subjects. As for the distribution by service, there was a near equality between the isolated MDR from external services n=88 (49%) (outpatients n=58; emergency n=30), versus the hospital services n=93 (51%) represented by medical services n=36; intensive care units n=30; surgical services n=27. Among the isolated cases, 152 (84%) cases did not have a urinary catheter, 157 (87%) and 141 (78%) cases were not associated with care and occurred in non-immunocompromised patients, respectively. Prior antibiotic therapy was observed in only n=58 cases. Table 1 shows the distribution of isolated species and the proportion of multi-drug-resistant strains among them. Table 2 shows the distribution of isolated multi-drug-resistant bacteria according to the risk factors of patients with UTIs.

UTI is a common infection in both communities and hospitals (Tan and Chlebicki, 2016). In our study, the frequency of UTIs was 5%. In the literature, this frequency varies according to the targeted populations and the designs of the different studies (Raka et al., 2004; Lahliou Amine et al., 2009; Moroh et al., 2014; Mohammed et al., 2016). Despite these differences in the frequency of UTIs, all studies, including our own, agreed on the frequency of UTIs in women (Randrianirina et al., 2006; Magliano et al., 2012). The female urinary system's anatomical characteristics, represented by the short length of the urethra and the proximity to the anal area, might explain this frequency (Randrianirina et al., 2006; Magliano et al., 2012). UTIs are one of the leading causes of the prescription and consumption of antibiotics (Aabenhus et al., 2017). The relationship between antibiotic consumption and the emergence of resistance has been well-established in the literature (Costelloe et al., 2010; Bell et al., 2014; Olesen et al., 2018; Mohareb et al., 2021).

This is more serious in the case of UTIs, which are almost exclusively due to bacteria originating from the intestinal flora (Chen et al., 2013; Ruppé and Andremont, 2013; Magrunder et al., 2019). Antibiotic resistance continues to evolve and causes severe problems for humanity (Reygaert, 2018); it results from the inappropriate use of antibiotics in humans, agriculture and the dissemination of resistant genes between humans, animals and the environment (Reygaert, 2018).
These mechanisms are the production of antibiotic hydrolyzing enzymes, target modification, membrane impermeability and efflux system, allowing the rejection of antibiotics out of the bacteria, as depicted in Table 3 (Reygaert, 2018). Our study showed a prevalence of MDR in our study. The prevalence of ESBL-E among Enterobacteriaceae in our series was slightly higher than in national studies (Marrakech 10%, Meknes 9%) (Lahlou Amine et al., 2009; El Bouamri et al., 2014). This could be mainly explained by the time and design of the study. Indeed, the prevalence rate of ESBL-E has been increasing over the last decade (Urbánek et al., 2007; Oz et al., 2014). This is principally due to the selective pressure exerted by the inappropriate use of broad-spectrum antibiotics, including third-generation cephalosporins and fluoroquinolones (Urbánek et al., 2007; Oz et al., 2014). The distribution of all multi-drug-resistant bacteria according to risk factors is modeled on Table 3.
Table 2: Distribution of 181 MDR isolated from UTI cases according to the recorded risk factors.

<table>
<thead>
<tr>
<th>MDR</th>
<th>Age groups</th>
<th>Gender</th>
<th>Departments</th>
<th>Presence of urinary catheter</th>
<th>Antibiotic therapy before CBEU</th>
<th>Healthcare-associated UTI</th>
<th>Immuno-depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children</td>
<td>Young adults</td>
<td>Elderly adults</td>
<td>Female</td>
<td>Male</td>
<td>Intensive care units</td>
<td>Medical</td>
</tr>
<tr>
<td>ESBL-E</td>
<td>37</td>
<td>69</td>
<td>38</td>
<td>61</td>
<td>83</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>CRE</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>n=11 (6%)</td>
<td>0</td>
<td>11</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>CRAB</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>n=14 (8%)</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>CRPA</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>n=2 (1%)</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>VRE</td>
<td>41</td>
<td>89</td>
<td>51</td>
<td>79</td>
<td>102</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>n=5 (3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Children: ≤15 years old; Young adults: 16–65 years old; Elderly adults ≥66 years old.

