

Assessment of Risk Factors, Treatment and Hospital Stay in Complicated Urinary Tract Infections in Men Caused by *Pseudomonas*: A Case-Control Study

Erkeklerde *Pseudomonas* ile Gelişen Komplike Üriner Sistem Enfeksiyonlarında Risk Faktörlerinin, Tedavi ve Hastane Yatış Sürelerinin Değerlendirilmesi: Olgu-Kontrol Çalışması

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What's known on the subject? and What does the study add?

It's known that the *Pseudomonas*, identified as the cause of health care-related complicated urinary tract infection (UTI), is an independent risk factor of mortality. Risk factors and antibiotic resistance data should be known for a proper empiric treatment. Nephrolithiasis and recurrent UTI were found independent risk factors of *Pseudomonas* related UTI. In such cases, anti-pseudomonal antibiotics should be taken into consideration. When resistance rates are taken into account, ciprofloxacin use should be limited. Also, it's thought that improper empiric treatment would increase costs by prolonging hospitalization.

Abstract

Objective: It is known that *Pseudomonas* has been isolated more frequently in health care-related urinary tract infections (UTIs). It was aimed to determine the risk factors and empiric therapies due to antibiotic resistance in *Pseudomonas*-related male UTIs, and assess the effect of *Pseudomonas* isolation on treatment and length of hospital stay.

Materials and Methods: The study was conducted between January 2011 and January 2013 with 228 male health care-related complicated UTI patients hospitalized in the Urology and Infectious Diseases Inpatient Clinics at Gazi University Faculty of Medicine. Three hundred UTI attacks in 228 patients were evaluated retrospectively with regard to agents.

Results: *Pseudomonas* was isolated in 37 of 300 complicated UTI attacks in 228 male patients. Nephrolithiasis, recurrent UTI and internal urinary catheterization were determined as the risk factors for *Pseudomonas* related with health care-related UTI. It was understood that nephrolithiasis increased *Pseudomonas* isolated UTI risk 3.5 fold and recurrent UTI increased the risk 8.9 fold. The antibiotic resistance of *Pseudomonas* was higher than other agents. *Pseudomonas* related UTIs prolonged the duration of hospital stay and antibiotic treatment.

Conclusion: In the presence of nephrolithiasis, recurrent UTI and internal urinary catheterization, drugs against *Pseudomonas* would be appropriate empiric treatment for health care-related complicated UTI. Ciprofloxacin use should be restricted when local antibiotic resistance, which leads empiric treatment, is taken into consideration. Increases in hospital stay and antibiotic treatment duration were thought to be associated with recurrent infection frequency and high antibiotics resistance in *Pseudomonas* related UTIs.

Keywords: *Pseudomonas*, complicated urinary tract infection, drug resistance

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Received: 09.10.2016

Accepted: 21.12.2016

Presented in: European Society Clinical Microbiology Infectious Diseases (ESCMID), 10 May 2014, in Barcelona, Spain.

Cite this article as: Özger HS, Kardeşin Ö, Kardeşin EF, Gaygusuz Ü, Şen İ, Dizbay M. Assessment of Risk Factors, Treatment and Hospital Stay in Complicated Urinary Tract Infections in Men Caused by *Pseudomonas*: A Case-Control Study. J Urol Surg 2017;4:48-52.

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Öz

Amaç: Sağlık bakımı ilişkili üriner sistem enfeksiyonlarında (ÜSE), *Pseudomonas*'ın artan sıklıklarda izole edildiği bilinmektedir. Bu çalışmada, erkeklerde *Pseudomonas* ilişkili komplike ÜSE'de risk faktörlerinin saptanması, antibiyotik dirençleri değerlendirilerek ampirik tedavi yaklaşımlarının belirlenmesi ile *Pseudomonas* izolasyonunun tedavi ve hastane yatış süresi üzerine etkisinin değerlendirilmesi amaçlanmaktadır.

Gereç ve Yöntem: Çalışmaya Ocak 2011-Ocak 2013 tarihleri arasında Gazi Üniversitesi Tıp Fakültesi, Üroloji ve Enfeksiyon Hastalıkları Servisleri'nde sağlık bakımı ilişkili komplike ÜSE tanısı konulan 228 erkek hasta dahil edilmiştir. Dahil edilen 228 hastada 300 ÜSE atağı izole edilen etkenler açısından retrospektif değerlendirilmiştir.

