Ventilator associated pneumonia; updated guidelines

Introduction

- Many of the critically ill patients are semiconscious or totally in coma.
- This requires a respiratory support to maintain their lives.
- Aggressive method of mechanical respiration is usually the solution of such patients.
- This method is called mechanical ventilation (endotracheal intubation or tracheostomy).
- However, this invasive device carries the risk for a serious infection that develops in the lungs called ventilator associated pneumonia (VAP).
- It is the second nosocomial infection (after urinary tract infection)
- Affecting approximately 15% of hospitalized patients.
- 90% of hospital acquired pneumonia is due to VAP.
- It is incidence is very high among ventilated patients: 10-65% of all ventilated patients
- VAP is defined as pneumonia due to mechanical ventilation for more than 48 h of intubation.
- It is a serious infection associated with increasing the length of mechanical ventilation (7-11 days), length of hospital stay (11-13 days), high mortality rate and increase in the overall cost.

Pathophysiology

It is main pathophysiology includes the entrance of the bacteria to the respiratory system. The entrance occurs through:

- Aspiration of the bacteria from the gastrointestinal system (most common cause)
- Direct colonization
- Inhalation of the bacteria
- Haematogeneous spread.

Diagnosis:

- It is diagnosed by: new progressive lung infiltrate on chest imaging with at least one of the following clinical findings:
- Fever, purulent sputum, excess sputum production, leukocytosis, reduce in oxygenation.
- The diagnosis should be confirmed by sampling (culture) from the respiratory system (sputum culture).
✓ VAP is not diagnosed by a normal radiologic finding with abnormal culture (because this could be colonization without infection).

**Microbiology:**

The most common pathogens that cause VAP include:


2- Gram-positive cocci (eg, *Staphylococcus aureus*, including methicillin-resistant *S. aureus* [MRSA], *Streptococcus* spp).

Viruses, fungi are rare causes, except for immunocompromised Patients.

-Microbiologic sampling (culture) should be obtained before initiation of the antimicrobial agents.

**Treatment approach**

✓ Not all patients should receive the same treatment.
✓ Some patients are at higher risk to have multi-drug resistant pathogens such as: *Pseudomonas aeruginosa*, *Acinetobacter*, Enterobacteriaceae and MRSA).
✓ These patients require more aggressive therapy than those who do not have risk factors for such aggressive pathogens.
✓ Assessing the risk factors for MDR pathogens should be identified before initiating the empiric therapy.
✓ According to the risk factors the patient has, he may require empiric therapy with triple or dual therapy.
✓ Antimicrobial resistance in the hospital setting is very important to determine the aggressiveness of the empiric therapy.
✓ Antimicrobial agents should be started as soon as VAP is suspected.
✓ Sputum culture and blood culture (if suspected blood spread) should be obtained prior to empiric antimicrobial therapy.
✓ Once pathogen is identified, tailoring of the therapy should be done.
Patients first should be assessed for the risk of MDR pathogens, if do not have risk for MDR pathogens, they should be assessed for the risk of MDR gram negative bacteria and the risk for MRSA.

It should be noted that the pattern of resistance in the hospital setting is very important, since many hospitals are known to have high MDR pathogens, and thus, patients admitted to such settings should be treated as having MDR bacteria.
# Empiric treatment of ventilator-associated pneumonia in patients with normal renal function

**Are any of the following risk factors for MDR VAP present?**
- IV antibiotic use within the previous 90 days?
- Septic shock at the time of VAP
- ARDS preceding VAP
- >3 days of hospitalization prior to the occurrence of VAP
- Acute renal replacement therapy prior to VAP onset

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**Does the patient have either of the following risk factors for resistant gram-negative bacilli?**
- Treatment in a unit in which >10% of gram-negative bacilli are resistant to an agent being considered for monotherapy
- Treatment in a unit in which the prevalence of resistance among gram-negative bacilli is unknown

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**Does the patient have either of the following risk factors for MRSA?**
- Treatment in a unit in which >20% of Staphylococcus aureus isolates are methicillin-resistant
- Treatment in a unit in which the prevalence of MRSA is not known

