A Review on The Causative Agents, Risk Factors and Management of Ventilator-Associated Pneumonia: South Asian Perspective

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Abstract

Ventilator-Associated Pneumonia (VAP) is common hospital-acquired pneumonia in ICU patients. Patients with pneumonia after 48 hours of mechanical ventilation are VAP affected. INICC found that VAP rates between 2012 to 2017 are 14.1 per 1000 episodes. The most common pathogens include Acinetobacter baumannii, Pseudomonas Aeruginosa *and* Klebsiella pneumoniae. *Developing countries seem to have a higher mortality rate compared to developed countries. Treatment protocol involves antibiotic therapy. For the early onset of VAP, cephalosporin (cefotaxime or ceftriaxone), fluoroquinolone, or piperacillin-tazobactam are found to be effective while for late-onset, ceftazidime, ciprofloxacin, meropenem, and piperacillin-tazobactam seems to have positive results. Apart from antibiotics, other options like bacteriophage therapy can offer a good alternative to fight the rapid emergence of MDR pathogens.*

Keywords: *Ventilator-Associated Pneumonia; indwelling mechanical ventilation; endotracheal aspirates; antibiotic susceptibility; antibiotic therapy.*

Introduction:

Ventilator-Associated Pneumonia (VAP) is a nosocomial disease considered fatal to critical care[1]. It is the most common form of infectious complication and mortality among patients in the intensive care unit (ICU)[2]. Without intubation, the incidence of pneumonia in 48 hours more after hospital admission is considered hospital-acquired/nosocomial pneumonia (HAP) based on the Infectious Diseases Society of America / American thoracic society (IDSA/ATS) guidelines (2016). A HAP that occurred after endotracheal intubation for more than 48-72hours is VAP[3]. Contamination of natural flora through aspiration of gastric

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or oropharyngeal contents is important for the pathogenesis. Further, the continual aspiration of subglottic secretion may also be a cause of VAP as seen in two randomized trials[3]. In Pediatric Intensive Care Units (PICU), it is the most often caused infection and has a pooled cumulative incidence of 22.8%, hence remaining a large cause of mortality with high healthcare-related costs[4]. VAP mortality rates range from 24-50% to even as high as 76% in cases with highly infectious pathogens. The most common organisms involved, include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*. However, other factors like ICU patient number, population, hospital stay period, age, gender, and previous exposure to antimicrobial therapy also affect the severity of the disease[5].

Prevalence:

VAP infections occur in 9% to 27% of mechanically ventilated patients[6]. The mortality rate in VAP is influenced by many factors and ranges between 27 and 76%[3]. The risk of getting a VAP infection is higher in the first 5 days of ventilation, and it has a mean duration of 3.3 days from intubation to the

development of the disease[7]. International Nosocomial Infection Control Consortium (INICC) conducted a surveillance study showing that, from January 2004 to December 2009, the ICUs of 36 countries in Latin America, Asia, Africa, and Europe had an overall infection rate of 15.8 per 1,000 ventilator-days and a crude unadjusted excess mortalities of 15.2% for ventilator-associated pneumonia[8]. Another data from the INICC surveillance study stated that the cases in developing countries may be as high as 16.8 cases per 1000 ventilator days[9]. In a US survey done on 183 US Hospitals in 2014, VAP and HAP (Hospital Acquired Pneumonia) take up 22% of diseases contracted from hospitals[1]. A summarized situation of VAP in different countries of Asia, based on recent studies, is shown in Table 1.

Infectious agents and Antibiotic Susceptibility:
VAP occurs in one of two ways, early-onset and late-onset. If infection occurs in the first four days of intubation and mechanical ventilation, it is early-onset, and commonly caused by antibiotic-sensitive bacteria, such as *Haemophilus spp*, streptococci including *Streptococcus pneumoniae*, and methicillin-sensitive *Staphylococcus aureus*[6]. In late-onset VAP, infection occurs after four days of intubation, where Multi-Drug Resistant (MDR) bacteria come into play. These include *Pseudomonas aeruginosa*, *Acinetobacter spp*, and methicillin-resistant *S aureus*[6]. Understanding and identifying the pathogens' susceptibility is crucial for combatting VAP.

VAP causing pathogens
Gram-negative bacilli cause 41-92% of VAP episodes. *Pseudomonas aeruginosa* makes up the most. Some reports showed *Candida spp* isolates are also dominant[10]. In one study, the common organisms isolated were *Klebsiella pneumonia* (16%), *Escherichia coli* (8.3%), *Pseudomonas aeruginosa* (2.7%), *Citrobacter* (2.7%), Coagulase-negative *Staphylococcus aureus* (2.7%). Imipenem and cefeperazone+sulbactum sensitive and ampicillin-resistant gram negatives, as well as cefoxitin sensitive gram positives were isolated. The presence of ESBL in the study was 5.5%[11].

