ORIGINAL ARTICLE

CLINICAL CHARACTERISTICS AND OUTCOME OF VENTILATOR ASSOCIATED PNEUMONIA IN PATIENTS WITH RENAL FAILURE

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ABSTRACT

Background: Ventilator associated pneumonia (VAP) causes significant morbidity and mortality. Data from patients with preexisting renal failure is limited. Our aim was to evaluate the clinical characteristics and outcome of VAP in patients with renal failure and/or on maintenance hemodialysis.

Material and Methods: A prospective observational study was conducted from February 2022 to February 2023. Patients ≥18 years, on mechanical ventilation (MV) for ≥48 hours, having underlying deranged renal function and who developed VAP were included. Demographics, cause of intubation, day of onset of VAP, clinical features, laboratory parameters and tracheal cultures were noted. Patients were followed till day 14 of VAP for mortality.

Results: Out of 165 MV patients, 67 (40.60%) developed VAP, 33 (49.25%) in ≤ 4 days. The cause of intubation was respiratory distress in 58(86.8%) patients. In 61(91%) patients tracheal cultures were positive with *Acinetobacter species* (64%) as the most common organism and 93% of which were carbapenem resistant. Carbapenem resistant organisms were more frequently in case of late onset VAP (91.2% versus 72.7% p=0.049). A total of 42 patients (62%) died, 76 % within 7 days of VAP and 13 patients (19.40%) recovered with successful extubation. There was no significant difference in 14 days mortality between early or late VAP.

Conclusion: VAP rates in patients with preexisting renal failure were 40%. Half of them developed in <4 days. *Acinetobacter* spp. was the predominant causative agent. Attributed mortality was high at 63% where two thirds of patients died within 14 days.

Keywords: Outcome, Renal failure, Ventilator associated pneumonia, Mechanical ventilator

BACKGROUND

Ventilator associated pneumonia (VAP) is defined as pneumonia that develops 48hours or longer after mechanical ventilation. VAP is classified further into two types, early onset VAP that occur within 4 days of ventilation, and late onset VAP that occur more than 4 days of initiation of mechanical ventilation.[1] VAP was found to be one of the most common hospital acquired and device associated infection according to a multistate point prevalence survey conducted in United States.[2] There is a significant morbidity and mortality associated with VAP. The 2016 clinical guidelines by Infectious Diseases society of America (IDSA) reported mortality rate of up to 30-50 %.[3] A study from France showed a significant morbidity with longer ventilator and hospital stay.[4] The incidence of VAP in Europe is between 5% to 60% and in US the incidence is 2-6 episodes per 1000 ventilator days.[5] A meta-analysis from China pointed out the cumulative incidence of VAP to be 23.8%.[1] In Pakistan the incidence of VAP was reported to be around 30% with a high mortality of 60%.[6,7] Zubair *et al* did a study on elderly population and found a significant high mortality among those who developed VAP.[8] The most common risk factors linked with VAP are advanced age, male gender, prolonged mechanical ventilation, patients with altered level of consciousness, burns, chronic diseases like chronic kidney disease, prior antibiotic therapy, invasive procedures like tracheostomy, fiber optic bronchoscopy, indwelling gastric tubes and thoracic tubes.[1,7]

Pneumonia in patients with renal failure is associated with increased hospitalization, and

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mortality.[9] The risk of pneumonia in chronic kidney disease is 1.97 times higher than in the general population.[10] A systemic review and meta-analysis reported that the mortality risk is doubled in patients with kidney disease having pneumonia.[11] Data on VAP among patients with renal failure is limited. Sindh Institute of Urology and Transplantation mainly caters to patients with renal failure. Our aim is to evaluate the incidence, risk factors and outcome of VAP in patients with renal failure and those on maintenance hemodialysis.

MATERIAL AND METHODS

We conducted a prospective observational study from February 2022 to February 2023. All patients ≥18 years of age, requiring mechanical ventilation (MV) for ≥48 hours and having deranged renal function (estimated glomerular filtration rate eGFR <60ml/min) and who developed VAP (defined below) were included. Patients who were diagnosed as pneumonia before MV and transplant recipients were excluded. Patient's demographics, comorbid conditions, cause of intubation, clinical features, laboratory parameters and tracheal cultures were noted at the time of diagnosis of VAP. Patients were followed till day 14 of VAP, whether alive and extubated, alive and intubated or died, whichever came first. The study was approved by institutional ethical review board for publication.

Ventilator associated pneumonia: Pneumonia diagnosed >48 hours after endotracheal intubation characterized by new lung infiltrates on chest X ray plus the new onset of fever, purulent sputum/tracheal secretions, leukocytosis, and decline in oxygenation. [12]

Early VAP is defined as pneumonia developed <4 days, while late onset was >4 days of intubation.[1]

End Stage Renal Disease (ESRD) diagnosed by nephrologists and defined as irreversible decline in kidney function with an estimated glomerular filtration rate less than 15 mL per minute per 1.73 m^2 body surface area, or those requiring dialysis irrespective of glomerular filtration rate.[13]

Acute renal failure diagnosed by nephrologists and defined as any of the following: increase in serum creatinine by ≥0.3 mg/dl within 48 hours; or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours.[14]

SPSS version 20 was used to analyze the data. Normally distributed continues variables were be reported as mean ± SD and non-normally distributed were reported as median with interquartile range [11]. To compare the mean difference between groups, for continues variables two sample t test was used whereas chi square, independent test or fisher exact test were used to determine proportion difference between groups. A cut off value of <0.05 was determined as statistically significant difference. Based on previous estimate of VAP as 30 % (7) with a margin of error 7% and 95% confidence level, a total of 164 patients were needed for this study.