Bulgular: İki yüz yirmi sekiz erkek hastada 300 komplike ÜSE atağının 37'sinde *Pseudomonas* izole edilmiştir. *Pseudomonas* ilişkili sağlık bakımı ilişkili komplike ÜSE için nefrolitiazis, rekürren ÜSE ve internal üriner kateterizasyon risk faktörleri olarak tespit edilmiştir. Nefrolitiazis varlığında 3,5 kat, rekürren ÜSE varlığında ise 8,9 kat riskin arttığı saptanmıştır. *Pseudomonas*'larda antibiyotik direncinin diğer suşlara göre daha yüksek olduğu belirlenmiştir. *Pseudomonas* etken olduğu ÜSE'lerin hastane yatış süreleri ve antibiyotik tedavi sürelerini uzattığı saptanmıştır.

Sonuç: Sağlık bakımı ilişkili komplike ÜSE ampirik tedavisinde, nefrolitiazis, internal üriner kateterizasyon ve rekürren ÜSE risk faktörleri varlığında *Pseudomonas*'a yönelik tedavinin uygun olacağı düşünülmektedir. Ampirik tedaviye yön verecek lokal antibiyotik direnç verileri göz önüne alındığında siprofloksasin kullanımının sınırlandırılması öngörülmektedir. *Pseudomonas* ilişkili ÜSE'lerde hastanede yatış süresi ve antibiyotik kullanım sürelerindeki artışın rekürren enfeksiyon sıklığı ve yüksek antibiyotik direnci ile ilişkili olduğu düşünülmektedir.

Anahtar Kelimeler: *Pseudomonas*, komplike üriner sistem enfeksiyonu, ilaç direnci

Introduction

Urinary tract infections (UTIs) constitute more than 30% of the nosocomial infections (1). Besides causing prolonging of hospital stay and increase in health expenditures, it also leads to bacteremia and mortality in case of improper empiric therapy (2). Therefore, it is important to determine agents early and start proper empiric therapy as soon as possible. Differentiation of increasing antibiotic resistances due to the agents requires risk factors of possible agents to be evaluated before therapy. Existence of urinary catheter, history of urological intervention, long hospital stay, male sex and existence of disease causing debility are risk factors for nosocomial UTI development (3). Especially in recent years, non-fermenter bacteria including *Pseudomonas* strains have an extensive place in health care-related infections (4).

It was aimed to determine the risk factors and empiric therapies due to the antibiotic resistance in *Pseudomonas* related male UTIs, and assess the effect of *Pseudomonas* isolation on treatment and length of hospital stay.

Materials and Methods

The study was conducted between January 2011 and January 2013 with 228 male health care-related complicated UTI patients hospitalized in our urology and infectious diseases inpatient clinics. Three hundred UTI attacks in 228 patients were evaluated retrospectively with regard to agents. UTIs were grouped as *Pseudomonas spp.* isolated and not and compared for the risk factors, hospital stay and treatment duration.

Statistical Analysis

Data was presented as number and percentage and continuous variables were presented by mean \pm standard deviation and

median (minimum, maximum). Chi-square test was used for comparisons. Logistic regression analysis was conducted with nephrolithiasis, recurrent UTI, prostatic hypertrophy, diabetes mellitus, internal and external catheter which were determined as risk factors. Antibiotic resistance of most identified agents were determined and presented as number and percentage.

Double J catheter use was accepted as internal catheterization and other urinary catheterization ways except double J catheter accepted as external catheterization.

Results

Three hundred complicated UTI attacks in 228 male patients were included. The mean age of the patients was 65.7 ± 15.18 years (median 69; 18-94). There was no statistically significant difference between the *Pseudomonas* isolated and non-isolated patient groups (67 ± 14.9 vs. 69 ± 15.2 ; $p=0.37$).

Pseudomonas was isolated in 37 of 300 UTI attacks. Isolated agents are presented in Table 1.

Table 1. Distribution of agents in urinary tract infections

Agent	n=300	%
<i>Pseudomonas spp.</i>	37	12.3
<i>Acinetobacter spp.</i>	5	1.6
<i>Candida spp.</i>	17	5.6
<i>Citrobacter freundii</i>	1	0.3
<i>Corynebacterium jeikeium</i>	1	0.3
<i>Escherichia coli</i>	154	51.3
<i>Enterococcus spp.</i>	22	7.3
<i>Klebsiella spp.</i>	35	11.6
Coagulase negative <i>Staphylococcus</i>	26	8.6
<i>Stenotrophomonas maltophilia</i>	2	0.6

UTI attacks grouped as *Pseudomonas* isolated and not, compared for the complicated UTI risk factors and are presented in Table 2.