In one study, *Pseudomonas aeruginosa* was seen to take up the highest, causing 22.9% of the total infection. *Klebsiella pneumonia* and *E. coli* and *Pseudomonas aeruginosa* had a significantly higher infection rate in the VAP group.[3]. In a retrospective study using 49 patients, it was seen that most patients who were infected with *Klebsiella spp*, died. *Enterobacter spp* and *Pseudomonas aeruginosa* had 80% and 70.6% mortality rates respectively[12].

For old and elderly patients, *Enterobacteriaceae, E. coli* and *Klebsiella* species seem to cause the most VAP. Among them,

E. coli significantly causes VAP following aspiration. Also, Gram-negative bacteria are responsible for 34.1% of pneumonia in patients above 65 and 20.5% in patients under 65[13].

In burn patients, in the first week, *S. aureus* was the most common. After 2 weeks, *P. Aeruginosa, A. baumannii*, and MRSA were dominant. *P. Aeruginosa* and *A. baumannii* combinedly accounted for nearly 20% of the VAP in the first 2 weeks[14].

In a study conducted with 49 patients, it was seen that VAP patients who had a longer ICU stay had five different microorganisms causing the VAP. The most common pathogen was, *Pseudomonas aeruginosa*[12]. A prospective cohort study in China found that the most common isolates from VAP patients were gram-negative bacteria (72.7%), gram-positive bacteria (15.3%) and fungi (12.0%). The common pathogens were *Pseudomonas aeruginosa* and *Acinetobacter baumannii,* then *Staphylococcus aureus* and *Stenotrophomonas maltophilia*[15].

Antibiotic Susceptibility of VAP causing pathogens
Studies show that the resistance to antibiotics for the following VAP organisms is *Acinetobacter baumannii* for Imipenem or meropenem (66.3%), *Klebsiella pneumoniae* for Ceftriaxone or Ceftazidime (68.9%) and Imipenem, Meropenem, or Ertapenem (7%). *Pseudomonas aeruginosa* for Fluoroquinolones (46.2%), Piperacillin or Piperacillin-Tazobactam (40.2%), Amikacin (28.3%), Imipenem or Meropenem (42.7%) and Cefepime (37.5%), *Escherichia coli* for Ceftriaxone or Ceftazidime (67.5%), Imipenem, Meropenem, or Ertapenem (4.2%) and Fluoroquinolones (54.9%); *Staphylococcus aureus* for Oxacillin (73.2%)[18]. *Acinetobacter baumannii* strains were found to have a Carbapenem resistance of 99.4% but it was found susceptible to Colistin[16]. The strain was found to be resistant rates like 99.7% to Meropenem, Piperacillin/ Tazobactam 99.3%, Amikacin 93.1%, Ciprofloxacin 99.7%, and Ceftazidime 99.3%[16]. *Pseudomonas Aeruginosa* isolated from VAP patients had antimicrobial resistance rates to 54.1% piperacillin/tazobactam 52.7%, amikacin 29.7%, ciprofloxacin 50%, ceftazidime 45.9%, and colistin 1.4%[16].

Meticillin-resistant *Staphylococcus aureus* was reported to have high rates, about 47.5%. Also high resistance is seen in imipenem resistant *P aeruginosa* (42.0%), imipenem-resistant *A. baumannii* (80.3%) and ciprofloxacin-resistant *P. aeruginosa* (58.6%)[16]. A prospective study in China found that some of the 92 *S. aureus* isolates were Methicillin-resistant (MRSA). Although no vancomycin-resistant enterococcus (VRE) or vancomycin-resistant/intermediate *S. aureus* (VRSA/VISA) was found[15].

K. pneumonia showed resistance to ampicillin. One of the extended-spectrum beta-lactamase (ESBL) producing strains showed high resistance to ampicillin, ampicillin-sulbactam, cefazolin, ceftriaxone and aztreonam. Some strains are found to be resistant to Imipenem and Ertapenem[17]. In this study, *Acinetobacter baumannii* was most common and among them, 96% were resistant to carbapenems. *Pseudomonas aeruginosa* which were also resistant to carbapenems were found. The third most common was *Escherichia coli* (7 isolates, that is 12%), among which 17% was ESBL (+)[18].

A .baumannii strains were found resistant to ceftazidime, imipenem but susceptible to colistin and piperacillin/tazobactam. Ceftazidime, piperacillin/tazobactam, imipenem and colistin were found to interfere with the biofilm formation of *A. baumannii*. Specific antibiotic therapy but in low concentrations is needed to kill *A. baumannii* strains. During VAP episodes, it can in some cases stimulate biofilm formation and cause potential and aggravate the infection. This is why it is important to find not only the strain but also its lethal doses, especially when using polymyxins, which are the last therapeutic alternative in the treatment of infections for MDR gram-negative bacteria[19].