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### One of the following:
- Piperacillin-tazobactam 4.5 g IV every 6 hours
- Cefepime 2 g IV every 8 hours
- Ceftazidime 2 g IV every 8 hours
- Levofoxacin 750 mg IV every 24 hours

**Plus one of the following:**
- Vancomycin 15 mg/kg IV (maximum 2 g per dose initially) every 8 to 12 hours with goal to target 15 to 20 mcg/mL trough level; consider a loading dose of 25 to 30 mg/kg (maximum 3 g) x 1 for severe illness
- Linezolid 600 mg IV every 12 hours

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- Ceftazidime 2 g IV every 8 hours
- Levofoxacin 750 mg IV every 24 hours
- Ciprofloxacin 400 mg IV every 8 hours
- Aztreonam 2 g IV every 8 hours

**Plus one of the following:**
- Amikacin 15 to 20 mg/kg IV daily
- Gentamicin 5 to 7 mg/kg IV daily
- Tobramycin 5 to 7 mg/kg IV daily
- Levofoxacin 750 mg IV every 24 hours
- Ciprofloxacin 400 mg IV every 8 hours
- Aztreonam 2 g IV every 8 hours

### One of the following:
- Piperacillin-tazobactam 4.5 g IV every 6 hours
- Cefepime 2 g IV every 8 hours
- Ceftazidime 2 g IV every 8 hours
- Imipenem 500 mg IV every 6 hours
- Meropenem 1 g IV every 8 hours

**Plus one of the following:**
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- Gentamicin 5 to 7 mg/kg IV daily
- Tobramycin 5 to 7 mg/kg IV daily
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1- Patients with no risk for MDR and no risk for psuedomonas or other MDR gram negative (hospital settings < 10 % resistant to monotherapy) and no risk for MRSA (< 10-20 % risk of methicillin resistant isolates) can be treated with one of the following:

- Piperacillin tazobactam: 4.5 gm IV q 6h
- Cefepime 2 gm IV q 8h
- Levofloxacin 750 mg IV once daily

2- Patients with at least one risk for MDR pathogens should receive a combination of triple therapy including two anti-pseudomonal agents plus one anti-MRSA:

ONE of the following:

- Piperacin-tazobactam, cefepime, ceftazidime, imipenem-cilastatin, meropenem

PLUS one of the following:

- Amikacin, gentamicin, tobramycin, levofloxacin, ciprofloxacin, aztreonam

PLUS one of the following:

Linezolid, vancomycin, telavancin

3- Patients without risk of MDR pathogen, but risk for gram negative MDR: resistance for monotherapy is greater than 10%, or the resistance is unknown, dual anti-psuedomonal should be started. Assess the risk for MRSA is very important to determine the need for the addition of anti-MRSA to the dual antimicrobial agents.

The combination consists of:

One of the following:

piperacillin tazobactam, cefepime, imipenem, meropenem

Plus one of the following:

Gentamicin, tobramycin, amikacin, ciprofloxacin, levofloxacin, aztreonam.

If risk for MRSA (> 10-20 % risk of s. aureus to be methicillin resistant or the resistance is unknown) add one of the following:

Vancomycin, linozolid, televancin.
4- Patients with no risk for MDR pathogen and no risk for MDR gram negative bacilli, but have risk for MRSA (as defined earlier) should be started on one anti-psuedomonal agent plus anti-MRSA.

One of the following:

Piperacillin-tazobactam, cefepime, ceftazidime, ciprofloxacin, levofloxacin, aztreonam

Plus one of the following agents:

Vancomycin, linozolid, televancin

✓ Once the empiric therapy is started, it should be reassessed after 2-3 days.
✓ Cultures are usually available after this period of time.
✓ For patients in whom a pathogen has been identified, the empiric regimen should be tailored to the pathogen based on its susceptibility pattern.
✓ For patients improving and do not have an identified pathogen, empiric treatment for MRSA or MDR gram-negative bacilli can be discontinued if these organisms have not grown in culture from sputum.
✓ Patients without improvement within 72 hours of starting the therapy should be reevaluated. If a drug-resistant pathogen is suspected, the empiric regimen should be expanded to cover the suspected organism.

