Ventilator Associated Pneumonia and SDD

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Introduction

- Most patients who receive mechanical ventilatory support for a protracted period develop microbial colonisation of the airway
- A subset of these patients develops invasive infection requiring antibiotics
- Infection occurs along a continuum of severity from purulent tracheobronchitis to progressive bronchopneumonia
- VAP is the commonest ICU acquired infection

Contentious subject

- How do we define it? Or diagnose it?
- What causes it?
- How can we prevent it?
- How many drugs should we use?
- When to start them? When to stop them?

Definition

- Pulmonary infection acquired in hospital, at least 48 hours after intubation and ventilation.
- Problems arise from confirming pulmonary infection.
- Traditional clinical features (pyrexia, leucocytosis, pulmonary infiltrates on CXR, positive endobronchial sputum culture) may be inadequate.

Incidence and Risk Factors

- Incidence: average of estimates is 17 cases per 1000 ventilator days.
- Risk Factors:
  - Duration of ventilation. 3% per day in first week, 2% per day in second, 1% per day after
  - Severity of illness: high APACHE II scores (>16) correlate with risk of VAP
  - Head injury or other cause of coma
  - Burns and trauma
  - Acute of chronic respiratory condition, ARDS
  - Male sex and increasing age.

Why are traditional features of pulmonary infection inadequate?

- They are common in ventilated patients and may reflect other pathologies:
  - Infiltrates: oedema, atalectasis, haemorrhage, or PE
  - Leucocytosis and fever – Large differential including any cause of SIRS
  - Purulent endobronchial secretions are common in intubated patients and may only indicate tracheobronchitis
  - Positive cultures: infection or colonisation?

Gold standards

- Lung biopsy showing abscess formation and neutrophil accumulation with positive quantitative culture of lung parenchyma ($>10^4$ microorgs/g lung tissue)…This is very rarely achieved
- Necropsy studies show poor histological correlation to clinical picture
- Histopathologists significantly differ when diagnosing VAP

Practical diagnosis

- Clinical features
- Microbiology, samples:
  - Expectorated sputum (not in intubated pts)
  - Tracheal aspirates
  - Semi-invasive endobronchial secretion sampling
  - Bronchoscopically obtained...

Invasive methods of sampling

- Using Bronchoscopy to obtain either bronchoalveolar lavage (BAL) or protected brush specimen (PBS) samples
- Quantitative bacteriological threshold for diagnosis (a specific number of colony forming units per ml of specimen)

Invasive sampling:

Advantages

- May exclude pneumonia
- May allow more specific diagnosis
- May allow antibiotic treatment to be optimised
- Other advantages of direct visualisation and manipulation of airway

Disadvantages

- Invasive
- Expensive
- Time consuming
- Potential airway trauma and/or infection risk

ATS statement (2002)

"Inadequate empiric therapy of VAP is associated with adverse outcome. However, prolonged broad spectrum antibiotic treatment is associated with emergence of multiresistant organisms, increased costs and, most importantly, masking non-pulmonary sites of infection. As it is difficult to obtain samples free of oropharyngeal contamination by conventional endotracheal aspiration, either bronchoscopic or nonbronchoscopic lower airway sampling is preferable. De-escalation of antibiotic therapy based on clinical response or culture results is recommended. If the techniques for lower airway sampling are not available discontinuing broad spectrum antibiotics early in patients with low risk of VAP may be an acceptable alternative"

Evidence for ATS statement

Fagon JY et al. Ann Intern Med. 2000 Apr 18;132(8):621-30.

- Multicenter randomized trial of invasive (bronchoscopic) diagnosis Vs usual care on 413 patients suspected of having VAP.
- The invasive group had a 14-day mortality rate of 16.2% Vs 25.8% in the usual care group ($P = 0.022$), and 28-day mortality 30.9% Vs 38.8%, respectively ($P = 0.09$).
- Antibiotic-free days at 14 days: 5.0 Vs 2.2 for the invasive and usual care groups ($P < 0.01$).
- There were 22 infections documented at other sites within first 3 days in invasive Vs only 5 in control.