ESBL was produced by 21.74% of *Enterobacteriaceae.* AmpC β lactamase was positive in 35.29% non-fermenters and 26.08% *Enterobacteriaceae*, Metallo-β-lactamase (MBL) was positive in 17.64% non-fermenters and 17.39% *Enterobacteriaceae*. 100% resistance to ceftazidime, amikacin and ciprofloxacin was shown by *Acinetobacter spp* while 75% was seen for *S. aureus* isolates, which were found to be MRSA[20]. A summarized view of antibiotic-resistant VAP-causing pathogens is shown in Table 2.

Risk Factors:
There are many factors related to the severity of VAP[3]. Individuals' age, gender and co-morbidities affect the disease manifestation. Conditions like burns, invasive operations, the disorder of consciousness, prior antibiotic therapy, etc. contribute to the disease's occurrence.

Age
In a study conducted with 417 patients, the maximum affected were in the age range between 69.9 ± 15.9 (range: 19–98) years[16]. In a multicenter study with 1735 patients, it was found that older age may not increase the risk for VAP. Although the mortality from VAP was high for elder patients, it did not seem to occur higher among the elderly[13].

Gender
In a retrospective study, it was found that of the 417 patients, 213 (51.1%) were males and 204 (48.9%) were females[16].

Another study with 58 cases of VAP found that the infection was more common among men (43 cases, that is 6%) than in women (15 cases, that is 3%). [18]. 854 patients with VAP are taken, of them, 676 males (79%) and 178 females (21%)[21]. The overall incidence of VAP between the genders, males and females were 3.8% and 2.6%. Males developed VAP more than females. However, it was seen that females have higher mortality with VAP compared with males (15% vs. 24%). This study also found that females have higher cases of severe episodes compared with males (49% vs. 61%). Females who developed early VAP had higher mortality than males (43% vs. 74%)[2].

Increased mechanical ventilation:
It has been reported that between the 5th and 9th day, the risk of VAP is high for patients in mechanical ventilation[12]. Therefore, to prevent risks, it is recommended to reduce intubation and decrease the use of invasive mechanical ventilation (MV) exposure[12]. The longer the ventilation, the more patients developed VAP[22]. Another study found an overall incidence of VAP in 20.8% of patients with MV[23]. A different study with 465 patients found that the mean duration for MV for all the patients was 13.4 ±4.4 days and that the duration was important because they statistically demonstrated that the patients with VAP had a longer mean MV duration compared with non-VAP patients[24]. In patients who receive mechanical ventilation, studies show that 28% of them get affected by VAP and the rate at with it occurs depends on the length of MV duration[3].

Disorder of consciousness:
Traumatic Brain Injury (TBI), a type of critical head injury, is associated with prolonged hospital admission. TBI patients with MV for >48hours, 24.3% developed early-onset VAP and 26.4% developed late-onset VAP[25]. Hemorrhagic shock, coma and pulmonary contusions were more common in patients with early VAP. This study showed that the VAP incidence in patients with TBI is 49.7% which is very high than average[25]. Aneurysmal subarachnoid haemorrhage (SAH) is a serious condition that in most cases requires mandatory mechanical ventilation (MV) and intensive care unit (ICU) hospitalization[26]. In this study, 47% of the patients were found positive for VAP. A significant association between constant sedation and VAP was also observed[26].

Burns:
VAP burn patients suffer from burn injury and inhalation injury and have higher mortality. They also need a longer duration of ICU and prolonged mechanical ventilation. Inhalation injury may also contribute to the higher risk of VAP in burned patients, as VAP rates are as high as 55 per

1000 ventilator days[14]. This study also found that patients with VAP had more inhalation injuries than non- VAP (44.6% vs 27%). The reason for this can be the immune, vascular, and organ changes that may occur due to severe burning[14].

Co-Morbidities:
Patients with cancer, major trauma injury, chronic obstructive pulmonary disease, acute respiratory distress syndrome and patients receiving Extracorporeal membrane oxygenation are reported to have higher VAP rates[12]. Other comorbid diseases associated with VAP are hypertension, Cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, coronary heart disease and chronic renal failure[16]. Renal failure (22.86%), and chronic obstructive pulmonary disease (14.29%) were seen in the majority of patients with VAP[20].

Prior Antibiotic Therapy:
Multivariate logistic analysis showed that prophylactic antibiotic application is an independent risk for MDR-caused VAP. Hence, by reducing prophylactic antibiotics, we can reduce the potentially modifiable factor for the development of MDR VAP in trauma patients[27]. This study showed that the majority of the patients had prior antibiotic therapy so it may be an independent risk factor[20].

