Upper Respiratory Tract Infection among Dialysis Patients

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ABSTRACT: **Background:** Upper respiratory tract infection (URTI) occurs frequently in the general population and is considered a benign self-limited disease. Dialysis patients constitute a high risk population whose morbidity and mortality rate as a result of URTI is unknown.

Objectives: To assess the local incidence, morbidity and mortality of URTI in dialysis patients compared to the general population.

Methods: In this retrospective cohort study we reviewed the charts of all chronic dialysis patients diagnosed with URTI at Meir Medical Center, Kfar Saba, Israel during the 2014–2015 winter season.

Results: Among 185 dialysis patients, 40 were found to be eligible for the study. The average age was 66.1 ± 15.7 years, and the co-morbidity index was high. Influenza A was the most common pathogen found, followed by rhinovirus, respiratory syncytial virus and para-influenza. Of the 40 patients 21 (52.5%) developed complications: pneumonia in 20%, hospitalization in 47.5%, and respiratory failure requiring mechanical ventilation in 12.5%. Overall mortality was 10%. General population data during the same seasonal period showed a peak pneumonia incidence of 4.4% compared to 20% in the study population ($P < 0.0001$).

Conclusions: The study findings show that compared to the general population, in dialysis patients URTI is a much more severe disease and has a higher complication rate. Influenza A, the most common pathogen, is associated with a worse prognosis.

IMAJ 2016; 18: 557–560

KEY WORDS: dialysis, upper respiratory tract infection (URTI), influenza, viral infection, influenza vaccination

Upper respiratory tract infection (URTI) occurs frequently in the general population, accounting for at least 10%–25% of visits to general practice and primary care physicians. URTI is an important cause of work loss and health care utilization and constitutes a substantial economic burden. The incidence varies, being highest among children and declining with age [1,2].

Clinical manifestations of URTI are characterized by an abrupt onset of respiratory and constitutional signs and symptoms (sneezing, nasal congestion and discharge, sore throat, cough, low grade fever, headache, malaise). The diagnosis is usually clinically based. The severity and type of symptoms might vary according to the infective agent involved and inter-individual differences (e.g., influenza causes more systemic and severe disease than other viruses). The typical duration of a URTI ranges from 7 to 10 days [3].

Usually, URTI is a benign self-limited disease caused by members of several families of viruses. Over 200 subtypes of viruses have been associated with URTI. Rhinovirus is the most common virus associated with cold symptoms, responsible for 25–50% of cases. Other identifiable viruses include coronavirus, influenza, para-influenza, and respiratory syncytial virus (RSV) [3-5]. No pathogen is identified in 30–75% of cases, usually due to poor collection techniques, late sampling or a low pathogen load. The clinical scenarios of these viruses overlap. This, combined with their high prevalence and benign ambulatory character make it difficult to assess the exact morbidity and mortality of each pathogen [6].

Complications of URTI include acute otitis media, epiglottitis, acute rhinosinusitis, lower respiratory tract infection, and exacerbation of chronic diseases such as chronic obstructive pulmonary disease and congestive heart failure [6-8]. Treatment in most cases of URTI is supportive [3], apart from influenza virus for which specific therapy (oseltamivir) is available and recommended for some subpopulations and specific circumstances [9,10].

Dialysis patients are considered a population in whom early diagnosis and treatment of influenza are of prime importance [10]. Patients with end-stage renal disease are predisposed to infection due to dysfunction of the immune systems (both innate and adaptive). In addition, they also exhibit reduced immune response to vaccination [11,12]. Infection is one of the leading causes of mortality in dialysis patients, second only to cardiovascular disease. Commonly encountered infections are bacteremia and pneumonia. Dialysis patients have higher mortality rates due to pneumonia than those seen in the general population [11]. Despite the decreased efficacy of influenza vaccine in these patients, the Centers for Disease Control (CDC) recommends annual influenza vaccination [10,11,13]. Part of the rationale for this recommendation is that dialysis patients are more prone to develop influenza complications [10]. As

such, they require immediate empiric treatment for any suspected or confirmed influenza (independent of the need for hospitalization). Specific diagnostic tests are also recommended in this patient population for patients in whom the tests might affect treatment decisions.

