Original Article

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Pathogenic Organisms Causing Respiratory Infections in Patients with Chronic Kidney Disease, Stage V on Maintenance Haemodialysis: A Cross-sectional Study

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ABSTRACT

Introduction: Pulmonary infections are the most common infectious cause of disability and mortality in Chronic Kidney Disease (CKD) stage V patients on haemodialysis after cardiovascular disease. The incidence of pathogenic invasion of the lungs causing pneumonia is markedly higher in CKD stage V patients undergoing haemodialysis as compared to the general population. The risk is due to various factors including immune dysfunction, prolonged hospital stays leading to contact exposure, and hospital-acquired infections. The other important factors are anaemia, uremic toxins promoting pulmonary oedema, age, and vascular access through the arteriovenous fistula and internal jugular vein leading to catheter-induced respiratory infections.

Aim: To study the common pathogens involved in causing lung infection in CKD stage V patients on maintenance haemodialysis.

Materials and Methods: This cross-sectional study was conducted in the Department of Medicine/Nephrology at Andhra Medical College and King George Hospital, Visakhapatnam, Andhra Pradesh, India. The duration of the study was two months, from June 2019 to July 2019. A total of 50 patients were included in the study with CKD stage V on haemodialysis. The samples were between ages 18 to 75 years with respiratory symptoms and signs including fever, productive cough, and shortness of breath being the major complaints. These patients were subjected to certain investigations to isolate the organism. The parameters assessed were blood culture and sputum culture, haemoglobin, and chest X-ray. Sputum examination for Acid-fast Bacilli (AFB) was done to rule out tuberculosis. Statistical Package for Social Sciences (SPSS) version 17.0 was used for statistical analysis and measurement, data were expressed as the Mean±Standard Deviation (SD).

Results: The majority of the subjects were in the mean age group of 49 years and males were predominantly affected. The commonly isolated organism was gram-negative bacilli-*Pseudomonas*, with access common through arteriovenous fistula as compared to *Escherichia coli (E.coli)*, which was common in patients with access through Internal Jugular Vein (IJV).

Conclusion: The respiratory infection, that posed the burden in the present study was pneumonia. The common organism isolated was gram-negative bacteria being *pseudomonas*. The respiratory infections identified, were more through Arteriovenous Fistula (AVF) access and common in patients with moderate to severe anaemia.

Keywords: Anaemia, Fistula, Jugular vein, Pneumonia

INTRODUCTION

The risk of lung infections for patients with CKD stage V on haemodialysis is markedly higher than that of the general population and as well in similar patients on conservative treatment. This is due to the proven fact of immune dysfunction following renal failure as supported by humoral immune abnormalities and a decline in cellular immune functions [1], thus, causing T cell dysfunction, enhanced phagocytosis, chemotaxis and airway mucosal barrier dysfunction. Further, leading to increased alveolar fibrin exudation with accumulation of respiratory secretions and thereby, enabling pathogenic invasion and respiratory infections [2]. The other possible clinical characteristics associated with increased respiratory infections in dialysis patients, include factors like prolonged duration of hospitalisation leading to hospital acquired infections, older age, anaemia, vascular access through AVF, internal jugular venous access, dialyser reprocessing and subsequent passage of pyrogens such as, bacterial endotoxin across the dialyser membrane [3]. Patients on haemodialysis are subjected to oxidative stress and exposure to foreign antigens in the process that potentially contribute to inflammation (type A allergic reaction). Moreover, the levels of acute-phase proteins are increased in dialysis patients. The main pathogenic mechanism underlying the development of dialysis related pulmonary infection is based on allergic reactions to the materials used in the devices and the endotoxins and peptidoglycans in the dialysate. They may be absorbed into the body, through inverse diffusion or inverse filtration via dialysis membrane and cause respiratory infections [4].

