INTRODUCTION

Pneumonia

Pneumonia is an inflammatory condition of the lung affecting primarily the microscopic air sacs known as alveoli.[1,2] It is usually caused by infection with bacteria or viruses and less commonly other microorganisms, certain drugs and other conditions such as autoimmune diseases.[3]

Typical symptoms include a cough, chest pain, fever, and difficulty breathing. Diagnostic tools include x-rays and culture of the sputum. Vaccines to prevent certain types of pneumonia are available. Treatment depends on the underlying cause. Pneumonia presumed to be bacterial is treated with antibiotics. If the pneumonia is severe, the affected person is, in general, admitted to hospital.[4]

Pneumonia affects approximately 450 million people globally per year, seven percent of population, and results in about 4 million deaths, mostly in third-world countries. Although pneumonia was regarded by William Osler in the 19th century as "the captain of the men of death", the advent of antibiotic therapy and vaccines in the 20th century has revealed improvements in survival. Nevertheless, in developing countries, and among the very old, the very young, and the chronically ill, pneumonia remains a leading cause of death.[5-6]

Imaging in VAP

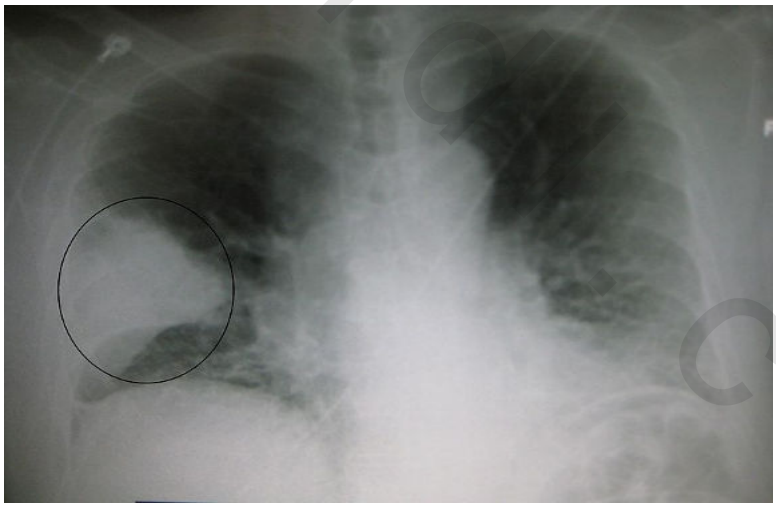


Figure (1): A chest X-ray showing a very prominent wedge-shape bacterial pneumonia in the right lung.[7]

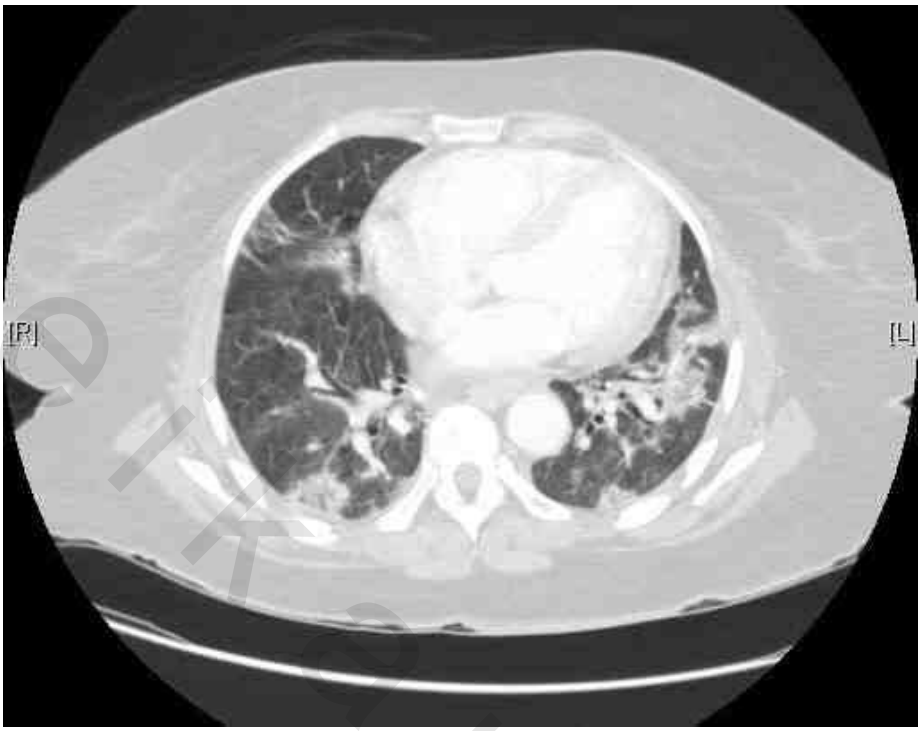


Figure (2): CT chest reveal bilateral VAP patches. [8]

There are many types of pneumonia including community acquired pneumonia CAP, health care associated pneumonia HCAP, hospital acquired pneumonia HCAP, and ventilator associated pneumonia VAP and the last is the main concern in this study. [9]

Community acquired pneumonia (CAP)

Community acquired pneumonia is a pneumonia acquired infectiously from normal social contact .not due to hospital stay or health care facility care it is one of the most common of infections of the human being.[10]

Health care–associated pneumonia (HCAP)

Health care–associated pneumonia is pneumonia that occurs in persons in one of the following groups:

- Patients who have been hospitalized in an acute care facility for 2 or more days within 90 days of the infection
- Residents of a nursing home or long-term care facility
- Patients who received intravenous antibiotic therapy, chemotherapy, or wound care within the last 30 days of the current infection
- Patients who receive hemodialysis in any setting. [11]

HAP) is pneumonia that develops 48 hours or longer after admission to a hospital. HAP is the second most common nosocomial infection. HAP increases a patient's hospital stay by approximately 7-9 days.[12]

Ventilator associated pneumonia (VAP)

VAP is pneumonia that develops 48 hours or longer after mechanical ventilation is given by means of an endotracheal tube or tracheostomy. VAP results from the invasion of the lower respiratory tract and lung parenchyma by microorganisms. Intubation compromises the integrity of the oropharynx and trachea and allows oral and gastric secretions to enter the lower airways.[13]

Epidemiology of VAP

VAP is a complication in as many as 28% of patients who receive mechanical ventilation. The incidence of VAP increases with the duration of mechanical ventilation.[14]

The crude mortality rate for VAP is 27-76%. *Pseudomonas* or *Acinetobacter* pneumonia is associated with higher mortality rates than those associated with other organisms. Studies have consistently shown that a delay in starting appropriate and adequately dosed antibiotic therapy increases the mortality risk. [15]

Risk factors

There are many of risk factors for vap but the main risk factor is endotracheal intubation that increase risk of pneumonia 6 to21 fold and this is due to formation of biofilm [16]

Biofilm is an aggregate of microbes with in ETT A biofilm is like a tiny city in which microbial cells invade the inner side of ETT and this facilitate transmission of bacteria to lower lung zone.[17]

