Epidemiology, etiology, and diagnosis of health care acquired pneumonia including ventilator-associated pneumonia in Nepal

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Abstract

Epidemiologic data regarding health care acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) from Nepal are negligible. We conducted a prospective observational cohort study in the intensive care unit (ICU) of a major tertiary hospital in Nepal between April 2016 and March 2018, to calculate the incidence of VAP, and to describe clinical variables, microbiological etiology, and outcomes. Four hundred and thirty-eight patients were enrolled in the study. Demographic data, medical history, antimicrobial administration record, chest X-ray, biochemical, microbiological and haematological results, acute physiology and chronic health evaluation II score and the sequential organ failure assessment scores were recorded. Categorical variables were expressed as count and percentage and analyzed using the Fisher’s exact test. Continuous variables were expressed as median and interquartile range and analyzed using Kruskal-Wallis rank sum test and the pairwise Wilcoxon rank—sum test. 46.8% (205/438) of the patients required intubation. Pneumonia was common in both intubated (94.14%; 193/205) and non-intubated (52.36%; 122/233) patients. Pneumonia developed among intubated patients in the ICU had longer days of stay in the ICU (median of 10, IQR 5–15, P<0.001) when compared to non-intubated patients with pneumonia (median of 4, IQR 3–6, P<0.001). The incidence rate of VAP was 20% (41/205) and incidence density was 16.45 cases per 1,000 ventilator days. Mortality was significantly higher in patients with pneumonia requiring intubation (44.6%, 86/193) than patients with pneumonia not requiring intubation (10.7%, 13/122, p<0.001, Fisher’s exact test). Gram negative bacteria such as Klebsiella and Acinetobacter species were the dominant organisms from both VAP and non-VAP categories. Multi-drug resistance was highly prevalent in bacterial isolates associated with VAP (90%; 99/110) and non-VAP categories (81.5%; 106/130). HAP including VAP remains to be the most prevalent hospital-acquired infections (HAI) at Patan hospital. A local study of etiological agents and outcomes of HAP and VAP are required for setting more appropriate guidelines for management of such diseases.
Introduction

Pneumonia is clinically defined as the presence of a new lung infiltrate with evidence that the infiltrate is triggered by an infectious agent such as, the new onset of fever, purulent sputum, or leukocytosis [1]. Healthcare acquired pneumonia (HAP) is an infection of the pulmonary parenchyma that develops >48 hours of admission to a health care facility and is commonly caused by pathogens that circulate in hospital settings [2]. In clinical practice, HAP is suspected when a patient presents with fever, impaired oxygenation, and supplicative secretions [3]. HAP is an important infectious disease worldwide and is associated with high morbidity, mortality, and additional health system expenditure [4]. In the US, the prevalence of HAP has been estimated to be 1.6% of all hospital admissions, representing a rate of 3.63 cases per 1,000 patient-days [5]. Epidemiologic data regarding HAP in Asia are scarce; however, the incidence of HAP is predicted to be high across Asia and especially problematic in intensive care units (ICUs), where the proportion of ICU-acquired respiratory infections ranges from 9% to 23% of admissions [6].

Ventilator-associated pneumonia (VAP) is a subtype of HAP that develops in ICU patients who have been mechanically ventilated for at least 48 hour [2, 7, 8]. VAP remains one of the most common infections in patients requiring invasive mechanical ventilation and is the leading cause of ICU mortality [2, 7]. The reported prevalence of VAP vary from 5 to 40% of ventilated patients depending on country, ICU type, and criteria used to diagnose VAP [9]. In high-income countries, a combination of surveillance, education, and tailored intervention and prevention bundles have led to a major reduction in VAP [10]. However, even with the implementation of such programs, VAP is still commonly reported in the US [7]. In Asia there are limited data on incidence of VAP, the causative pathogens, and their antimicrobial susceptibility profiles [6, 11]. A meta-analysis which encompassed 88 studies from 22 Asian countries from 2008 to 2018 indicated that the pooled incidence density of VAP in low-middle-income countries (LMICs) (18.5 per 1,000 ventilator-days) was more than twice that in high-income countries (9.0 per 1,000 ventilator-days) [12].