Invasive Operations:
Bacterial biofilm develops on the internal layer of the endotracheal tube becomes resistant to systemic antibiotics over time, and acts as a nodule for infection. The biofilm size and the type of bacteria greatly contribute to the risk factors of infection[6]. The host's strength of immunity will decide whether ventilator-associated pneumonia and parenchymal infection will occur[6]. Another study found that invasive medical treatments like tracheostomy, bronchoscopy, reintubation, enteral and parenteral nutrition, analgosedation, tube, aspiration, chest drainage influence the occurrence of VAP[18]. 16 of 27 patients involved in this study, developed VAP after bronchoscopy was performed. Tube thoracostomy was also found to be a risk factor for VAP. Patients who were given this treatment, all developed VAP at least on the lateral lung. Lung parenchyma injury caused by pneumothorax or hemothorax can also be a cause of development[22]. Tracheostomy was also shown to be higher in VAP and a 20.8% estimated ICU mortality for all mechanically ventilated patients[3]. This study however showed no important difference in mortality for patients with re-intubation or ICU re-admission between the groups[3].

Gene Polymorphism:
A study showed that single nucleotide polymorphisms within the promoter region of the tumour necrosis factor gene are responsible for susceptibility to infections[28]. Tumor necrosis factor (TNFá) single nucleotide polymorphism (SNP) alleles cause proinflammatory cytokine to be produced. Although this does not predict the severity of the VAP[28].

Other factors
Intra-Abdominal Hypertension was found in 19.5% of the patients with VAP in a study with 123 patients[29]. Smoking was also found to be a strong predictor of VAP development. A study conducted showed that current smokers were 4.37 times more likely to have VAP than non-smokers[24]. When compared with patients without VAP, patients with VAP showed a higher chance of severe sepsis/septic shock, ARDS, atelectasis and infection with MDR organisms. However, the occurrence of pneumothorax and tracheobronchitis were similar[3].

Diagnosis:
The way to clinically diagnose a patient suspected of VAP is by symptoms of pulmonary infections which are fever, purulent secretions, and leukocytosis. Bacterial pulmonary infection and radiology also confirm the pulmonary infection[3]. American Thoracic Society (ATS) guideline suggests sampling should be done in a non-invasive way, with semiquantitative cultures. Suspected VAP patients who have below diagnostic culture results, should be withheld from continuing their antibiotics. Using clinical criteria alone to decide or initiate antibiotic therapy is recommended[30].

Clinical empiric diagnosis:
Fever at temperatures higher than 38.3°c, leukocytosis > 10000mm[3,] or leucopenia < 4000 per mm^3, secretions of purulent tracheal, and new or continuous radiographic infiltrate are clinical signs of VAP[11]. Acute physiology and chronic health evaluation (APACHE) is a classification system that works by the idea that acute diseases' severity can be calculated by finding the degree of changes in physiological variables. APACHE II is the revised prototype system of APACHE[31]. APACHE score greater than 16 predicted the mortality of patients with VAP[2]. APACHE II scores were significantly higher in non-surviving patients with VAP than in patients who survived[2]. In one study it was determined that clinical diagnosis to make postmortem studies of VAP suspected patients has a chance of producing 30-35% false-negative results and 20-25% false-positive results[6].

Phenotypic/Cultural diagnosis
Broncho-alveolar lavage (BAL), protected specimen brushing and "mini-BAL" (which is a method that takes samples from the distal airways through the tracheal tube using a specially designed catheter) are some of the ways to

test for VAP. Blind bronchial sampling is a method where a sterile catheter is randomly inserted through the tracheostomy tube and endotracheal aspirates are taken. The aspirates can then be tested using Gram's staining to find the phenotypes of the bacteria. Kirby Bauer's disc diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines are often used to determine the Antimicrobial susceptibility of the organism[11]. For *K. pneumoniae*, a string test can be used where a strain with mucoviscous string >5 mm can be considered a positive string test. BioMerieux VITEK-2 system can be used to both identify and find the antimicrobial susceptibility of microorganisms including ESBL[17] *A. baumanii* MIC (minimum inhibitory concentration) can be calculated by a micro-dilution technique using a 96-well polystyrene plate and a serial two-fold dilution of 50 µL between 0.5 and 512 µg/mL ranges for each antibiotic[19]. Endotracheal tube aspirate can be serially diluted and plated on sheep blood agar, chocolate agar, MacConkey agar and Saboraud's dextrose agar (SDA) to test the growth and identify possible isolates present. Then based on that, it can be separately tested for AST using Kirby Bauer's disk diffusion method. Ceftazidime and ceftazidime + clavulanic acid disk can used in combination disk test to confirm the presence of suspected ESBL organisms[20]. For finding imipenem susceptibility test, the following minimum inhibitory concentration is used for detection, ≥2 µg/ml for *E. coli* or *Klebsiella spp*; for *Enterobacter spp.*, *Serratia spp*. and *Citrobacter spp* ≥4 µg/ml; for *Acinetobacter spp*, MIC of e"8 and *P. aeruginosa*, and imipenem MIC of ≥16 µg[32] Carba NP test detects the presence of carbapenem-resistant strains. Carba NP test is a biochemical test that is used to detect the presence of carbapenemase production in gram-negative bacilli[33].