Risk factors [18] includes

- Age >70 years
- Chronic lung disease
- Depressed consciousness
- Aspiration
- Chest surgery
- The presence of an increased intracranial pressure
- monitor or nasogastric tube
- H2 blocker or antacid therapy
- Transport from the intensive care unit (ICU) for diagnostic
- or therapeutic procedures
- Previous antibiotic exposure, particularly to third generation cephalosporins
- Reintubation or prolonged intubation
- Mechanical ventilation for acute respiratory distress syndrome

- Frequent ventilator circuit changes
- Paralytic agents

Pathophysiology

VAP primarily occurs because the endotracheal or tracheostomy tube allows free passage of bacteria into the lower segments of the lung in a person who often has underlying lung or immune problems. Bacteria travel in small droplets both through the endotracheal tube and around the cuff. Often, bacteria colonize the endotracheal or tracheostomy tube and are embolized into the lungs with each breath. Bacteria may also be brought down into the lungs with procedures such as deep suctioning or bronchoscopy. Another possibility is that the bacteria already exist in the mucus lining the bronchial tree, and are just kept in check by the body's first line of defenses.[19]

Once inside the lungs, bacteria then take advantage of any deficiencies in the immune system (such as due to malnutrition or chemotherapy) and multiply. A combination of bacterial damage and consequences of the immune response lead to disruption of gas exchange with resulting symptoms.[20]

Pathogenesis

The pathogenesis of VAP, is related to the number and virulence of microorganisms entering the lower respiratory tract and the response of the host (eg, mechanical, humoral, and cellular host defenses). The primary route of infection of the lungs is through microaspiration of organisms that have colonized the oropharyngeal tract (or, to lesser extent, the gastrointestinal tract). [21]

Percent of healthy subjects aspirate during sleep, and an even higher proportion of severely ill patients aspirate routinely.[22]

presence of an endotracheal tube Although frequently regarded as partially protective, the breaks the integrity of the upper airway and permits the aspiration of oropharyngeal material or bacteria of gastrointestinal origin to lower lung zone. [23]

Depending upon the number and virulence of the organisms reaching the lung, pneumonia may ensue.[24]

In addition, the near sterility of the stomach and upper gastrointestinal tract may be disrupted by alterations in gastric pH due to illness, medications, or enteric feedings. For this reason, much attention has been paid to the possible adverse effect of peptic ulcer prophylaxis regimens that raise the gastric pH. Less frequently, pneumonia results from inhalation of infectious aerosols or from bacteremia originating in a distant focus. [25]

Microbiology

The microbiologic flora responsible for VAP is different from that of the more common community-acquired pneumonia (CAP). In particular, viruses and fungi are uncommon causes in

people who do not have underlying immune deficiencies. Though any microorganism that causes CAP can cause VAP, there are several bacteria which are particularly important causes of VAP because of their resistance to commonly used antibiotics. These bacteria are referred to as multidrug resistant (MDR).[26]

- *Pseudomonas aeruginosa* is the most common MDR Gram-negative bacterium causing VAP. *Pseudomonas* has natural resistance to many antibiotics and has been known to acquire resistance to every antibiotic except for polymyxin B. Resistance is typically acquired through up regulation or mutation of a variety of efflux pumps which pump antbiotics out of the cell.
- *Klebsiella pneumoniae* has natural resistance to some beta-lactam antibiotics such as ampicillin. Resistance to cephalosporins and aztreonam may arise through induction of a plasmid-based extended spectrum beta-lactamase (ESBL)
- *Enterobacter* as a group also have an inducible ampC gene. Enterobacter may also develop resistance by acquiring plasmids.
- *Acinetobacter* are becoming more common and may be resistant to carbapenems such as imipenem and meropenem
- *Methicillin-resistant Staphylococcus aureus*(MRSA) is an increasing cause of VAP. As many as fifty percent of *Staphylococcus aureus* isolates in the intensive care setting are resistant to methicillin. [27-31]

Clinical feature

Presentation — VAP typically presents with a new or progressive pulmonary infiltrate and one or more of the following findings: fever, purulent tracheobronchial secretions, leukocytosis, increased respiratory rate, decreased tidal volume, increased minute ventilation, and decreased oxygenation. These symptoms and signs may develop gradually or suddenly.[32]

Patients with VAP are typically unable to provide any history because they are either sedated or their ability to communicate is impaired by the endotracheal or tracheostomy tube. [33]

Physical examination

Fever and an increased volume of purulent tracheobronchial secretions are common among patients with VAP. On auscultation, patients typically have diffuse, asymmetric rhonchi due to the tracheobronchial secretions that the patient is unable to mobilize. The rhonchi are often accompanied by focal findings, such as crackles and decreased breath sounds. In addition, many patients are tachypneic with increased respiratory effort and they may have bronchial breathing. Bronchospasm (wheezing and increased expiratory time) and hemoptysis are also common. These pulmonary signs may be accompanied by systemic abnormalities, such as encephalopathy or sepsis, septic shock .[34]

Ventilator associated events:

Ventilator associated event (VAE) is based on objective steam lined and potentially automatable criteria that will intationally identify a broad range of conditions and complication occur in mechanically ventilated adult patients. [35]

There are 3 main component of VAE

1. Ventilator associated condition (VAC).
2. Infection related ventilator associated conditions (IVAC)
3. Possible and probable VAP. [36]

These data are easy implemented and make use of electronic health record system recording system to automate event detection and identify clinically important events associated with outcome as ICU stay length and mortality rate. [37]

The main ventilator associated event are VAP, ARDS, atelecatasis, pulmonary edema and this significant condition may be preventable.

Definitions included in ventilator associated events

VAEs are identified by using combination of objective criteria.

1. Deterioration of respiratory status after period of stability.
2. Evidence of respiratory infection clinically and laboratory. [38]

To apply this criteria patients must be ventilated invasively by ETT more than 2 days to be eligible for VAE and the earliest date for evaluating event is day number 4 calendar day provided that the day of intubation is no 1 calendar day and worsening of oxygenation is day 3 calendar day.[39]

Period of stability on a mechanical ventilator is a period of 2 calendar days immediately preceding the first day of increasing minimum PEEP or FIO_2 and characterized by 2 or more days of stable or decreasing daily minimum FIO_2 or PEEP.[40]

Date of event is the date of onset of worsening oxygenation and this is defined as day in which the day minimum PEEP or FIO_2 increased above the threshold that present in the first 2 days. [41]

VAE window period

This is a period of days around the event date (the day of onset worsening oxidization) within which other VAE criteria must be met. It is usually 5 days period include 2 days before, the day of, and 2 days after VAE event date. [42]

Ventilator associated event based on changes in the 2 main components:

1. FIO_2 is a fraction of oxygen in inspired gas and it's one of the key parameters in VAE it's could be adjusted depending on the patients oxygenation needs it's typically ranged from 30% to 100 %. A sustained increase in the minimum FIO_2 of 20 following a period of stability or improvement is the first of 2 criteria that can be used in meeting VAC. [43]
2. PEEP it's a technique used in respiratory therapy in which airway pressure greater than atmospheric pressure is achieved at the end of exhalation by the introduction of a

mechanical impedance to exhalation. It's a one of key parameters that can be adjusted depending on the patient's oxygenation needs. A sustained increase in the daily minimum PEEP of > 3 cm H_2O following a period of stability or improvement on the second criterion applied to met VAE. (44)

Daily minimum FIO_2: The lowest value of FIO_2 requirement during a calendar day that asset on ventilator for 1 hour duration and this requirement ensure that unit monitoring for an hour is important to detect minor VAE. (45)

Daily minimum PEEP: is the lowest value of PEEP during a calendar day that is set on a ventilator and maintained for 1 hour duration and this requirement will ensure monitoring and is important to detect minor VAE. (46

Figure (7); ventilator associated events (VAE) surveillance algorithm.

