Ventilator Associated Pneumonia (VAP)

November 9, 2020 by Josh Farkas

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Ventilator associated pneumonia (VAP) is pneumonia occurring more than two days after intubation. Clinicians must walk several fine lines regarding VAP:

- **Undertreatment versus overtreatment**
  - Undertreatment: Overlooking the diagnosis until the patient develops septic shock.
  - Overtreatment: Treating every patient with possible VAP using numerous broad-spectrum antibiotics.

- **Underinvestigation versus overinvestigation**
  - Underinvestigation: Assuming the diagnosis of VAP without any sophisticated studies.
  - Overinvestigation: Broad use of bronchoscopy and CT scan for every patient with a pulmonary infiltrate.

This is not easy. Studies consistently show that among patients who are clinically diagnosed with VAP, only ~40-50% will eventually be found to have VAP based on microbiological studies. Likewise, all of the early diagnostic indicators of VAP have poor test performance (e.g., fever, leukocytosis, sputum production, and chest radiograph). Consequently, we are doomed to *usually be wrong* when we make the initial diagnosis of VAP. To make matters even more complicated, VAP may have a significant attributable mortality (perhaps ~10%) – so we *do* need to take it seriously, and treat it properly.

The fact that our clinical diagnosis of VAP will often be wrong should lead to some *restraint* regarding the initial antibiotic regimen. Specifically, if the patient probably doesn’t have VAP, then it may not be wise to unleash a toxic cocktail of vancomycin, cefepime, and an aminoglycoside. The probability of harming the kidneys with these antibiotics is substantial, whereas the probability of randomly hitting a multidrug-resistant pathogen may be lower.

To make the topic even more confusing, there is no gold-standard diagnostic study for VAP (other than autopsy – which isn’t an attractive approach). Nearly all tests available have only intermediate performance. Consequently, in clinical practice it’s impossible to make a diagnosis of VAP with 100% certainty.

Given these uncertainties, it should come as little surprise that guidelines disagree about how to approach the diagnosis and treatment of VAP. European and American guidelines disagree substantially regarding the use of bronchoscopy and the selection of empiric antibiotic regimens. ([30601179](https://pubmed.ncbi.nlm.nih.gov/30601179/), [30063491](https://pubmed.ncbi.nlm.nih.gov/30063491/), [30390750](https://pubmed.ncbi.nlm.nih.gov/30390750/)). These disagreements don’t imply that either guideline is wrong, but rather that the optimal approach to VAP remains unknown. Numerous reasonable approaches exist. The approaches explored below are more consistent with American guidelines (with the recognized limitation that no single approach will be universally appropriate for every ICU).

Ultimately, where does this leave us? In a place of diagnostic and therapeutic humility. We must recognize that our clinical acumen will frequently fail us. Consequently, we must continuously be re-evaluating the data and reconsidering our diagnoses. Likewise, our initial therapies will frequently be suboptimal, requiring ongoing revision. The best that we can hope for is to be systematic, thoughtful, right more than we are wrong, and to cause more benefit than iatrogenic harm.
Mirroring the uncertainty surrounding VAP, our approach to it is a stepwise and recursive process. Let’s walk through these steps...

**step #1 – consider rapidly available information**

There are roughly four sources of clinical information which should be rapidly available, when considering the possibility of VAP. Try to consider all evidence, rather than anchoring on a single bit of evidence. Additionally, trends in vital signs and data are often more informative than any single data point (since VAP occurs in the context of critical illness, we will always know the patient's baseline values).

**(a) Evidence of inflammation**

- Leukocytosis (sensitivity ~64%; specificity ~59%; positive likelihood ratio (+LR) 1.6; negative likelihood ratio (-LR) of 0.6) [32306086](https://pubmed.ncbi.nlm.nih.gov/32306086/)
- Bandemia, left-shift, and neutrophil/lymphocyte ratio.
- Fever (sensitivity 66%; specificity 54%; +LR 1.4; -LR -0.6) [32306086](https://pubmed.ncbi.nlm.nih.gov/32306086/)
- Hypothermia.
- Septic shock.