According to the result of logistic regression analysis, it was found that recurrent UTI increased complicated UTI risk 2.97 (95% confidence interval: 1.45-6.09) fold ($p=0.003$).

Antibiotic resistances of most common isolated agents (*Escherichia coli*, *Pseudomonas* and *Klebsiella*) were determined. Ciprofloxacin resistance was 72% and 51.4% in *Escherichia coli* and *Klebsiella* isolates, respectively. Trimethoprim-sulfamethoxazole resistance was 59% and 60%; extended-spectrum beta-lactamase (ESBL) positivity was 48% and 45.7%,

respectively. Antibiotic resistance of *Pseudomonas* isolates are shown in Table 3.

UTI attacks grouped as *Pseudomonas* isolated and not, compared for length of hospital stay and antibiotic treatment duration (Table 4).

Discussion

Pseudomonas is one of the most common agents determined in complicated UTIs related with gram negative enteric bacteria and especially more often determined in health care-related UTIs (1,2,5,6,7). A study assessing the differentiation of UTI

Table 2. Distribution of complicated urinary tract infection risk factors by agents

	<i>Pseudomonas</i> isolated (%)	Non- <i>Pseudomonas</i> agents isolated	p
Urinary tract malignancy			
Yes	17 (45.9)	98 (37.3)	0.30
No	20 (54.1)	165 (62.7)	
Diabetes mellitus			
Yes	7 (18.9)	63 (23.9)	0.65
No	30 (81.1)	200 (76.1)	
Internal urinary catheterization			
Yes	9 (24.3)	32 (12.1)	<0.05
No	28 (75.7)	231 (87.9)	
External urinary catheterization			
Yes	9 (24.3)	89 (33.9)	0.24
No	28 (75.7)	174 (66.1)	
Prostatic hypertrophy			
Yes	16 (43.2)	132 (50.1)	0.42
No	21 (56.8)	131 (49.9)	
Nephrolithiasis			
Yes	11 (29.8)	37 (14.0)	<0.05
No	26 (70.2)	226 (86.0)	
Urological intervention			
Yes	19 (51.3)	147 (55.9)	0.60
No	18 (48.6)	116 (44.1)	
Recurrent urinary tract infection			
Yes	22 (59.4)	82 (31.2)	<0.05
No	15 (40.6)	181 (68.8)	
Two and more attacks			
Yes	14 (37.9)	49 (18.6)	<0.05
No	23 (62.1)	214 (81.4)	
Neurogenic bladder			
Yes	3 (8.1)	10 (3.9)	0.41
No	34 (91.9)	253 (96.1)	

Table 3. Antibiotic resistance of *Pseudomonas isolates*

Antibiotic	Resistance (n)	(%)
Ciprofloxacin	24	64.8
Cefepime	19	51.3
Ceftazidime	12	32.4
Cefoperazone-sulbactam	17	45.9
Piperacillin-tazobactam	7	18.9
Aminoglycoside	7	18.9
Carbapenem	5	13.5

Table 4. Comparison of hospital stay and treatment duration in urinary tract infection attacks by agents

	<i>Pseudomonas</i> UTI	Non- <i>Pseudomonas</i> UTI	p
Therapy duration (day)	14±5.5	10±3.5	<0.05
Hospital stay duration (day)	14±8.8	10±8.0	<0.05

UTI: Urinary tract infection

agents at intensive care units (ICUs) over a 10-year period showed a significant increase in UTIs caused by *Pseudomonas* and *Klebsiella* isolates (8).

Determining the risk factors for UTI agents is very important to predict the real agent and start treatment with proper empiric antibiotic therapy (1). Djordjevic et al. (9) identified female gender, previous hospitalization and beta-lactam antibiotic use as independent risk factors for UTIs caused by *Pseudomonas*. Venier et al. (10) found that *Pseudomonas* UTIs in ICU patients were associated with male gender, length of hospital stay and antibiotic therapy. A study assessing UTIs developed in males showed that the frequency of *Pseudomonas* originated from UTIs increase with age (11). Urinary stone and catheter were found to be risk factor for *Pseudomonas* related UTI by Johansen et al. (12). Association of bacteria except *Escherichia coli* with recurrent UTIs in male gender was proven in a study by Amna et al. (13) assessing community-acquired bacteriuria. A study assessing recurrent UTIs after renal transplantation found that the most common identified agent was multi-drug resistant *Pseudomonas* after ESBL-positive *Klebsiella* and ESBL-negative *Escherichia coli* strains (14). In accordance with the literature, our study proved that anti-pseudomonal antibiotics should be used in empiric treatment of health care-related complicated UTIs when there are risk factors such as nephrolithiasis and recurrent UTI.