Patient has a baseline period of stability or improvement on the ventilator, defined by ≥ 2 calendar days of stable or decreasing daily

FiO2 or PEEP values. The baseline period is defined as the 2 calendar days immediately preceding the first day of increased daily minimum PEEP or

FiO*

After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:

1) Increase in daily minimum* FiO2 of ≥ 0.20 (20 points) over the daily minimum FiO2 in the baseline period, sustained for ≥ 2 calendar days.

2) Increase in daily minimum* PEEP values of ≥ 3 cmH2O over the daily minimum PEEP in the baseline period†, sustained for ≥ 2 calendar days

*Daily minimum defined by lowest value of FiO2 or PEEP during a calendar day that is maintained for at least 1 hour (49)

Ventilator-Associated Condition (VAC)

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets both of the following criteria:

1) Temperature > 38 °C or < 36°C, OR white blood cell count ≥ 12,000 cells/mm3 or ≤ 4,000 cells/mm3.

AND

Possible versus probable VAP criteria

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections)

• Defined as secretions from the lungs, bronchi, or trachea that contain >25 neutrophils and <10 squamous epithelial cells per low power field [lpf, x100].

• If the laboratory reports semi-quantitative

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections—and defined as for possible VAP)

AND one of the following:

• Positive culture of endotracheal aspirate*, ≥ 105 CFU/ml or equivalent semi-quantitative result

• Positive culture of bronchoalveolar lavage*, ≥ 104

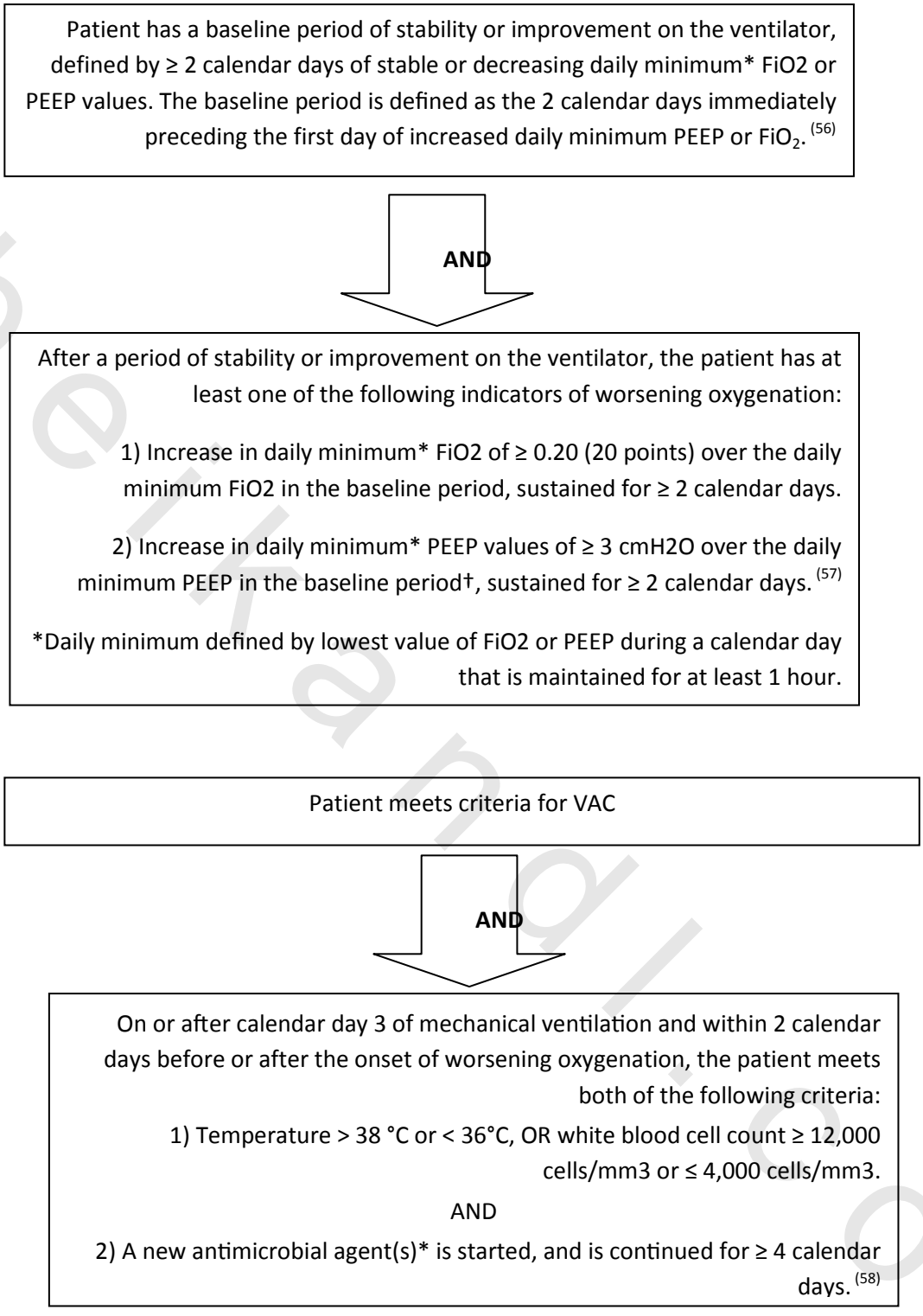


Figure (9): Infection-related Ventilator-Associated Complication (IVAC)

Patient meets criteria for VAC and IVAC

AND

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections)

• Defined as secretions from the lungs, bronchi, or trachea that contain > 25 neutrophils and < 10 squamous epithelial cells per low power field [lpf, x100].

• If the laboratory reports semi-quantitative results, those results must be equivalent to the above quantitative thresholds.

