NOSOCOMIAL INFECTION IN NEUROCRITICAL CARE

OVERVIEW

- Introduction.
- Pneumonia.
- Bacteremia.
- Urinary tract infection.
- Ventriculitis.
- Subdural empyema.
- Brain abscess.
- Meningitis and encephalitis.

INTRODUCTION

- **Nosocomial infections** can be defined as those occurring within 48 hours of hospital admission, 3 days of discharge or 30 days of an operation.

- The reported incidence in the neurointensive care unit (NICU) ranges from **20% to 30%.**

- The incidence of **post neurosurgical wound infection** is from <1 to 8%, with reported mortality as high as 14%

- Infection risk **is increased** in NICU patients **due to –**
  - ✓ Medication side-effects
  - ✓ Catheter and line placement
  - ✓ External ventricular drains and ventilators
  - ✓ Neurosurgical procedures
  - ✓ Acquired immune suppression secondary to steroid/barbiturate use and brain injury itself.

- These infections are associated with **increased length of hospital stay and increased morbidity and mortality.**

- The **blood–brain barrier** presents a challenge to antimicrobial selection and infection treatment.
- **Prevents large molecules** from penetrating into cerebrospinal fluid (CSF).
- **Limits** the number of antimicrobials available for treating CNS infection.
- This makes it critical to identify whether a infection is **intra-axial or extra-axial**.
- Antibiotics that effectively enter the CNS are unfortunately often associated with **CNS toxicities –**

✓ **Encephalopathy** are beta-lactam antibiotics (penicillins, cephalosporins, and carbapenems), quinolones, and metronidazole.

Table 1 CNS properties of selected antimicrobials and antivirals by class. Adapted from Mayo Clinic Antimicrobial Guide [2]

Antibiotic class	Degree of CNS penetration	Dose adjustment required for CNS infections
Aminoglycosides	Poor	Not applicable
Carbapenems	Fair	No
Cephalosporins		Higher-range dosing needed for selected agents
First generation	Poor	
Second generation	Poor	
Third generation	Fair	
Fourth generation	Fair	
Aztreonam	Fair	No
Beta-lactams	Poor to fair	Higher-range dosing needed for selected agents
Penicillin		
Aminopenicillins		
Beta-lactam/beta-lactamase inhibitors		
Quinolones	Fair	No
Tetracyclines		No
Doxycycline	Fair to good	
Minocycline	Fair to good	
Tetracycline	Poor	
Tigecycline	Insufficient data	

Colistin	Poor	Unknown
Daptomycin	Unknown	Unknown
Linezolid	Good	No
Metronidazole	Good	No
Trimethoprim/sulfamethoxazole	Good	No
Vancomycin	Poor to fair	Yes, aim for serum trough of 15–20 mcg/mL to achieve higher levels in the CNS
Antitubercular agents		
Ethambutol	Fair	No
Isoniazid	Good	No
Pyrazinamide	Good	No
Rifamycins	Fair	No
Antifungals		
Amphotericin B (liposomal or conventional)	Poor	No; use in concert with other agents (e.g., flucytosine)
Echinocandins	Poor	Not applicable
Azoles		No
Fluconazole	Good	
Itraconazole	Poor	
Voriconazole	Good	
Posaconazole	Poor	

Flucytosine	Good	No
Antivirals		
Acyclovir	Good	No
Cidofovir	Poor	Not applicable
Foscarnet	Fair	No
Famciclovir	Unknown	Not applicable
Ganciclovir	Unknown	Not applicable
Valacyclovir	Fair	No

CNS Central nervous system

- ✓ Fortunately, the **encephalopathy is reversible** with discontinuation of the medication.
- ✓ **Seizures** have been reported with beta-lactams and fluoroquinolones.
- ✓ Aminoglycosides and polymyxins (colistin, polymyxin B) can cause a **neuromuscular blockade -like effect.**
- ✓ **Older age, renal failure, and higher doses** are risk factors that increase neurotoxicity.

PNEUMONIA
(Ventilator Associated Pneumonia)

- **Ventilator-associated pneumonia (VAP)** is defined as pneumonia that occurs 48 hours after endotracheal intubation.

- **Early VAP** occurs **within 5–7 days** of mechanical ventilation.

- **Late VAP** occurs more than 5–7 days of mechanical ventilation.

- It contributes to **half of all cases of hospital acquired pneumonia** (HAP).

- VAP is estimated to occur in **9–27% of all mechanically ventilated patients**.

- All-cause mortality associated with VAP ranges from **20 to 50%** in different studies, but the **attributable mortality is 9–13%.**

- **The factors associated with increased mortality are:**
  - ✓ Bacteraemia,
  - ✓ Shock,
  - ✓ Coma,
  - ✓ Respiratory failure,
  - ✓ ARDS,
  - ✓ Severe underlying comorbid disease, and
  - ✓ Infection with MDR organisms.

- The **risk of VAP is approximately 1%/day, being higher in initial days**, and this decreases as time passes to 3% in the first 5 days, then 2% between the fifth to tenth days, and then 1%/day of mechanical ventilation.

- The United States Centre for Disease Control and Prevention (CDC) has adopted a new method of ICU surveillance.

- Employing **ventilator-associated events (VAE)** as a potential metric to **assess quality of care in ICU.**

- **VAE include –**
  - ✓Ventilator-associated complications (VAC),
  - ✓Infection-related ventilator-associated complications (IVAC),
  - ✓Possible and probable VAP.

- These definitions are **used for surveillance** and quality improvement of the ICUs.