VAP has received little attention in LMICs until relatively recently [13]. In a low income country, like Nepal, where the incidence of infectious disease is high and strategies for control and prevention are weak, the opportunity for nosocomial infection is significantly higher [11, 14–16]. This problem is further exacerbated by antimicrobial resistance (AMR) in organisms such as Acinetobacter baumannii and Klebsiella pneumoniae, which are responsible for a large proportion of nosocomial infections and commonly multi-drug resistant (MDR) [17, 18].

A delayed diagnosis and delay in initiating appropriate therapy in VAP may be associated with poor outcomes [2, 19–21]. Therefore, an early and accurate diagnosis is fundamental in the management of patients with VAP. In order to develop effective therapeutic strategies to optimize the use of antimicrobial agents we need a better understanding of the local pathogens causing. Therefore, we performed a prospective study to describe some epidemiological features of HAP among patients admitted to the ICU of major tertiary hospital in Kathmandu, Nepal. We measured the incidence rate of VAP, investigated the antimicrobial susceptibility profiles of the etiological agents, and compared clinical profiles associated with HAP/VAP mortality.

Materials and methods

Ethics approval and consent to participate

This study was approved by Nepal Health Research Council (NHRC) (Reference number 11/2016, Date: 11 March 2016) and Oxford Tropical Research Ethics Committee (OxTREC 32–16,
Date: 19 October 2016. Adult patients admitted in the ICU or next-of-kin of the patient were approached for written informed consent to participate in this study.

**Setting and study design**

This was a prospective observational cohort study conducted in the ICU of Patan hospital between April 2016 and March 2018. Patan hospital is a 450-bed tertiary care referral teaching hospital with 15 ICU beds, located in the Lalitpur Metropolitan area of the Kathmandu valley in Nepal.

**Study structure**

All adult patients, ≥ 18 years of age admitted to the ICU were eligible to participate in the study. Adult patients admitted in the ICU or next-of-kin of the patient were approached for written informed consent to participate. Patients who denied consent and under the 18 years of age were not included in the study. Upon recruitment, demographic data, medical history, antimicrobial administration record, chest X-ray or other imaging findings, biochemical, microbiological and haematological results, and clinical parameters were recorded in a case report form (CRF). The acute physiology and chronic health evaluation (APACHE) II score and the sequential organ failure assessment (SOFA) score were recorded from the biochemical findings of the day of admission. Daily observation of the individual was conducted and CRF completed until an outcome of discharge, death, transfer to another ward or development of VAP.

VAP was defined by following the modified US Centers for Disease Control and Prevention criteria which requires to fulfill radiographic, systemic, and pulmonary criteria [16, 22–24] “Fig 1”.

The day when the patient fulfilled the criteria of VAP was taken as day 0 of VAP diagnosis. These VAP confirmed patients were followed up on day 3, day 7, and day 14. During these visits comparable clinical information was collected via hospital records. The final follow up was conducted on day 30 by phone if the patient was discharged, or in person if the patient was still in the hospital. Final diagnosis or working diagnosis if still under admission were recorded in the patient CRF.

**Sample collection for microbiological culture**

Respiratory samples [either tracheal aspirates (TA), bronchoalveolar lavage (BAL), or sputum] and blood samples were obtained from enrolled patients for microbiological culture. A respiratory sample of either TA or BAL was obtained from all patients before the diagnosis of VAP. The decision for BAL or TA samples was at the discretion of the treating physician.

**Collection of TA sample**

TA samples were collected as previously described, following local standard operating procedures [25]. Specimens were transported to the microbiology laboratory, and processed within 2 hours of collection. The tracheal aspirate specimens were examined by Gram staining, and the aspirate fluid was diluted 1:1 with Sputasol (Oxoid) and incubated at 37°C, with periodic agitation, until liquefaction. The sample was diluted (1:1, 10−1 and 10−2) using maximum recovery diluent (Oxoid), and 20 ml 1:1 diluent was inoculated onto blood agar and chocolate agar plates. Additionally, 20μl of the 10−1 and 10−2 dilutions was plated onto MacConkey media and blood agar base (Mast diagnostics, UK). Inoculated media were incubated at 37°C and examined after 24 and 48 h of incubation. The threshold used to discriminate between infection and colonization was ≥1x10⁵ colony forming unit (CFU)/ml (i.e., 20 colonies on either media from the 10−2 dilution). Colonies above this threshold were identified

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Daily minimum PEEP reduce or stabilize ≥ 2 days, followed by a daily increase minimum PEEP ≥ 2.5 cm H₂O, sustained for ≥ 2 days