Genetic Diagnosis:
Polymerase chain reaction (PCR) can detect the presence of resistant genes like KPC, NDM, IMP, VIM and OXA48 [17]. Repetitive extragenic palindromic (REP)-PCR methodology can investigate the clonal profile of *Klebsiella* isolates through molecular typing[34]. A PCR test specific to the *mecA* gene confirms the Methicillin resistance. Molecular analysis using pulsed-field gel electrophoresis (PFGE) can be used to find the genetic profile[35]. If there is a positive EDTA-imipenem disc synergy test, it can be a further test for the presence of the *blaVIM* gene by PCR amplification[34]. Three-dimensional extract tests and AmpC disc tests are used to screen for plasmid-mediated AmpC â-lactamases. For control, Plasmid-mediated AmpC-producing strains of *K.*

pneumoniae HVAMC 39 (high-level ACT-1) and *K. pneumoniae* UMJMH14 (low-level DHA-1) and phenotypically β-lactamase-negative *E. coli* ATCC 25922 may be used. *E. coli* or *Klebsiella spp* with plasmid-mediated AmpC genes can be detected using multiplex PCR[32].

Management and Prevention
For early-onset infections, the British Society for Antimicrobial Chemotherapy Guidelines recommends co-amoxiclav or cefuroxime if patients weren't previously prescribed antibiotics or have any risk with the multi-drug-resistant patients. Patients with an early-onset infection that received antibiotics and have other risk factors may be prescribed third-generation cephalosporin (cefotaxime or ceftriaxone), a fluoroquinolone, or piperacillin-tazobactam. Other treatment antibiotics can be ceftazidime, ciprofloxacin, meropenem, and piperacillin-tazobactam. Vancomycin or linezolid can be added if methicillin-resistant *S. aureus* is present. In late-onset pneumonia, the most common MDR is *P. aeruginosa*. Acceptable treatment regimes include ceftazidime, ciprofloxacin, meropenem, and piperacillin-tazobactam although there is no specific or superior management. Vancomycin or linezolid are possible treatments for methicillin-resistant *S aureus*. Although linezolid is found to be able to penetrate lung tissues better, studies found no difference in results with vancomycin[6]. American Thoracic Society has some recommendation for the management and treatment of patients suspected of VAP that is shown in detail in Figure 1. If Methicillin-resistant *Staphylococcus aureus* (MRSA) is present, they recommend the use of vancomycin or linezolid for treatment. If methicillin-susceptible *Staphylococcus aureus (MSSA)* is indicated, then a regimen including piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem should be used. If oxacillin, nafcillin, or cefazolin are used for the treatment of MSSA then empiric treatment is not needed. Empiric treatment of suspected VAP patients with 2 antipseudomonal antibiotics from different classes can only be done if the patient has risk factors like prior intravenous antibiotic use within 90 d, septic shock at the time of VAP ARDS preceding VAP, before VAP spending 5 or more days in the hospital, Acute renal replacement therapy before VAP onset. For MRSA and MDR *Pseudomonas spp.* this treatment can be used when prior intravenous antibiotic use is done within 90 days. Patients without risk of antimicrobial resistance but empirically suspected VAP with *P. aeruginosa* can receive one antibiotic against it if they are in an ICU where d"10% of gram-negative isolates are resistant to the agent being