• See additional instructions for using the purulent respiratory secretions criterion in the VAE Protocol. [59]

OR

2) Positive culture (qualitative, semi-quantitative or quantitative) of sputum*, endotracheal aspirate*, bronchoalveolar lavage*, lung tissue, or protected specimen brushing*

*Excludes the following: [60 -63]

• Normal respiratory/oral flora, mixed respiratory/oral flora or equivalent

• Candida species or yeast not otherwise specified

Figure (10): Possible Ventilator-Associated Pneumonia (VAP)

Patient meets criteria for VAC and IVAC

AND

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections—and defined as for possible VAP)

AND one of the following (see Table 2):

- Positive culture of endotracheal aspirate*, ≥ 105 CFU/ml or equivalent semi-quantitative result
- Positive culture of bronchoalveolar lavage*, ≥ 104 CFU/ml or equivalent semi-quantitative result
- Positive culture of lung tissue, ≥ 104 CFU/g or equivalent semi-quantitative result
- Positive culture of protected specimen brush*, ≥ 103 CFU/ml or equivalent semi-quantitative result

***Same organism exclusions as noted for Possible VAP.** [64-67]

OR

2) One of the following (without requirement for purulent respiratory secretions):

- Positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
- Positive lung histopathology
- Positive diagnostic test for Legionella spp.
- Positive diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

respiratory rate, decreased tidal volume, increased minute ventilation, or decreased oxygenation. Many patients will require more ventilatory support or inspired oxygen than they did previously.[68]

Diagnostic evaluation.

Clinical criteria used in diagnosing ventilator-associated pneumonia

Evaluation is required any time that VAP is suspected because clinical features alone are nonspecific. The goal is to confirm VAP and to identify the likely pathogen, so that the appropriate treatment can be initiated. The evaluation begins with a chest radiograph. Patients who have an abnormal chest radiograph should have their respiratory tract sampled and specimens sent for microscopic analysis and culture.[69]

These steps are ideally performed prior to the initiation of antibiotic therapy because antibiotic therapy reduces the sensitivity of both the microscopic analysis and culture, these steps are ideally performed prior to changing the antibiotic regimen of patients suspected of developing VAP while receiving antibiotic. Once the respiratory specimens have been obtained, empiric antibiotic therapy is indicated for all cases of suspected VAP, unless the clinical suspicion is low and the microscopic analysis of lower respiratory tract samples is negative (ie, few neutrophils).[70]

Table (1): Clinical criteria used in diagnosing ventilator-associated pneumonia

Johanson criteria	• Presence of a new or progressive radiographic infiltrate • Plus at least two of three clinical features: - fever > 38°C - leukocytosis or leucopenia - purulent secretions		
Clinical Pulmonary Infection Score (CPIS)112	• Temperature	Oxygenation (PaO2/FiO2)	• Temperature • Oxygenation (PaO2/FiO2) • Tracheal secretions (score)
	0 point: 36.5–38.4 C	- 0 point: PaO2/FiO2 > 240 or ARDS	- -0 point: < 14
	1 point: 38.5–38.9 2 points: PaO2/FiO2 < 240 and no	- 2 points: PaO2/FiO2 < 240 and no evidence of	- -1 point: > 14

		ARDS	
	2 points: < 36 or > 39 -		-2 points: purulent sputum
	• Blood leukocytes (cells/µL)		• Culture of tracheal aspirate
	- 0 point: 4000–11000		-0 point: minimal or no growth
	1 point: < 4000 or > 11000 -		-1 point: moderate or more growth
	2 points: > 500 band forms -		-2 points: moderate or greater growth
		• Pulmonary radiography	
		point: no infiltrate 0 -	
		1 point: diffuse or patchy infiltrates -	
		2 points: localized infiltrate -	
Total score of > 6 points suggests ventilator-associated pneumonia			
ARDS = acute respiratory distress syndrome			

Chest imaging:

A chest radiograph should be performed on all patients with suspected VAP . A normal chest radiograph excludes VAP, while an abnormal radiograph should prompt the collection of respiratory tract secretions. Those finding could be obtained by plain x ray of chest. but computerized tomographic scan have a great importance not only to diagnose but also to follow up minor changes as basal effusion or atelectasis or cavitations. Ultrasound chest can also diagnose this to a lesser extent because it is an operator dependent procedure. But it is easier to be performed bedside easier than CT as the critical patients situations limit transmission to perform CT scan. Common radiographic abnormalities could be detected in VAP include alveolar infiltrates, air bronchograms. Patchs uni/bilateral.[71]

While an abnormal chest radiograph is required to diagnose VAP, it is not sufficient. The reason that radiographic abnormalities alone are insufficient to diagnose VAP is that they are nonspecific (ie, they frequently exist in the absence of VAP. [72]

Additional benefits of the chest radiograph are that it can help determine the severity of the disease (multilobar versus unilobar) and identify complications, such as pleural effusions or cavitation.

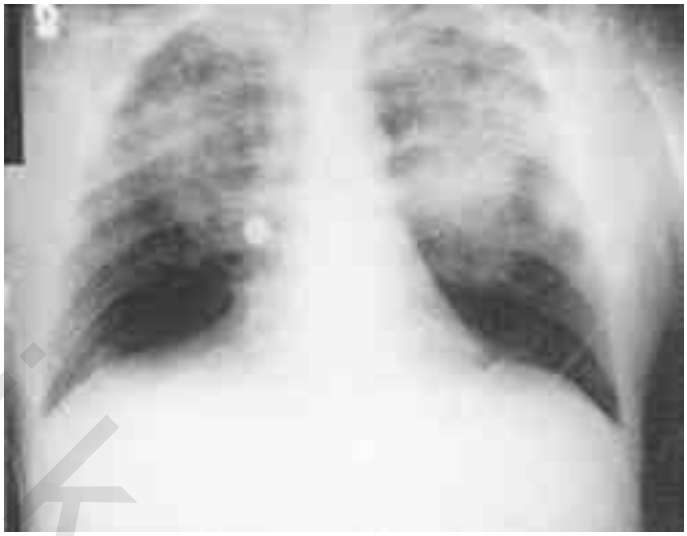
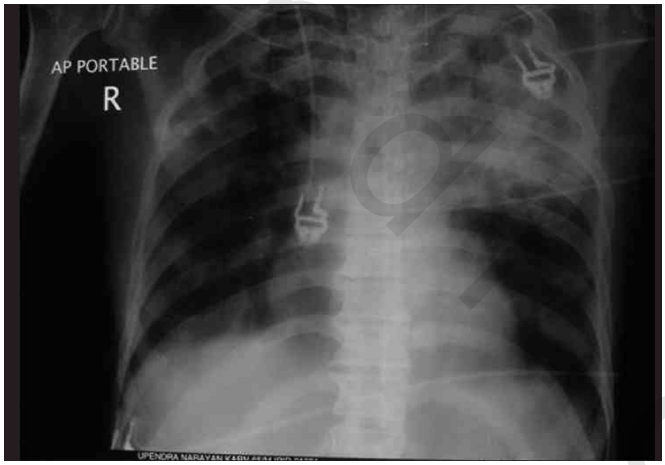


