HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA IN ADULTS

DEFINITIONS

- HAP (or nosocomial pneumonia) is pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission.
- VAP is a type of pneumonia that develops ≥48 hours after endotracheal intubation.

- The concept of health care-associated pneumonia (HCAP) was included in the 2005 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines and referred to pneumonia acquired in health care facilities such as nursing homes, hemodialysis centers, outpatient clinics, or during a hospitalization within the past three months and used to identify patients at risk for infection with multidrug-resistant (MDR) pathogens .

- this categorization may have been overly sensitive and may have led to increased, inappropriately broad antibiotic use.

- Thus, the category of HCAP was purposefully not included in the 2016 IDSA/ATS guidelines.
- For similar reasons, the combined 2017 European and Latin American guidelines on the management of HAP and VAP did not categorize HCAP as a distinct type of pneumonia.

ANTIMICROBIAL RESISTANCE

- Multidrug resistant (MDR) refers to acquired nonsusceptibility to at least one agent in three different antimicrobial classes.

- Extensively drug resistant (XDR) refers to nonsusceptibility to at least one agent in all but two antimicrobial classes.

- Pandrug resistant (PDR) refers to nonsusceptibility to all antimicrobial agents that can be used for treatment.

EPIDEMIOLOGY

- HAP is one of the most common and morbid hospital-acquired infections .
- Most cases of HAP occur in nonventilated patients . However, the highest risk for HAP is in patients on mechanical ventilation.
- According to the United States Center for Disease Control and Prevention's National Healthcare Safety Network (NHSN), there has been a steady decline in reported VAP rates in the United States; between 2006 and 2012.

- VAP is associated with long hospital stays and significant costs .
- Two studies estimated that VAP prolongs the length of mechanical ventilation by 7.6 to 11.5 days and prolongs hospitalization by 11.5 to 13.1 days compared with similar patients without VAP.

PATHOGENESIS

- The primary route of infection of the lungs is through microaspiration of organisms that have colonized the oropharyngeal tract (or, to a lesser extent, the gastrointestinal tract).
- Approximately 45 percent of healthy subjects aspirate during sleep and an even higher proportion of severely ill patients aspirate routinely.

- Hospitalized patients often become colonized with microorganisms acquired from the hospital environment, and as many as 75 percent of severely ill patients will be colonized within 48 hours.
- An additional mechanism of inoculation in mechanically ventilated patients is direct contact with environmental reservoirs, including respiratory devices and contaminated water reservoirs .
- Disposable tubing used in respiratory circuits or tracheostomy or endotracheal tubes may become contaminated.

- 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 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.

MICROBIOLOGY

- Common pathogens include aerobic gram-negative bacilli (eg, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp, *Pseudomonas aeruginosa*, *Acinetobacter* spp) and gram-positive cocci (eg, *Staphylococcus aureus*, including methicillin-resistant *S. aureus* [MRSA], *Streptococcus* spp)
- There is increasing recognition that a substantial fraction of nosocomial pneumonias may be due to viruses in general medical and surgical patients and both viruses and fungi in immunocompromised patients .
- suggests that anaerobes may play a relatively minor role in the pathogenesis of VAP.

MDR RISK FACTORS

- Prolonged hospitalization and recent exposure to antibiotics are two of the most important risk factors for MDR pathogens

Risk factors for MDR pathogens:
•IV antibiotic use within the previous 90 days
•Septic shock at the time of VAP
•ARDS preceding VAP
•≥5 days of hospitalization prior to the occurrence of VAP
•Acute renal replacement therapy prior to VAP onset
Risk factors for MDR *Pseudomonas* and other gram-negative bacilli:
•Treatment in an ICU in which >10 percent of gram-negative isolates are resistant to an agent being considered for monotherapy
•Treatment in an ICU in which local antimicrobial susceptibility rates are not known
•Colonization with OR prior isolation of MDR *Pseudomonas* or other gram-negative bacilli
Risk factors for MRSA:
•Treatment in a unit in which >10 to 20 percent of *Staphylococcus aureus* isolates are methicillin resistant
•Treatment in a unit in which the prevalence of MRSA is not known
•Colonization with OR prior isolation of MRSA