- These definitions fail to detect many patients with VAP and **do not aid in management at the bedside level.**

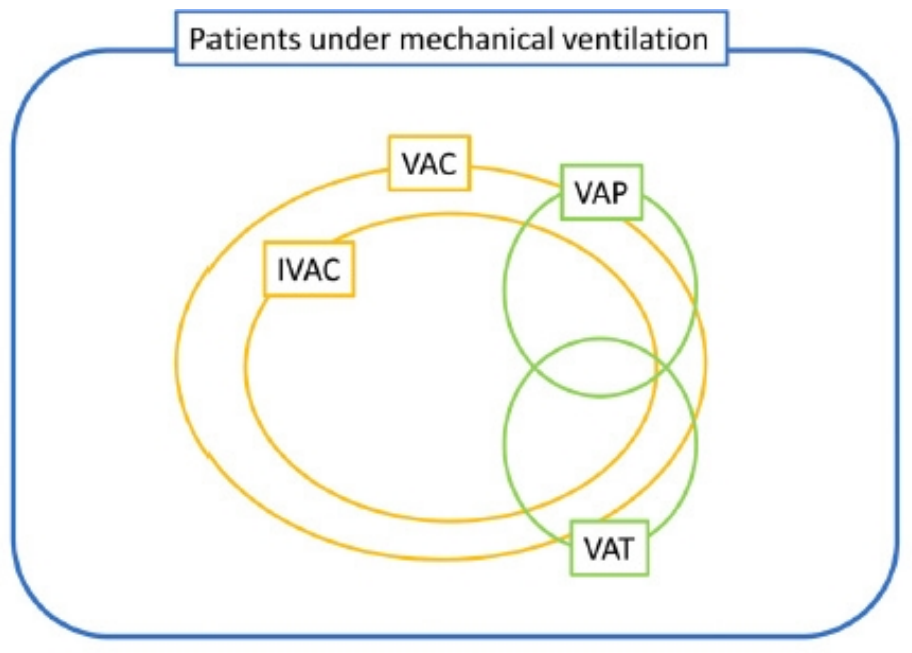


Figure 2. Ventilator-associated events, definitions, and nosology. *Ventilator-associated conditions (VACs)*: at least 2 calendar days of stable or decreasing daily minimum positive end-expiratory pressure (PEEP) or fraction of inspired oxygen (FiO_2) followed by rise in PEEP of at least 3 cm H_2O or rise in FiO_2 of at least 20 points sustained for at least 2 days. *Infection-related ventilator-associated complications (IVACs)*: VAC plus: temperature of less than 36°C or more than 38°C OR white blood cell (WBC) count of not more than 4 or at least 12×10^3 cells/mm^3 AND at least one new antibiotics continued for at least 4 days WITHIN 2 days of VAC onset EXCLUDING first 2 days on the ventilator. *Possible ventilator-associated pneumonia (VAP) (Centers for Disease Control and Prevention [CDC] definitions)*: IVAC plus: criterion 1: Positive culture meeting specific quantitative or semi-quantitative threshold; criterion 2: Purulent respiratory secretions AND identification of organisms NOT meeting the quantitative or semi-quantitative thresholds; criterion 3: Organisms identified from pleural fluid specimen, positive lung histopathology, and positive diagnostic test for Legionella species or selected respiratory viruses WITHIN 2 days of VAC onset EXCLUDING first 2 days on the ventilator. (The updated January 2017 definitions and comprehensive examples are detailed in the CDC National Healthcare Society Network website; https://www.cdc.gov/nhsn/pdfs/pscmanual/10-vae_final.pdf; accessed 23 October 2017.) *VAP*: radiographic criteria (new or progressive and persistent infiltrates or consolidation or cavitation); systemic criteria (temperature of less than 36°C or more than 38°C OR WBC count of not more than 4 or at least 12×10^3 cells/mm^3); pulmonary criteria (at least one of the following: (1) new onset or increase of purulent aspirates and (2) worsening gas exchange). *Ventilator-associated tracheobronchitis (VAT)*: criteria for VAP but without radiographic criteria.

Table 1. Risk factors of ventilator-associated pneumonia.

Host-related risk factors	Intervention-related risk factors
Medical history and underlying illness	Peri-operative transfusion of blood products
Male gender	Duration of the mechanical ventilation
Extreme age	Reintubation
Prior central nervous system disorder	Supine head position in patients receiving enteral nutrition
Immunocompromised	Antibiotic therapy[a]
Acute underlying diseases	Enteral nutrition
Emergent surgery	Absence of subglottic secretion drainage[b]
Neurosurgery	Intra-hospital transports
Thoracic surgery	Continuous sedation, use of paralytic agents
Cardiac surgery	Nasogastric tubes
Burns	Tracheostomy
Re-intervention	Frequent ventilator circuit changes
Acute severity factors	Intracuff pressure of less than 20 cm H_2O
Organ system failure index of at least 3	
Acute renal failure	
Acute respiratory distress syndrome	
ECMO, intra-aortic support	
Ulcer disease	

Adapted from 2,35–38. [a]Antibiotic therapy protects from early-onset pneumonia due to susceptible bacteria but is a risk factor for late-onset pneumonia due to more resistant organisms. [b]Protective impact of subglottic secretion drainage is mainly demonstrated for cardiac surgery patients. ECMO, extra-corporeal membrane oxygenation.

Intravenous antibiotic use within the previous 90 days
Septic shock at the time of VAP
Acute respiratory distress syndrome (ARDS) preceding the development of VAP
More than 5 days of hospitalisation prior to the development of VAP
Patient requiring acute renal replacement therapy prior to the development of VAP

Table 2. Risk Factors for Multidrug–resistant Ventilator-associated Pneumonia (VAP)[6]

- The presence of **neurologic disease** has been identified as an **independent risk** factor for development of VAP and **for failure of VAP resolution** with initial antibiotic therapy.

- Neurologic patients are particularly vulnerable to pneumonia due to **decreased consciousness, dysphagia, and impaired protective airway reflexes**.

- **Pathogenesis –**

✓ **Micro and macro aspiration** of the colonized oropharyngeal secretions across the tracheal tube cuff.

✓ The bacteria can also **adhere to the internal surface of the tube** forming a biofilm and translocate into the lungs with inspiration.

✓ Patients can be **colonized** either –

- **Exogenously** from the hand, equipment, invasive devices and hospital environment, or
- **Endogenously** from the organisms present in the oropharynx, tracheal tube and gastrointestinal tract.

✓ In normal individuals, there are **various defence mechanisms** to prevent translocation of pathogen in the lower airways like -

- Adduction of true and false vocal cords,
- Cough reflex,
- Mucociliary clearance in the upper airways.

✓ However, these body defence mechanisms are **impaired in intubated patients.**

- **Causative organisms –**

✓ **Early-onset VAP, occurring within 4 days** of intubation, is usually attributed to antibiotic sensitive pathogens.