Figure (2): Another chest x ray that demonstrate VAP as bilateral apical and middle patches [(73)]



ray that reveal left

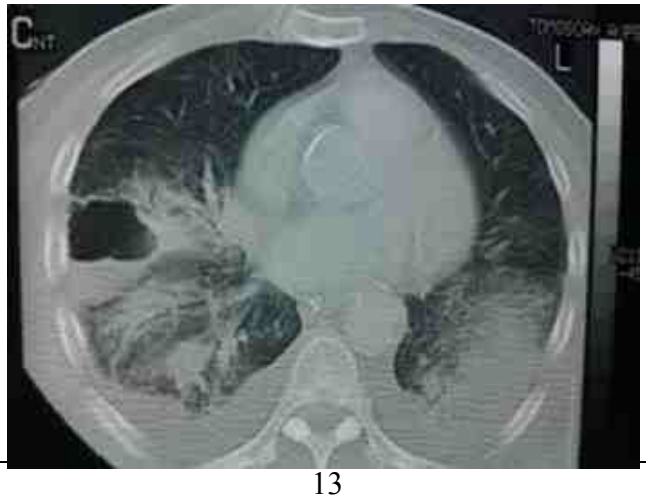


Figure (3): Chest X upper lobe patch[(74)]

Figure (4): Bilateral VAP patches and right lung abscess in ct scan of the chest. [75]

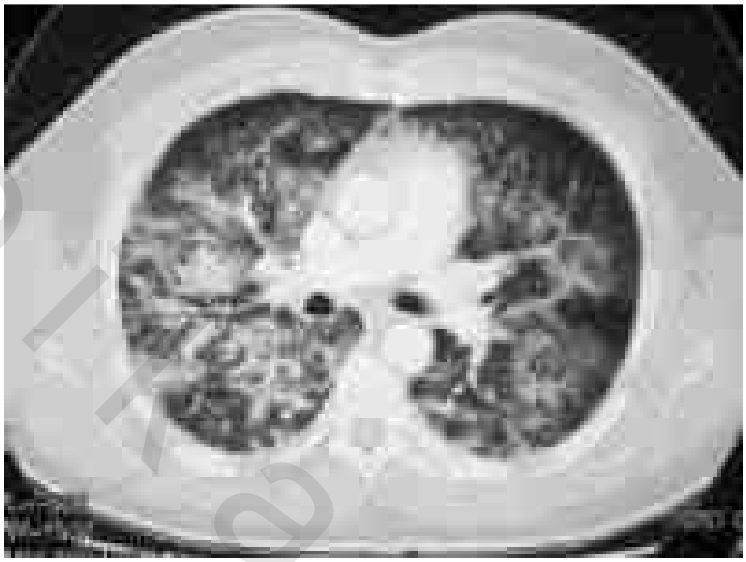


Figure (5): ARDS following protracted VAP course.[76]

Respiratory sampling

Lower respiratory tract sampling is indicated for all patients who are suspected of having VAP and have an abnormal chest radiograph. There are a variety of methods available to sample material from the airways and alveoli, including nonbronchoscopic and bronchoscopic samples.[77]

Nonbronchoscopic lower respiratory tract sampling includes tracheobronchial aspiration and mini-BAL Tracheobronchial aspiration is performed by advancing a catheter through the endotracheal tube until resistance is met and then applying suction.Mini-BAL is performed by advancing a catheter through the endotracheal tube until resistance is met, infusing sterile saline through the catheter, and then aspirating. A clinician is not necessary to perform or supervise non bronchoscopic sampling. This reduces the cost, allows specimens to be obtained quickly, and facilitates serial sampling when necessary.[78]

BAL explores large areas of the alveolar compartment zone. providing cells as well as non cellular constituents of lower respiratory tract . it open window to lung. alteration in bronchial fluid nature and cells means pathological changes .it was done using the bronchoscopy (rigid, flexible) and must be done by a physician because it is advanced technique .its common side effect includes fever, bronchospasm, wheezes, hypoxia, bleeding.[79]

Protected specimen brush (PSB) or blind BAL also done with bronchoscopy help.and have a wide acceptance diagnostic accuracy. however limitations like bronchospasm, wheezes, need for a physician to perform always present. .[80]

Microscopic analysis

The lower respiratory specimens should be sent for microscopic analysis. The most common microscopic analysis is the Gram stain. It can be used to semi-quantitate polymorphonuclear leukocytes and other cell types, as well as to characterize the morphology of bacteria. The presence of abundant neutrophils is consistent with VAP and the bacterial morphology may suggest a likely pathogen. Gram stain analysis may decrease the incidence of inappropriate antimicrobial therapy and improve diagnostic accuracy when correlated with culture results.[81]

A differential cell count can also be performed by microscopic analysis following a mini BAL.
It determines the proportion of total nucleated cells in the spun sediment of BAL fluid that are neutrophils, lymphocytes, macrophages, eosinophils, basophils, or other nucleated cells.[82]

Table 2. Threshold values for cultured specimens used in the Probable VAP definition

Specimen collection/technique	Values
Lung tissue	$\geq 10^4$ cfu/g tissue*
Bronchoscopically (B) obtained specimens	
Bronchoalveolar lavage (B-BAL)	$\geq 10^4$ cfu/ml*
Protected BAL (B-PBAL)	$\geq 10^4$ cfu/ml*
Protected specimen brushing (B-PSB)	$\geq 10^3$ cfu/ml*
Nonbronchoscopically (NB) obtained (blind) specimens	
NB-BAL	$> 10^4$ cfu/ml*
NB-PSB	$\geq 10^3$ cfu/ml*
Endotracheal aspirate (ETA)	$\geq 10^5$ cfu/ml*

cfu = colony forming units, g = gram, ml = milliliter

*Or equivalent semi-quantitative result. [83]

Respiratory culture

The lower respiratory specimens should also be sent for culture. Quantitative or semi quantitative cultures are both acceptable, with the choice depending largely upon availability.[84]

Quantitative culture

Quantitative cultures can be performed on bronchoscopic or nonbronchoscopic specimens.
VAP is supported when an established threshold of bacterial growth is exceeded. Only bacteria that are pulmonary pathogens should be counted. As examples, Staphylococcus epidermidis, enterococci, and most gram positive bacilli (except actinomycosis and nocardia) should not be counted.[85]

Thresholds of 1,000,000 colony forming units (cfu)/mL for samples obtained by tracheobronchial aspiration, 10,000 cfu/mL for samples obtained by BAL, or 1000 cfu/mL for samples obtained by protected specimen brush (PSB) are most accurate because they are sufficiently high that patients with tracheobronchial colonization are unlikely to be mistaken for patients with VAP lower thresholds are reasonable if the risk of a missing a VAP (ie, a false-negative result) exceeds the risk of unnecessary treatment (ie, a false-positive result .[86]

Biological markers

Biologic markers are sometimes used to try to distinguish between bacterial and non-bacterial causes of pneumonia. [87]