Causative organisms

Early (<72 hrs)

- Staph. Aureus
- Strep. Pneumoniae
- other Strep
- H. Influenzae

Late (>72 hrs)

- Pseudomonas aeruginosa
- MRSA
- Acinetobacter baumanii

- > 50% comprise of 'normal' respiratory flora
- > 50% have more than one organism
- Anaerobes are often co-pathogens in early VAP
- MRSA has the worse mortality

Pathogenesis

- Normal microflora of the oropharynx does not include enteric gram-negative bacteria (EGNB)
- Oropharynx - EGNB colonise 73% of critically ill patients
- Tracheobronchial tree - EGNB colonise 45-100% of intubated patients
- Also colonisation of the sinuses, dental plaque, biofilm on endotracheal tube and trachea.
- Traumatised tracheobronchial surface from suctioning, promotes mucus stagnation and colonisation

How it happens

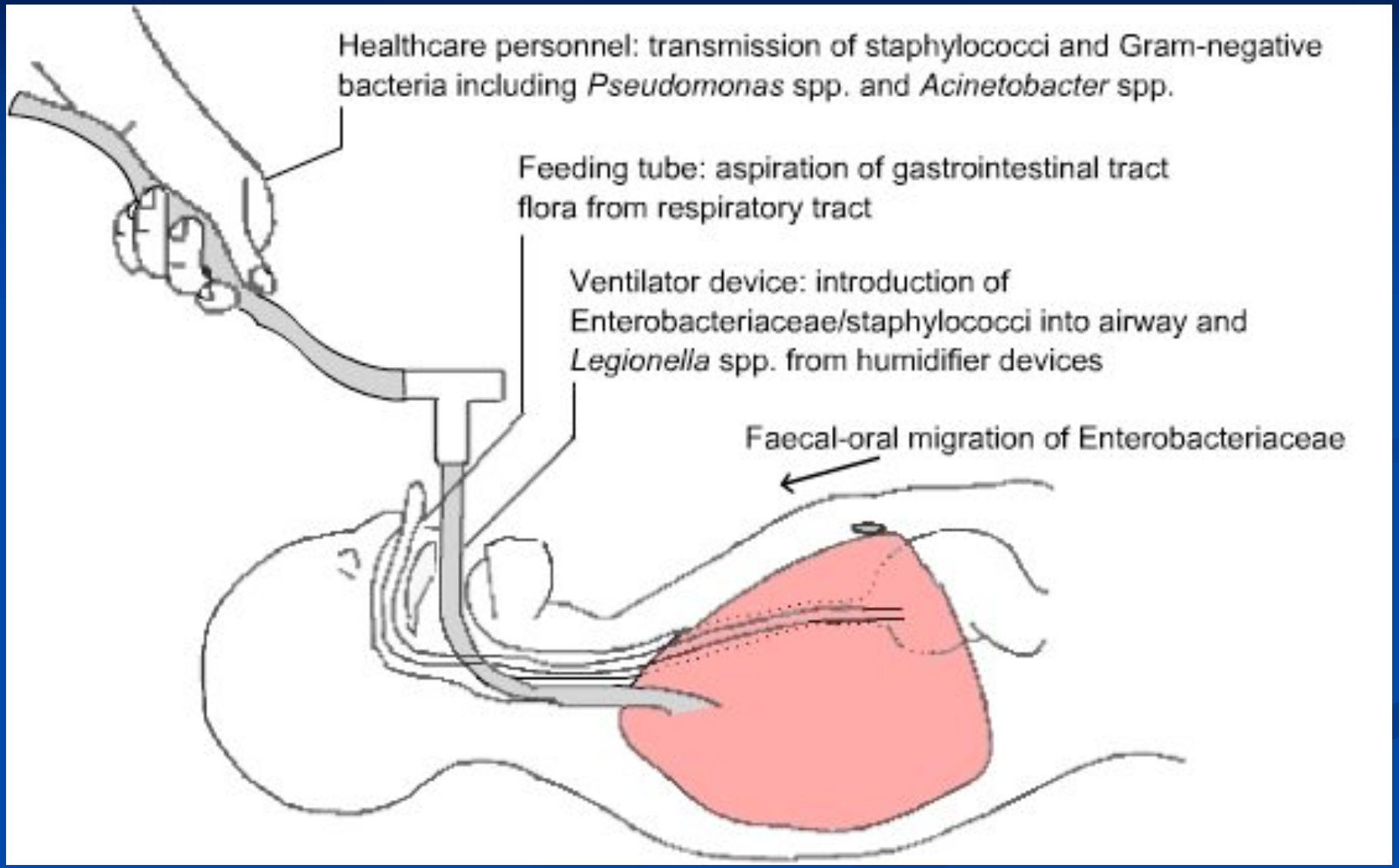
1. Upper respiratory tract becomes colonised
2. Bugs get to the lower respiratory tract from the upper respiratory tract: ventilator/suctioning
3. Pneumonia can result if large inoculum, virulent microbes, or impaired host defences
4. If bacterial infection becomes severe or invasive the inflammatory response causes systemic features of SIRS.

How does the upper airway become colonised?