RESULTS

Out of 165 patients on MV, 67 (40.60%) were diagnosed with VAP. Table-1 shows their demographics and clinical characteristics. A total of 33patients (49.25%) developed VAP ≤ 4 days and 54 patients (80.59%) within 7 days of MV. The median age of the study population was 35 years, 25 (37.3%) were females. The cause of intubation was respiratory distress in 58 (86.8%) patients in our cohort.

Respiratory culture results were obtained in 61 (91%) patients. The most common pathogen isolated was *Acinetobacter species* (64%). In addition, 55 of 59 (93%) isolates of gram-negative bacteria were carbapenem resistant. A total of 14 (20.8%) patients had concomitant bacteremia pre and post intubation. The source of bacteremia was central line infection in 8 cases (57%), urinary tract infection in 2 cases (14%) and unknown origin in 4

cases (28.5%). None of the bacteremia was attributable to VAP.

A total of 42 (62%) patients died. Thirty-two (76.19%) died in <7 days of VAP diagnosis. A total of 13 (19.40%) were alive with successful extubation.

The comparison of early and late onset VAP is shown in Table-2. Male patients developed VAP early compared to females, however did not reached statistically significant difference. Episodes of fever were seen more frequently in patients who developed VAP after 4 days (p value= 0.035), in contrast, mean TLC was high in early than in late VAP (19% vs 14.8 % p=0.06). Carbapenem resistant gram-negative bacteria were more frequently isolated from patients suffering from late onset VAP (91.2% versus 72.7% p value=0.049). There was no significant difference in 14 days mortality between early or late onset VAP.

Table-1: Demographics and baseline characteristics of patients with ventilator associated pneumonia (n=67).

Characteristics	n (%)
Age median (IQR)	35 (25-50)
≤30 years	27 (40.3)
30-50 years	24 (35.8)
>50 years	16 (23.9)
Female	25 (37.3)
Recent hospitalization within one month	25 (37.3)
Duration of hospitalization before intubation median (IQR)	1(0-3)
Duration of intubation before VAP days median (IQR)	5.0 (3.0-7.0)
Early VAP (≤4 days)	33 (49.25)
Late VAP (>4 days)	34 (50.74)
Clinical presentation at the time of intubation	
Pulmonary edema	24 (35.8)
Advanced uremia	6 (9)
Sepsis	23 (34.32)
Seizures	6 (9)
Others	19 (28.35)
Cause of intubation	
Respiratory distress	58 (86.8)
Low Glasgow coma scale	4 (6)
Cardio-pulmonary resuscitation	11 (16.6)
Arrhythmias or cardiac arrest	13 (19.4)
Others	5 (7.5)
Renal failure types	
Acute renal failure	31 (46.26)
Acute on chronic renal failure	19 (28.35)
End stage renal disease	11 (16.41)
Comorbidities	
Diabetes mellitus	15 (22.4)
Chronic lung diseases	2 (3)
Immunocompromised	9 (13.4)
Ischemic heart diseases	1 (1.5)
Stroke	2 (3)
Laboratory parameters	
Leucocytosis	46 (68.7)
Leucopenia	5 (7.5)
Thrombocytopenia	44 (65.7)
Microbiology characteristics	
Respiratory culture isolated	61 (91.04)
Acinetobacter spp.	43(64.17)
Klebsiella spp.	12 (17.91)
Pseudomonas aeruginosa	3 (4.47)

MRSA	2 (2.98)
Carbapenem resistant gram-negative bacteria	55/59 (93.22)
Bacteremia not attributable to VAP	14 (20.89)
Before intubation (n=6)	6/14 (42.85)
After intubation (n=8)	8/14 (57.14)
Outcome at day 14 of VAP	
Death	42 (62.68)
Within 7 days	32 (76.19)
After 7 days	10 (23.80)
Alive and intubated	12 (17.91)
Alive and extubated	13 (19.40)

Table-2: Comparison between early vs late onset VAP.