✓ **Late-onset VAP occurring later than 4 days** after intubation is more likely caused by multidrug resistant (MDR) pathogens.

Pathogens that caused ventilator-associated pneumonia (VAP) with their frequency in hospital-acquired pneumonia

VAP pathogens	Frequency
Pseudomonas	24.4%
Staphylococcus aureus	20.4%
Enterobacteriaceae (*Klebsiella* spp., *Escherichia coli*, *Proteus* spp., *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp.)	14.1%
Streptococcus species	12.1%
Haemophilus species	9.8%
Acinetobacter species	7.9%
Neisseria species	2.6%
Coagulase-negative staphylococcus	1.4%
Others (*Corynebacterium*, *Moraxella*, *Enterococcus*, fungi, virus)	4.7%

Organisms	Frequency
Gram-Negative Bacilli	56.5%
Pseudomonas aeruginosa	18.9%
Escherichia coli	9.2%
Hemophilus spp	7.1%
Enterobacter spp	3.8%
Proteus	3.8%
Klebsiella pneumoniae	3.2%
Others	10.5%
Gram-Positive Cocci	42.1%
Staphylococcus aureus	18.9%
Streptococcus pneumoniae	13.2%
Hemophilus spp	1.4%
Others	8.6%
Fungal Isolates	1.3%

From Chastre J. et al. JAMA 2003; 290:2558.

- **Diagnosis –**

✓The clinical diagnosis of VAP is difficult because clinical findings are **non-specific.**

✓At present, there is **no universally accepted gold standard** criteria for VAP.

✓**IDSA/ATS 2016 guidelines** for management of VAP recommend **clinical diagnosis** of VAP based upon -

- ➢A new lung infiltrate **PLUS**
- ➢Clinical features suggesting infectious nature of the infiltrate like new onset of fever, purulent secretions, leukocytosis and decline in oxygenation.

✓Unfortunately, in patients who are suspected of having VAP based on these clinical criteria, the incidence of pneumonia on post-mortem exam is **only 30% to 40%.**

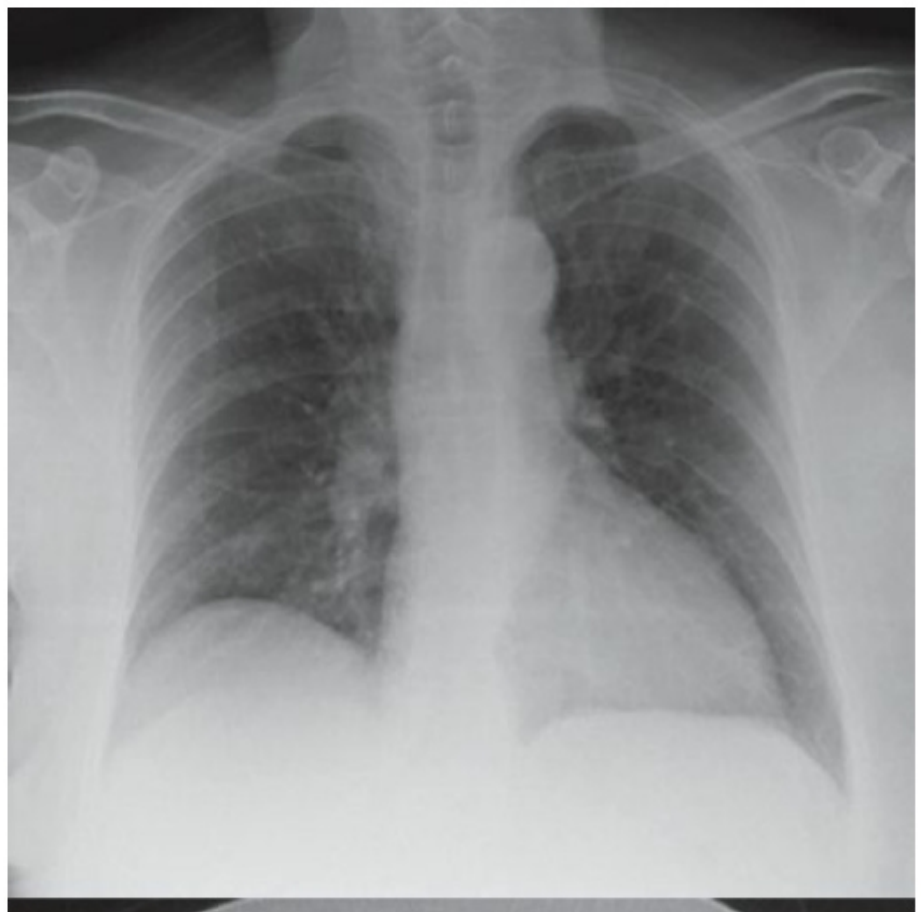
✓**The limited diagnostic accuracy** in VAP is primarily due to the **nonspecific nature of pulmonary infiltrates**.

✓Pneumonia accounts for **only one-third** of all pulmonary infiltrates in ICU patients.

✓**Differential diagnosis of pulmonary infiltrates** includes –

- ➢Aspiration pneumonitis
- ➢Pulmonary embolism
- ➢Pulmonary hemorrhage
- ➢Acute respiratory distress syndrome
- ➢Infiltrative tumor
- ➢Lung contusion
- ➢Radiation pneumonitis
- ➢Congestive heart failure.

- ✓ The **other limitation of chest radiography** is a limited sensitivity for the detection of pulmonary infiltrates.