"The gastropulmonary hypothesis"

- Stomach is a reservoir of EGNB, overgrowth moves retrogradely up into oropharynx and then may be aspirated into the lower respiratory tract
- Whose EGNB?
  - Patient's own endogenous EGNB
  - In ~50% cases from other patients on the ITU!

Probable routes of transmission of pathogens leading to VAP

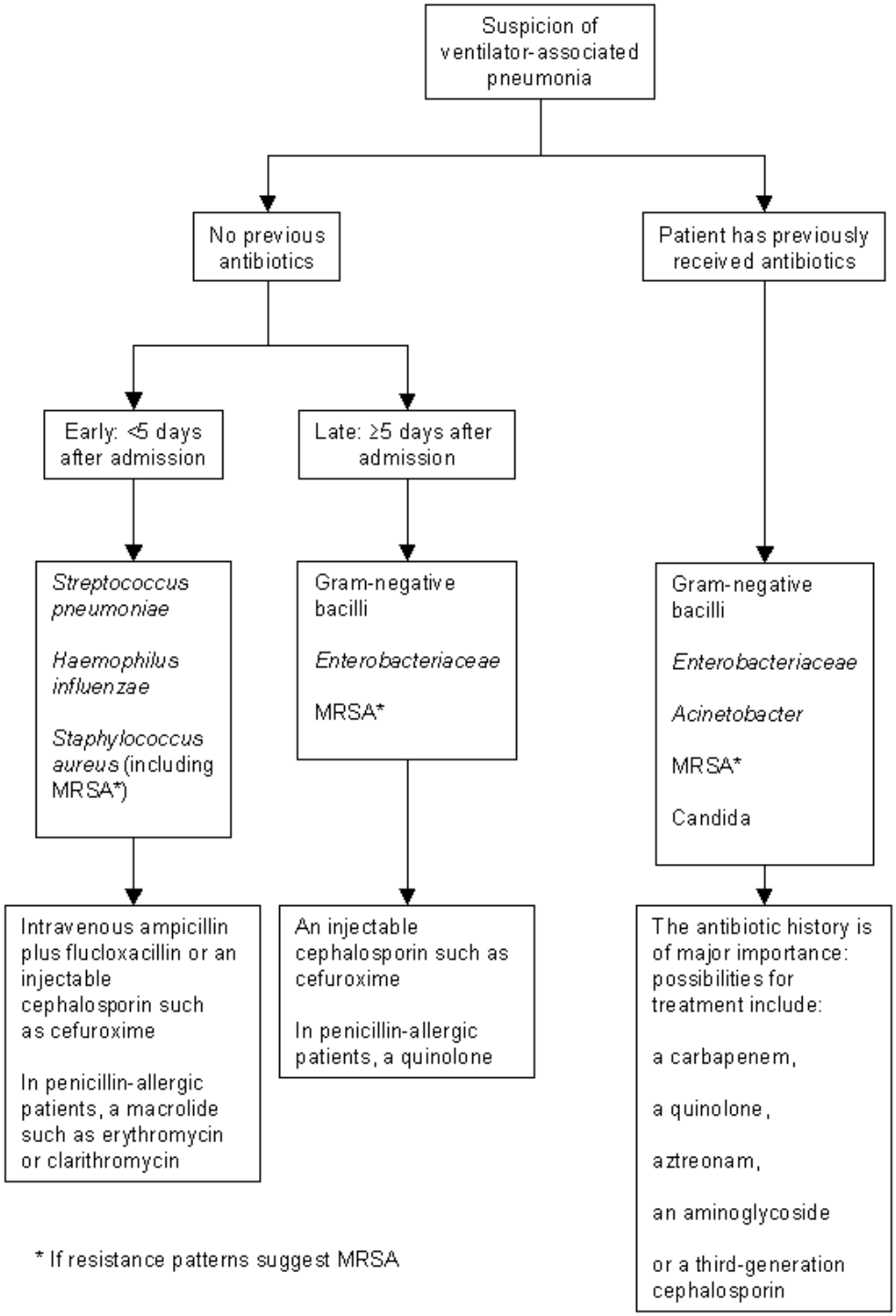


Antibiotic treatment

- When to start: Increased mortality if delays in Abx administration. Excess mortality of inappropriate Abx is not reduced on correction of regimens when culture results arrive 24-48hrs later.
- How long: However, there was a clear lack of consensus on the optimum duration of antibiotic treatment. Nearly all participants chose a seven- to 14-day range.
- How many Abx: Monotherapy for early, Combination therapy in late onset (>72 hrs)