Many biological markers have been studied in an effort to improve the rapidity and performance of current diagnostic procedures in VAP. When the anatomical and mechanical defense mechanisms that prevent microorganisms from reaching alveoli are overwhelmed, a complex host response develops. Microbial products activate alveolar macrophages, which release multiple endogenous mediators locally. Among these mediators, tumor necrosis factor alpha, interleukin-1β, and other cytokines are increased in various types of pulmonary infections and thus have potential prognostic implications. However, there is no cutoff value for such mediators that could be used to diagnose pneumonia. Several biomarkers have been investigated for diagnosing VAP . The presence of elastin fiber (EF), a marker of parenchymal lung destruction, in tracheal secretion has been proposed to differentiate colonization from infection of the lung. However, the presence of EF in tracheal aspirates had only reasonable specificity in diagnosing VAP. And indicates lung tissue damage. [88]

Procalcitonin (PCT) and C-reactive protein (CRP) measurements have been shown to improve the clinical accuracy in identifying patients with SIRS caused by infection from SIRS of other causes. Serum PCT levels had a better performance than alveolar PCT concentrations, with a high specificity upto 100%. In patients after cardiac arrest and return of spontaneous circulation, PCT had a sensitivity of 100% and a specificity of 75% for the diagnosis of VAP. CRP (>9.6 mg/dl) had a good accuracy for VAP in a population of general ICU patients. In addition, in patients with microbiologically confirmed VAP, high CRP levels were associated with poor outcome. The detection of soluble triggering receptor expressed on myeloid cells (sTREM)-1 in BAL fluid may be useful in establishing or excluding a diagnosis of bacterial or fungal pneumonia. It was discovered in patients with suspected pneumonia and measured sTREM-1 in their BAL fluid. These authors showed that the presence of sTREM by itself was more accurate than any clinical findings or laboratory values in identifying the presence of bacterial or fungal pneumonia. In critically ill mechanically ventilated patients, it was reported an increase in sTREM-1 levels in non-directed BAL fluid obtained from patients who developed VAP in contrast to those who did not. A cutoff value for BAL fluid sTREM-1 levels of 200 pg/ml had a high specificity in diagnosing pneumonia. The value of endotoxin measurements in BAL fluid was also investigated, as approximately 70% of cases of VAP are caused by Gram-negative bacteria. It was reported an increased concentration of endotoxin in bronchoscopic BAL and non-directed BAL fluid of patients with VAP. [89]

An endotoxin concentration of 6 EU/ml yielded the optimal operating characteristics. In samples of BAL fluid from patients with multiple trauma requiring prolonged mechanical ventilation, it was showed a relation between the concentration of endotoxin in lavage fluid and the quantity of Gram-negative bacteria. An endotoxin level greater than or equal to 6 EU/ml distinguished patients with Gram-negative bacterial pneumonia from colonized patients, and from those with pneumonia due to Gram-positive cocci. The studies evaluating the value of the previously mentioned biomarkers are limited by the lack of a gold standard used to diagnosis VAP. EF and sTREM-1 were compared to clinical diagnosis ad hoc, PCT was compared to mini-BAL, and CRP to Johanson criteria. [90]

Other biomarkers, such as C-reactive protein (CRP), Sequential organ failure assessment SOFA score on admission was initially considered promising marker for improving diagnostic strategies for VAP. [91]

Prevention

In addition to minimizing mechanical ventilation, the recommendations included reducing colonization of the upper respiratory tract and/or the digestive tract, as well as preventing aspiration.[92]

Among the various strategies that have been evaluated for preventing VAP, decontamination of the oropharynx (with or without decontamination of the digestive tract) has been demonstrated to improve patient outcomes by preventing VAP this has primarily been demonstrated in settings of low antimicrobial resistance and may not apply to intensive care units with higher rates of resistance, preventing aspiration-aspiration is a major predisposing mechanism for both hospital-acquired pneumonia (HAP) and VAP. Appropriate patient positioning and subglottic drainage in ventilated patients are two important modalities for the prevention of aspiration.[93]

VAP bundle

The bundle includes the following components: [94]

1. Elevation of the head of the bed (HOB)
2. Daily sedation vacations and assessment of readiness to extubate.
3. Peptic ulcer disease prophylaxis.
4. Deep vein thrombosis (DVT) prophylaxis.
5. Daily oral care with chlorhexidine.

Implementation of the VAP Bundle Components

Although the VAP definition was not clear, the VAP bundle was introduced, and implementation was expected. 2 To evaluate the effectiveness of the VAP bundle in its entirety,

clinicians must evaluate the evidence used to support the effectiveness of each component of the bundle. [95]

1. HOB Elevation

Elevation of the HOB to prevent aspiration has been a nursing standard for many years. Although intuitively this intervention seems logical, the evidence to support its efficacy in patients being treated with mechanical ventilation is not clear. In the original IHI proposal, the suggested elevation for HOB was a range of 30 ° to 45 °.[96]

2. Oral Hygiene Care

Oral hygiene care is another nursing domain that can affect development of VAP. The oropharynx is colonized with potential pathogens such as Staphylococcus aureus, Streptococcus pneumoniae, Prevotella species, Bacteroides fragilis, and more than 700 other microbes, many of which have not been identified yet. Within 48 hours after a patient is admitted to the ICU, the flora of the oral cavity undergoes a transformation to predominantly gram-negative microbes, which can be more virulent. Oral hygiene care methods, including mouthwashes, gel, toothbrush, or combination techniques, have been used to combat possibly pathogenic flora. [97]

3. Prophylaxis Interventions

Two interventions in the bundle are specifically directed at prevention of complications associated with mechanical ventilation: DVT and peptic or stress ulcer disease. Deep vein thrombosis can be a complication of mechanical ventilation due to increased venous stasis in the lower extremities, but it also can be a complication of other conditions such as sepsis, cancer, trauma, postoperative course, peripheral vascular disease, and immobility. Prophylaxis for DVT has been shown to reduce the incidence of venous thromboembolism in hospitalized patients. Stress ulcer prophylaxis is a component of the VAP bundle that also may or may not have a direct impact on VAP rates, but it does impact associated risk factors that are related to patients being treated with mechanical ventilation in the ICU. [98]

4. Daily Sedation Vacations and assessment of Readiness to Extubate

Early extubation may decrease incidence of VAP. Daily sedation vacations allow for proper assessment of the patient's readiness to be extubated. It is concluded that patients who received daily interruption of sedative drug infusions had decreased number of mechanical ventilator days as well as decreased length of stay in the ICU. Appropriate timing of sedation interruptions depends on a patient's stability, including evaluation of hemodynamics and the ability of the patient to protect the airway. Daily sedation vacations were paired with spontaneous breathing trials, resulting in earlier extubation and fewer ventilator days as well as decreased ICU and hospital days. 39 Of the 5 interventions proposed in the VAP bundle, this intervention is the most likely to help decrease the occurrence of VAP, because it has been demonstrated that it expedites earlier extubation. The sooner the ET tube is removed, the possibility of infection developing is lower. [99]