considered for therapy. Amino-glycosides should be avoided if the gram-negative activity was present. Instead, colistin can be used for the treatment. The choice of antibiotic therapy for patients with VAP due to *P. Aeruginosa* should be based on the results of the antibiotic susceptibility test. This should include the sensitivity assessment of the *P. aeruginosa* isolate to polymyxins, (colistin or polymyxin B) in situations that have a high prevalence of extensively resistant organisms. Aminoglycoside therapy should not be used for the treatment of *P. Aeruginosa*. For patients having *P. aeruginosa* with unknown AST, who are not in septic shock or at high risk for death, monotherapy can be done rather than combination therapy. For patients who remain in septic shock or at a high risk of death and have the results of AST known, combination therapy can be suggested. If the VAP patient has ESBL-producing gram-negative bacilli isolate, the results of antimicrobial susceptibility testing and patient-specific factor should be used to create a definitive therapy. For *Acinetobacter* species, treatment with carbapenem or ampicillin/ sulbactam can be used if the isolate is susceptible to these agents. If sensitive to only polymyxin, then intravenous polymyxin (colistin or polymyxin B) should be given. If the pathogen is sensitive to only colistin, then adjunctive rifampicin can be used for treatment. Tigecycline should not be used against *Acinetobacter* species. Intravenous polymyxins (colistin or polymyxin B) can also be used for the treatment of patients with carbapenem-resistant pathogens[30]. In one study, Cefuroxime has been shown to reduce the occurrence of VAP in patients with head injuries[3].

Current and futuristic approach to combat VAP:
One promising treatment can be bacteriophage treatment which uses bacterial viruses to treat of patients[36]. Bacteriophage therapy or phage therapy involves the usage of live, lytic bacteriophage in the treatment of infections for bacterial infections[37]. Phages are pathogen-specific and remain localized at certain parts of the body[38]. A test with an animal model showed a significant decrease in mortality in rats treated with anti-*S. aureus* phage cocktail when compared with the placebo group. 58% of the animals treated with phages survived at the end of the experiment and lived at least 12 hours after being infected[36]. In another experiment, rat models with VAP were treated with a prophylactic application of a nebulized phage. The animal models that lived had a significant reduction in bacterial load in the lungs and less lung tissue damage[38]. A 15-year-old VAP patient was treated with bacteriophage treatment. The patient had comorbidities of pancreatic insufficiency, insulin-dependent diabetes, cystic fibrosis (CF)-related liver disease, Nissen fundoplication and gastrostomy, CF-related osteoporosis and was expected for a lung transplant. Before the transplantation, the patient was treated for *Pseudomonas aeruginosa* and *M. abscessus* for 8 years with anti-NTM (non-tuberculosis mycobacterium) treatment. After the transplant, the patient was administered immunosuppressive drugs and multiple intravenous (iv) antibiotics. After one week of stopping intravenous antibiotics, the patient was found to be infected with *M. abscessus*. The patient was then treated a cocktail of phage, a single topical test and IV therapy every 12 hours for at least 32 weeks. After 6 months of treatment using phage, the patient clinically improved with slow healing of wounds and skin lesions. This is the first case where bacteriophage was used for treatment.[39]

VAP Care bundle can be adopted in hospitals. Bundles are a group of evidence-based clinical methods that when performed individually, was found to be effective for treatment[40]. Oral care using chlorhexidine solution can be included. Adequate endotracheal tube cuff pressure (20-30 mmHg) and endotracheal tube with an in-line suction system and subglottic suctioning can be used[9]. A randomized trial stated in the literature showed a reduction in the occurrence of VAP of 3 -fold if the treatment was performed in a semi-recumbent position compared to a supine position [3]. After compliance with VAP prevention bundle from 2010 to 2012, the VAP rate per 1000 days decreased from 15.4 ± 11 in 2008 to 9.1 ± 10.9 in 2012[14].

The bacterial load of the digestive tract can be reduced through selective decontamination of the digestive tract and oral. Antiseptics such as chlorhexidine can be used for oral decontamination and can help reduce ventilator-associated pneumonia. Oral decontamination can also involve the intravenous administration of broad-spectrum antibiotics and, oral and gastric non-absorbable oral antibiotics such as polymyxin, tobramycin, and amphotericin B. A study showed that endotracheal tubes which were silver-coated tend to have a risk reduction of 35.9% (3.6%-69%). The length of time spent in tracheal intubation may also help in the reduction of the occurrence of pneumonia[6].

Topical oropharyngeal antimicrobial prophylaxis has been shown to reduce the chance VAP. As the oropharynx is known to be a source of microbes, having a continuous aspiration in the subglottic secretion showed the reduced occurrence of VAP in two randomized studies[3]. Treatment using histamine-2-receptor blockers and proton pump inhibitors reduces the acid production, which in turn allows the pathogens to grow on the oropharynx and endotracheal tube. This is elevated due to aspiration[1].