Interesting antibiotics

- **Linezolid** is a oxazolidinone. Anti Gram positive only. Much better than Vanc for MRSA VAP (improved cure and survival), resistance has already been found. Vanc has poor lung penetration and problems with administration and VRSA. £450/day
- **Meropenem**, a carbapenem, Broad spectrum of activity which includes many aerobic and anaerobic Gram-positive and Gram-negative bacteria £60/day
- **Teicoplanin**, a glycopeptide, suitable for aerobic and anaerobic Gram-positive bacteria, £40-80/day
- **Aztreonam** is a monocyclic beta-lactam (‘monobactam') antibiotic with an antibacterial spectrum limited to Gram-negative aerobic bacteria . Up to £80/day
- **Tazocin** (piperacillin with the beta-lactamase inhibitor tazobactam) is an anti-pseudomonal penicillin. Good G negative cover. Synergistic with aminoglycosides. £45/day.


Suspicion of ventilator-associated pneumonia
No previous antibiotics
Patient has previously received antibiotics
Early: <5 days after admission
Late: ≥5 days after admission
Streptococcus pneumoniae
Haemophilus influenzae
Staphylococcus aureus (including MRSA*)
Gram-negative bacilli
Enterobacteriaceae
MRSA*
Gram-negative bacilli
Enterobacteriaceae
Acinetobacter
MRSA*
Candida
Intravenous ampicillin plus flucloxacillin or an injectable cephalosporin such as cefuroxime
In penicillin-allergic patients, a macrolide such as erythromycin or clarithromycin
An injectable cephalosporin such as cefuroxime
In penicillin-allergic patients, a quinolone
The antibiotic history is of major importance: possibilities for treatment include:
a carbapenem,
a quinolone,
aztreonam,
an aminoglycoside
or a third-generation cephalosporin
* If resistance patterns suggest MRSA

The Tarragona strategy

- **Start broad spectrum ABx immediately, high doses, tissue penetration paramount.**
- **De-escalate ABx once sensitivities known**
- **Specific agents should be based on previous treatments and responses i.e. individualised treatment.**

- Prolonged treatment does not prevent recurrences – don't do it
- Use direct staining of samples to guide initial therapy (if available)
- If COPD / more than 1 week ventilation – cover pseudomonas
- If GCS<8 suspect MSSA. Only suspect MRSA is patient previously had it
- Only cover yeasts if neutropenic, even if Candida grown
- Vancomycin for MRSA VAP never works well, use alternatives
- Guidelines should be updated regularly and customised to local bugs

Prognosis

- Crude mortality estimates from 24 to 76%
- Relative risk of in-hospital death (relative to patients who do not get VAP) of 1.7 to 4.

- Many studies in this area, conflicting results.
- Easy to show association between label of VAP and mortality but difficult to prove causal relationship.

Prevention of VAP

- What has evidence that it helps?
  - Avoiding Intubation, use NIV. Reintubation
  - Avoiding Supine posture - always 30-45° head up.
  - Physiotherapy (small trial)
- No good evidence with respect to:
  - Oral or nasal tracheal intubation
  - Type/route of enteral feed
  - Gastric pH increasing drugs (may increase risk)
  - Frequency of suctioning
  - Humidification of ventilator gases (heated wire worse)
- Systemic antibiotics and SDD...

Selective Digestive Decontamination

- VAP often have an endogenous source of infection. Colonisation of the digestive tract and the oropharynx correlates with development of VAP
- SDD = Selectively eliminating potentially pathogenic organisms (not normal anaerobic flora) in the digestive tract and oropharynx with the aim of decreasing the incidence of VAP and it's associated mortality

- SDD usually involves:
  - Topical application of non absorbable agents (such as polymyxin B, tobramycin and amphotericin B) that have activity against G negative organisms and fungi.
  - Initial use of broad spectrum IV antibiotics for 3-4 days, such as cefotazime.
- Potential benefits:
  - Decreased VAP, improved mortality, less time in ITU
- Potential problems:
  - Increased resistant organisms, cost, side effects.

24% vs 31% mortality (p=0.02)

- E de Jonge, The Lancet, 2003
- 934 mixed (med and surg) ITU patients
- Prospective randomised non blinded
- Control (standard) vs SDD (daily oral/enteral Abx, 4 days IV cefotaxime)
- Endpoints: ITU and hospital mortality, days in ICU.
- All significantly decreased in SDD group
- Also found no increase in resistant organisms
- BUT: Hospital in Netherlands, MRSA incidence 0%

Summary

- VAP is common and serious and requires aggressive treatment with broad spectrum antibiotics, these should be de-escalated once sensitivities known
- Interpret tracheal aspirates results with caution
- Sit patients head up and avoid intubation (or reintubation) if possible
- SDD would be recommended if MRSA and VRE rates were low enough

Thanks

References

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