The previous 4 components either have marginal evidence to support a role in decreasing VAP or had no relationship to VAP. With this lack of clear evidence, clinicians started to challenge the validity of the VAP bundle and its effectiveness. [100]

Reconstruction of the VAP Bundle to Promote Best Care

As the efficacy and validity of the VAP bundle has been examined, expert clinicians have called for a deconstruction of the bundle. This argument hinges on the issue that surveillance and clinical definitions are in conflict, but the expectation of regulatory bodies is that this bundle be implemented even though the evidence behind the bundle components is variable. Organizing care around a specific diagnosis is a valid concept. The positive results of the bundle implementation have been attributed to the fact that it heightened awareness of VAP with the multidisciplinary team and focused on the care of patients being treated with mechanical ventilation. However, careful consideration must be given to the specific care that is recommended to help prevent and/or combat that diagnosis. Regulatory bodies are now reconsidering the adherence to the VAP bundle as a reportable statistic. The Joint Commission has decided not to include the bundle in the 2014 National Patient Safety Goals, and the Centers for Medicare & Medicaid Services has not included VAP on the list of nonreimbursable diagnoses at this time, which is an opportunity for nursing and advanced practice nurses to assist with the reconstruction of best care for patients being treated with mechanical ventilation. Nursing interventions may primarily focus on prevention. Clinicians must recognize that measures to prevent a condition will be different but complementary to measures used to combat or treat a condition. [101]

Body Position

Body position has an impact on gravitational forces that influence the leakage of secretions around the ET tube. 50 The semirecumbent position has been the standard practice, but the best degree of HOB elevation has not been determined by the evidence. The 30 ° HOB elevation is the recommended position that may decrease aspiration. The weakness of this rationale is that secretions above the ET tube balloon can pool and lead to microaspiration. [102]

Two other aspects of this intervention should be considered: (1) what is the role of HOB elevation to help prevent skin breakdown and (2) is the semirecumbent position the best position to prevent leakage around the ET tube it is described the conflict between guidelines for HOB elevation to prevent aspiration (recommendation of 45 ° elevation) and guidelines for pressure ulcer prevention (recommendation of no more than 30 ° elevation). Ironically, the goal is prevention of health care–associated pressure ulcers. the VAP bundle or prevention of pressure ulcer formation. The recommendation of the Bed Head Elevation Study Group is to maintain HOB elevation at 30 ° or more, as long as this positioning does not pose risks or conflicts with other nursing or medical interventions or patients' wishes. 18 Measuring compliance with HOB elevation could be seen as a poor use of time and resources. This HOB position would seem to be a prudent compromise with the many conflicts in the evidence and compliance with the intent of regulatory directives. [103]

Searching for a new paradigm also may be an alternative solution for the HOB elevation issue. semirecumbency is the best position for patients being treated with mechanical ventilation and better than head down position. The fact is that using gravitational force may move secretions away from the ET tube by maintaining the ET tube/trachea orientation at or below horizontal position. [104]

Supine positioning appears to predispose to aspiration and the development of HAP.it was shown that patients in the supine position are predisposed to microaspiration of gastric contents as compared with patients in the semi recumbent position. Although no effect of positioning on mortality has been demonstrated, it seems prudent to preferentially place intubated patients in the semi recumbent position unless contraindicated.[105]

Reconstructing Other Bundle Components

The other components of the VAP bundle also should be evaluated in the reconstruction effort. Oral care is important for this patient population for 2 reasons: control of bacterial flora and maintenance of patient comfort. Use of chlorhexidine may help control bacterial growth, but the current technology used to detect microbes may not be able to identify all species. Drugs to suppress gastric acid should not be included in any plan to prevent VAP, because the use of these drugs may increase gram negative bacterial growth. The International Nosocomial Infection Control Consortium reported that the international. Drugs that suppress gastric acid are effective in preventing GI bleeding and treating gastric reflux disease and may need to be included in the care of patients with a history of gastric issues or GI bleeding. Physical examination and closer evaluation for gastric distension on chest radiographs are easy additions to a VAP prevention plan. Prophylaxis for DVT is important and monitored separately. It should not be included in a VAP prevention program because it will not influence VAP development. [106]

Daily interruption in sedation and assessment of readiness for extubation are probably the most productive interventions in the VAP bundle. Process-improvement relations to moderating the use of sedative agents should continue. Removing the ET tube as soon as safely possible will eliminate an important factor that contributes to the cascade of events that may lead to VAP. Decreasing the number of days of treatment with mechanical ventilation may decrease the risk of VAP. Even if a decrease in VAP is not clear, decreasing the use of sedative agents may help decrease the occurrence of delirium and its associated complications. Advanced practice nurses play a pivotal role in enhancing the communication and implementation of this intervention, and further research should be pursued. [107]

Advances in Technology

Advances in technology also need to be included in a VAP prevention plan. Subglottic suctioning using a specialized ET tube with a separate dorsal lumen designed to suction secretions collected around the ET tube cuff was not included in the original VAP bundle but has been recommended by various organizations. The difficulty with this tube is maintaining patency, because the dorsal lumen has a tendency to clog as a result of the tenacious nature of the secretions. Microbiological and molecular biological techniques

continue to evolve and are becoming increasingly more effective in the detection of new microbes of the presumed 700 + species in the mouth. Interventions to prevent biofilm formation are another area of research that may play a role in VAP prevention. Biofilm, a community of microorganisms that attaches to a surface and develops a structure to support replication, may play a significant role in the development of VAP. Silver-coated ET tubes have been shown to decrease or delay VAP but not ventilator or ICU days. Novel inventions such as a mucus shaver, a catheter that is inserted into an ET tube and shaves mucus/secretions from the inner lumen of the tube, may assist with decreasing the formation of biofilm. These types of technological innovations will continue to evolve and may provide solutions. [108]

Treatment

Treatment of VAP should be matched to known causative bacteria. However, when VAP is first suspected, the bacteria causing infection is typically not known and broad-spectrum antibiotics are given (empiric therapy) until the particular bacterium and its sensitivities are determined. Empiric antibiotics should take into account both the risk factors a particular individual has for resistant bacteria as well as the local prevalence of resistant microorganisms. If a person has previously had episodes of pneumonia, information may be available about prior causative bacteria. The choice of initial therapy is therefore entirely dependent on knowledge of local flora and will vary from hospital to hospital.[109]

Risk factors for infection with an MDR strain include ventilation for more than five days, recent hospitalization (last 90 days), residence in a nursing home, treatment in a hemodialysis clinic, and prior antibiotic use (last 90 days).[110]

Possible empirical therapy combinations include (but are not limited to):

- Vancomycin/linezolid and ciprofloxacin,
- Cefepime and gentamicin/amikacin/tobramycin
- Vancomycin/linezolid and ceftazidime
- A carbapenem (e.g., imipenem or meropenem)

