

THE EFFECT OF DIABETES MELLITUS ON THE CLINICAL AND MICRO-BIOLOGICAL OUTCOMES IN PATIENTS WITH ACUTE PYELONEPHRITIS

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Received 2014-03-26; Revised 2014-04-08; Accepted 2014-05-06

ABSTRACT

There is some published evidence which suggests that the clinical outcomes and pathogens associated with Acute Pyelonephritis (AP) differ between diabetics and non-diabetics. However, current guidelines do not make treatment distinctions based on Diabetes Mellitus (DM) status. The objectives of this study were to identify the microbiological and clinical characteristics of hospitalized patients with AP and investigate differences between patients with and without DM. A retrospective cohort study of adult patients admitted with AP at The Brooklyn Hospital Center was conducted. Patient information was accessed through the hospital's electronic medical record system and patients were identified through primary discharge diagnosis ICD-9 codes for AP within the past three years. Patients were then screened for DM; all DM patients were randomly matched in a 2:1 manner to patients without DM admitted with AP during the same time period. A total of 48 patients were included in this analysis, 16 with DM and 32 without DM. There was a significantly greater median length of stay among diabetics (6 (3-8) Vs. 3 days (2-5), $P = 0.02$). There was a greater rate of antimicrobial resistance among DM patients, with a significantly greater rate of infection by Multi-Drug Resistant Organisms (MDRO) (4/16 [25%] Vs. 1/32 [3%], $P = 0.036$). *Escherichia coli* was the overall most common uropathogen, in 50% of the DM patients and 53% of the non-DM patients. Ceftriaxone monotherapy was the most commonly used empiric regimen in both groups (10/16 [63%] Vs. 19/32 [59%]) and there were similar rates of ceftriaxone sensitivity (8/10 [80%] Vs. 19/19 [100%]). Patients with DM were at greater risk of infection from MDRO and required longer lengths of hospitalization than patients without DM. Further investigation is warranted to guide effective empiric treatment of AP among patients with DM.

Keywords: Acute Pyelonephritis, Urinary Tract Infections, Diabetes Mellitus

1. INTRODUCTION

Patients with Diabetes Mellitus (DM) have been found to be at an increased risk of developing Urinary Tract Infections (UTI) (Patterson and Andriole, 1997; Hirji *et al.*, 2012; Muller *et al.*, 2005; Scholes *et al.*, 2005). The etiology of this increased risk is multifactorial and includes incomplete bladder emptying secondary to autonomic neuropathy and high urinary glucose concentration; both of which promote microbial growth (Ronald and Ludwig, 2001). For these reasons, patients with DM are known to have an increased rate of

recurrent UTIs (Patterson and Andriole, 1997). Additionally, severe complications such as emphysematous pyelonephritis and abscess formation may occur more commonly in patients with DM (Joshi *et al.*, 1999).

The microbiological patterns of UTIs may differ between patients with DM and those without DM. While *Escherichia coli* is the causative pathogen for the majority of UTIs (Saeed and Mohammed, 2010), *Klebsiella spp.*, *Streptococcus spp.* and *Candida spp.* are also common uropathogens among diabetic patients (Kofteridis *et al.*, 2009; Horcajada *et al.*, 2003). Patients with DM may be at an increased risk of infection by

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Multi-Drug Resistant Organisms (MDRO), however few trials have assessed microbiological differences in uropathogens between DM and non-DM patients and further investigation is necessary (Kofteridis *et al.*, 2009; Horcajada *et al.*, 2003). While it is known that patients with DM disproportionately suffer from more frequent and severe UTIs, current treatment guidelines do not distinguish treatment recommendations for patients with DM and those without DM (Gupta *et al.*, 2011; Kofteridis *et al.*, 2009). The Infectious Disease Society of America and The European Society for Microbiology practice guidelines for the treatment of hospitalized patients with AP recommend empiric regimens including a fluoroquinolone or aminoglycoside with or without ampicillin, an extended spectrum penicillin or cephalosporin with or without an aminoglycoside, or a carbapenem (Gupta *et al.*, 2011). In practice, clinicians often turn to consensus guidelines for assistance with antibiotic selection, however these guidelines do not provide recommendations for the optimal management of AP in diabetic patients. The wide range of antibiotic recommendations complicates treatment selection and further heightens the need for the reevaluation of evidence supporting empiric treatment. Additionally, it is unknown what degree of glycemic control can mitigate the risk of developing a UTI and further complications. Better understanding of clinical and microbiological characteristics in this patient population will help clinicians manage AP.

