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Health care-associated pneumonia: Pathogenesis Diagnosis and Preventions

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ABASTRACT:*Pneumonia has been ancientdisease, pneumonia referred as captain of the men of death and the old man's friend. Health care–associated pneumonia (HAP) and ventilator -associated pneumonia (VAP) has high morbidity and mortality. Wide spectrum of bacteria, viruses, fungi, parasites and multidrug resistant (MDR) pathogens are frequent cause of HAP and VAP. Over the years tremendous progress has been made in reducing health care-associated infections and antibiotic management and implementation of prevention strategies. Noninvasive positive-pressure ventilator support without need for intubation and is an effective alternative for patients with chronic pulmonary* disease.*Limiting the use of continuous sedation, paralyticagents, use of Silver-coated Endotracheal Tube, oralantiseptic, modulation of oropharyngeal colonization by oral antibiotics, and use of quantitativemicrobiologiccultures to assess lower airway colonizationand infection. Prevention is cost effective and the key to reduced mortality and morbidity. Old proverb, "prevention is better than cure".*

KEYWORDS:*Health care-associated pneumonia,Pathogenesis, Diagnosis, and Preventions.*

I. INTRODUCTION

Pneumonia has been a common disease throughout human history. The symptoms were described by Hippocrates(460-370,BC).Hippocrates referred pneumonia as a disease "named by the ancients"[1,2].Maimonides(1135-1204 AD) observed "The basic symptoms that occur in pneumonia, such as Acutefever, sticking pleuritic pain in the side, short rapid breaths, serrated pulse and cough[3].Edwin Klebs was first to observe bacteria in the airways of persons having died of pneumonia in 1875[4].Initial work identifying two common bacterial causes, *Streptococcus pneumoniae* and *Klebsiella pneumoniae*,was performed by Carl Friedlander and Albert Frankel in 1882[5,6].Health care-associated or hospital acquired pneumonia(HAP) is defined as an infection that occurs in a patient who has been hospitalized more than 48 hours, and ventilated pneumonia(VAP) is an infection that occurs in an intensive care unit(ICU) patient more than 48 hours after endotracheal intubation and mechanical ventilation[7].Rates of HAP have varied between 5 and 10 episodes per 1000 hospital admissions and tend to be higher in university versus nonteaching hospitals[7]Mortality rates for HAP estimates are approximately 10% and are higher for VAP with range of 20% to 60% depending on the patient, severity of disease, specific pathogen isolated, and management[7].An average episode of VAP has been estimated to increase hospitalization by 12 days, ventilation days by 6 days,ICU stay by 6 days, and hospital costs by $12,000 to $40,000 per episode[7].Frequent pathogens causing HAP and VAP include wide spectrum of bacteria, viruses,fungi,parasites, multidrug resistant(MDR) pathogens[7].MDR pathogens of concern include gram-bacilli(extended spectrum β lactamase producing *Klebsiella pneumonia,Acinetobacterbaumannii,Pseudumonas aeruginosa)* or methicillin-resistant *Staphylococcus aureus* (MRSA)[8].Gram-negative bacilli have been implicated in more than 60% of reported episodes of HAP and VAP ,but pneumonia due to *S.aureus* now accounts for 20% to 40% of episodes, most of which are now MRSA[9].Increasing resistance to vancomycin and identification of glycopeptide or vancomycin intermediate-resistant *S.aureus* isolates seem to be emerging worldwide[10].Prevention strategies for HAP and VAP reduce patient mortality ,morbidity, and health care costs[11].The paper reviews the pathogenesis, diagnosis, and prevention of health care-associated pneumonia(HAP) and ventilator associated pneumonia(VAP).

II. PATHOGENESIS

The prognosis of HAP and VAP depends on the number and types of colonizing pathogens that enter the lower respiratory tract and the host's mechanical, cellular and humoral defenses [12].For HAP, micro aspiration is the primary route of bacterial entry into the lower respiratory tract; risk factors include sedation, intubation for operative procedures, vomiting, and impaired swallowing[7].For VAP,leakage of bacteria and oral secretions around the endotracheal cuff, inhalation of the contaminated aerosols, or reflux of contaminated ventilator tubing condensate are the primary routes of bacterial entry into the lower respiratory[12].Local trauma and inflammation from the endotracheal tube increase tracheal colonization and reduce clearance of organisms from the lower respiratory tract. Not widely appreciated is the impact of biofilm-encased in the endotracheal

tube lumen. These bacteria increase over time and may be transported into the distal lung alveoli after routine suctioning or bronchoscopy. These biofilm – incased bacteria are protected against killing by antibiotics and host mechanical cellular, and humoral defenses[13].The outcome of the pathogen-host battle determines whether the outcome will be tracheal colonization, tracheobronchitis, or HAP/VAP[11].