OR

Daily minimum FiO₂ decrease or stabilize ≥ 2 days, followed by a daily increase minimum FiO₂ ≥ 0.15 points

Yes

Temperature > 38°C or < 36°C

OR

Leukemia > 12x 10⁹/L or < 4x 10⁹/L

No

No VAP: Continue filling up daily review form

Yes

Increased Secretion

OR

On a sputum/tracheal aspirate Gram stain: ≥ neutrophils and epithelial cells ≤ 10/low power field

No

Yes

New infiltrates on chest radiograph

OR

New antibiotic started for respiratory tract infections in the past 48 hours

Yes

VAP enrollment

Day 0

No
using biochemical tests following standard operating protocol of Patan Hospital. In the interpretation of results, each colony corresponded to 20,000 CFU/ml, and it was considered to be TA positive when the count was $\geq 10^5$ CFU/ml [26].

**Antimicrobial susceptibility testing**

Antimicrobial susceptibility testing was performed using the Kirby Bauer disc diffusion method. The inhibitory zone sizes were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) 2018 guidelines. Mueller–Hinton agar and antimicrobial discs were purchased from Mast Diagnostics, UK. *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923 were used as controls for these assays. The antimicrobials tested against *Acinetobacter* spp., *Pseudomonas* spp., and the Enterobacteriaceae were amikacin (30 mg), piperacillin/tazobactam (100/10 mg), imipenem (10 mg), ofloxacin (5 mg), and ceftriaxone (30 mg). An isolate was defined as MDR when it was non-susceptible to at least one agent in $\geq$ 3 antimicrobial categories [CLSI guidelines (2018)] [27]. Gram positive organisms were tested against co-trimoxazole (1.25/23.75 mg), penicillin (10 mg), gentamicin (10 mg), erythromycin (15 mg) and oxacillin (1 mg).

**Statistical analysis**

Data recorded onto a case record form were entered into a CliRes database system protecting participant information. Verification was done by double entry. Data analysis was performed in R Software (version 3.2). Categorical variables were expressed as count and percentage and analyzed using the Fisher’s exact test. Continuous variables were expressed as median and interquartile range and analyzed using Kruskal-Wallis rank sum test and the pairwise Wilcoxon rank—sum test. Each variable with a $p$-value $< 0.05$ was considered a significant variable. VAP incidence was calculated as follows: (Number of cases with VAP/Total number of patients who received MVx100) = VAP rate per 100 patients. VAP incidence density was calculated as follows: (Number of cases with VAP/Number of ventilator days) x 1000 = VAP per 1,000 ventilator days. Flow diagram of the study enrollment procedure and categorization into five categories is shown in “Fig 2”.

**Results**

**Baseline characteristics**

Four hundred and thirty-eight patients between April 2016 and March 2018 were hospitalized in the ICU and enrolled in the study. The patients were between the ages of 18 and 95 years and 48.9% (214) were male and 51.1% (224) were female “Table 1”.

The total numbers of participants in each of the five categories were I-P-V- = 111, I-P+V- = 122, I+P-V- = 12, I+P+V- = 152, and I+P+V+ = 41, who had median ages of 48, 62.5, 35.5, 57.5, and 59.5 years, respectively. More than 50% of participants in all five categories had co-morbidities at the time of admission in the ICU with $> 15\%$ of the participants in each category...
Fig 2. Flow diagram of the study enrollment procedure and categorization into five categories. Patients enrolled in the study were into five groups depending upon intubation, pneumonia development, and VAP development: These were: I-P-V- (not intubated, no pneumonia), I-P+V- (not intubated, but pneumonia developed), I+P-V- (intubated but no pneumonia), I+P+V-(intubated and pneumonia developed, but VAP not confirmed), and I+P+V+(VAP confirmed). The flow diagram of the study enrollment procedure and categorization into five categories is shown in “Fig 2”.

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having had a history of hospital admission in the past 90 days with antimicrobial use ranging from 9.8% (4/41 in the I+P+V+ group) to 35.5% (54/152 in the I+P+V- group). The median SOFA scores ranged from 3 to 10, with the highest scores being observed in the VAP group (median of 10, IQR 7–11). The median APACHE II score ranged from 10 to 18; the highest score was observed in the non-VAP group 18 (IQR 13–24).