Characteristics	**Early VAP (≤4 days) n=33**	**Late VAP (>4 days) n=34**	**P-value**
Age median (IQR)	40(26-56)	35(25-45.75)	0.551
Male	24(72.7)	18(52.9)	0.094
Recent hospitalization	12(36.4)	13(38.2)	0.874
Days of hospitalization before intubation median (IQR)	1(0-4)	0(0-3)	0.704
Cause of intubation			
Respiratory arrest	30(90.9)	30(82.4)	0.253
Coma	2(6.1)	2(5.9)	0.975
CPR	3(9.1)	8(23.5)	0.111
Cardiac arrest	8(24.2)	5(14.7)	0.324
Comorbidities			
Diabetes mellitus	9(27.3)	6(17.6)	0.345
Acute Renal Failure	13(39.4)	18(52.9)	0.266
Acute on Chronic Renal Failure	11(33.3)	8(23.5)	0.373
End stage renal disease	6(18.2)	5(14.7)	0.701
Bacteremia unrelated to VAP	5(15.2)	9(26.5)	0.255
Clinical parameters			
Fever	16(48.5)	25(73.5)	0.035
TLC mean± SD	19.11±9.37	14.88±8.79	0.06
Thrombocytopenia	20(60.6)	24(70.6)	0.390
Respiratory culture isolates			
Acinetobacter spp.	20(60.6)	23(67.6)	
Klebsiella spp.	5(15.2)	7(20.6)	
Morganella Morganii	1(3)	0	0.396
MRSA	1(3)	1(2.9)	
Pseudomonas aeruginosa	1(3)	2(5.9)	
Carbapenem resistant organisms	24(72.7)	31(91.2)	0.049
Mortality	22(66.7)	20(58.8)	0.507

DISCUSSION

Ventilator associated pneumonia is one of the most common complication of mechanical ventilation and renal dysfunction is a major risk factor.[1,15] We found a very high rate of VAP (around 40%) in our cohort of patients with renal dysfunction. Furthermore, half of our patients developed VAP in less than 4 days of intubation. Cook *et al* reported the risk of development of VAP was higher in 5 days as compared to10 days of MV (3%/day vs 1%/day).[16] A study from Thailand have shown higher MDR organisms, length of hospital stay, mechanical ventilation and mortality in late onset VAP as compared to early onset VAP. [17] In contrast late onset VAP was found to have high morbidity and mortality due prolonged hospital stay and multiple comorbidities.[15] However in our study there was no difference in mortality between early and late onset VAP. Hosamirudsari *et al* in a retrospective study showed similar results with no risk difference of mortality in terms of early and late VAP.[18]

We found a very high mortality of 63% where two third of our patients died within 7 days of diagnosis. Overall

both crude and attributable mortality of VAP has been reported to be around 30-50%. [15,19] A study from Pakistan in trauma related mechanically ventilated patients showed a mortality of 65.8%.[7] There is scanty data on the outcome of VAP in patients with preexisting renal disease or those on maintenance hemodialysis. Data of all types of pneumonia in patients with kidney diseases reported a two times higher mortality.[20] Chronic kidney disease is prevalent in South Asia with alarming numbers in Pakistan (23.3%) involving both younger and older population due to diabetes mellitus and renal stone disease.[21,22] CKD patients have higher burden of comorbidities and require more frequent interaction with critical care leading to increased mortality.[23] In this study, we noticed pulmonary edema and sepsis as leading cause of intubation.

The microbiology of respiratory isolates of our patients is similar as reported in literature with predominance of gram-negative organisms and Acinetobacter *spp* as the most common pathogen isolated.[17,24] In addition, carbapenem resistance was seen significantly more seen in patients with late onset VAP. This is in agreement with various studies where late onset VAP was found to be due to multidrug resistant organisms (MDR).[17,25] The reason being prolonged hospitalization may lead to colonization of hospital acquired resistant organisms leading to infection with resistant bugs Studies have shown antibiotics exposure in preceding 90 days, hospital stay >5 days, mechanical ventilation and immunocompromised patients are the risk factors for colonization and infection with MDR organisms.[18] Patients with CKD or on renal replacement therapy are also colonized with drug resistant bacteria due to frequent exposure to healthcare setting and repeated admissions.[23]

During ICU stay, patients with renal dysfunction are more prone to develop blood stream infection due to usage of indwelling access catheter and arteriovenous fistula for hemodialysis.[23] In our cohort, we found nearly one fourth of our patients developed blood stream infection prior to or after development of VAP mostly originating from central line. Basseti *et al* reported 15% of patients with VAP develop bacteremia and it is the second most important source of blood stream infection in critically ill patients.[26] Baber *et al* from our institute also found 6.8% of patients had bacteremia caused by pneumonia.[27] However we did not find bacteremia attributed to VAP in our cohort.

Conclusion: In conclusion, this is the first reported data from Pakistan on clinical features and outcome of VAP in patients with preexisting renal disease. Our cohort of renal failure patients were young, intubated due to pulmonary edema, 40% of them developed VAP, more than half in less than 4 days. *Acinetobacter* spp. remained the predominant causative agent and two third of patients died within 14 days of VAP.

LIMITATIONS

There are several limitations. This was a single center observational study with a small sample size. Inclusion of all ventilated patients with or without VAP for comparison is needed for risk factors assessment.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

AUTHOR CONTRIBUTION:

Muhammad Hassan, Zaheer Udin Babar: Contributed to manuscript writing, study methodology, data analysis.

Sanjay Kumar, Muhammad Kashif Farooq: Involved in data collection, results analysis

Sunil Kumar Dodani, Asma Nasim: Contributed in conceptualization, final manuscript writing, and results analysis.

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