In intubated patients, lower respiratory tract colonization may progress to ventilator-associated tracheobronchitis(VAT),which may be a precursor to VAP or, in selected patients, difficult to distinguish from VAP[14].Nseir and colleagues define VAT as the presence of clinical signs of lower respiratory infection,(fever, leukocytosis and purulent sputum),with a quantitative endotracheal sputum sample having a respiratory tract pathogen at a concentration of more than 10^5 organisms per milliliter and the absence of a new or progressive infiltrate on chest x-ray[14].Others may prefer different quantitative thresholds or use a semi quantitative endotracheal aspirate having moderate to heavy growth of a respiratory tract pathogen[11].

III. CLINICAL SYMPTOMS

WilliamOsler in the 19th century regarded pneumonia as "the captain of the men of death"[15].In the terminally ill and elderly, especially those with other conditions, pneumonia is often the immediate cause of death. In such cases, particularly when it cuts short the suffering associated with lingering illness, pneumonia has often been called "the old man's friend"[16].People with infectious pneumonia often have a productive cough, fever accompanied by shakingschills, shortness of breath, sharp or stabbing chest pain during deep breaths, and increased respiratoryrate. In the elderly, confusion may be the most prominent sign [17].The typical signs and symptoms in children under five are fever,cough,and fast or difficult breathing[18].Fever is not very specific, as it occurs in many other common illnesses, and may be absent in those with severe disease or malnutrition. In addition, a cough is frequently absent in children less than 2 months old[18].More severe signs and symptoms may include blue-tinged skin, decreased thirst, convulsion, persistent vomiting, extremes of temperature, or a decreased level of consciousness[18].

Bacterial and viral cases of pneumonia usually present with similar symptoms [19].Some causes are associated with classic, but non-specific, clinical characteristics. Pneumonia caused by *Legionella* may occur with abdominal pain, diarrhea, or confusion, while pneumonia caused by *Streptococci pneumoniae* is associated with rusty colored sputum [20,21],and pneumonia caused by *Klebsiella* may have bloody sputum often described as "currant jelly"[22].Bloody sputum(known as hemoptysis)may also occur with tuberculosis. Gram-negative pneumonia, and lung abscesses as well as more commonly with acute bronchitis[23].*Mycoplasma* pneumonia may occur in association with swelling of the lymph nodes in the neck, joint pain, or a middle ear infection[23].Viral pneumonia presents more commonly with wheezing than does bacterial pneumonia[19].

IV. INFECTIOUS ETIOLOGIES

Infectious agents causing HAP and VAP include a wide spectrum of bacteria,viruses,fungi, and parasites. Over the past 20 years, there has been a dramatic increase in health care-associated (hospital associated) respiratory infections due to antibiotic- resistant or multidrug resistant (MDR) pathogens [7].Bacteria causing HAP and VAP may originate from patient's endogenous flora, otherpatients, hospitalstaff, contaminateddevices, or the inanimate environments[24].The spectrum of bacterial pathogens in the ICU are dynamic and may vary with time, by hospital, type of ICU,and specific patient population emphasizing the importance of up-to date surveillance data[7].Early onset of HAP(occurring during the first 5 days of hospital stay) is more likely to be caused by antibiotic-sensitive pathogens, such as *Streptococcus pneumoniae,Moraxella catarrhalis,Haemophilus influenza,*anaerobic bacteria*or Legionella pneumophila*[7].

Predisposing, factors for patient colonization and infection with MDR pathogens that require a different spectrum of initial empirical antibiotic therapy include recent hospitalization, residence in a long term health care facility, the presence of significant chronic disease, debility, and recent antibiotic therapy [7].MDR pathogens of concern include gram-negative bacilli(extended spectrum β lactamase producing *Klebsiella pneumonia,Acinetobacter baumannii,Pseudomonas aeruginosa)*or methicillin- resistant *Staphylococcus aureus* (MRSA) [7].*P.aeruginosa,*the most common MDR,gram-negative pathogen causing VAP, and some isolates that are pan-resistant(sensitive only to polymixin) or having exotoxin 111 have been associated with increased patient mortality[8].Also, outbreaks of VAP due to other MDR gram-negative bacilli, especially*A.baumannii,*have been reported over the past decade and have been difficult to control and eradicate[7].