Phenotypic characteristics of *Pseudomonas* such as pyoverdine, protease, and phospholipase A production in combination with quorum sensing activity and biofilm formation were revealed to ease the development of catheter related UTIs (15). In our study, internal catheter (double J catheter) presence was found to be more frequent in *Pseudomonas* related UTI.

Antibiotic resistance in *Pseudomonas* was declared to be higher than other strains in UTIs (8). In our study, ciprofloxacin resistance was detected quite high in *Pseudomonas* strains and it was observed that the oral therapy chance decreased gradually. Resistance to phosphomycin which can be used in oral therapy was found in 56% of *Pseudomonas* strains in Turkey (16). Fu et al. (17) showed that there was 30-40% resistance to parenteral administrable anti-pseudomonal antibiotics. In our study, frequency of anti-pseudomonal cephalosporin resistance in *Pseudomonas* strains was detected to be 30% and higher. Also, it is known that carbapenem resistance is increasing gradually. Carbapenem resistance in *Pseudomonas* strains in invasive device-related infections was determined as 42%, 4% in a study conducted in 43 countries from Latin America, Asia, Africa and Europe (18). In our study, carbapenem resistance was 13% in *Pseudomonas* which caused UTIs. Especially, a rise in recurrent infections associated with *Pseudomonas* causes a rise in frequency of antibiotic therapy, thereby, it eases the development of antibiotic resistance. The frequency of multi-drug resistant *Pseudomonas aeruginosa* in UTI was shown to be increased in half between 2000 and 2009 by Zilberberg and Shorr (19). Clinical guidelines indicate that optimal therapy should be given according to the clinical evaluations and local antibiotic resistance data, because of the differences in data regarding resistance (20,21). Increases in length of hospital stay and antibiotic treatment duration were thought to be associated with recurrent infection frequency and high antibiotics resistance in *Pseudomonas* related UTIs.

Frequency of recurrent infection and increase in drug resistance of *Pseudomonas* chains make the infection treatment difficult. A study made in India showed that *Pseudomonas* related nosocomial UTIs increased the hospital stay duration (21). In our study, antibiotic therapy and hospital stay duration in *Pseudomonas* isolated UTIs were found to be higher than in UTIs originated from other agents.

Horino et al. (22) showed that the important part of the *Pseudomonas* bacteremia was secondary to UTI derived from the same bacteria. Moreover, improper empiric antibiotic therapy in UTI attacks was shown to be associated with bacteremia and mortality (2).

Study Limitations

The most favorable limitation of our work is retrospective construct. It is also thought that increasing the number of agents in order to determine the risk factors for complicated UTI associated with *Pseudomonas* in men will increase the power of future studies.

Conclusion

Empiric treatment should be started after assessing the risk factors of health care-related complicated UTI. Improper empiric antibiotic selection without consideration of risk factors and local resistance data in *Pseudomonas* related UTI especially, is thought to be the reason of recurrence and increase in resistance. Anti-pseudomonal antibiotics should be used as empiric treatment in the presence of nephrolithiasis, recurrent UTI and internal urinary catheter. However, when the resistance rates are taken into account, ciprofloxacin use should be limited. In addition, it is thought that improper empiric treatment would increase health care-related costs by prolonging hospitalization.

Ethics

Ethics Committee Approval: The study was retrospectively reviewed by examining patient files. For this reason, ethical approval was not received.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.S.Ö., Ö.K., Ü.G., Concept: H.S.Ö., Ö.K., E.F.K., Ü.G., İ.Ş., M.D., Design: H.S.Ö., Ö.K., M.D., Data Collection or Processing: H.S.Ö., Ö.K., E.F.K., Ü.G., Analysis or Interpretation: E.F.K., Literature Search: H.S.Ö., Ö.K., E.F.K., Ü.G., İ.Ş., M.D., Writing: H.S.Ö., Ö.K., E.F.K., Ü.G., İ.Ş., M.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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