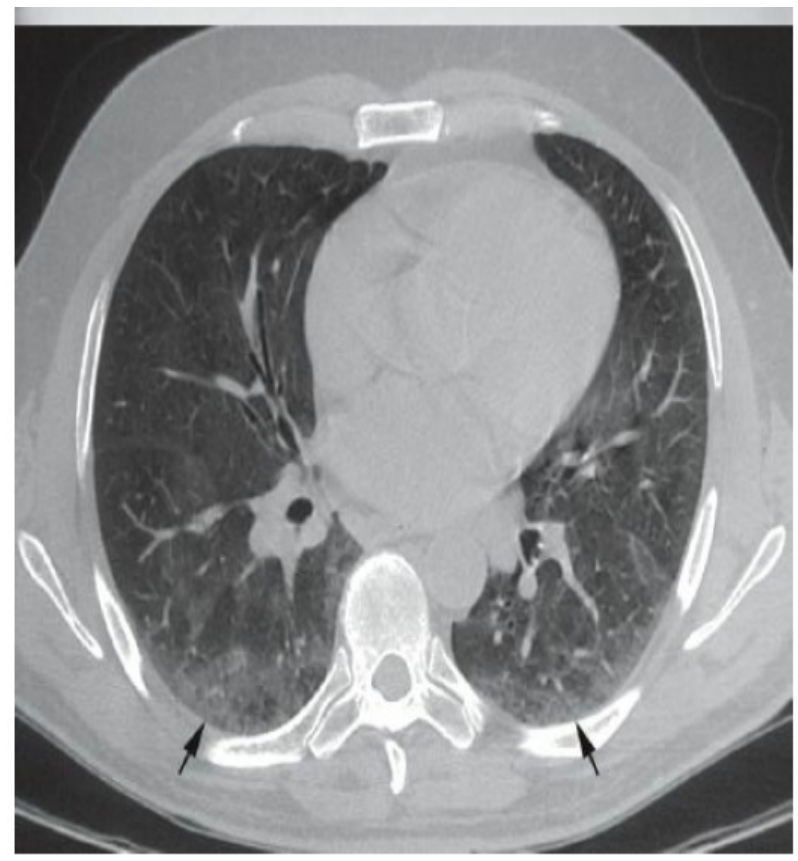


FIGURE 29.3 Demonstration of the limited sensitivity of portable chest radiography in the detection of pulmonary infiltrates. A portable chest x-ray of a patient with fever shows no apparent pulmonary infiltrates, while the CT image from the same patient reveals infiltrates in the posterior region of both lungs (indicated by the arrows).

- ✓ **Blood cultures have limited value** in the diagnosis of VAP because organisms isolated from blood in cases of suspected VAP are often from extrapulmonary sites of origin.

- ✓ Diagnosis is confirmed when **lower respiratory tract sampling identifies a pathogen**.

- ✓ Guidelines recommend obtaining **lower respiratory tract samples** for culture and microbiology, ideally before antibiotics are started or when it is changed.

- ✓ There are two methods of sampling of the respiratory tract—**invasive and non-invasive.**

  - ➢ **Non-invasive** sampling refers to endotracheal aspirates.

  - ➢ **Invasive** involves bronchoscopic bronchoalveolar lavage (BAL), protected specimen brushing (PSB) and blind bronchial sampling, i.e., miniBAL.

Qualitative Cultures

The standard practice is to perform qualitative cultures on endotracheal aspirates (where the growth of organisms is reported, but there is no assessment of growth density). These cultures have a high sensitivity (usually >90%) but a very low specificity (15–40%) for the diagnosis of VAP (22). This means that for qualitative cultures of tracheal aspirates, a negative culture can be used to exclude the diagnosis of VAP, but a positive culture cannot be used to confirm the presence of VAP. The poor predictive value of positive cultures is due to contamination of tracheal aspirates with secretions from the mouth and upper airways.

Quantitative Cultures

For quantitative cultures of tracheal aspirates (where growth density on the culture plate is reported), the threshold growth for the diagnosis of VAP is 10^5 colony-forming units per mL (CFU/mL). This threshold has a sensitivity and specificity of 76% and 75%, respectively, for the diagnosis of VAP (see Table 29.3) (2,22). Comparing these results to the sensitivity and specificity of qualitative cultures (i.e., sensitivity >90% and specificity ≤40%) shows that, for cultures of tracheal aspirates, quantitative cultures are less sensitive but more specific than qualitative cultures for the diagnosis of VAP.

Table 29.3 Quantitative Cultures for the Diagnosis of Pneumonia in Ventilator-Dependent Patients

	TA	PSB	BAL
Diagnostic Threshhold (CFU/mL)	10^5	10^3	10^4
Sensitivity (mean)	76%	66%	73%
Specificity (mean)	75%	90%	82%
Relative Performance	Most Sensitive	Most Specific	Most Accurate

Abbreviations: TA = tracheal aspirates; PSB = protected specimen brushings; BAL = bronchoalveolar lavage.