ESBL-E: Extended-spectrum beta-lactamase-producing Enterobacteriaceae; CRE: Carbapenem-resistant Enterobacteriaceae; CRAB: Carbapenem-resistant Acinetobacter baumannii; CRPA: Ceftazidime-resistant Pseudomonas aeruginosa; VRE: Vancomycin-resistant Enterococcus faecium; MRSA: Methicillin-resistant Staphylococcus aureus.

was similar in hospital- and community-acquired infections (n=93, 51.4%) and (n=88, 48.6%), respectively. These high levels of resistance in community-acquired infections are mainly due to the large number of ESBL-E strains found in outpatients (n=75, 52.1%). The shared resistance between hospitals and community settings is a real public health problem. This rate varies considerably from one country to another and within the same country, indicating an extensive reservoir of resistance in these two settings (Bouchillon et al., 2012). The presence of the urinary catheter is associated with an increased risk of urinary tract infections from multi-drug-resistant bacteria (Clarke et al., 2020; Werneburg et al., 2022). The catheter inhibits the defense mechanisms of the urinary tract epithelium against bacteria and facilitates the rapid invasion of the bladder by colonizing microorganisms (Clarke et al., 2020; Werneburg et al., 2022). In addition, it promotes the development of bacterial biofilm, where antibiotics do not reach significant concentrations (Werneburg et al., 2022). However, we did not find an association between the notion of urinary catheter and bacterial resistance because urine collection in the middle of the stream is the method most used by outpatients, and we had a few patients with urinary catheters n=29 (16%). Similarly, the infection associated with care represented only n=24 (13%) of UTIs with MDR. This confirms the increase
of resistance in the community. Likewise, probabilistic antibiotic therapy was administered in only 32% (n=58) of patients with MDR, probably due to the lack of situations requiring empirical administration of antimicrobials, especially immunosuppression observed in just 22% (n=40).

Overall, the involvement of different risk factors in MDR-UTIs varies from study to study and according to the study design (Tenney et al., 2018). However, regardless of the context, MDR-UTI prevention must consider all known risk factors (Ikram et al., 2015). Thus, preventive measures are based on global UTI prevention and multi-drug-resistance prevention (Warzecha et al., 2021). Regarding the first component, preventative measures are aimed at combating the risk factors. They include abundant hydration, prevention and treatment of constipation, behavioral rehabilitation/frequent urination, promote mobilization, rules of intimate hygiene, urinating after sex, treatment of any abnormalities of the urinary tree functional or organic and specific measures recommended in patients with urinary catheters (Lajoso et al., 2018). Other alternatives can be used: Cranberry products (Jepson et al., 2012), herbal therapy with Canephron N (Naber, 2013), probiotics (Gupta et al., 2017), nonsteroidal anti-inflammatory drugs (Gágyor et al., 2015), estrogen use (Rosenthal, 2020), vitamins C (Hudson et al., 2022), D-mannose (Altarac and Papeš, 2014) and immunotherapy (Wade et al., 2020). Concerning the second part, the fight against bacterial resistance must break the chain of acquisition of resistance genes and their propagation (Levent et al., 2003).

To manage the challenges posed by AMR, the entire health system must be engaged in the "One World, One Health" concept (Ryu, 2017; Badau, 2021). The "One World, One Health" concept has been presented as a paradigm for introducing and promoting multidisciplinary collaboration. It is an effort to integrate many local, national, and global disciplines to achieve optimal health for humans, animals and the environment (Ryu, 2017; Badau, 2021). The objectives of the WHO in its action plan against bacterial resistance are to improve knowledge through effective education and training, to promote surveillance and research, to adopt hygienic and preventive measures to reduce the incidence of infections, to rationalize antibiotic therapy in humans and animals, and to increase investment in the development of new antibiotics and diagnostic tools (Badau, 2021).

CONCLUSION
Research findings highlight the critical and alarming increase in the incidence of multi-drug-resistant urinary tract infections, both in the community and in the hospital setting, covering a variety of phenotypes. This emerging crisis calls for a combined effort from all stakeholders to take immediate and coordinated action to solve the complex problem of antimicrobial resistance.

CONFLICTS OF INTEREST
We declare no conflict of interest.

DATA AVAILABILITY
All data used to support the findings of our study are available from the corresponding author upon request.

REFERENCES