Duration:

✓ Course duration of seven days is as effective as longer duration as confirmed by most studies
✓ However, patients with sepsis, bacteremia, critically ill patients, metastatic infection, immunocompromised patients, aggressive pathogens such as MRSA, psuedomonas and acinetobacter require longer duration (14-21 days).
✓ Short course of therapy (7 days) was not associated with high mortality.
✓ Seven day course therapy is preferred to reduce the risk of resistance.

Conversion to oral antimicrobial agents:

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 be the same (or in the same drug class) as the intravenous agent and should have adequate lung penetration.

**Specific antimicrobial consideration:**

- In critically ill patients, in those receiving antibiotics prior to the onset of pneumonia and in institutions where these pathogens are frequent, coverage of MRSA, *P. aeruginosa*, and antibiotic-resistant gram-negative bacilli such as *Acinetobacter* spp should be considered.

- **Allergy to penicillins or cephalosporins:** aztreonam can be given for patients who have immediate hypersensitivity for the β-lactam (penicillins, cephalosporins, carbapenems: imipenem and meropenem). Aztreonam has cross reactivity with ceftazedime, so patients allergic to ceftazedime should not receive aztreonam.

**Some agents are generally not preferred for the treatment of VAP:**

* Daptomycin: does not achieve sufficiently high concentrations in the respiratory tract.

* Ceftaroline (anti-MRSA) but not for pneumonia caused by MRSA.

* Tigecycline is a broad-spectrum antibiotic (anti-MRSA), it has a **warning box**: increase the risk of death. So should be reserved for use in situations when alternative agents are not suitable.

* Ceftobiprole (anti-psuedomonal and anti-MRSA). Cure rate with this agent is lower in VAP compared with other agents.

* Doripenem: higher rate of mortality compared to imipenem-cilastatin.

**Notes for gram negative bacteria:**

- To reduce the risk of resistance and the side effects, combination therapy is usually recommended.
✓ **P. aeruginosa**: For patients with VAP due to *P. aeruginosa* who are not in septic shock or at high risk of death and for whom susceptibility results are known, monotherapy can be given.

✓ Aerosolized antibiotics can be used as adjunctive therapy (in combination with IV antibiotics) in patients with VAP caused by MDR *P. aeruginosa* that is failing to improve on IV therapy.

✓ Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae – (ESBL+) In ICU settings in which ESBL producing Enterobacteriaceae are found, cephalosporins should be avoided as monotherapy due to the selection of resistant organisms when these agents are used. The most reliable agent in this setting is a carbapenem.

✓ **Acinetobacter baumannii** – For patients with VAP caused by A. baumannii, a carbapenem or ampicillin-sulbactam should be used if the isolate is susceptible. If the isolate is susceptible only to polymyxins (colistin or polymyxin B) one of these agents should be given intravenously together with inhaled colistin (since intravenous colistin yields low lung concentrations): IV colistin, meropenem, rifampin, tigecycline.

✓ ceftolozane-tazobactam and ceftazidime-avibactam: are new cephalosporin B lactamase antimicrobials approved for urinary tract and intra-abdominal infections but not for pneumonia.

✓ **Aerosolized antibiotics**: Aerosolized colistin or aminoglycosides can be used as adjunctive therapy (in combination with IV antibiotics) in patients with VAP caused by multidrug-resistant gram-negative bacilli, such as A. baumannii or P. aeruginosa.

✓ Aerosolization may increase antibiotic concentrations at the site of infection.

✓ It is useful for the treatment of organisms that have high minimum inhibitory concentration (MIC) to systemic antimicrobial agents. However, the evidence of aerosolized antibiotics is conflicting (in a meta-analysis to compare colistin IV alone versus IV with aerosolized colistin: no improvement in outcome or microbiologic eradication seen with the combination over IV colistin alone.
- **Legionella** — Patients who have diabetes mellitus, renal disease, structural lung disease, or have been recently treated with glucocorticoids may require coverage for *Legionella* spp (fluoroquinolone).

- **Anaerobes** — Patients who have aspirated or had recent abdominal surgery may warrant coverage for anaerobes (clindamycin, beta-lactam-beta-lactamase inhibitor, or a carbapenem).