Hospital-acquired pneumonia: Risk factors for MDR pathogens and/or increased mortality in adults

Risk factors for increased mortality:
•Ventilatory support for HAP
•Septic shock
Risk factor for MDR *Pseudomonas*, other gram-negative bacilli, and MRSA:
•IV antibiotics within the past 90 days
Risk factors for MDR *Pseudomonas* and other gram-negative bacilli:
•Structural lung disease (bronchiectasis or cystic fibrosis)
•A respiratory specimen Gram stain with numerous and predominant gram-negative bacilli
•Colonization with OR prior isolation of MDR *Pseudomonas* or other gram-negative bacilli
Risk factors for MRSA:
•Treatment in a unit in which >20 percent of *Staphylococcus aureus* isolates are methicillin resistant
•Treatment in a unit in which the prevalence of MRSA is not known
•Colonization with OR prior isolation of MRSA

DIAGNOSIS

- The 2016 Infectious Diseases Society of America/American Thoracic Society guidelines for the management of HAP and VAP recommend a clinical diagnosis based upon a new lung infiltrate plus clinical evidence that the infiltrate is of infectious origin, which includes the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation.
- presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever >38ºC, leukocytosis or leukopenia, and purulent secretions) has a 69 percent sensitivity and 75 percent specificity for VAP

- Cultures of pulmonary secretions (sputum, endotracheal aspirates, bronchoalveolar lavage) are also prone to false positives and false negatives.
- When compared with histology, quantitative endotracheal aspirate cultures had a pooled sensitivity of 48 percent and positive predictive value of 81 percent .
- quantitative bronchoalveolar lavage cultures had a sensitivity of 75 percent and positive predictive value of 77 percent .

- Molecular diagnostic tests for detection of respiratory pathogens are being developed and offer promise for more rapid identification of the causes of HAP or VAP
- . Although there are limitations regarding the sensitivity and specificity of these tests (eg, colonization or true pathogen).
- As an example, a multiplex polymerase chain reaction assay, which detects an array of respiratory bacterial pathogens including *Streptococcus pneumoniae* and several antibiotic-resistance genes, is approved for the diagnosis of pneumonia using bronchoalveolar lavage specimens in the United States.

EMPIRIC THERAPY

- Empiric therapy for HAP and VAP should include agents with activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli.
- The choice of a specific regimen for empiric therapy should be based upon knowledge of the prevailing pathogens and susceptibility patterns within the patient’s health care setting as well as the patient's individual risk factors for multidrug resistance.

APPROACH TO THERAPY

- Once HAP or VAP is suspected clinically, diagnostic specimens should be obtained as soon as possible in all patients and antimicrobial therapy started as soon as possible in patients with signs of septic shock or rapidly progressive organ dysfunction.

- Establishing the diagnosis of HAP and VAP can be difficult, especially for hospitalized patients in whom clinical, radiologic, and microbiologic findings can be due to numerous etiologies besides pneumonia.
- The difficulty in diagnosis may lead to overtreatment and its attendant risks of *Clostridioides difficile* infections, antimicrobial resistance and antibiotic toxicity.
- If the diagnosis of HAP and VAP is uncertain and the patient is not in sepsis or septic shock, then it appears to be safe and potentially beneficial to gather more data and await culture results before treating .