Therapy is typically changed once the causative bacteria are known and continued until symptoms resolve (often 7 to 14 days). For patients with VAP not caused by nonfermenting Gram-negative bacilli (like Acinetobacter, Pseudomonas aeruginosa) the available evidence seems to support the use of short-course antimicrobial treatments (< or =10 days).[111] People who do not have risk factors for MDR organisms may be treated differently depending on local knowledge of prevalent bacteria. Appropriate antibiotics may include ceftriaxone, ciprofloxacin, levofloxacin, or ampicillin/sulbactam.[111-113]

There is ongoing research into inhaled antibiotics as an adjunct to conventional therapy. Tobramycin and polymyxin B are commonly used in certain centres but there is no clinical evidence to support their use.[114]

Statins

statin is in a group of drugs called3 hydroxyl 3methyl glutaryl HMG CoA reductase inhibitors, It reduces levels of "bad" cholesterol (low-density lipoprotein, or LDL) and triglycerides in the blood, while increasing levels of "good" cholesterol (high-density lipoprotein, or HDL).[115]

Statin is also used to lower the risk of stroke, heart attack, and other heart complications in people with diabetes, coronary heart disease, or other risk factors.[116]

This medicine is used in adults and children who are at least [**10)** years old. (statin) is an agent that is derived synthetically from a fermentation product of *Aspergillus terreus*[117]

Statins have multisystem effect other than lipid lowering agents actions as below:

Effect of statins on the leucocyte response in sepsis

Sepsis results in a significant and time-dependent increase in leucocyte recruitment, adherence, and transmigration of leucocytes and P-selectin expression on vascular endothelium. Statins greatly reduce both lipopolysaccharide (LPS)-induced and *Staphylococcus aureus* α-toxin-induced leucocytes migration and leucocytes recruitment.[118]

Statins result in a significant reduction of leucocytes adhesion to endothelium by down-regulation of surface expression of endothelial cell adhesion molecule P-selectin, CD11b, and CD18 and by inhibition of lymphocyte function antigen-1 (LFA-1)-mediated leucocyte adhesion.[119]

Statins also affect monocyte function. LPS meauserment (20 IU kg^{-1}), showed that simvastatin attenuated up-regulation of toll-like receptors (TLR) 4 and 2 on the surface of monocytes by more than half after LPS challenge . Suppressed TLR4 and TLR2 expression was associated with decreased circulating concentrations of TNF-α and monocyte chemo attractant protein-1. [120]

Effect of statins on the drivers of sepsis

Statins affect the production of many acute phase reactants, such as IL-6, IL-8, TNF-α, monocyte chemoattractant protein-1 (MCP–1), and C-reactive protein (CRP). [121]

CRP is mainly produced by hepatocytes in response to IL-6. In human hepatocytes were stimulated with IL-6 in the presence or absence of simvastatin and atorvastatin. Hepatocytes treated with statins showed significant inhibition of IL-6-induced CRP production. The reduction of CRP levels was more pronounced with atorvastatin than with other statins.[122]

Effect of statins on coagulation cascade

Statins improve platelet function and diminish procoagulant activity by a reduction in platelet aggregation, TF activity, reduced conversion of prothrombin to thrombin with resultant reduced thrombin activity, and a decline in levels of fibrinogen.[123]

Statins also seem to stimulate fibrinolysis by altering the level and activity of tissue plasminogen activator (tPA) and PAI-1, indicating a potential role in the treatment of protein C

deficiency. This raises the possibility that statins, particularly atorvastatin, could offer a potential pharmacological treatment for severe sepsis.[124]

Effect of statins on endothelial cell function

The microvascular circulation and particularly endothelial cell dysfunction is central to the pathogenesis of sepsis. As sepsis develops, EC become activated, participating in the inflammatory process and generating multiple inflammatory mediators and up-regulating adhesion molecule expression. Endothelial cell adhesion molecules not only act as docking structures for leucocytes, but also activate the signalling cascades required for successful leucocyte transmigration. The weight of evidence suggests that statins inhibit this process.[125]

A reduction in the activation of pro-inflammatory transcription factors in EC also represents a key mechanism by which statins exert their immunomodulatory effects. This appears to be due to reduced levels of NF-kappaB and so statins can block the effects of cytokines such as TNF-α upon EC. These effects of statins on vascular endothelium have been closely associated with their ability to up-regulate endothelial NO synthase (eNOS) activity and enhance NO production.[126]

Physiologically, eNOS is activated by the protein kinase to produce endothelium-derived NO for controlling vasomotor activity sepsis results in a decrease in eNOS function and an increase in inducible NO synthase (iNOS) expression, contributing to the hypotension and resistance to vasopressor drugs that occur in septic shock.[127]

Statins increase eNOS activity by inducing mediated phosphorylation of eNOS, up-regulating eNOS expression, and activating eNOS directly. This may be anti-inflammatory locally on EC as NO prevents leucocyte chemotaxis and reduces endothelial adhesion molecule expression, which in turn attenuates leucocyte migration. Activation of this pathway by statins may also be important as it leads to reduced endothelial cell apoptosis.[128]

Statins have also been found to increase the number of circulating endothelial progenitor cells (EPCs) so statins induce angiogenesis by promoting the proliferation, migration, and survival of circulating EPC. [129]

Simvastatin

It is one of statin group of drugs and it have multiple effects as anti-inflammatory drug**s.**

After oral ingestion, statins, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is a one of (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol [130]

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2Hpyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S- [1α,3α,7β,8β(2S*,4S*),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:

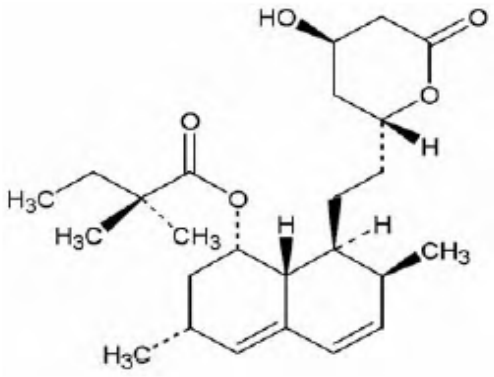


Figure (12): Structural formula of simvastatin

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.[131]

Tablets for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: ascorbic acid, citric acid, hydroxypropyl cellulose, hypromellose, iron oxides, lactose, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Butylated hydroxyanisole is added as a preservative.[132]

Simvastatin in addition to previously metioned as belongs to HMG coA reductase inhibitiors group it is also act as protease inhibitors and in addition to well known cholesterol lowering effect, statins regulates the immune and coagulation systems and prevent endothelial cell dysfunction and have potent anti-inflammatory effect. These occurs through various mechanisms includes decreasing alveolar and pulmonary capillaries permeability, improving gas exchange, and endothelial barrier protection through stabilization of endothelial junction by polymerization of cortical actin. This also will lead to decrease incidence of microvascular leakage and improve endothelial functions and decrease incidence of lung injury. These beneficial pleiotropic effect)LDL(means production of multiple effects of a simvastatin not related to low density lipoprotein mediated effect of simvastatin treatment.[133-134]