This study undertook to assess the local incidence of upper respiratory tract infection as well as morbidity and mortality in dialysis patients compared to the general population.

PATIENTS AND METHODS

The charts of all chronic dialysis patients at Meir Medical Center, Kfar Saba, Israel, during the winter season October 2014 to April 2015 were retrospectively reviewed for a diagnosis of URTI. Meir Medical Center is a university-affiliated hospital with a dialysis unit providing dialytic care to 185 patients: 150 on hemodialysis (HD) and 35 on peritoneal dialysis (PD).

URTI was diagnosed when patients exhibited a combination of the following signs and symptoms: sneezing, nasal congestion and discharge, sore throat, cough, fever, headache, and general malaise. Patients with either clinical or radiological evidence of lower respiratory tract infection from the outset (bronchitis and/or pneumonia) were excluded.

DEMOGRAPHIC AND CLINICAL DATA

Data gathered from patient charts included age, gender, co-morbidities, baseline laboratory data, complications, need for hospitalization, and mortality. Similar data for the general population were obtained from the Israel Ministry of Health, ICDC report of June 2015. The course of the acute disease was further characterized by the presence of fever, oxygen saturation at room air, and C-reactive protein (CRP). The above data were compared between patients who survived and those who died. Viruses were identified from nose and throat swabs by polymerase chain reaction (PCR) of the common respiratory pathogens.

Patients were managed according to their clinical status and guideline recommendations. Thus, those with a clinical suspicion of influenza were empirically treated with oseltamivir and underwent a diagnostic test for influenza. Continuation or cessation of oseltamivir was determined based on the test result. Patients with clinically severe disease (high fever, dyspnea, hypoxemia) were hospitalized. The Meir Medical Center Ethical Review Committee approved the study.

STATISTICAL ANALYSIS

Data are expressed as mean ± standard deviation for continuous variables and as numbers and percentage for non-metric parameters. Metric data were checked for normality with the Shapiro-Wilk test. As some of the variables were not normally distributed, the *t*-test or the Mann-Whitney non-parametric test was used to compare between the two groups for the different blood markers. Chi-square or Fisher's exact test were used to compare between categorical parameters. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS-22.

RESULTS

From a total 185 dialysis patients, 40 (37 HD and 3 PD) were eligible for inclusion in the study (incidence of 21.6%). Only three were on peritoneal dialysis due to the fact that PD is a home treatment modality and patients are usually seen only monthly. Additional cases of URTI in the PD population were presumably seen by their local general practitioner. Therefore, the prevalence of URTI in PD patients compared to the HD patients in this study is probably an underestimation.

Demographic data, co-morbidities and baseline laboratory parameters of the study participants are shown in Table 1. The average age was 66.1 years. Patients had a high morbidity index, 72.5% were diabetic, and more than half had a diagnosis of congestive heart failure. About half the patients experienced complications, including pneumonia in 8 (20%), hospitalization in 19 (47.5%), and development of respiratory failure requiring mechanical ventilation in 5 (12.5%).

In 37 of the 40 patients, specimens for virus identification were sent in accordance with the CDC guidelines regarding the need for virus identification. The remaining three patients did not comply with these indications. As such, specimens from these three patients were not sent in and they were included in the group in which no pathogen was isolated.

Distribution of the viral pathogens is shown in Figure 1. Influenza A was the most common pathogen isolated (33%), followed by rhinovirus, RSV and para-influenza. No pathogen was isolated in 35% of the patients.

Table 1. Demographic data, co-morbidities and baseline laboratory parameters of the study patients (n=40)

Parameter	Value
Age (years)	66.1 ± 15.7
Dialysis duration (years)	3.39 ± 4.9
Gender: male (%)	20 (50%)
Co-morbidity	
Chronic pulmonary disease*	11 (27.5%)
Diabetes mellitus	29 (72.5%)
Ischemic heart disease	18 (45%)
Congestive heart failure	23 (57.5%)
Baseline laboratory data	
Albumin (g/dl)	3.35 ± 0.56
Hemoglobin (g/dl)	10.8 ± 1.37
Alanine aminotransferase (U/L)	15.56 ± 7.22
Calcium (mg/dl)	8.53 ± 0.74
Phosphorus (mg/dl)	5.1 ± 1.70
Parathyroid hormone (pg/ml)	238.38 ± 163.8
Kt/V	1.46 ± 0.25