- Empiric treatment choices should be informed by the local distribution of pathogens causing HAP and VAP and their antimicrobial susceptibility patterns .
- As noted above, all hospitals should regularly create and disseminate local antibiograms, ideally ones that are specific to their different units.
- In addition to awareness of local pathogen distribution, antimicrobial selection should also be based upon risk factors for multidrug-resistant (MDR) pathogens.
- Additional considerations include Gram stain results, potential toxicities, potential drug interactions, cost, availability, and clinician familiarity with different antibiotics

- Reassessing a patient's status 48 to 72 hours after the initiation of therapy with consideration of discontinuing antibiotics or narrowing the regimen (de-escalating therapy) based upon appropriate culture results may reduce the selective pressure for antimicrobial resistance and appears to be safe

- Patients with VAP who have **any** of the following risk factors for MDR VAP should receive **two** agents with activity against *P. aeruginosa* and other gram-negative bacilli and **one** agent with activity against MRSA:

•IV antibiotic use within the previous 90 days

•Septic shock at the time of VAP

•ARDS preceding VAP

•≥5 days of hospitalization prior to the occurrence of VAP

•Acute renal replacement therapy prior to VAP onset

NO MDR RISK FACTORS

- For patients with VAP who have **no** known risk factors for multidrug-resistant pathogens and who are in a unit in which ≤10 percent of gram-negative isolates are resistant to an agent being considered for monotherapy.

- Piperacillin-tazobactam 4.5 g IV every 6 hours
- Cefepime 2 g IV every 8 hours
- Levofloxacin 750 mg IV daily

MDR RISK FACTORS

- **ONE of the following**:
- ●Piperacillin-tazobactam 4.5 g IV every six hours
- ●Cefepime 2 g IV every eight hours
- ●Ceftazidime 2 g IV every eight hours
- ●Imipenem 500 mg IV every six hours
- ●Meropenem 1 g IV every eight hours
- ●Aztreonam 2 g IV every eight hours
- **PLUS one of the following**:
- ●An aminoglycoside –
- •Amikacin 15 to 20 mg/kg IV daily
- •Gentamicin 5 to 7 mg/kg IV daily
- •Tobramycin 5 to 7 mg/kg IV daily

- An antipseudomonal fluoroquinolone such as ciprofloxacin (400 mg IV every eight hours) or levofloxacin (750 mg IV daily)
- A polymyxin – Addition of an alternative agent, such as intravenous colistin or polymyxin B, may be appropriate if highly resistant *Pseudomonas* spp, *Acinetobacter* spp, Enterobacteriaceae (including *Klebsiella pneumoniae*) is suspected .
- Aztreonam 2 g IV every eight hours

- **PLUS one of the following**:
- ●Linezolid 600 mg IV every 12 hours, which may be administered orally when the patient is able to take oral medications.
- ●Vancomycin
- ●Telavancin 10 mg/kg IV every 24 hours is an alternative agent when neither linezolid nor vancomycin can be used.
- The combination of vancomycin and piperacillin-tazobactam has been associated with acute kidney injury

TAILORING THERAPY

- All patients with HAP or VAP should be evaluated for clinical response and results of microbiologic studies after initial empiric antimicrobial therapy.
- For patients in whom a pathogen has been identified, the empiric regimen should be tailored to the pathogen's susceptibility pattern
- For patients who are clinically improving who do not have an identified pathogen, empiric treatment for *S. aureus* or multidrug-resistant gram-negative bacilli can be discontinued if these organisms have not grown in culture from a high-quality sputum specimen within 48 to 72 hours.

- Patients who have not improved within 72 hours of starting empiric antibiotics should be evaluated for complications, other sites of infection, and alternate diagnoses.