Association of different variables with intubation and pneumonia

In total, 29.7% (130/438) of patients had a diagnosis of pneumonia when admitted in the ICU and 46.8% (205/438) of patients required intubation. The most common requirement for intubation was failure to oxygenate (24.4%; 50/205), followed by failure to maintain or protect the airway (99%; 39/205). Pneumonia was common in both the intubated (94.14%; 193/205) and the non-intubated (52.36%; 122/233) patients. Pneumonia in intubated patients in the ICU was associated with longer days of stay (median of 10, IQR 5–15, \( p < 0.001 \)) when compared to non-intubated patients with pneumonia (median of 4, IQR 3–6, \( p < 0.001 \)). SOFA and APACHE II scores were also significantly higher among the patients that then on-intubated patients (\( p < 0.05 \); Kruskal-wallis rank sum test) “Table 2”.

Table 2. Kruskal-wallis rank sum test for the variables associated with intubation and pneumonia.

| Variables          | IntPosPneum | NonIntPosPneum | \( p \)-value |
|--------------------|-------------|----------------|--------------|
| Days in Hospital   | 11 (7–17)   | 5 (3–7)        | <0.001       |
| Days in ICU        | 10 (5–15)   | 4 (3–6)        | <0.001       |
| Days in Intubation | 9 (5–15)    | NA             | NA           |
| FiO2               | 50 (40–80)  | 36 (29–41)     | <0.001       |
| PaO2               | 79 (48.2–114)| 68.1 (53.7–88) | 0.056        |
| Temperature        | 98 (97.2–99.2)| 98 (97.2–98.4) | 0.027        |
| SOFA               | 8 (5–11)    | 3 (2–5)        | <0.001       |
| APACHE             | 18 (13–23)  | 11 (7.25–14)   | <0.001       |
| Mortality          | 86/193 (44.6%) | 13/122 (10.7%) | <0.001       |

Values given are median (IQR) or count (percent). Kruskal-Wallis rank sum test for median (IQR). Fisher’s Exact Test for count (percent). I+P+ (intubated, pneumonia) and I-P+ (non-intubated, pneumonia developed).
Incidence density of VAP

Out of 205 patients requiring mechanical ventilation during their stay in ICU, 41 patients were diagnosed with VAP (20%), equating with a total incidence density of 16.45 cases per 1,000 ventilator days.

Factors associated with VAP confirmed cases

We aimed to identify factors associated with VAP in the VAP confirmed group (I+P+V+) “Table 3”. VAP was significantly associated with the duration of stay in the hospital (median 18 days, IQR 11–27, p < 0.001), the duration of stay in ICU (median 16 days, IQR 10–25, p < 0.001), number of days of intubation (median 17 days, IQR 11–27, p < 0.001), fraction of inspired oxygen (FiO2) (median 60, IQR 40–100, p < 0.001), APACHE II score (median 17, IQR 13–22 p < 0.001), SOFA score (median 10, IQR 7–11, p < 0.001) and PaO2 (median 70.6, IQR 52.3–102, p < 0.001).

A pairwise Wilcoxon signed rank test was performed among the five defined categories to identify significance between the groups “Fig 3”. The number of days of hospital stay, the number of days of ICU stay, APACHE II score, and SOFA score were all significantly higher in the I+P+V+ and I+P+V− groups than in the I−P−V− group (p < 0.001).

Mortality

Mortality was significantly higher in patients with pneumonia requiring intubation than patients with pneumonia not requiring intubation (44.6% (86/193) vs. 10.7%, (13/122) p < 0.001, Fisher’s exact test) “Table 2”. Between the groups, the highest mortality (58.5%; 24/41) was observed among VAP patients (I+P+V+) followed by non-VAP (I+P+V−) patients (40.8%; 62/152); and lowest mortality (3.7%; 4/109) was observed among patients who neither required intubation nor had pneumonia during their stay in the ICU (I−P−V−)(p < 0.001; Kruskal wallis test) “Table 3”.