However, more recently indirect toxic effect via protein/albumin carbamylation, a risk factor for the infections in CKD dialysis patients and a direct toxic effect have been attributed to urea. Urea was found to induce the generation of Reactive Oxygen Species (ROS) and insulin resistance in an in-vitro study by Lau WL and Vaziri ND [5]. Guanidine been considered as uraemic toxins having respiratory and cardiovascular toxicity based on their leucocyte activation, proinflammatory at uraemic concentrations. They are also responsible for the generation of other uraemic toxins like Tumour Necrosis Factor alpha (TNF-α) and Interleukin 6 (IL-6). These proinflammatory cytokines are believed to be the hallmark of microinflammation and further respiratory infections. In addition, a reduced number and dysfunction of T-lymphocytes (T4), as well as, enhanced phagocytosis, chemotaxis and bacterial capacity, which decrease monocytes and neutrophils may result in a decline in cellular immune function in CKD patients on haemodialysis thus, causing respiratory infections [6].

The occurrence of fever, productive cough and shortness of breath are noted as suspicion to infectious respiratory process. Anorexia,

night sweats and unexplained weight loss are additionally noted in case of tuberculosis. Following cardiovascular, infection is the most common cause of mortality in haemodialysis patients, particularly lung infections. This has been shown in a study by Delmez JA et al., [7]. In a similar study by Sarnak MJ and Jaber BL and Rayner HC et al., [8,9], lung infection was found to be the major cause of mortality in haemodialysis patients. According to a study by Hakim RM and Himmerlfarb J, the cost, as well as, the morbidity associated with the maintenance of haemodialysis access is increasing rapidly [10]. In a study by Feldman HI et al., reported that, access through either AVF or IJV related morbidity accounted for approximately 15% of hospital stays prior to 1989 however, the most recent evidence suggests that, access related morbidity accounts for atleast 25% of all hospital stays [11].

In a case report by Peddi S et al., an end stage renal disease patient on haemodialysis with fever was reported to have developed a cavity in the left lung, whose primary source was the right IJV catheter [12]. This showed development of pulmonary infections, due to vascular access creation as proven in the present study considering the mode of vascular access as the parameter to differentiate the distribution of the pathogenic organisms causing respiratory infections, where the patients with AVF were noted to be more common. The novelty of the present study was evaluating the subjects taking the symptomatology, blood, and sputum culture reports into primary consideration. The present comprehensive study also, revealed a strategical association of anaemia, age, vascular access with respiratory infections in CKD stage V patients on maintenance haemodialysis.

Hence, the present study aimed to study the clinical characteristics, common pathogenic bacteria associated and the distribution of lung infections in CKD stage V haemodialysis patients and to isolate the specific and common organisms, affecting lung and causing infection with each mode of access either with AVF or IJV. Also, to know the pathogenic impact upon age and anaemia in CKD and stage V patients on haemodialysis.

MATERIALS AND METHODS

This was a hospital based cross-sectional study conducted in the Department of Medicine/Nephrology at Andhra Medical College and King George Hospital, Visakhapatnam, Andhra Pradesh, India. The duration of the study was two months, from June 2019 to July 2019. Ethical clearance was obtained from the Institutional Ethics Committee with serial no: 60/IEC KGH/MAY 2019. An informed consent was taken prior to the study from all the subjects.

Sample size calculation: A total of 50 patients were taken upon consecutive sampling.

The number of patients with CKD stage V on haemodialysis (n=50) +new cases emerged during the two months of study (n=15)

Number of cases recruited=50

$$\text{Prevalence}=\frac{\text{The number of patients with CKD Stage V on haemodialysis+new cases emerged during the two months of study}}{\text{Number of cases recruited}\times 1000}$$

$$\frac{50+15}{50}=\frac{65}{50}\times 1000=1.3 \text{ per } 1000 \text{ population}$$

Inclusion criteria: Patients with CKD stage V on maintenance haemodialysis with respiratory infection symptoms which include fever, productive cough and shortness of breath [13]. Patients who were aged between 18 years to 75 years and undergoing haemodialysis of two cycles/week and three cycles/week for past one and two years, were included in the study and other adventitious respiratory findings like rhonchi and wheeze upon auscultation were also taken into consideration.