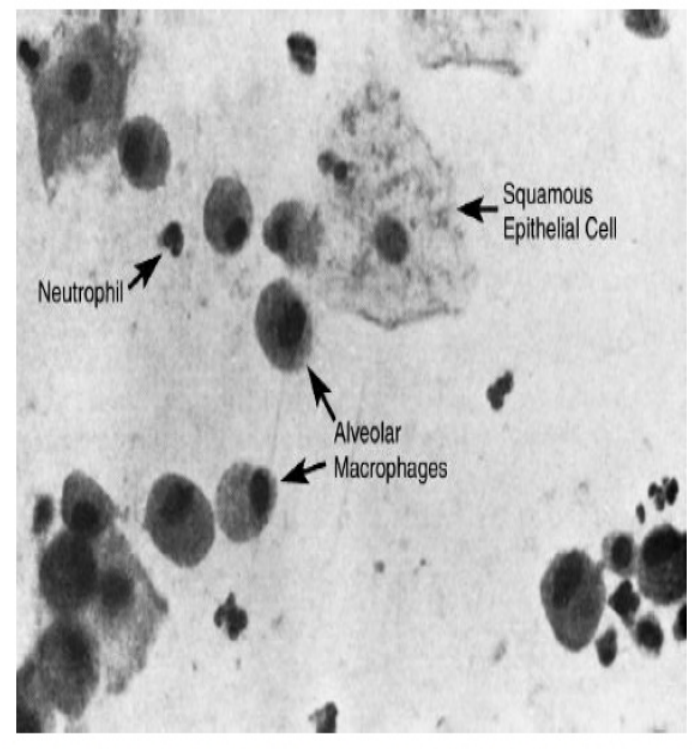
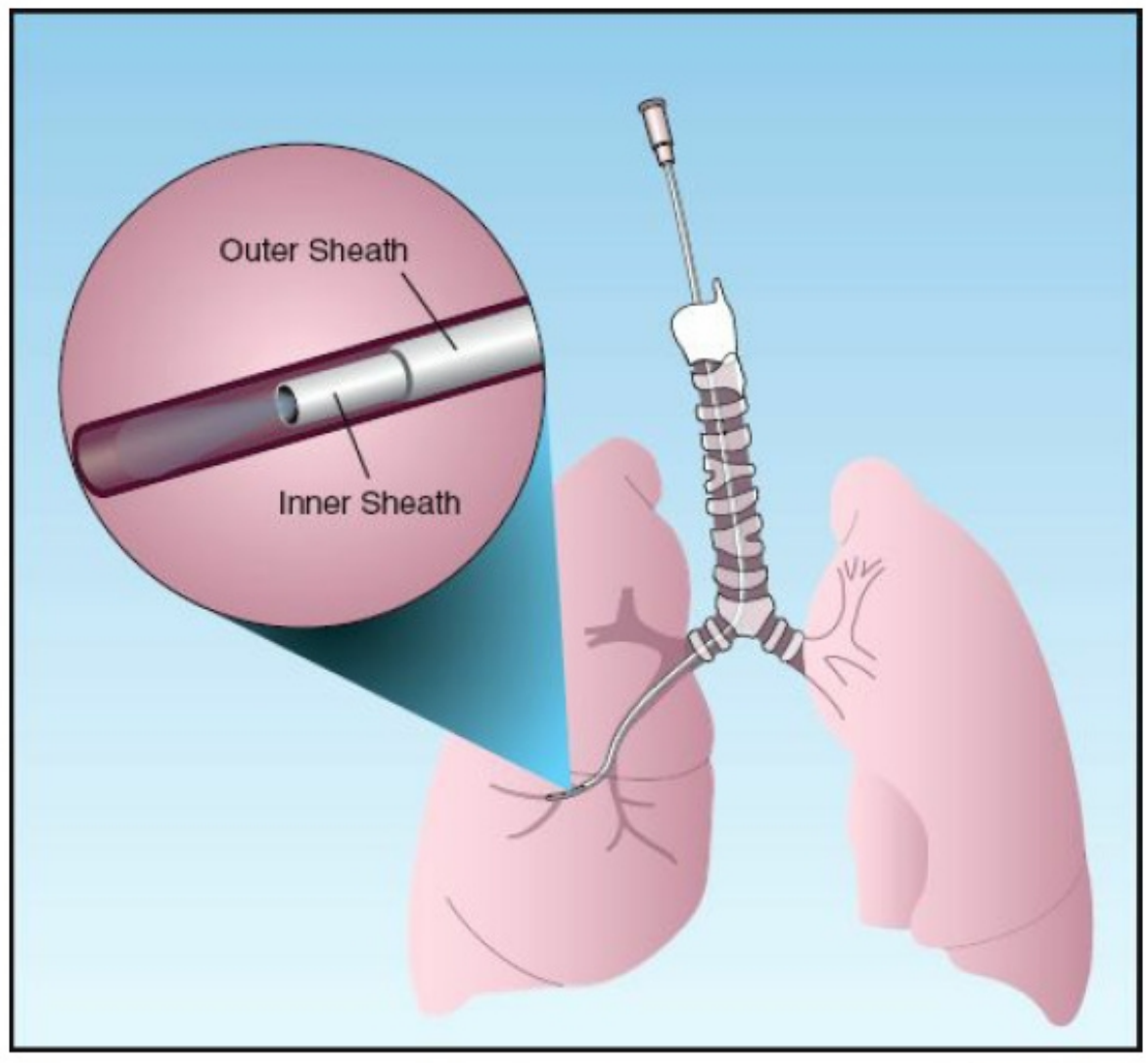


FIGURE 29.5 Microscopic appearance (magnification 400) of bronchial brushings from a ventilator-dependent patient. The paucity of squamous epithelial cells and the presence of alveolar macrophages is evidence that the specimen is from the distal airways (and thus would be an appropriate specimen for culture in a case of suspected VAP).

- ✓ **A positive microbiological sample in a patient with normal chest radiograph suggests tracheobronchitis.**



- ✓ IDSA 2016 guidelines recommend using clinical criteria alone for starting antibiotics in patients with suspected VAP and **not on serum procalcitonin level plus clinical criteria**.

- ✓ **Procalcitonin levels can be useful -**
  - ➢ To stop/discontinue antibiotic therapy in patients with confirmed VAP, and
  - ➢ Can also be used as a prognostic marker.

- ✓ **Other diagnostic methods** which have been in use to diagnose VAP include –
  - ➢ Clinical pulmonary infection score (CPIS),
  - ➢ HELICS criteria, and
  - ➢ Johannson criteria.

- ✓ **Clinical pulmonary infection score (CPIS) –**
  - ➢ The maximum score is 12 and a score > 6 is diagnostic of VAP.
  - ➢ Sensitivity and specificity of only 65% and 64%, respectively.

Table 20.1

The clinical pulmonary infection score (CPIS)

Assessed parameter	Result	Score
Temperature (°C)	36.5–38.4°C	0
	38.5–38.9°C	1
	≤36 or ≥39°C	2
Leukocytes in blood (cells/mm^3)	4000–11 000/mm^3	0
	<4000 or >11 000/mm^3	1
	≥500 band cells	2
Tracheal secretions (subjective visual scale)	None	0
	Mild/nonpurulent	1
	Purulent	2
Radiographic findings (on chest radiography, excluding CHF and ARDS)	No infiltrate	0
	Diffuse/patchy infiltrate	1
	Localized infiltrate	2
Culture results (endotracheal aspirate)	No or mild growth	0
	Moderate or florid growth and pathogen consistent with Gram stain	2
Oxygenation status (defined by Pa_{O_2}: Fi_{O_2})	>240 or ARDS	0
	≤240 and absence of ARDS	2

Adapted from Kalanuria et al. (2014).
CHF, congestive heart failure; ARDS, acute respiratory distress syndrome.