Gram- negative bacilli have been implicated in more than 60% of reported episodes of HAP and VAP, but pneumonia due to *S.aureus* now accounts for 20% to 40% of episodes, most of which are now MRSA[7].HAP and VAP due to hospital acquired MRSA have been increasing worldwide for the past 10 years, and there is also a cause of HAP and VAP[25].In contrast to the hospital MRSA strains, community acquired MRSA isolates are genetically distinct and almostuniformly carry the Panton-Valentine leucocidin and factors that seem to increase damage to lung tissue[25].In addition, increasing or creeping resistance to vancomycin and

identification of glycopeptide or vancomycin intermediate-resistance *S.aureus* isolates seem to be emerging worldwide. Of greater concern is the lack of detection of these isolates with the techniques currently used in many microbiology laboratories [26].

Viruses.In adults viruses account for approximately a third and in children for about 15% of pneumonia cases[27,28].Commonly implicated agents includerhinoviruses coronaviruses, influenza virus, respiratorysyncytial virus(RSV),adenovirus, and parainfluenza[27].Herpes simplex virus rarely causes pneumonia, except in groups such as: newborns, persons with cancer, transplant recipients, and people with significant burns[29].Patients with viral infections may be secondarily infected with the bacteria *Streptococcus pneumonia*,*Saphylococcus aureus*,or *Haemophilus influenzae*,particularly when other health problems are present[28].

Fungi. Fungal pneumonia is uncommon, but occurs more commonly in individuals with weakened immune system due to AIDS, immunosuppressivedrugs, or other medical problems [16].It is most often caused by *Histoplasma capusulatum ,blastomyces, Cryptococcus neoformans*,*Pneumocystitis jiroveci*,and *Coccidio immitis*,Histoplasmosis is most common in the Mississippi River basin, and coccidioidomycosis is most common in the Southwestern United States[16].The number of cases have been increasing in the later half of 20^{th} century due to increasing travel and rates of immunosuppression in the population[30].

Parasites.A variety of parasites can affect the lungs, including *Toxoplasma gondii, Strongyloides stercoralis,Ascaris lumbrocoides*,and *Plasmodium malariae*[31].These organisms typically enter the body through direct contact with skin ,ingestion, or via an insect vector[31].Except for *Paragononimus westermani* most parasites do not affect specifically the lungs but involve the lungs secondarily to other sites[31].Some parasites, in particular those belonging to the *Ascaris* and *Strongyloides*genera, stimulate a strong eosinophilic reaction, which may result eosinophilic pneumonia[31].In other infections, such as malaria, lung involvement is due primarily to cytokine-induced systemic infection[31].

Idiopathic.Idiopathic interstitial pneumonia or noninfectious pneumonia are a class of diffuse lung diseases. They include diffuse alveolar damage, organizing pneumonia, nonspecific interstitial pneumonia, lymphocyticinterstitial pneumonia, desquamatepneumonia respiratorybronchiolitis interstitial lung disease, and usual interstitial pneumonia [32,33].

V. DIAGNOSIS

The best sensitivity(identifying patients with pneumonia) and specificity(accuracy of the diagnosis) combine clinical signs and symptoms with microbiologic sputum smear(Gram stain)and bacterial culture[9].Clinical signs and symptoms suggesting HAP and VAP include at least two of three clinical features(temperature>38^{o}Cor hypothermia) leukocytosis, leukopenia, increased immature neutrophils("bandemia") or purulent respiratory secretions, and the presence of a new or progressive radiographic infiltrate. Blood cultures may be helpful but positive cultures are uncommon, except in patients with pneumococcal and *S.aureus*pneumonia. The clinical pulmonary infection score used in some ICUs,gives points for clinical, radiographic, andmicrobiologic, data for a single numerical result. The ratio of alveolar partial pressure of oxygen ($Pa0_2$)to the fractional inhaled oxygen partial pressure of oxygen ($Fi0_2$) is a key physiologic parameter. A clinical pulmonary infection score of more than 6 correlates well with the presence of clinical pneumonia [7].

The major route of bacteria into and out of lung is via the trachea.The presence of bacteria and polymorph nuclear cells on sputum Gram stain and a sputum culture having significant growth of bacterial pathogen by semi quantitative or quantitative bacteriologic techniques help to confirm the clinical suspicion of pneumonia or tracheobronchitis[7].In patients with HAP, it may be more difficult to obtain and interpret sputum samples than VAP patients. Thediagnosis of VAP has greater specificity than HAP, but can be limited by increased bacterial colonization in the endotracheal aspirates or the presence of VAT than may mimic VAP,especially in patients with previous or increasing pulmonary infiltrates due to congestive heart failure, adult respiratory distress syndrome, pulmonary emboli or atelectasis[11].