Exclusion criteria: Patients without respiratory symptoms and patients with pulmonary tuberculosis (with prior history of pulmonary tuberculosis and also, after examination of sputum for AFB and chest X-ray findings) were excluded from the study.

Study Procedure

The shortness of breath was graded according to New York Heart Association (NYHA) classification [14] [Table/Fig-1].

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (feeling heart beats), or dyspnoea (shortness of breath).
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

[Table/Fig-1]: New York Heart Association (NYHA) classification.

These patients were subjected to the following investigations-haemoglobin, total and differential counts, blood culture for gram-stain, for AFB and culture sensitivity to isolate the microbial organisms. Sputum specimens were also sampled for gram-stain, AFB to isolate the microbial organism, chest X-ray was done to note the lung invasion. Patients without respiratory symptoms were excluded after subjecting to complete blood counts and chest X-ray. Anaemia was evaluated and categorised into mild, moderate and severe with Hb% of 11 gm%-12.9 gm%, 8 gm%-10.9 gm% and less than 8 gm%, respectively, as per the World Health Organisation (WHO) classification [15].

STATISTICAL ANALYSIS

The statistical analysis was done using SPSS version 17.0 (Chicago, IL, USA) and the data was expressed as the mean±SD.

RESULTS

The number of patients with CKD stage V on haemodialysis (n=50) and new cases emerged during the two months of study (n=15) with the prevalence of 1.3 per 1000 population. Among the 50 haemodialysis patients with pulmonary infections, that were recruited into the study, majority of them were in the age group between 35-55 years (n=37, accounting for 74%), followed by patients in the age group between 56 to 75 years (n=13, accounting for 26%) with mean of 49.09±9.165 years [Table/Fig-2]. In the present study, predominant clinical feature was dyspnoea, present in 50 (100%) cases, followed by cough 30 (60%) cases, expectoration 30 (60%) cases, and fever 23 (46%) cases. Shortness of breath was present in all the patients and graded according to NYHA classification as described with a majority of class II dyspnoea in 16 (32%) cases, followed by class I 14 (28%), class III 11 (22%), and class IV 09 (18%) [Table/Fig-3]. A total of 50 patients with CKD, mild degree of anaemia was found in three patients (two males and

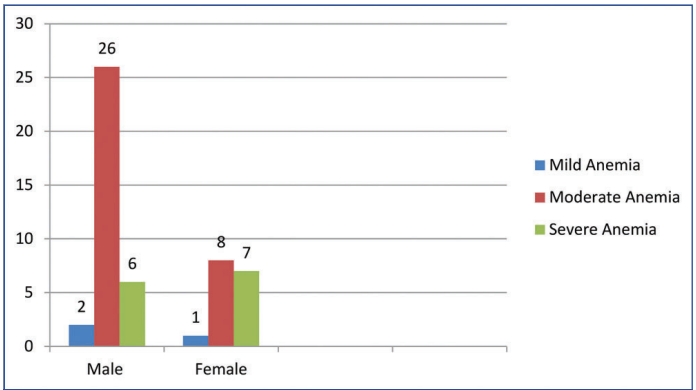
Age (in years)	Number of cases (n)	Percentage (%)
35-45	21	42
46-55	16	32
56-65	11	22
66-75	2	4

[Table/Fig-2]: Age-wise distribution of cases with pulmonary infections (N=50).

Grading of dyspnoea	Number of cases (n)	Percentage (%)
Class I	14	28
Class II	16	32
Class III	11	22
Class IV	09	18

[Table/Fig-3]: Distribution of cases with grading of dyspnoea (N=50).

one female), moderate anaemia was found in 34 patients (26 males and eight females) and severe degree of anaemia was found in 13 patients (six males and seven females) [Table/Fig-4].