In this study, we sought to investigate differences based on DM status in the setting of AP. Our primary objectives were to evaluate the clinical and microbiological characteristics of AP among hospitalized patients. We hypothesized that among hospitalized patients with AP, those with DM may be at a greater risk of infection by MDRO and suffer worse clinical outcomes than those patients without DM. Our secondary objective was to investigate potential risk factors for developing infection by MDROs and assess differences based on DM status. The implications of these findings may be important to guide treatment recommendations for DM patients with AP.

2. MATERIALS AND METHODS

2.1. Study Design and Patient Population

A retrospective cohort study was conducted of patients with and without DM diagnosed with AP and admitted between January 2010 and August 2012 to The Brooklyn Hospital Center, a 463-bed community teaching hospital in Brooklyn, NY. Patients were

identified using ICD-9 codes for AP. The study protocol was approved by the hospital's institutional review board. Inclusion criteria: (1) Adult patients ≥ 18 years (2) Patients with AP as primary discharge diagnosis for hospitalization. If a patient was admitted for AP on multiple occasions within the study period, only the first episode of infection was included. Exclusion criteria: (1) patients with indwelling urinary devices. We randomly matched all identified patients with DM to non-DM patients in a 2:1 manner; all non-DM patients were admitted for AP during the same time period.

2.2. Data Collection and Study Definitions

The medical and laboratory records of eligible patients were retrospectively reviewed for pertinent demographic, laboratory and clinical data. A structured data collection form was used to record the abstracted data and all data were compiled into a single database using Microsoft Access (Microsoft Corp, Redmond, Wash). Demographic data included age, gender, place of residence prior to hospitalization (home, or transferred from an outside hospital or facility), admission to ICU, total length of stay, length of stay after isolation of organism and co-morbid conditions.

Infections were defined according to criteria established by the Centers for Disease Control and Prevention (Horan *et al.*, 2008). AP infection was confirmed based on clinical signs and symptoms of infection and we considered the AP diagnosis accurate if patients had fever (>38 C), flank pain, or flank tenderness associated with pyuria (>10 WBC mL^{-1}). Then, patients were screened for DM by assessing the past medical history for DM. Diagnosis of DM was made based on American Diabetes Association criteria, Hb A1c $\geq 6.5\%$, fasting plasma glucose ≥ 126 mg dL^{-1} , 2 h plasma glucose ≥ 200 mg dL^{-1} during an oral glucose tolerance test, or a random glucose level of ≥ 200 mg dL^{-1} with symptoms of hyperglycemia (ADA, 2013).

Time to achieve clinical stability was defined as return of altered mental status and abnormal vital signs to normal baseline values (heart rate ≤ 100 beats min^{-1} , systolic blood pressure ≥ 90 mm Hg, respiratory rate ≤ 24 min^{-1} , oxygen saturation $\geq 90\%$ and temperature $\leq 37.2^\circ\text{C}$ [99°F]). Response included complete and partial responses. A complete response was defined as resolution of fever, leukocytosis and local signs of infections; a partial response was improvement of some but not all of these conditions. Non-response included failure, relapse and death. Failure was defined as no improvement or worsening of signs and symptoms of infections; relapse was recurrence of infection with the same organism at anybody site within 1 month after discontinuation of therapy.

Risk factors for MDRO were defined according to criteria described by clinical practice guideline (ATS, 2005). Uropathogens were deemed to be MDRO if resistant to two or more classes of antibiotics.

2.3. Outcome Analysis

Primary outcomes measures were clinical and microbiological characteristics. The clinical outcomes assessed were length of stay, rate of complications and time to clinical stability. The microbiological characteristics assessed were uropathogen identified and drug susceptibilities. Standard microbiological methods were used to identify isolates; the Vitek 2 automated system (BioMérieux) was used to determine isolate susceptibilities. Our secondary outcome was to identify risk factors for developing infection by MDROs. For both outcomes analysis, patients were compared by DM diagnosis.

2.4. Statistical Analysis

GraphPad Prism, version 6.0 (GraphPad Software, Inc., San Diego, Calif), was used to perform statistical analyses. The cohort group variables were compared using the *t* test, Mann-Whitney *U* test, χ^2 test, or Fisher exact test where applicable. All statistical tests were 2-tailed; $p \leq 0.05$ denotes statistical significance.

3. RESULTS

As this study was retrospective our sample size was predetermined. During our study period, there were 156 patients with AP. Of these, we excluded 15 pediatric patients less than 18 years old and 8 patients with indwelling urinary devices. We included in our study 16 patients with DM and we matched these patients in a 2:1 manner with 32 randomly selected patients without DM for comparison of the clinical and microbiological course of AP between these 2 groups.