- ✓ **The HELICS criteria** are used for VAP surveillance in Europe –

HELICS case definition of pneumonia (2003) – also in ECDC PPS protocol

X-ray(s) + clinical symptoms (t°/wbc + sput./ronchi…)

- PN1: protected sample + quantitative culture (10^4 CFU/ml BAL/10^3 PB,DPA)
- PN2: non-protected sample (ETA) + quantitative culture (10^6 CFU/ml)
- PN3: alternative microbiological criteria
- PN4: sputum bacteriology or non-quantitative ETA
- PN5: no microbiological criterion

- ✓ **The Johannson criteria –**
  - ➢ Sensitivity and specificity of these criteria are 69% and 75%, respectively.
  - ➢ New/progressive infiltrates on chest X-ray associated with at least 2 of 3 clinical features—leucocytosis, purulent secretions and temperature greater than 38 °C.
- ✓ The **diagnosis of VAP is more problematic in neuro-ICU** due to ubiquitous nature of clinical findings related to primary brain injury.

- **Differential diagnosis -**

1. Ventilator-associated tracheobronchitis (VAT): VAT is characterized by signs of respiratory infection such as increase in volume and purulence of the secretions, fever, leukocytosis but no radiological infiltrates suggestive of consolidation in chest X-ray. No antibiotic therapy is recommended for patients with VAT. It leads to more antibiotic resistance than benefits.
2. Aspiration pneumonitis: This can be differentiated from VAP by history and microscopic analysis of respiratory secretions. Aspiration pneumonitis can get secondarily infected with organisms leading to aspiration pneumonia.
3. Pulmonary embolism with infarction: The clinical features in embolism may suggest risk factors for embolism in these cases.
4. Acute respiratory distress syndrome (ARDS): The patients with ARDS will have negative cultures of respiratory secretions.
5. Pulmonary haemorrhage: There will be frank bleeding in cases of pulmonary haemorrhage and blood mixed with purulent secretions in VAP.
6. Lung contusion: The patient would have history of trauma along with negative cultures.

- **Treatment –**

- The **duration of therapy** is guided by clinical response.

✓For early-onset VAP is 8 days.

✓For late-onset VAP it is 8 to 14 days.

Comparison of recommended initial empiric therapy for ventilator-associated pneumonia (VAP) according to time of onset

Early-onset VAP	Late-onset VAP
Second- or third-generation cephalosporin, e.g.: Ceftriaxone: 2 grams daily Cefuroxime: 1.5 grams every 8 hours Cefotaxime: 2 grams every 8 hours or Fluoroquinolones e.g., Levofloxacin: 750 mg daily Moxifloxacin: 400 mg daily or Aminopenicillin+beta-lactamase inhibitor, e.g., Ampicillin+sulbactam: 3 grams every 8 hours or Ertapenem 1 gram daily	Cephalosporin e.g., Cefepime: 1–2 grams every 8 hours Ceftazidime 2 grams every 8 hours or Carbapenem e.g., Imipenem+cilastin: 500 mg every 6 hours or 1 gram every 8 hours Meropenem: 1 gram every 8 hours or Beta-lactam/beta-lactamase inhibitor e.g., Piperacillin+tazobactam: 4.5 grams every 6 hours plus Aminoglycoside e.g., Amikacin: 20 mg/kg/day Gentamicin: 7 mg/kg/day Tobramycin: 7 mg/kg/day or Antipseudomonal fluoroquinolone e.g., Ciprofloxacin 400 mg every 8 hours Levofloxacin 750 mg daily plus Coverage for MRSA e.g., vancomycin 15 mg/kg every 12 hours or Linezolid 600 mg every 12 hours

Table 2. Empirical treatment of hospital-acquired pneumonia/ventilator-associated pneumonia.

Not at high risk of mortality and no risk factors[a]	Not at high risk of mortality but with factors increasing the likelihood of Gram-negative bacteria	High risk of mortality or receipt of intravenous antibiotics during the prior 90 days
One of the following: Piperacillin-tazobactam 4.5 g IV q6h OR Cefepime 2 g IV q8h Levofloxacin 750 mg IV daily	Piperacillin-tazobactam 4.5 g IV q6h OR Cefepime or ceftazidime 2 g IV q8h OR Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h OR Imipenem 1g IV q8h Meropenem 1 g IV q6h	Piperacillin-tazobactam 4.5 g IV q6h OR Cefepime or ceftazidime 2 g IV q8h OR Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h OR Imipenem 1g IV q8h Meropenem 1 g IV q6h AND Amikacin 25 (30) mg/kg IV daily OR Gentamicin 5–7 mg/kg IV daily OR Tobramycin 5–7 mg/kg IV daily
Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness) OR Linezolid 600 mg IV q12h		Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness) OR Linezolid 600 mg IV q12h

Adapted from Infectious Diseases Society of America/American Thoracic Society guidelines[7]. [a]Risk factors of multidrug-resistant ventilator-associated pneumonia (VAP) are prior intravenous use within 90 days, septic shock at VAP onset, acute respiratory distress syndrome preceding VAP, five or more days of hospitalization prior to VAP onset, and acute renal replacement therapy prior to VAP onset. IV, intravenous; q, every.

- **Prevention:**

The various modalities used to prevent VAP are as follows:

1. Head-up position: As aspiration of pathogens is the main cause of VAP, preventing aspiration in intubated patients must be a priority. There is evidence that patients in supine position have more chances of aspiration of gastric contents than patients in head-up position [64, 65]. The head end of the bed should be elevated to 30–45° [66].
2. Subglottic suction device: Endotracheal or tracheostomy tubes with subglottic suction tube should be used in patients who are expected to require more than 48 h of mechanical ventilation [66]. The secretions pooled over the cuff of the tube may get aspirated. Studies have shown that patients with these tubes have lesser VAP rate, reduced duration of mechanical ventilation and reduced ICU stay [67].
3. Oral care: Oral care with chlorhexidine mouthwash has proven its role in reducing VAP [68] and so should be used regularly in intubated patients.
4. Strict hand hygiene: The biofilm formation on the tube can be reduced by strict hand hygiene practices, closed suction systems and use of heat and moisture exchangers.
5. Reducing the duration of mechanical ventilation: This can be achieved by daily sedation vacation and spontaneous breathing trials and assessment of readiness to extubate.