DURATION

- We treat most patients with HAP or VAP for seven days, in agreement with the 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines and the combined 2017 European and Latin American guidelines on HAP a. Seven days appears to be as effective as longer durations in most circumstances and may reduce the emergence of resistant organism

- For selected patients with severe illness, bacteremia, metastatic infection, slow response to therapy, immunocompromise, and pyogenic complications such as empyema or lung abscess, the duration of therapy should be individualized and courses longer than seven days may be warranted.
- Monitoring serial procalcitonin level
- a low or declining procalcitonin level (eg, <0.25 ng/mL or ≥80 percent decrease from peak) in a patient who has clinically responded to antibiotics provides additional reassurance that antibiotics can be safely stopped

CONVERSION TO ORAL ANTIBIOTICS

- Generally, patients can be switched to oral therapy when they are hemodynamically stable, clinically improving, and able to tolerate oral medications.
- If a pathogen has been identified, the choice of antibiotic for oral therapy should be based on the organism's susceptibility pattern.
- If a pathogen has not been identified, the oral antibiotic selected should have similar antimicrobial coverage as the intravenous agent and should have good lung penetration.

ALLERGY TO PENICILLINS OR CEPHALOSPORINS

- For patients who are allergic to penicillin, the type and severity of reaction should be assessed.
- The great majority of patients who are allergic to penicillin by skin testing can still receive cephalosporins (especially third-generation cephalosporins) or carbapenems.

- If there is a history of a mild reaction to penicillin (**not** an immunoglobulin [Ig]E-mediated reaction, Stevens-Johnson syndrome, or toxic epidermal necrolysis), it is reasonable to administer a cephalosporin or an antipseudomonal carbapenem using a simple graded challenge:
- 1/10 dose followed by a one-hour period of observation; if no symptoms, give the full dose followed by another hour of observation

POTENTIAL TOXICITIES

- Aminoglycosides are nephrotoxic and ototoxic.
- Polymyxins (polymyxin B and colistin) are nephrotoxic.
- The combination of vancomycin and piperacillin-tazobactam has been associated with acute kidney injury

In patients with renal insufficiency, imipenem and cefepime have been associated with seizures

- The fluoroquinolones have multiple potential toxicities, including QT interval prolongation, tendinitis and tendon rupture, and neurotoxicity.

METHICILLIN-RESISTANT S. AUREUS

- If MRSA is a frequent nosocomial pathogen in the institution (ie, >20 percent local prevalence), linezolid or vancomycin should be included as part of the initial regimen to provide antistaphylococcal coverage but should be discontinued if MRSA is not isolated.
- Telavancin, tedizolid, and ceftaroline are alternatives when neither linezolid nor vancomycin can be used.

- If a sputum culture reveals MSSA, empiric therapy for MRSA should be replaced with nafcillin (2 g IV every four hours), oxacillin (2 g IV every four hours), or cefazolin (2 g IV every eight hours)

PROLONGED INFUSIONS

- Because of increasing resistance of pathogens associated with VAP and HAP, one potential strategy to enhance the antimicrobial potential of a given agent is to optimize the pharmacodynamic effect.
- As an alternative to traditional intermittent dosing (eg, administered over 30 minutes), prolonged infusions of certain beta-lactam antibiotics may be given in critically ill patients when MDR pathogens are suspected.
- Suitable agents for prolonged infusions include piperacillin-tazobactam, meropenem, imipenem, and cefepime.

AEROSOLIZED ANTIBIOTICS

- Aerosolized colistin, polymyxin, or aminoglycosides can be used as adjunctive therapy (in combination with IV antibiotics) in patients with VAP or HAP caused by MDR gram-negative bacilli, such as *P. aeruginosa* .

- **Legionella** Patients who have compromised immune systems, diabetes mellitus, renal disease, structural lung disease, or have been recently treated with glucocorticoids may require coverage for *Legionella* spp (eg, with azithromycin or a fluoroquinolone). Nosocomial cases of HAP and VAP due to *Legionella* spp attributable to contamination of the hospital water supply have been reported.
- **Anaerobes** Patients who have aspirated or had recent abdominal surgery may warrant coverage for anaerobes (clindamycin, beta-lactam-beta-lactamase inhibitor, or a carbapenem).
- In general, anaerobes are rarely implicated in VAP, and some retrospective analyses suggest little difference in outcomes in patients with aspiration pneumonitis treated with and without anaerobic coverage .