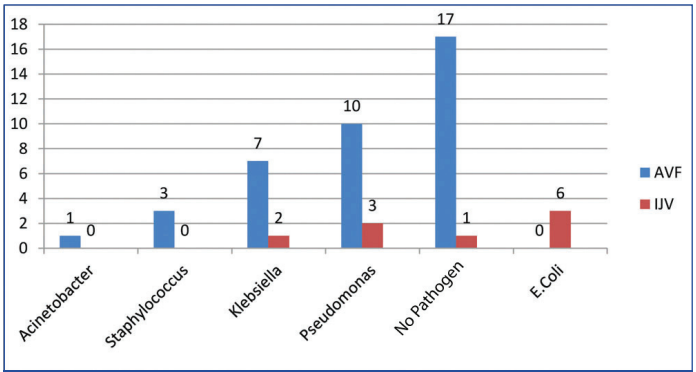


[Table/Fig-4]: Distribution of Chronic Kidney Disease (CKD) stage V patients on haemodialysis with anaemia.

Chest X-ray showed the presence of inflammatory lung pathology with infiltrates suggesting pneumonia, which was unilateral in 42 (84%) cases and bilateral in 8 (16%) cases. Increased White Blood Cells (WBC) counts were observed in all the patients. A total of 32 (64%) patients, showed the presence of pathogens obtained following sputum and blood culture, while in 18 (36%) patients, no pathogen could be obtained on sputum and blood culture. Both, the sputum and blood culture sampling isolated the same organisms. Sputum for AFB was also done as routine to all the 50 subjects though the prior history or active patients with tuberculosis were excluded and no AFB were isolated. The organisms isolated were commonly Gram-negative organisms with *Pseudomonas aeruginosa* (n=13), followed by *Klebsiella pneumoniae* (n=9), E.coli (n=6), and *Acinetobacter baumannii* (n=1), while three cases were isolated with Gram-positive *staphylococcus* aureus [Table/Fig-5]. Vascular access as a source of infection: In the present study, all the 50 patients on haemodialysis had a vascular access with 38 patients upon AVF and 12 patients upon IJV [Table/Fig-6]. The above figure shows that, while pseudomonas was the most common pathogen in patients, whose vascular access was an AVF, *E.coli* was the common pathogen that was isolated in those patients, whose vascular access was the internal jugular venous catheter.

Pathogen	Number of cases (n)	Percentage (%)
Gram-negative organisms		
Pseudomonas aeruginosa	13	26
Klebsiella pneumonia	9	18
Escherichia coli	6	12
Acinetobacter baumannii	1	2
Gram-positive organisms		
Staphylococcos aureus	3	6
No organism obtained	18	36

[Table/Fig-5]: Distribution of bacteria isolated from blood and sputum culture (N=50).



[Table/Fig-6]: Organisms prevalent in AVF and IJV.

Among the study population, patients of CKD stage V on haemodialysis, 29 of them were undergoing dialysis at a frequency of two cycles per week since one year. The other 21 patients were old cases of CKD stage V who were undergoing dialysis at a frequency of three cycles per week past two years. Pathogenic organisms causing pneumonia was isolated from 17 subjects, undergoing twice weekly sessions of dialysis past one year, as compared to 15 subjects undergoing thrice weekly sessions past two years [Table/Fig-7].

Pathogen	Frequency of twice weekly sessions n=29 (%)	Frequency of thrice weekly sessions n=21 (%)
Gram-negative organisms	6 (20.7%)	3 (14.3%)
Klebsiella pneumonia		
Pseudomans aeruginosa	4 (13.8%)	9 (42.8%)
Escherichia coli	3 (10.3%)	3 (14.3%)
Acinetobacter baumanii	1 (3.4%)	-
Gram-positive organisms	3 (10.3%)	-
Staphylococcus aureus		
No pathogen obtained	12 (41.4%)	6 (28.6%)

[Table/Fig-7]: Pathogens isolated in patients of Chronic Kidney Disease (CKD) stage V on haemodialysis based on frequency of dialysis.