Various studies have been conducted on other modalities but no conclusive results were presented. Selective decontamination of the digestive tract may increase the growth of resistant bacteria and so it is not widely practiced [69, 70]. Similarly, administration of probiotics and use of silver-coated endotracheal tubes have not shown promising results in the form of any significant decrease in the VAP rate or days on mechanical ventilation or hospital stay and are not recommended.

Preventative Aim	Preventative Measure
Reducing aspiration	Nurse in a semirecumbent position (30°-45°) Maintain tracheal tube cuff pressure >20 cm H_2O Subglottic tube insertion for patients requiring mechanical ventilation >72 hours Avoid unnecessary endotracheal tube changes
Optimising the patient's microbial ecology	Stop stress ulcer prophylaxis in low-risk patients Basic oral hygiene Infection control (eg, hand hygiene) Avoid unnecessary circuit changes
Minimising the duration of mechanical ventilation	Daily sedation breaks Daily assessment for extubation
Optimising unit microbial ecology	Monitor VAP rates Local input from Microbiology regarding antimicrobial selection and antimicrobial resistance patterns

Table 3. Example of Ventilator-associated Pneumonia (VAP) Prevention Bundle

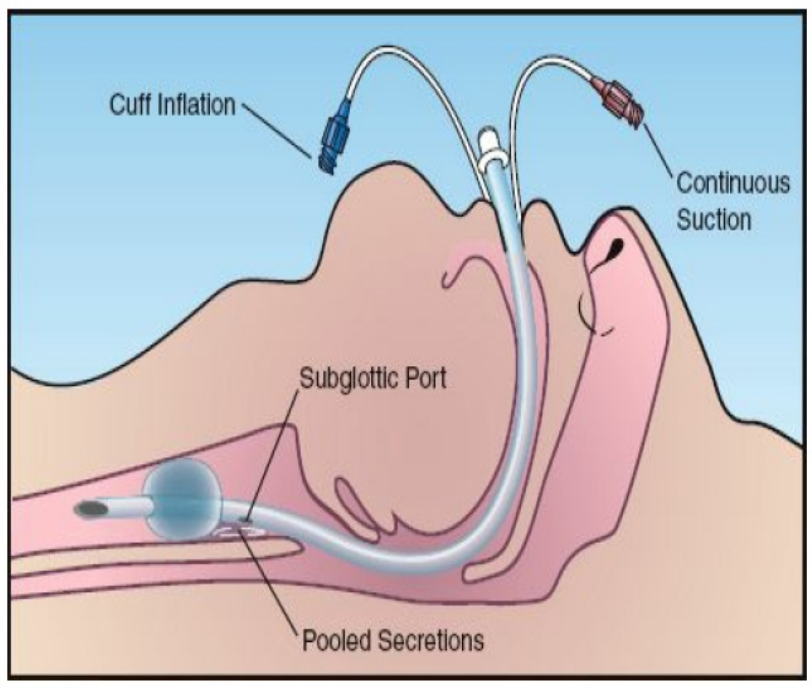


FIGURE 29.1 Endotracheal tube with a suction port placed just above the cuff to clear secretions that accumulate in the subglottic region.

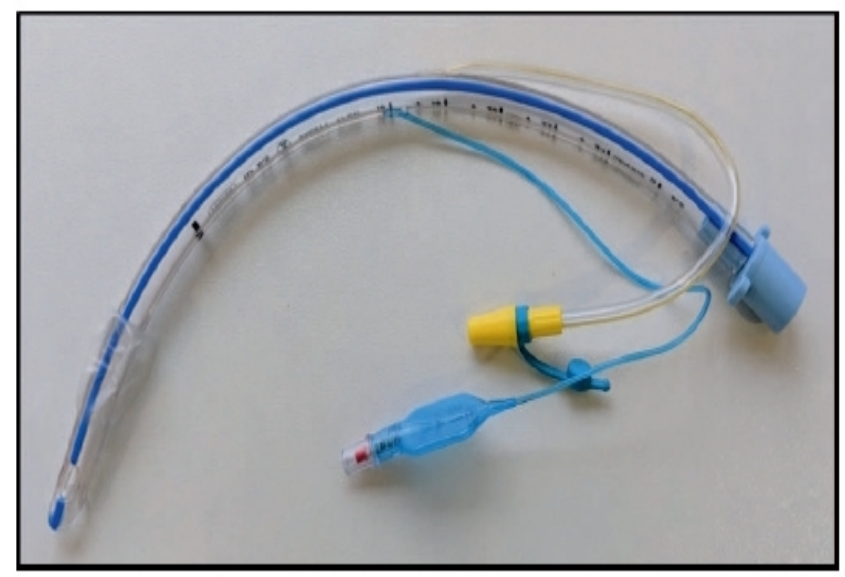


Figure 1. Endotracheal tube with the yellow subglottic suction line (manufactured by Smiths Medical).

BACTEREMIA

- Bacteremia is the **second most common HAI** in the NICU.
- The **crude mortality rate** resulting from bacteremia has been estimated at **27%.**
- **Risk factors** for bacteremia include –
  - ✓Intravascular catheter placement
  - ✓Host factors such as immunosuppression, older age, malnutrition, and total parenteral nutrition.
- The **risk** for catheter-related bacteremia (CRB) (per 1000 catheter days, with 95% confidence intervals) has been estimated at –
  - ✓2.7 (2.6–2.9) for noncuffed CVCs,
  - ✓1.7 (1.2–2.3) for arterial catheters,
  - ✓1.6 (1.5–1.7) for cuffed and tunneled CVCs, and
  - ✓1.1 (0.9–1.3) for peripherally inserted central catheters.

- **Aseptic technique** is essential for avoidance of infection.

- A meta-analysis of randomized controlled trials favours the use of **cutaneous chlorhexidine over povidone-iodine** for optimal antiseptic technique.