Microbiology of VAP and non-VAP

A total of 110 samples from those with confirmed VAP(I+P+V+) and 130 samples from those without-VAP category (includes all categories except I+P+V+) were subjected to microbiological cultured. The majority of these samples were TA samples; 81/110 in VAP category and 63/130 in non-VAP category.
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I = Intubated  
P = Pneumonia  
V = VAP

- p-value from pairwise wilcoxon-test with bonferroni correction

### Days in Hospital (p-value)

|          | I-P-V | I-P-Vv | I-P-Vi | I-P-Vii | I-P-Viii |
|----------|-------|--------|--------|---------|----------|
| NA       | 1     | 0.64   | 1      | <0.001  | <0.001   |
| NA       | 1     | 0.64   | 1      | <0.001  | <0.001   |
|          | <0.001| 0.001  | 0.005  | 1       | <0.001   |
|          | <0.001| 0.001  | 0.001  | 1       | <0.001   |

### Days in ICU (p-value)

|          | I-P-V | I-P-Vv | I-P-Vi | I-P-Vii | I-P-Viii |
|----------|-------|--------|--------|---------|----------|
| NA       | 1     | 1      | 1      | <0.001  | <0.001   |
| NA       | 1     | 1      | 1      | <0.001  | <0.001   |
|          | <0.001| 0.001  | 0.02   | 0.02    | 0.01     |
|          | <0.001| 0.001  | 0.001  | 0.001   | 0.001    |

### Days in Intubation (p-value)

|          | I-P-V | I-P-Vv | I-P-Vi | I-P-Vii | I-P-Viii |
|----------|-------|--------|--------|---------|----------|
| NA       | 1     | 0.66   | 1      | 1       | 1        |
| NA       | 0.66  | 1      | 0.34   | 0.44    | 1        |
|          | 0.34  | 0.44   | 1      | 1       | 1        |
|          | 0.44  | 1      | 1      | 1       | 1        |

### PaO2 (p-value)

|          | I-P-V | I-P-Vv | I-P-Vi | I-P-Vii | I-P-Viii |
|----------|-------|--------|--------|---------|----------|
| NA       | 1     | 0.005  | 0.39   | <0.001  | <0.001   |
| NA       | 0.005 | 0.39   | <0.001 | <0.001  | <0.001   |
|          | 0.39  | <0.001 | <0.001 | <0.001  | <0.001   |
|          | <0.001| 0.19   | 1      | 0.14    | 0.24     |
|          | <0.001| 0.24   | 0.34   | 0.48    | 1        |

### Temperature (p-value)

|          | I-P-V | I-P-Vv | I-P-Vi | I-P-Vii | I-P-Viii |
|----------|-------|--------|--------|---------|----------|
| NA       | 1     | 1      | 1      | 0.28    | 0.28     |
| NA       | 1     | 1      | 1      | 0.04    | 0.04     |
|          | 1     | 1      | 1      | 1       | 1        |
|          | 1     | 1      | 1      | 1       | 1        |

### APACHE II score (p-value)

|          | I-P-V | I-P-Vv | I-P-Vi | I-P-Vii | I-P-Viii |
|----------|-------|--------|--------|---------|----------|
| NA       | 1     | 1      | 1      | <0.001  | <0.001   |
| NA       | 1     | 1      | 1      | <0.001  | <0.001   |
|          | 1     | 1      | 0.05   | 0.14    | 0.14     |
|          | <0.001| 0.001  | 0.01   | 0.1     | 0.1      |
|          | <0.001| 0.001  | 0.14   | 0.34    | 1        |

### SOFA score (p-value)

|          | I-P-V | I-P-Vv | I-P-Vi | I-P-Vii | I-P-Viii |
|----------|-------|--------|--------|---------|----------|
| NA       | 1     | 1      | 1      | 0.01    | <0.001   |
| NA       | 1     | 1      | 1      | <0.001  | <0.001   |
|          | 1     | 1      | 0.05   | 0.14    | 0.14     |
|          | <0.001| 0.001  | 0.01   | 0.1     | 0.1      |
|          | <0.001| 0.001  | 0.14   | 0.34    | 1        |
|          | <0.001| 0.001  | 0.14   | 0.34    | 1        |

### Other data

- Data from a study on health care acquired pneumonia in Nepal.
Gram negative bacteria were the dominant organisms from both VAP and non-VAP patients "Table 4", "Fig 4"). Klebsiella species was the most common bacteria associated with VAP (n = 36, 32.7%) followed by Acinetobacter species (n = 35, 31.8%). Acinetobacter species was the predominant organism (n = 48, 36.9%) isolated from those without-VAP, followed by Klebsiella species (n = 28, 21.5%). Klebsiella species was more likely to be isolated from VAP patients (OR 1.76, 95% CI 0.96–3.3, p value 0.05).