- **Anti-inflammatory effects of macrolides** — there has been interest in the nonantibiotic anti-inflammatory effects of macrolides.

### Prognosis

The absolute mortality cannot be assessed because many patients die due to their actual illness. However, it is ranged from 20-50 % according to several studies. The attributed risk among patients with VAP is 13%.

### Variables associated with increased mortality include in patients with VAP:

1. Serious illness at the time of diagnosis (eg, sepsis, shock, coma, respiratory failure, bacteremia)

2. Severe comorbid disease

3. Infection caused by MDR organisms

4. Rapidly progressive infiltrates on lung imaging

5. Delay in the institution of effective antimicrobial therapy

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score has been considered the best system to predict mortality in patients with VAP. Higher APACHE score indicated higher mortality among critically ill patients.

### Prolonged infusion

Usually antibiotics are given intravenously as bolus or intermittent infusion (over 30 minutes). However, prolonged infusions of certain beta-lactams (piperacillin, imipenem, meropenem, cefepime) is recommended to optimize their pharmacodynamics to achieve higher rate of eradication, patients with infections caused by gram-negative bacilli that have elevated but susceptible minimum inhibitory concentrations (MICs) to the chosen agent are the best candidates for such approach.
Prolonged infusion administration strategies for intravenous beta-lactams may: either as continuous infusion (over the entire dosing interval) or an extended infusion (over 3 to 4 hours).

<table>
<thead>
<tr>
<th>medication</th>
<th>Creatinine clearance</th>
<th>Dose</th>
<th>interval</th>
<th>Infusion duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin tazobactam</td>
<td>CrCl&gt;20 ml/min</td>
<td>4.5 gm IV</td>
<td>Q.8 h</td>
<td>Over 4 h</td>
</tr>
<tr>
<td>cefepime</td>
<td>CrCl&gt; 50 ml/min</td>
<td>2 gm IV</td>
<td>Q.8 h</td>
<td>Over 4 h</td>
</tr>
<tr>
<td>Imipenem cilastatin</td>
<td>CrCl&gt; 70</td>
<td>500, 1000 mg</td>
<td>Q.6 h</td>
<td>Over 3 h</td>
</tr>
<tr>
<td>meropenem</td>
<td>CrCl&gt; 50</td>
<td>1, 2 gm</td>
<td>Q.8 h</td>
<td>Over 3 h</td>
</tr>
</tbody>
</table>

**Antimicrobial toxicity**

- Almost all antibiotics used for VAP increase the risk of *C. difficile* infection: fluoroquinolones and broad-spectrum cephalosporins /penicillins are most commonly implicated.
- Aminoglycosides are nephrotoxic and ototoxic: preferred to be used as a combination, and preferably to be discontinued after 2-3 days and continue on the other agent.
- Polymyxins (polymyxin B and colistin) are very nephrotoxic. Should be avoided if alternative agents are available.
- The combination of vancomycin and piperacillin-tazobactam increase the risk of acute kidney injury. Using linezolid instead of vancomycin, or cefepime/ceftazedime instead of piperacillin-tazobactam.
- In patients with renal insufficiency, imipenem and cefepime have been associated with seizures.
- The fluoroquinolones side effects: QT interval prolongation, tendinitis and tendon rupture and neurotoxicity
- Telavancin is an alternative anti-MRSA agent when neither linezolid nor vancomycin can be used (high rate of mortality in patients with CrCl< 50 ml/min also increase the risk of acute renal impairment).
- Linezolid is more likely to cause GI side effects compared to vancomycin.
- Nephrotoxicity occurred more commonly with vancomycin than linezolid (18 versus 8 percent)
- Aztreonam is rarely used because of the risk of resistance.
**Prevention**

Some preventing methods may reduce the risk of VAP, these methods do not provide 100% risk reduction of VAP. These preventing methods (VAP bundle) are:

1- Stress ulcer prophylaxis
2- Head of bed elevation
3- Daily interruption of the sedation if possible
4- Avoid gastric distention
5- Chlorhexidine mouthwash.
References:


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