Examination of endotracheal aspirates by Gram stain allows rapid insight into the number and types of bacteria, as well as the number of polymorph nuclear leukocytes and macrophages that are suggestive of inflammation and infection. The presence of bacteria on Gram stain(smear)correlates with cultures of approximately 10^5 bacteria per milliliter of sputum and also provides a clue to the offending bacteria(i.e.,gram-positive bacteria in clusters suggest *S.aureus* and gram negative bacilli may suggest *Klebsiella* spp.,*Escherichia* coli or *P.pseudomonas*).Endotracheal aspirate cultures, using the semi quantitative endotracheal aspirates, are reported as moderate or heavy growth of pathogen, which helps to confirm a diagnosis of VAP or VAT.Endotracheal aspirate growth is reported as rare or few probably represents tracheal colonization. Some microbiology laboratories report quantitative endotracheal aspirates in which a pathogen growth of morethan$10^{5\text{-}6}$colony-forming units per milliliter (CFU/ml) is consistent with a diagnosis of VAP[11].

Quantitative distal airways samples obtained by bronchoscopyBroncho alveolar lavage(BAL)(>10^4 CFU/ml) or protective specimen brush(>10^5 CFU/ml),or nonbronchoscopic BAL or protective specimen brush have good diagnostic sensitivity and probably a higher specificity than endotracheal aspirate samples, but these techniques are not widelyavailable, are more expensive and require expertise[34].The advantages of using semi quantitative or quantitative endotracheal aspirates versus distal lung parenchyma sampling by BAL/protective specimen brush for diagnosis of VAP remain controversial. Most hospitals in the United States use semi quantitative endotracheal aspirates for the diagnosis of VAP[34].Biological markers, such as procalcitonin and soluble triggering receptor expressed on myeloid cells, may be helpful adjunct for the diagnosis and management of VAP[35].Although they both have greater diagnostic accuracy than most commonly used clinical parameters and other biomarkers of infection, such as C-reactive protein, they can be increased in noninfectious conditions or remain low in patients with true infection[34].Furthermore these assays cannot determine the causative organisms and associated patterns of antibiotic susceptibility[11].

VI. MANAGEMENT

The basic principles of antibiotic management of HAP and VAP emphasized in the American Thoracic Society and Infectious Diseases society of America Guidelines include (1) selection of antibiotic regimen (2) de-escalation of initial antibiotic therapy when possible (3) stopping antibiotic therapy in responders, and (4) further evaluation of nonresponses.Other guidelines have also been provided similar recommendations for management of HAP and VAP [7].

Data suggest that delay in initiating appropriate antibiotic therapy increase patient morbidity and mortality[7].Blood cultures and respiratory sputum samples should be collected before antibiotics are initiated to ensure proper therapy and to provide better de-escalation of antibiotics 36 to 48 hours later[7].Initial empirical antibiotic regimen should be appropriate (pathogen is sensitive to the antibiotic in vitro),based on the presence or absence of risk factors for MDR bacterial pathogens that have been emerging over the past two decades, and administered without delay[7].

Initial empirical therapy for patients with MDR risk factors for VAP should include coverage for suspected pathogens endemic in the ICU,which should include for gram negative bacilli either third or fourth generation cephalosporin(e.g.,ceftazidime,cefpime),βlactamβ lactamase inhibitor (e.g.,piperacillin-tazobactam) or a carbepenem(e.g.,imipenem, meropenem)plus an aminoglycoside(e.g.,gentamicin,tobramycin,amikacin)or an anti pseudomonal fluoroquiolone(e.g.,levoflaxacine,ciprofloxacin)is recommended for 48 hours until sputum culture and sensitivity data are available[7].Ideally, concentrations of antibiotics should remain above the minimal inhibitory concentration(MIC) of the pathogen as long as possible to have maximal effect in reducing the bacterial burden in the lung[7].

Although initial antibiotic coverage should be liberal and sufficiently broad to cover all suspected pathogens, narrowing the spectrum or streamlining antibiotic therapy at 24 hours or 48 hours should be based on the patient's clinical response(fever,oxygenation,leukocyte count, appearance and vital signs) and microbiologic data(Gram stain, culture and antibiotic data[7].Narrowing the spectrum improves patient outcomes by minimizing the complications of broad spectrum use ,such as *C.difficile,* selection of MDR pathogens and superinfections [35].Evidence based data support limiting the total duration of antibiotic therapy to 7 days in responders who do not have other complications, such as empyema or bacteremia with MRSA that may seed other tissues[36].Serum markers such a procalcitonin may also be helpful to guide antibiotic treatment[7].The use of procalcitonin levels and changes in oxygenation may provide important clues for patients who are more likely to relapse or need a longer duration of antibiotic therapy[37].