MDR in VAP and non-VAP categories
MDR was prevalent in all bacterial isolates from both VAP and non-VAP categories. The distribution of MDR isolates from various VAP and non-VAP samples are presented in "Fig 5". 90% (n = 99/110) of the isolates from various VAP samples and 81.5% (n = 106/130) of the non-VAP isolates were MDR. The data was suggestive of association of MDR with the VAP isolates but this was none significant (OR 2.03, 95% CI 0.90–4.85, p 0.07).

Discussion
The data on HAP from prospective studies are scant notably from LMIC setting. Our study showed that HAP was common in our ICU setting regardless of intubation requirement [94.14% (193/205) among intubated and 52.36% (122/233) among non-intubated patients] indicating that these pneumonia cases may be a common HAI at Patan hospital. In addition to this, at least 16% of the patients from all the categories have had a visit to the hospital in the past 90 days and 50% of the patients had co-morbidities "Table 1" mainly chronic respiratory illness such as chronic obstructive pulmonary disorder. As a result, antibiotic usage was also common. Pneumonia as HAP was also common in a Malaysian study where,21% of HAP infections were pneumonia [6].

The complex interplay between the endotracheal tube, presence of risk factors, virulence of the invading bacteria and host immunity largely determine the development of VAP [28]. The diagnosis of VAP is traditionally based on clinical symptoms and radiographic criteria that require further bacteriological confirmation. However, it has been demonstrated that these criteria are not sensitive or specific [8]. There is no gold standard for the diagnosis of VAP however, the qualitative method of culturing the tracheobronchial aspirate samples is said to be better at differentiating colonization and actual infection.

Despite recent advances in microbiological tools, the epidemiology and diagnostic criteria for VAP are still controversial, complicating the interpretation of treatment, prevention, and

| Isolates                     | VAP (n = 110) | Non-VAP (n = 130) | OR (95%CI)  | p-value |
|------------------------------|--------------|------------------|-------------|---------|
| Acinetobacter spp            | 35 (31.8%)   | 48 (36.9%)       | 0.8 (0.45–1.4) | 0.42    |
| Klebsiella spp               | 36 (32.7%)   | 28 (21.5%)       | 1.76 (0.96–3.3) | 0.05    |
| Pseudomonas spp              | 14 (12.7%)   | 17 (13.1%)       | 0.97 (0.42–2.21) | 1       |
| E. coli                      | 11 (10%)     | 18 (13.8%)       | 0.69 (0.28–1.64) | 0.43    |
| Enterobacter spp             | 5 (4.5%)     | 8 (6.2%)         | 0.73 (0.18–2.61) | 0.78    |
| Coagulase negative Staphylococcus (CoNS) | 7 (6.4%) | 3 (2.3%) | 2.9 (0.6–17.6) | 0.19    |
| S. aureus                    | 0 (0%)       | 5 (3.8%)         | NA          | NA      |

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Fig 4. Etiology of VAP and non-VAP specimen.

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Fig 5. MDR isolates in VAP and non-VAP specimen.

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outcomes studies [9]. Data on rates of VAP, the common associated pathogens, and their antimicrobial susceptibility profiles from Asia are limited [12]. Pooled incidence density of VAP was 18.5 per 1000 ventilator days in high in Asian LMIC countries [12]. This finding is similar to our study where we observed the incidence rate of VAP of 20% (n = 41/205) with a total of incidence density of 16.45 per 1000 ventilator days. However, some other Asian countries have reported a lower VAP incidence (9.9%) and VAP density (8.7/1000 ventilator days) [16].

Meta-analysis study from mainland China reported that the cumulative incidence of VAP was 23.8% [29]. In contrast, studies from India have reported the higher incidence density of VAP of 39.6% to 40.1% [30, 31]. Such reported incidences vary widely from 5 to 40% depending on the setting and diagnostic criteria [9] indicating that the incidence rates vary not only between countries but also among different settings within a country. In high-income countries, a combination of surveillance, education, and tailored intervention and prevention bundles have led to a reduction in the incidence of VAP [32].

Gram negative bacteria were the dominant organisms from both VAP and non-VAP categories. *Klebsiella* species was the most common bacteria associated with VAP followed by *Acinetobacter* species. Among non-VAP category, *Acinetobacter* species was the predominant organism followed by *Klebsiella* species (n = 28, 21.5%). *Klebsiella* species was more likely to be isolated from VAP category. We did not find major differences in the etiologic agents of VAP and non-VAP organism and their antimicrobial susceptibility profiles. However, there was a suggestive association of MDR with VAP isolates. Similar findings have been reported from other studies where the leading pathogens are *A. baumannii, P. aeruginosa* and *K. pneumoniae* [33, 34]. In a large meta-analysis of 88 studies analyzing VAP in adults in Asia, it was revealed that *A. baumannii* was the most common organism in the LMIC group and the proportion due to this organism gradually reduced as income levels increased, and *S. aureus* and *P. aeruginosa* were the most common in the high income country group [12]. Studies on VAP from other Asian countries also have reported *A. baumannii* to be the most common isolate [35].