Table 1 shows the demographic characteristics of our sample. The median age of DM patients was significantly greater than non-DM patients (49 [37-62] Vs. 27 [23-39], $P = 0.006$). The overwhelming majority of patients in both groups were female. DM patients had greater BMIs than non-DM patients however; this was not statistically significant different (30 [24-36] Vs. 26 [24-28], $P = 0.18$). We were only able to assess long-term glycemic control in the DM group, as we did not have HbA1C values for patients without DM. All but one diabetic patient had a HbA1C level collected during the AP admission or within three months earlier; the median

HbA1C was elevated at 8.7, therefore, this group had very poor glycemic control.

We next assessed the clinical outcomes of this sample (**Table 2**). We found that days until clinical stability was similar between the two groups, with a median of one day for both groups. There was a trend towards an increase in complications among the DM group but this did not achieve statistical significance (5/16 [31%] Vs. 3/32 [9.4%], $P = 0.13$). The most common complication was bacteremia. Diabetic patients were found to require longer LOS when compare to non-diabetics (6 days [3-8] vs. 3 days [2-5], $P = 0.02$). Lastly, we analyzed final response at discharge. We found that 25% (12/48) of our sample and within each group had a complete response at discharge and 75% (36/48) had a partial response meaning they showed some clinical improvement but were either discharged with antibiotics or had some signs or symptoms of infection at discharge.

As shown in **Table 3**, we analyzed microbiological differences between patients with DM and those without. We found that for both populations, *E. coli* was the primary uropathogen identified. We found that among these *E. coli* isolates, those from DM patients were significantly more likely to have antimicrobial resistance to ampicillin (100% [8/8] Vs 24% [4/17], $P = 0.002$) and levofloxacin (63% [5/8] Vs. 6% [1/17], $P = 0.009$) but there were similar rates of resistance to sulfamethoxazole trimethoprim (50% [4/8] Vs. 12% [2/17], $P = 0.11$) and there was one patient in each group with Extended Spectrum Beta Lactamase (ESBL) producing *E. coli*. There were similar rates of infection from *Klebsiella* sp. (6% [1/16] Vs 6% [2/32], $P = 0.5$) and *Enterococcus* sp. (13% [2/16] Vs. 3% [1/32], $P = 0.24$) between the two groups. Although there was greater antimicrobial resistance among the *E. coli* isolates from DM patients, the rates of resistance to the empiric regimen selected by clinicians was similar between the two groups (19% [3/16] Vs 3% [1/32], $P = 0.096$). The most common empiric regimen was ceftriaxone, which the majority of uropathogens were susceptible.

Table 4 shows risk factors for MDRO and active infection, 25% (12/48) of our sample had at least one risk factor including immunosuppression, antibiotics or hospitalization >2 days in the past 90 days, or nursing home residence. There was a greater rate of patients with risk factors in the DM group but this was not statistically significantly different, (38% [6/16] Vs 19% [6/32] $P = 0.178$). Although there was no difference in risk factors for MDRO infection, we found that AP infection by an MDRO was significantly greater in the DM group (25% [4/16] Vs 3% [1/32], $P = 0.036$).

Table 1. Patient demographics

	Overall N = 48	With DM N = 16	Without DM N = 32	P-value
Age, years				
Median (IQR)	35 (23-47)	49 (37-62)	27 (23-39)	0.006
Male gender, n (%)	2 (4)	1 (6)	1 (3)	0.61
BMI, median (IQR)	26 (23-30)	30 (24-36)	26 (24-28)	0.18
HbA1c, median (IQR)	N/A	8.7 (7.2-12)	N/A	N/A
Nursing home residence, n (%)	1 (2)	0	1 (3)	0.12

Table 2. Clinical characteristics and outcomes

	Overall N = 48	With DM N = 16	Without DM N = 32	P-value
Time to clinical stability (days), median (IQR)	1	1 (1-3)	1 (1-2)	0.13
Complications, n (%)	8 (17)	5 (31)	3 (9.4)	0.13
Bacteremia	6	3	3	
Abscess formation	1	1	0	
Emphysematous pyelonephritis	1	1	0	
Length of stay, median (IQR)	4 (2-6)	6 (3-8)	3 (2-5)	0.02
Final response, n (%)	12 (25)	4 (25)	8 (25)	1.00
Complete partial	36 (75)	12 (75)	24 (75)	1.00