In most patients, clinical improvement takes 24 hours to 48 hours [7].Therefore; the selected antimicrobial regimen should not be changed during this time unless there is evidence of progressive deterioration. Possible causes for clinical deterioration or failure to improve include wrong diagnosis(pulmonary embolism with infarction,atelectasis,pulmonary hemorrhage, neoplastic or connective tissue disease, acute respiratory distress syndrome with diffuse alveolar damage, other source of infection)[7].

VII. PREVENTIONS

Tremendous progress has been made in reducing health care-associated infections in last 5 years [[9].Prevention in the ICU has become a high priority. It is now a "team support "that require leadership,organization, goals, clearly defined roles, checklist, quality improvement targets,and data feedback at multidisciplinary staff meeting [38].

Endotracheal tube is a primary target for prevention strategies because it facilitates bacterial entry into the lower respiratory tract and limits effective removal of secretions from the lower respiratory tract by cough [9].In addition, the endotracheal tube may be biofilm encased bacteria that are sheltered from killing by antibiotics and host cellular defences.These bacteria may be embolized to the distal lung during suctioning [7].

Noninvasive positive- pressure ventilator support without the need for intubation and is an effective alternative for patients with acute exacerbation of chronic obstructive pulmonary disease or acute hypoxemic respiratory failure. Noninvasive positive- pressure ventilation is associated with decreased rates of pneumonia, antibioticuse, and patientmortality [39]

Limiting the use of continuous sedation and paralytic agents that depress cough coupled with sedation vacations and weaning protocols that facilitate removal of the endotracheal tube are strongly recommended to reduce days of mechanical ventilation and lower rates of VAP [40].Continuous aspiration of subglottic through of specially designed endotracheal tubes with a wider elliptical hole helps facilitate drainage of subglottic secretions and bacteria entering the trachea[41].

The North American Silver-Coated Endotracheal Tube (NASCENT) Study was a randomized study comparing a colloidal silver-coated endotracheal tube with control endotracheal tube [42].The incidence of VAP using microbiologic confirmation by BAL with more than 10^4 organisms per milliliter, was significantly lower in silver-coated endotracheal tube group(4.8% vs.7.5%,*P*=0.3),with relative risk reduction for VAP of 36%[42].

Oral antiseptic chlorhexidine has demonstrated efficacy in reducing VAP,especially in cardiac surgery patients[43].In a recent multicenter, double-blind, randomized clinical trial of VAP outcomes subjects treated with 2% chlorhexidine paste were compared with patients randomized to 2% chlorhexidine plus 2% colistin (paste)or placebo. Although the risk of VAP was reduced by 65% in the chlorhexidine group (P=.01), no difference was noted in ventilatordays, length of hospital stay, ormortality [44].

Modulation of oropharyngeal colonization by combination of oral antibiotics, with or without systemic therapy or selective decontamination of the digestive tract is effective in preventing VAP,but data are difficult to assess because of methodologic study quality, spectrum of regimens used, and differences in study populations [39].Clinical evidence of the efficacy of selective decontamination of the digestive tract was recently reported in a Cochrane review [45].

Accurate diagnosis of VAP is limited by the lack of a common diagnostic gold standard [46].Intubated patients have ready access to lower airway sputum, which can be evaluated by smear and microbiologicculture. Routine use of serial quantitative microbiologic cultures to assess lower airway colonization, to increase the clinical suspicion for VAP,and to help clinicians distinguish between colonization and infection [14].There has been tremendous progress in understanding of HAP and VAP,antibiotic management, and implementation of prevention strategies[46].HAP and VAP are dynamic and complex diseases with associated morbidity and mortality and that will require constant surveillance and efforts to improve therapy and prophylaxis[11].Investing in prevention is cost effective and the key to reduced mortality and morbidity. The Institute for Healthcare Improvement has been a force for "sowing seeds for change", but other methods of prevention may be needed to further reduce VAP in high risk population [47]

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VIII. CONCLUSION

HAP and VAP are dynamic and complex diseases with associated morbidity and mortality and that will require constant surveillance and efforts to improve therapy and prophylaxis.

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