One of the differences between our data and reports from Western countries was the proportion of gram-negative and gram-positive bacterial causes of VAP. We found a much lower proportion of gram-positive organisms as causative agents of VAP and non-VAP [35, 36].

ICUs often have the highest levels of infections due to antimicrobial resistant pathogens as a result of the environment that is under constant pressure with high antimicrobial usage due to the presence of severely ill patients. Etiologic agents of VAP are generally associated with pathogens with high levels of antimicrobial resistance, resulting in the need to treat with broad-spectrum antibiotics, which further drives antibiotic resistance [12].

Early onset VAP is usually attributed to antibiotic sensitive pathogens whereas late onset VAP is more likely caused by MDR bacteria and emerges after 4 days of intubation [37, 38]. However, this scenario seems to be different in the LMIC settings. This study revealed that MDR isolates were slightly higher in VAP than in non-VAP categories. Although significant association was not observed, there was an indication of association of VAP with MDR organisms. This further highlights the need to have infection control protocol guidelines in order to control such HAIs. s Guidelines for VAP prevention, including hand washing, elevation of the head of the bed, oral care with chlorhexidine, optimized endotracheal tube cuff pressure, respiratory circuit manipulation, and weaning protocols to early extubation were established in our hospital. These are cost effective control and preventive measures of VAP. Strict compliance, staff training, and regular monitoring of implementation of such guidelines will be effective in the prevention of VAP.

Mortality attributable to HAP is estimated between 5 and 13% [39]. Even in HAP, generally considered to be less severe than VAP, serious complications occur in approximately 50% of
patients [40]. Mortality was significantly higher in patients with pneumonia requiring intuba-
tion (44.6%, 86/193) than patients with pneumonia without intubation (10.7%, 13/122, p<
0.001). Highest mortality of 58.5% (24/41) was observed among VAP patients (I+P+V+) fol-
lowed by non VAP (I+P+V-) patients (40.8%, 62/152) and lowest mortality of 3.7% (4/109) was
observed among patients who neither required intubation nor had pneumonia during their
stay in the ICU (I-P-V-) category. The mortality in our ICU due to VAP was still lower than
reported in other studies where it was as high as 68.4% [31].

Development of pneumonia increased the number of days of intubation. Intubated patients
with pneumonia had to spend a median of 7.5(4–11) (I+P+V-) to 17(11–27) (I+P+V+) days
being intubated as in comparison to those without pneumonia (I+P-V-) {4(2.75 to 7.25)}. In
addition, VAP confirmed patients spent a median of 16 days in ICU ranging from 10 to 27
days. 24.6% (50 / 203) patients required intubation due to the reduction in exchange of oxygen
(low PaO2), followed by cognitive impairment and airway obstruction (19.2%, 39/203).

Conclusion

Pneumonia was one of the common infections in our ICU setting. Pneumonia developed
among intubated patients in the ICU had longer days of stay in the ICU when compared to
non-intubated patients with pneumonia. We found high VAP incidence in this study and
highest mortality was observed among VAP patients followed by non VAP (I+P+V-) patients.
MDR Gram negative bacteria were the dominant organisms from both VAP and non-VAP
categories.

HAP including VAP remains to be the most prevalent HAIs at Patan hospital. One of the
limitations of this study was that it was conducted at a single hospital. Surveillance studies on
HAIs at various hospitals within the country are required in identifying the etiological agents.
Antimicrobial susceptibility profiles of the etiological agents and outcomes of HAP and VAP
would be beneficial for setting more appropriate guidelines for management of such diseases.
In addition, countries like Nepal lack proper protocols of infection control and implementa-
tion for minimizing such infections in the hospital. Therefore, a suitable surveillance programs
should be implemented, analyzing differences in VAP rates between different ICUs, and evalu-
ating potential therapeutic approaches, and prevention strategies.

Supporting information

S1 Dataset.
(XLSX)

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