**(b) Evidence of pulmonary dysfunction**

- Secretions
  - ? Purulent secretions (sensitivity 77%; specificity 39%; +LR 1.3; -LR 0.6) [32306086](https://pubmed.ncbi.nlm.nih.gov/32306086/)
  - ? Volume of secretions.
- Respiratory dysfunction
  - Decline in oxygenation (requirement for higher FiO2 or PEEP).
  - Possibly: decline in ventilation (increased minute ventilation requirement).
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(c) Radiographic evidence

- Chest X-ray (CXR)
  - Infiltrate on chest X-ray is fairly sensitive (89%), but it's nonspecific (26%). Consequently, the +LR is 1.2 and the -LR is 0.4. ([32306086](https://pubmed.ncbi.nlm.nih.gov/32306086/))
  - Imperfect sensitivity is due partially to portable films that often miss infiltrates hiding behind the heart or diaphragms. Among patients with pre-existing X-ray abnormalities (e.g., ARDS), detecting a new infiltrate is even harder.
  - Poor specificity is the major problem with chest radiography. Infiltrates may also represent atelectasis, aspiration pneumonitis, pulmonary infarction, chronic pulmonary fibrosis, or cardiogenic pulmonary edema.
  - Repeat CXR may sometimes help clarify the diagnosis. A true pneumonia will resolve very slowly, whereas atelectasis or aspiration can often resolve within 1-2 days.

- Lung ultrasonography
  - Ultrasonography is less useful for VAP than for community-acquired pneumonia, because many patients in the ICU will have dependent consolidation and B-lines due to atelectasis.
  - However, ultrasonography may remain useful (e.g., to distinguish pleural effusion vs. consolidation at the lung bases).

- CT scan
  - This remains the gold-standard imaging study for thoracic infection. CT scan is superior to chest X-ray at differentiating between atelectasis versus pneumonia. The main drawback of CT scanning is the logistic challenge of transporting the patient to the CT scanner.
  - Absence of an infiltrate on CT scan excludes pneumonia.
  - Presence of pulmonary infiltrates doesn't prove the diagnosis of VAP. CT scan is exquisitely sensitive for mild infiltrates, so the presence of an infiltrate may be nonspecific. As with any radiologic study, be sure to review the images yourself and compare them to prior studies (radiologists may err on the side of safety by overcalling "possible pneumonia").

(d) Alternative diagnostic considerations

- It's important to avoid falling into the trap of anchoring on a binary diagnostic approach (e.g. does the patient have VAP – yes or no?). A more fruitful approach is to consider all possibilities (e.g. what process does the patient have?). If an alternative diagnosis is established (e.g. empyema), this makes VAP far less likely. Some common alternative diagnoses to consider include the following:
  - Pulmonary embolism with infarction (this may produce infiltrates).
  - The combination of two processes:
    - #1 = Pulmonary process that doesn't cause inflammation: Atelectasis, asymmetric pulmonary edema, transudative pleural effusion.
    - #2 = Extra-pulmonary inflammatory process: Infection elsewhere (e.g., line infection, Clostridioides difficile) or noninfectious fever (e.g., drug fever).
  - Empyema.
  - Fibroproliferative ARDS (persistent fevers can last for days in the remodeling/subacute phase of ARDS).
  - Cryptogenic organizing pneumonia (COP).
  - Aspiration pneumonitis.
  - Medication-induced pneumonitis.

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**Step #2 – when to pull the trigger on antibiotics and cultures**

Based on the above information, an initial clinical decision needs to be reached regarding whether VAP is a likely diagnosis.

- If VAP is considered likely, then cultures should be sent and antibiotics initiated.
- If VAP is considered unlikely, then neither cultures nor antibiotics are indicated. Cultures will often be positive among intubated patients, so obtaining cultures without a suspicion of infection may lead to false-positive cultures and inappropriate therapy.