*Including chronic obstructive lung disease, asthma and obstructive sleep apnea

Figure 1. Distribution of the viral pathogens

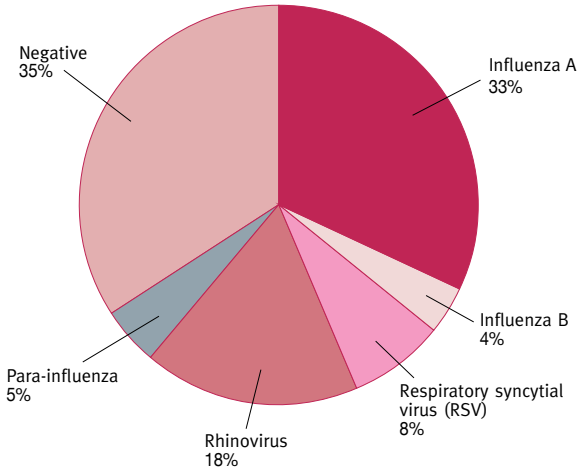

Table 2. Characteristics of patients with influenza vs. other pathogens

Characteristic	Influenza (n=14)	Other pathogens (n=26)	*P* value
Age (years)	68.79 ± 16.6	64.69 ± 15.31	0.439
Influenza vaccine	38.50%	87%	0.006
The acute disease			
Fever at presentation	36.96 ± 0.61	36.89 ± 0.77	0.787
Room air saturation	91.86 ± 7.54%	93.78 ± 5.7%	0.421
CRP at presentation	8.44 ± 7.08	5.21 ± 5.54	0.142
Complications			
Pneumonia	21.40%	19.20%	1.00
Hospitalization	78.60%	30.80%	0.007
Mechanical ventilation	28.60%	3.80%	0.043
Mortality	21%	3.80%	0.115

CRP = C-reactive protein

Despite no significant differences in age, co-morbidities and baseline laboratory data, infection with influenza caused a worse outcome and carried a higher complication rate compared to other pathogens [Table 2]. Specifically, hospitalization and mechanical ventilation rates were significantly higher (78.6 vs. 30.8%, $P = 0.007$; 28.6 vs. 3.8%, $P = 0.043$, respectively). Mortality also tended to be higher in influenza patients but did not reach statistical significance (21% vs. 3.8%, $P = 0.115$), probably due to the small number of patients who died. Four patients (10%) died from URTI complications and exacerbation of chronic medical diseases. Characteristics of the patients who survived vs. those who died are depicted in Table 3. As can be seen, patients who died were significantly older, had lower oxygen saturation at room air, and a higher CRP value at presentation. Patients who had contracted the influenza virus compared to other pathogens were significantly less likely to have received influenza vaccination (38.5% vs. 87%, $P = 0.006$) [Table 2].

Table 3. Characteristics of patients who survived vs. those who died

Characteristic	Survived	Died	*P* value
Age (years)	63.9 ± 14.9	86.5 ± 4.7	0.005
Dialysis duration (years)	3.5 ± 5.1	2.0 ± 1.8	0.557
Influenza vaccine (yes)	66.7%	100%	0.538
Co-morbidities			
Chronic pulmonary disease	22.2%	75%	0.056
Diabetes mellitus	69.4%	100%	0.56
Congestive heart failure	52.8%	100%	0.123
Ischemic heart disease	41.70%	75%	0.310
Baseline laboratory			
Albumin (mg/dl)	3.4 ± 0.6	2.9 ± 0.4	0.073
Hemoglobin (g/dl)	10.9 ± 1.4	10.2 ± 0.4	0.356
Calcium (mg/dl)	8.5 ± 0.8	8.4 ± 0.4	0.714
Phosphorus (mg/dl)	5.2 ± 1.8	4.8 ± 0.6	0.66
PTH (pg/ml)	246.8 ± 170.6	165.0 ± 44.0	0.351
Kt/V	1.4 ± 0.2	1.7 ± 0.3	0.097
Baseline CRP	1.5 ± 1.4	1.5 ± 0.9	0.955
The acute disease			
Fever at presentation	36.9 ± 0.7	36.9 ± 0.8	0.961
Room air saturation	94.1 ± 5%	84.8 ± 10.6%	0.006
CRP at presentation	5.5 ± 5.4	13.1 ± 9.4	0.021
Complications			
Pneumonia	16.7%	50%	0.172
Hospitalization	41.7%	100%	0.042
Mechanical ventilation	8.3%	50%	0.069