Table-1: *Prevalence of VAP (VAP rate –episodes/ 1000 ventilation) in different countries of Asia*

Country	Study design	Type of ICU	Criteria to diagnose	VAP rate –(episodes/ 1000 ventilation)	Reference
India	Prospective study	MICU and CCU	CDC	14.35 to 8.1	[46]
India	Prospective study	Neurosurgery and Polytrauma	CDC	11.9	[32]
Bangladesh	Prospective cohort	CCU	CDC	35.73	[47]
Thailand	Prospective study	SICU	CPIS	6.3 to 2.8	[48]
Thailand	Surveillance study	ICU	(N/A)	12.6-13.6	[49]
Nepal	Prospective study	MICU and SICU	CDC	21.4	[50]
Kuwait	Prospective surveillance study	(N/A)	CDC	4	[51]
South Korea	Retrospective study	Cancer ICU	(N/A)	2.13	[52]
Pakistan	(N/A)	Medical and surgical	(N/A)	26	[53]
Saudi Arabia	(N/A)	Medical surgery	(N/A)	16.8	[54]
Japan	Cohort study	Medical and surgical	(NNIS)	6.5	[55]
China	Prospective study	(N/A)	(N/A)	4.5	[56]

(N/A) means no usable data found. Abbreviations used: ICU- Intensive Care Unit; MICU-Medical Intensive Care Unit; CCU-Critical Care Unit; CDC-Centers of Disease Control and Prevention; SICU- Surgical Intensive Care Unit; NNIS- National Nosocomial Infection.

Table-2: *VAP causing pathogens and their resistance to antibiotics*

| Organism	Resistance	Reference
Acinetobacter baumannii	Imipenem, meropenem, piperacillin, tazobactam, amikacin, ciprofloxacin, ceftazidime	8,15,16,20
Klebsiella Pneumonia	Ceftriaxone, ceftazidime, Imipenem, meropenem, ertapenem, ampicillin	8,17
Pseudomonas Aeruginosa	Fluoroquinolones, Piperacillin, piperacillin-tazobactam, Amikacin, ciprofloxacin, ceftazidime, colistin	8,15,16
Escherichia Coli	Ceftriaxone, ceftazidime, Imipenem, meropenem, ertapenem, Fluoroquinolones	8
Staphylococcus Aureus	Oxacillin, Methicillin	8,15,20
Enterobacteriaceae	Ampicillin	20
Extended spectrum beta-lactamases (ESBL)	Ampicillin, ampicillin-sulbactam, cefazolin, ceftriaxone, aztreonam, Imipenem, Ertapenem	17
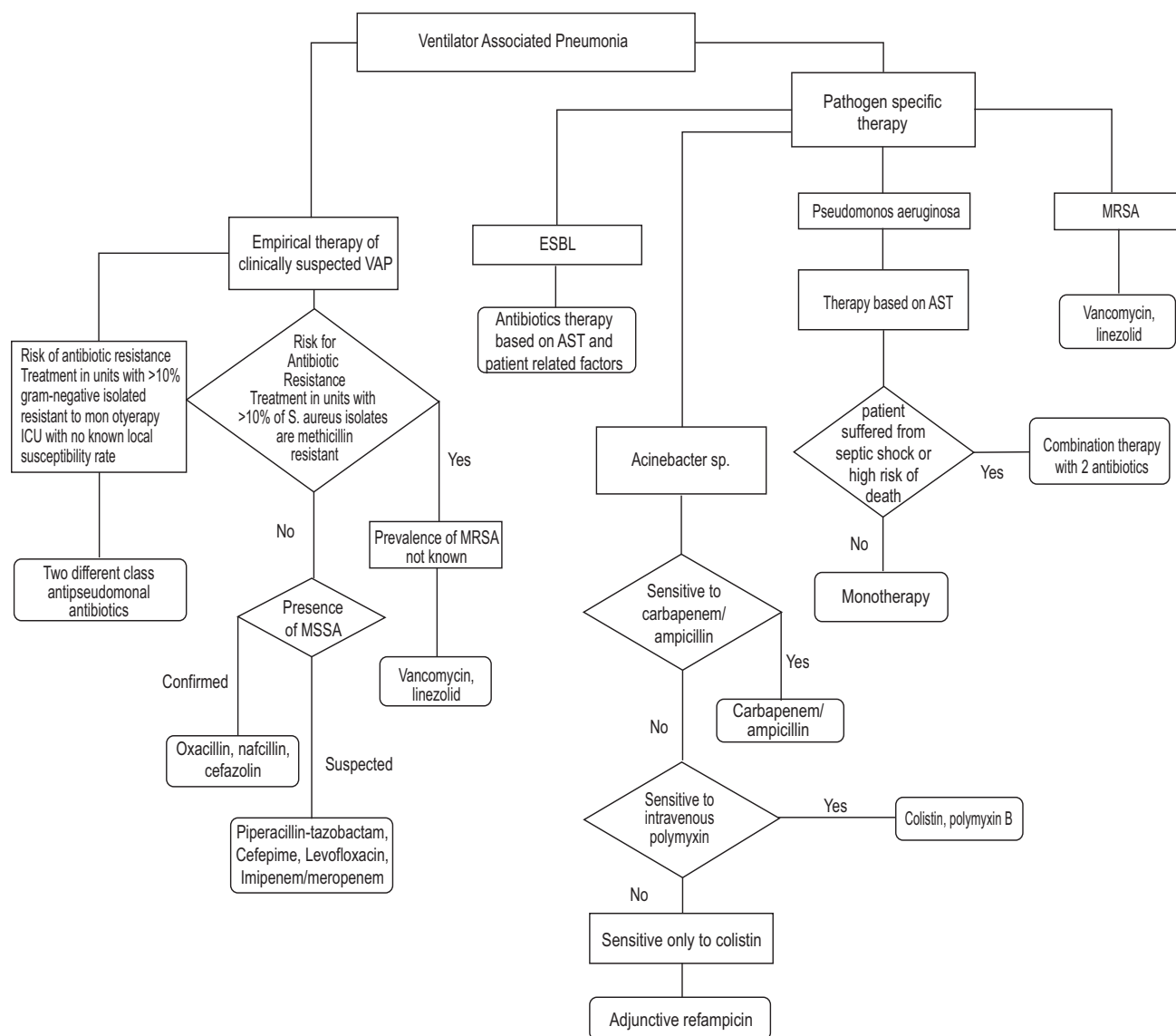
Figure 1: *American Thoracic Society guideline to antibiotic therapy for VAP*