There are no validated criteria regarding how exactly to establish this diagnosis. Clinical judgement is required.
Previous, the Clinical Pulmonary Infection Score (CPIS) was used to adjudicate the diagnosis of VAP. Unfortunately, meta-analysis demonstrated that the Clinical Pulmonary Infection Score doesn’t have adequate performance and thus it is no longer recommended. (32306086)

Alternative courses of action, other than antibiotic initiation, may also be considered:

- Obtain more data (e.g., chest CT scan).
- Attempt to treat other problems (e.g., diuresis or ventilator strategies to improve lung recruitment).
- Close clinical and radiological monitoring without intervention.

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**step #3a – management of suspected VAP – cultures & repeat imaging**

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**additional diagnostic studies for a patient with suspected VAP**

- (1) Blood cultures (two peripheral cultures, plus cultures of any central line in place >72 hours).
- (2) Tracheal aspirate for gram stain and culture.
- (3) PCR studies for influenza and COVID-19, if appropriate.
- (4) Nasal PCR for MRSA (if not recently performed).
- (5) Procalcitonin levels may be useful (in the absence of severe immune compromise).
- (6) A repeat chest X-ray after 24-48 hours may be helpful.
- (7) Consider evaluation for *Invasive Aspergillus*.

**Potential indications (more detail in below table):**

- ARDS due to influenza or COVID-19
- Prolonged neutropenia
- Prolonged steroid use
- Organ transplantation

**Investigation may include:**

- CT scan
- Serum galactomannan antigen and beta-D-glucan
- Bronchoalveolar lavage for culture & fungal stain, PCR, and galactomannan (if it can be accomplished safely and there is high suspicion)

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**Integrative diagnosis of invasive aspergillosis among ICU patients (without biopsy evidence)**

[Image](https://emcrit.org/ibcc/aspergillosis/attachment/asptablematrix/)

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**step #3b – management of suspected VAP – antibiotics**
occasionally, a treatment regimen for community-acquired pneumonia (CAP) is appropriate:

- This is appropriate if all of the criteria listed below are met (32157357): (a) Patient admitted within <5 days (“early VAP”). (b) Not recently admitted to the hospital or treated with IV antibiotics (within 90 days). (c) Not immunosuppressed. (d) Structurally normal lungs (e.g., no bronchiectasis or severe COPD). (e) Not in septic shock. (f) No ARDS or acute dialysis prior to VAP onset. (g) No prior colonization with multidrug-resistant bacteria.
- For more on appropriate antibiotics for community-acquired pneumonia, look [here](https://emcrit.org/ibcc/pneumonia/#antibiotic_selection).

For most other patients, the following approach is taken:

(i) **Backbone agent: Antipseudomonal beta-lactam**

- A broad-spectrum antipseudomonal agent is the backbone of therapy.
- This is generally cefepime or piperacillin/tazobactam (more on comparison of these antibiotics [here](https://emcrit.org/ibcc/antibiotics/#piperacillin-tazobactam)). Meropenem may occasionally be considered if there is concern for an extended-spectrum beta-lactamase resistance organism (ESBLs).
- For patients with recent antibiotic exposure, an agent which they weren't exposed to might be preferable. Additionally, prior microbiologic data should be reviewed (e.g., prior infection or colonization with drug-resistant organisms).
- Double coverage of pseudomonas isn’t evidence based [here](https://emcrit.org/pulmcrit/double-coverage-vap/) and may increase toxicity. In units with exceptionally high rates of multidrug-resistant bacteria (e.g., ongoing Acinetobacter outbreak), broader empiric therapy may be considered.