PTH = parathyroid hormone, CRP = C-reactive protein

Data pertaining to the general population during the same seasonal period, October 2014 through April 2015 (Israel Ministry of Health-ICDC Report, June 2015), showed an overall influenza vaccination rate of 21%. Vaccination rate of the elderly population (> 65 years) was considerably higher. Influenza infection was detected by nasal swab in 28.6% of tests performed, followed by RSV (13%). The incidence of pneumonia in the general population was significantly lower, reaching a peak of 4.37% vs. 20% in our study population ($P < 0.0001$).

DISCUSSION

The incidence of URTI in our dialysis cohort during the 2014–2015 winter season was 21.6%. This underestimates the true incidence, as URTI was recorded in only 3 of 35 PD patients. As mentioned above, since PD is a home-based dialysis modality, additional cases of URTI in our PD patients were either self-treated at home or by the local family physician and thus they were not brought to our attention.

In the general population, URTI is typically a mild, self-limiting catarrhal syndrome of the nasopharynx. However, this may not be the case among immunocompromised patients. End-stage renal disease can be viewed as an acquired immunodeficiency state. The adverse consequences of the uremic milieu include defects in both humoral and cellular immunity. This

is borne out by the fact that in dialysis patients, infection is a major cause of mortality, second only to cardiovascular disease.

Our study results indeed show that compared to the general population, the course of URTI among dialysis patients is far more sinister. Complications, in particular the development of pneumonia, the need for hospitalization and the need for mechanical ventilation, were significantly increased. Four patients (10%) died from URTI complications and exacerbation of chronic medical diseases. Risk factors for mortality were older age, lower oxygen saturation, and a higher CRP value at presentation. The complication rates were higher than those reported for elderly patients not on dialysis [14,15]. A review of the influenza A pandemic in the dialysis population documented a hospitalization rate of 34% (103/306 patients) [16]. Although this is lower than the 78.6% found in our patients with influenza, it can be attributed to the fact that the cohort was younger (mean age 52.7 ± 17.7 years) and had fewer co-morbidities.

Similar to the ICDC report, influenza A was the most common viral pathogen isolated in our patients (28.6% vs. 33%, respectively). Compared to other viruses, influenza infection was associated with more hospitalizations and greater need for mechanical ventilation. Notably, patients who were vaccinated against influenza were less likely to contract the virus. This finding is all the more remarkable considering that dialysis patients have a decreased response to vaccination [11,12], and the vaccine of that particular season was known to have a lower efficacy [17]. It lends support to the CDC recommendation for influenza vaccination in dialysis patients. Although treatment with oseltamivir did not benefit our patients, a definite conclusion regarding its usefulness cannot be made due to the small number of patients treated (12 of 14 patients with influenza), lack of a control group, and differing initiation times of oseltamivir from disease onset. Nevertheless, our results seem to justify the CDC guidelines advocating immediate empiric antiviral treatment for any suspected or confirmed case of influenza in dialysis patients, independent of the need for hospitalization [10].

In conclusion, this study indicates that in comparison to the general population, URTI in dialysis patients is far from a benign disease. Complications are frequent, leading to increased morbidity and possibly mortality. This is particularly true when the offending agent is influenza. The study therefore lends further credence to the CDC recommendation to annually vaccinate the dialysis population against influenza. Despite the lack of benefit of treatment with oseltamivir (for reasons mentioned above), due to the high complication rate, we recommend that empiric antiviral treatment in confirmed or suspected cases of influenza be given to dialysis patients.

Acknowledgments

We thank Dr. Eliezer Golan, Head of the Hemodialysis Unit and Dr. Andy Kotliroff, Head of the Peritoneal Dialysis Unit, for their cooperation in performing this study; the language editor, Faye Schreiber, for her help in preparation of the manuscript, and Nava Jelin for statistical analysis.

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"I dream of giving birth to a child who will ask, "Mother, what was war?"

Eve Merriam (1916-1992), American poet and writer