Discussion:

Developing countries tend to have a higher rate of VAP when compared to developed, varying from 10- 41.7 per 1000 MV-days[15]. From table 01, it can be seen that developing countries like Bangladesh, Nepal, India, and Pakistan showed a higher VAP rate of 35.73, 21.4,11.9 and 26 per 1000 respectively.

In the diagnosis, most of the papers used bronchoscopic BAL and blind BAL to collect endotracheal aspirates which were then further tested. As qualified operators and other resources like fiberoptic bronchoscopes are not easily available, NB (Non-bronchoscopic)-BAL can be a good alternative as it is not only less invasive but also requires less compromise of oxygenation than B-BAL. In the study

conducted, it was found that Non-bronchoscopic protected BAL sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 89%, 75%, 77% and 88% respectively, whereas Bronchoscopic BAL had a sensitivity of 85% and specificity of 77%, PPV and NPV were 74% and 82% respectively[41].

VAP is mainly diagnosed through empiric treatment. Beginning the empirical antibiotic therapy as soon as the patient was found to have VAP, was considered the right approach but the problem is that there aren't any diagnostic techniques that quickly identify the affected patient[42]. Broad antibiotics are often used before treatment of the intubated patients as most have concomitant infections[43]. So the patient's natural flora is already resistant to them. There is a

great ecologic impact, especially in ICU patients where broad-spectrum antibiotic therapy is used, as it can change the microflora in the patient's body. Antibiotic pressure is found to be the main reason leading to most nosocomial outbreaks in patients in ICU[43]. VAP is often caused by patients' natural flora, which means it can resistant to previously used antibiotics[44]. So, for every patient, a unique antibiotic regime has to be made.

When APACHE II was tested with CPIS to check the discrimination and calibration for predicting 30-day mortality in patients with VAP, APACHE II showed promising results. The possible reasons can be because APACHE II was designed to classify the severity of a disease. So, when taking data, APACHE II includes values like acute physiology score, age points, and chronic health points while CPIS uses six parameters like temperature, white blood cell count, tracheal secretions, PaO2/FiO2, chest radiography, and microbiology are related to the disease. So testing mortality using CPIS for VAP may not be a good option since many of the patients may also die from other factors like multiple organ failure[45].

Conclusion

Ventilator-associated pneumonia is one of the frequent causes of mortality in intensive care units. From the information collected, it can be understood that developing countries have a higher VAP rate. The classification of VAP is of two types, early-onset pneumonia which is caused by antibiotic-sensitive bacteria, and late-onset pneumonia which is caused by multidrug-resistant pathogens. The majority of VAP is caused by gram-negative bacilli and the most dominant ones are A. *baumannii, P. Aeruginosa* and *K. pneumoniae* with *P aeruginosa* is the most commonly found. In one study, *P. aeruginosa* is found to be resistant to colistin. ATS suggests empirical diagnosis VAP and immediately start antibiotic therapy. A range of antibiotics can be used to treat patients based on the type of VAP. Other approaches to combat VAP can be, the use of VAP bundle, bacteriophage treatment etc. Some methods to reduce the occurrence of VAP, can be selective decontamination of the digestive tract and oral, topical oropharyngeal antimicrobial prophylaxis, use of passive humidifiers and use of histamine-2 receptor blockers and proton pump inhibitors.

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