(ii) **MRSA coverage?**

- Not all patients with VAP require MRSA coverage.
  - Only ~40% of patients with suspected VAP will end up truly having a genuine VAP. MRSA is the cause of only ~10-20% of VAP infections. Consequently, only ~4-8% of patients with suspected VAP may have a true MRSA VAP infection. Depending on individual risk factors, this may or may not be worth covering empirically.
  - It’s conceivable that MRSA VAP is substantially over-diagnosed, due to difficulties sorting out colonization versus invasive infection. Cunha has suggested that in the absence of necrotizing pneumonia, MRSA may be more likely to be a colonizer.
  - General indications for considering MRSA coverage, based on IDSA guidelines, are listed below. These criteria are sensitive, but not specific. Nearly all patients with VAP will have at least one criterion, so covering for MRSA in anyone with one risk factor will tend to cover MRSA unnecessarily.
    - Receipt of intravenous antibiotics within the last 90 days.
    - Hospitalized in a unit where >20% of *Staph aureus* isolates are MRSA (or the rate of MRSA is unknown).
    - Patients at high mortality risk (e.g., septic shock).
    - Known colonization with MRSA.
    - Five or more days of hospitalization prior to the occurrence of VAP.
• MRSA coverage may not be necessary in patients with a recent nares PCR which was negative for MRSA (33004324, 29340593).

- Nares PCR is only ~70% sensitive for MRSA, so this doesn't entirely exclude the diagnosis of MRSA pneumonia. However, for patients at an average risk of MRSA (e.g., ~6% likelihood), a negative nares PCR reduces the likelihood of MRSA to ~2%. At this level, the risk of antibiotic toxicity may overshadow the benefits of antibiotic therapy.

- MRSA PCR performed on sputum samples likely has a greater sensitivity than nares specimens.(25942570, 23919575) However, this requires further clinical validation.

- In ICUs with extraordinarily high rates of MRSA, MRSA coverage may be considered even among patients with a negative nares PCR.

• If MRSA coverage is indicated, this is generally achieved with linezolid, vancomycin, or ceftaroline (note that daptomycin cannot be used to treat pneumonia).

- Given superior pulmonary penetration and more predictable pharmacokinetics, linezolid may be superior to vancomycin for treatment of MRSA VAP. One RCT found that linezolid led to improved clinical resolution and less nephrotoxicity compared to vancomycin. (22247123) More on vancomycin versus linezolid here.

(iii) Atypical coverage?

• Atypical bacteria (e.g. *Mycoplasma, Chlamydiae, Legionella*) don't generally cause VAP. Consequently, atypical coverage is generally not utilized.

- If your hospital water system is known to harbor Legionella, add coverage for it (e.g., azithromycin) and obtain a *Legionella* urinary antigen test.

(iv) Anaerobic coverage is not indicated

• Anaerobic coverage for pulmonary infections is generally indicated only in the context of empyema or lung abscess.

step #4 – data review & diagnosis adjudication

Among patients who are started on antibiotics for VAP, only ~40-50% are eventually diagnosed with it after all the data is available (18091545, 31754887) Therefore, it's essential to re-consider the diagnosis as additional information becomes available. If emerging evidence is inconsistent with a diagnosis of pneumonia, antibiotics should be discontinued and the diagnosis should be discarded.

tracheal aspirate gram stain & culture

• Tracheal sampling basics

- Unlike community-acquired pneumonia, VAP is almost always due to gram-positive or gram-negative organisms which can be cultured in the microbiology lab. Additionally, compared to community-acquired pneumonia, VAP is more likely to represent a *bronchopneumonia* (rather than lobar pneumonia) – which is more amenable to sputum sampling (more on types of pneumonia here). Bronchoscopic or quantitative culture methods are generally unnecessary. Qualitative tracheal aspirates are cheaper, easier, and more sensitive. (More on the role of bronchoscopy below.)

• Gram stain interpretation

- If the gram stain shows no evidence of inflammation (i.e., no leukocytes) – this strongly argues against a diagnosis of VAP.

- If the gram stain is of high quality (e.g., <10 squamous epithelial cells and >25 neutrophils per high power field) and it shows a single dominant bacterial morphology (e.g., gram-positive cocci or gram-negative rods), this is likely reliable information which can be used to adjust antibiotic selection.