DISCUSSION

Pulmonary infections are the commonly encountered cause of morbidity and mortality in patients with CKD on haemodialysis and among which pneumonia is diagnosed to be the commonest. This was reportedly 10-fold higher, as established in earlier studies [7,8,16]. The results were consistent with the previous studies related to the subject [16-18]. The present study has a lot of positive outcomes focusing upon certain parameters including anaemia and vascular access with duration. Dramatically greater pneumonia incidence rates in dialysis patients, were detected probably as a result of multiple interacting factors. According to Jha V et al., the incidence and prevalence of CKD differ substantially across countries and regions [17]. Projected worldwide population changes suggest that, the potential number of cases of CKD will increase disproportionately in countries like China and India. The mean age of patients in India was 51 years whereas, it was 66.6 years in China. In India, patients with CKD of unknown origin, were younger and more likely to present with advanced CKD than people with known causes [17]. In a study by Rayner HC et al., the mean age ranged from 58 years in the United Kingdom (UK), 62.4 years in Italy, and 60.9 years in Spanish patients with a similar disease [9].

Among the gender-wise distribution of cases in the present study, out of the 50 patients with chronic renal disease stage V on haemodialysis, 16 (32%) were females and 34 (68%) were males. Based on the most recent United States Renal Data System (USRDS) annual data report [19], men have always had a higher incidence of End-Stage Renal Disease (ESRD) than women, and despite declines in adjusted incidence in men and women since 2009, the relative difference continues to increase. Furthermore, 56.3% of the prevalent dialysis patients were males. In the present study, predominant clinical feature was dyspnoea 50 (100%) cases followed by cough 30 (60%) cases, expectoration 30 (60%) cases, and fever 23 (46%) cases. This is similar to the clinical findings of the study by Suresh H et al., where dyspnoea was the most common respiratory symptom (89%) followed by cough (64%) [20].

Anaemia has been linked to higher morbidity and a higher risk of complications during dialysis and hospitalisation [21]. In the present study, anaemia was seen in all the patients and as a risk factor in developing pneumonia in patients with CKD stage V on maintenance haemodialysis. It was observed in a majority of 34 (68%) cases presented with moderate anaemia (7-9 gm/dL).

The vascular access related infections in the present study, showed a majority of respiratory illness with AVF 38 (76%) cases as compared with IJV catheter 12 (24%) cases, which was proven otherwise in prior studies. This can be substantiated because, there is a near doubling of the use of AVFs. The study being an observational study, showed more number of patients on AVFs due to the prolonged duration of dialysis access required and hence, was reported as such. The Dialysis Outcomes and Practice Patterns Study (DOPPS) described that, there was no clear benefits of AVFs over IJVs worldwide [22]. Moreover, the present study is similar to the outcome based on the study by Murray EC et al., at the renal unit, western infirmary, Glasgow, UK wherein, their cross-sectional data averaged the dominant vascular access as 64.8% AVFs versus 35.2% by other methods with lesser incidence of pulmonary infections [18].

Limitation(s)

It was a single centre based study. The sample size and duration of the study were small. The blood culture from the access sites of AVF or IJV nor the microbiological culture of the dialysate was not analysed to isolate the organism. A study with a larger sample size and longer duration with a control group, may be needed to look further into the incidence, prevalence, etiology, risk factors, and outcomes of pulmonary infections in patients with CKD stage V on maintenance haemodialysis.

CONCLUSION(S)

Overall the results of the present study, demonstrate that pneumonia poses significant morbidity among CKD stage V patients on haemodialysis with the common pathogenic organism being Pseudomonas followed by *Klebsiella* and *E.coli*. Male preponderance was observed and a higher risk of pneumonia was present in CKD stage V patients on haemodialysis with moderate to severe anaemia. Lung involvement is predominantly unilateral. The age group of 35 to 55 years, had a higher incidence of respiratory illness causing pneumonia, due to early vascular stiffness as compared to the elderly of 56 to 75 years.

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