Table 3. Microbiological characteristics

	Overall N = 48 (%)	With DM N = 16 (%)	Without DM N = 32 (%)	P-value
<i>Escherichia coli</i>	25 (52)	8 (50)	17 (53)	0.830
Resistant to Ampicillin	12 (48)	8 (100)	4 (24)	0.002
Resistant to TMP-SMX	6 (24)	4 (50)	2 (12)	0.110
Resistant to Levofloxacin	6 (24)	5 (63)	1 (6)	0.009
ESBL +	2 (8)	1 (12)	1 (6)	1.000
<i>Klebsiella</i> spp.	3 (6)	1 (6)	2 (6)	0.500
ESBL +	1 (33)	1	0	0.200
<i>Enterococcus</i> spp.	3 (6)	2 (13)	1 (3)	0.240
VRE	1 (33)	1 (50)	0	0.200
Ceftriaxone empiric monotherapy	29 (60)	10 (63)	19 (59)	1.000
Sensitive to ceftriaxone	27 (93)	8 (80)	19 (100)	10.110
Uropathogen resistant to empiric regimen	4 (8)	3 (19)	1 (3)	0.096

Table 4. MDRO risk factors

	Overall N = 48 (%)	With DM N = 16 (%)	Without DM N = 32 (%)	P-value
MDRO Risk Factor	12(25)	6 (38)	6 (19)	0.178
Immunosuppression	3 (6)	2 (12)	1 (3)	1.000
Antibiotics in prior 90 days	5 (10)	2 (12)	3 (9)	1.000
Hospitalization >2 days in past 90 days	4 (8)	2 (12)	2 (6)	1.000
Nursing home residence	1 (2)	1 (6)	0	1.000
Infection by MDRO	5 (10)	4 (25)	1 (3)	0.036
ESBL + <i>E. coli</i>	2 (42)	1 (6)	1 (3)	1.000
ESBL + <i>Klebsiella</i> spp.	1 (21)	1 (6)	0	1.000
VRE	1 (21)	1 (6)	0	1.000
MRSE	1 (21)	1 (6)	0	1.000

4. DISCUSSION

This study assessed the impact of DM status on the course of AP among hospitalized patients. In this sample of patients, we found that those with DM had a

longer LOS, however other clinical outcomes were similar including time to clinical stability and rates of complications. As for microbiological outcomes, uropathogen antimicrobial resistance was greater in patients with DM; however, empiric regimen

susceptibility was similar between the two groups with ceftriaxone being the most common empiric regimen. This study provides evidence of microbiological differences between patients with DM and those without DM as we observed increased rates of uropathogen resistance among DM patients compared to non-DM patients.

This is the first trial to date to investigate AP differences by DM status across a general population of adult patients. To our knowledge, the only other study to investigate these differences was limited to elderly patients hospitalized with AP in Greece (Kofteridis *et al.*, 2009). Kofteridis *et al.* (2009) found that DM patients had a greater rate of bacteremia, increased LOS and increased mortality compared to elderly patients without DM while microbiological outcomes were similar between groups. In contrast, our trial found that the clinical course of AP was similar between the groups but there were significant differences in microbiological patterns of AP infection. This may be due to the fact the population in our study cohort were relatively young and healthy and therefore less susceptible to complications and mortality from AP. As for microbiological differences, (Kofteridis *et al.*, 2009) found in their study that almost 30% of their patients with DM had negative urine cultures likely due to the common practice of self medicating with antibiotics available as over the counter medications in Greece. Therefore, they could not accurately draw conclusions on microbiological differences as such a large portion of the sample did not have a uropathogen identified. In our sample, we found that *E. coli* was the most common uropathogen in both groups but there was significantly greater antimicrobial resistance observed among those with DM. Despite these differences in antimicrobial resistance, there were similar rates of isolate susceptibility to the empiric regimen with ceftriaxone monotherapy the most commonly used. While these differences in antimicrobial resistance did not affect empiric treatment at our institution, it may vary by institution and local antibiotic resistance patterns.

There are some potential limitations of this study. Our analysis included only 48 patients admitted with AP over a period of 3 years. This small sample size may not be representative of the overall population of patients admitted for AP, however, the size of this sample is similar to other studies investigating AP (Kofteridis *et al.*, 2009; Horcajada *et al.*, 2003). Since this was a retrospective study, we had to rely on

information documented in the patient's medical record, which may be inaccurate or incomplete.

5. CONCLUSION

In conclusion, we found among this sample of patients hospitalized with AP, those with DM required longer hospital lengths of stay and were more susceptible to infection from MDROs. Potential limitations include this study's small sample size and retrospective design. Further study is warranted to replicate these findings as well as assess the impact of glycemic control since those with uncontrolled DM may be at a greater risk of infection by MDRO and suffer worse clinical outcomes than those patients with controlled DM.

6. ACKNOWLEDGEMENT

We thank Dr. Georgeta Vaidean, MD, MPH, PhD, for her expertise and recommendations on the statistical tests used in this investigation.

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