- If the gram stain shows multiple different organisms, this is nonspecific and cannot be relied upon to modify therapy.

• Negative culture interpretation

- If cultures don't grow a pathogenic bacteria associated with VAP, this strongly argues against a diagnosis of VAP (unless antibiotics were initiated before cultures were obtained).

• Positive culture interpretation
• Positive cultures from a tracheal aspirate alone *don’t* prove the presence of pneumonia (e.g., they may result from *colonization* rather than infection).
• Certain species may be more likely to represent *colonization* than invasive infection: Enterobacter, Proteus, Citrobacter, Flavobacterium, Stenotrophomonas, Burkholderia and Enterococcus. ([Cunha](https://www.amazon.com/Infectious-Diseases-Antimicrobial-Stewardship-Critical-ebook/dp/B08COJBRXS/))

**blood cultures**

• Blood culture data in patients with suspected VAP:
  • 15% of patients with VAP will have positive blood cultures.
  • Up to 25% of patients with suspected VAP will have positive blood cultures originating from a *nonpulmonary* source (e.g., line infection)!
  • If blood cultures turn up positive, be thoughtful about looking for a nonpulmonary focus of infection – especially if blood cultures reveal an organism which doesn’t usually cause pneumonia (e.g., *Candida*, *Enterococcus*).[33004324](https://pubmed.ncbi.nlm.nih.gov/33004324/)

**additional imaging**

• Repeat chest X-ray
  • A repeat chest X-ray after 1-2 days may be helpful.
  • If infiltrates rapidly disappear (within <24-48 hours), this suggests atelectasis rather than pneumonia. In true pneumonia, infiltrates take many days to weeks to resolve.
  • Stable or worsening infiltrates may support a pneumonia diagnosis.
• Chest CT scan
  • CT scan may be indicated if there is suspicion of pulmonary embolism, fungal pneumonia, or interstitial lung disease.
  • CT scan can also help differentiate between more common entities (e.g., pneumonia vs. atelectasis vs. heart failure).

**procalcitonin**

• Procalcitonin may be helpful among patients who are not immunosuppressed.
• A procalcitonin value of <0.5 argues strongly against VAP. This should prompt consideration of discontinuing antibiotics, even if the sputum cultures are positive (positive sputum cultures with a negative procalcitonin may represent colonization rather than infection).

**step #5 – narrowing the antibiotic regimen based on microbiological studies**

*For patients with persistent evidence supporting pneumonia, microbiological data should be reviewed to adjust the antibiotic regimen.*

**MRSA coverage**

• MRSA is typically easy to grow in culture (MRSA pneumonia produces lots of sputum and doesn’t sterilize rapidly following therapy).
• Do not continue MRSA coverage for >48 hours unless there is some evidence of MRSA!
  • Nares PCR negative for MRSA suggests that MRSA coverage can be discontinued.
  • Absence of MRSA growth in tracheal aspirates is conclusive evidence that MRSA coverage should be discontinued.

**if an organism is detected**

• Ideally, a causative bacteria will be identified.
• Antibiotic therapies should be tailored for that organism (with discontinuation of unnecessary antibiotics).

**if no organism is detected**

• Sometimes, no pathogenic organism is detected. If this is the case, the diagnosis of VAP should be reconsidered and probably discarded. However, in some situations, VAP can occur without an organism being cultured from the sputum:
  • i) Antibiotics initiated prior to sputum culture.
  • ii) *Early-onset VAP* leading to infection with atypical or fastidious organisms (e.g., *Pneumococcus* or *Legionella*).
• If the concern for VAP remains high despite negative cultures, it may be reasonable to continue antibiotics. However, in the absence of evidence supporting *Pseudomonas*, antibiotic therapy may generally be narrowed down (e.g. to ceftriaxone).
step #6 – duration of therapy

- The IDSA/ATS guidelines generally recommend a seven-day course of antibiotics (even for *Pseudomonas*). (https://pubmed.ncbi.nlm.nih.gov/27418577)
  - Empyema
  - Lung abscess
  - Necrotizing pneumonia
  - Bacteremia with certain gram-positive organisms (e.g., *Staph. aureus*)
  - Severe immunodeficiency
  - Cystic fibrosis
- Procalcitonin may occasionally be useful to shorten the duration of therapy:
  - Procalcitonin levels falling below 20% of the initial value or <0.25 ng/ml suggests that it is safe to discontinue antibiotics.
  - Procalcitonin should only be used as an antibiotic-stopping tool. Therefore, a low procalcitonin may support discontinuation of antibiotics before seven days. Antibiotics should generally be discontinued after a seven day course, regardless of the procalcitonin level.

step #7 – treatment failure

The causes and investigation of this are similar to community-acquired pneumonia (link here).

bronchoscopy

**why bronchoscopy isn't generally indicated to investigate VAP**

- Bronchoscopy hasn't been shown to affect mortality or length of stay in VAP. (https://pubmed.ncbi.nlm.nih.gov/25354013/)
  Consequently, routine bronchoscopy is not recommended by the IDSA/ATS guidelines. (https://pubmed.ncbi.nlm.nih.gov/27418577/)
- Bronchoscopy with protected specimen brush and quantitative culture has only a 61% sensitivity and 77% specificity (for a positive likelihood ratio of 2.6 and a negative likelihood ratio of 0.5). (https://pubmed.ncbi.nlm.nih.gov/32306086/)
  Clinicians may overestimate the value of hard-earned bronchoscopic data, leading to misdiagnosis.
- Bronchoscopy may lead to delays in therapy, if antibiotics are delayed until a bronchoscopy can be performed.
- Bronchoscopy is an invasive procedure which exposes patients to risks of sedation and desaturation (due to saline instillation).
- Blind mini-BAL involves blindly inserting a catheter into the lungs until it wedges in a terminal bronchus, then performing a bronchoalveolar lavage. Compared to bronchoscopy, this provides less diagnostic information (e.g. no inspection of the bronchial tree or directed aspiration) while exposing patients to a similar level of risk.

**when bronchoscopy is indicated**

- Bronchoscopy may be indicated when there is a concern for *Pneumocystis* pneumonia or invasive *Aspergillus*. Among these, *Aspergillus* is the primary concern as a nosocomial pathogen causing pneumonia.
  - More on *Pneumocystis pneumonia*.
  - More on invasive pulmonary aspergillosis.
- If sampling is required, bronchoscopy is superior to mini-BAL for the following reasons:
  - Visualization of the mucosae is possible, to evaluate for tracheal aspergillosis.
  - Targeting of involved areas of lung is possible.
- If bronchoscopy is performed, a differential cell count should be obtained. If <50% of the cells are neutrophils, this probably excludes pneumonia.
**summary**

[https://emcrit.org/ibcc/vap/attachment/vappath/]

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**podcast**

[https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/apps.40518.14127333176902609.7be7b901-15fe-4c27-863c-7c0dbfc26c5c.5c278f58-912b-4af9-88f8-a65ff2da477.jpg]


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**questions & discussion**

To keep this page small and fast, questions & discussion about this post can be found on another page [here](https://emcrit.org/pulmcrit/vap/).

[https://i0.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif]
- Continuation of MRSA coverage >48 hours despite there being zero evidence that the patient actually has a MRSA pneumonia.
- Use of fluoroquinolones for VAP (they have no role, as explained here [https://emcrit.org/pulmcrit/double-coverage-of-gram-negatives-with-a-fluoroquinolone/]), here [https://emcrit.org/pulmcrit/fluoroquinolone-critical-illness/], and especially here [https://emcrit.org/pulmcrit/double-coverage-vap/].
- Failure to re-evaluate all data 24-48 hours after starting antibiotics. Remember, 40-50% of patients started on antibiotics will ultimately not be diagnosed with VAP.

**references**