- **Diagnosis and microbiology –**

✓ The **most frequent pathogens associated with CRB** are -
- ➢ Staphylococcus epidermidis (37%),
- ➢ S. aureus (13%),
- ➢ Enterococcus (13%),
- ➢ Enterobacter-Klebsiella (11%),
- ➢ Candida spp. (8%),
- ➢ Serratia (5%), and
- ➢ Others (Escherichia coli, Pseudomonas spp.).
- ➢ Gram-negative organisms are especially common in patients with malignancies

✓ **True confirmation of a catheter source** requires the following:

- ➢ **Same organism** is grown from peripheral blood and the catheter tip culture with growth of >15 CFUs; or

- ➢ Central blood sample is read as **positive 2 hours earlier** than a peripheral blood sample inoculated at the same time; or

- ➢ Both catheter and peripheral cultures grow the same organisms and the colony count from the catheter-drawn blood is **three to five times greater** than that drawn by venepuncture.

- **Treatment –**

✓ Short- and long-term **catheters should be removed from patients with CRB when** associated with any of the following conditions:

- Hemodynamic instability or sepsis,
- Endocarditis,
- Suppurative thrombophlebitis, or
- Infections.

✓ **Catheter tip culture** should be performed when a catheter is removed for suspected CRB.

✓ For patients in **whom catheter salvage is attempted**, additional blood cultures should be obtained.

✓ If blood cultures remain **positive despite 72 hours** of antimicrobial therapy, the **catheter should be removed**.

✓ **Antimicrobial therapy** is often initiated **empirically.**

✓ **Vancomycin** is the empiric therapy of choice.

✓ The addition of empiric therapy **against Pseudomonas (e.g., cefepime, piperacillin-tazobactam, meropenem)** is indicated in patients who are –

- Critically ill,
- Have sepsis or neutropenia, or
- Have a femoral catheter in place.

✓ If **candidemia** is suspected. Fluconazole or echinocandin (e.g., caspofungin) should be started.

✓ **Blood cultures should be redrawn** after initiation of therapy to assure clearance of bacteremia.

✓ The **recommended duration of therapy is 14 days**, with day 1 defined as the first day with negative cultures.

✓ **Four to six weeks of therapy** is recommended when –

- Bacteremia or fungemia **persists for more than 72 hours after catheter removal**,
- Bacteremia resulting from **infection with S. aureus** in patients with diabetes, immunocompromised state, or with a prosthetic intravascular device;
- **Endocarditis, suppurative thrombophlebitis, or metastatic infectious** foci are Identified.

✓ Antibiotic treatment is **not recommended** in some situations involving positive cultures associated with an indwelling or recently removed CVC. These include –

- Positive culture from a removed catheter tip **not accompanied by clinical signs** of infection,
- Positive cultures from an indwelling CVC associated with **negative associated peripheral blood cultures**, and
- **Phlebitis in the absence of infection** (topical antimicrobials are preferred).

URINARY TRACT INFECTIONS

- Second most common HAI in patients admitted to ICUs.
- **Third most common in patients admitted to NICUs**, accounting for 22.7–36.6% of HAIs.
- Approximately **20% of hospital-acquired bacteremias,** arise from the urinary tract, and the mortality associated with this condition is 10%.
- **Risk factors** include –
  - ✓ Indwelling urethral catheters (80%),
  - ✓ Diaabetes mellitus,
  - ✓ Older age,
  - ✓ Female sex,
  - ✓ Severe underlying illness, and
  - ✓ Bacterial colonization of the drainage bag.

- **Diagnosis and microbiology –**

✓ Most ICU-acquired catheter-associated UTIs (CAUTI) are **monomicrobial** (88–95%).

✓ The **predominant pathogens are**:

- ➢ E. coli (39%),
- ➢ P. aeruginosa (22%),
- ➢ Enterococcus (15%),
- ➢ Acinetobacter spp. (11%),
- ➢ Klebsiella spp. (11%), and
- ➢ Proteus (11%).
- ➢ Candida spp (account for one-third of all ICU-acquired UTIs).

- ✓ CAUTI is **defined** as culture growth of **> 1000 CFU/mL** of uropathogenic bacteria in the presence of **symptoms or signs** compatible with UTI with no other identified source of infection in a patient with an indwelling urethral or suprapubic catheter, or intermittent catheterization.

- ✓ **Signs and symptoms** compatible with CAUTIs include –
  - ➢ New-onset or worsening fever,
  - ➢ Rigors,
  - ➢ Altered mental status,
  - ➢ Malaise, or lethargy with no other identified cause.
  - ➢ Flank pain,
  - ➢ Costovertebral angle tenderness,
  - ➢ Acute hematuria, and
  - ➢ Pelvic discomfort.

- ✓ Catheter associated **asymptomatic bacteriuria** is defined by culture growth of **>10,000 CFU/mL** of uropathogenic bacteria in patients with an indwelling urethral or suprapubic catheter, or intermittent catheterization in a patient **without clinical symptoms.**

- ✓ **Pyuria** (white blood cell count 10 cells/mL) can be present in catheterized patients with asymptomatic bacteriuria, and **has a low sensitivity**.

- ✓ It is **not recommended** to use the degree of pyuria to differentiate CAUTI from catheter-associated asymptomatic bacteriuria.

- ✓ A **urine culture** should be obtained prior to initiating treatment.

- ✓ The **urine culture** should be obtained from the **freshly placed catheter** prior to the initiation of antimicrobial therapy in patients with **long-term indwelling catheters**.

✓ In patients with **short-term catheterization**, it is recommended that –
  - ➢ Specimens be obtained by sampling through the catheter port using aseptic technique or,
  - ➢ If a port is not present, by puncturing the catheter tubing with a needle and syringe.

✓ Culture specimens should **not be obtained from the drainage bag.**

- **Treatment –**

✓ Uncomplicated UTI (not CAUTI) - Trimethoprim/sulfamethoxazole or ciprofloxacin.

✓ For empiric treatment of CAUTI with Gram-negative rods - third generation cephalosporins (e.g., ceftriaxone) or a fluoroquinolone (ciprofloxacin or levofloxacin) are recommended.

✓ Vancomycin is the drug of choice for empiric treatment of Gram-positive cocci.

✓ Attention to bacterial susceptibility is important. Follow-up of culture results is essential.

✓ **Candida albicans and C. glabrata** are the most frequent uropathogens associated with CAUTI.

✓ Parenteral fluconazole for 14 days for C. albicans.

✓ Voriconazole is more effective against non-C. albicans.

✓ Severe illness who have uncomplicated UTI - **3–7 days** of antibiotic treatment is sufficient.

✓ **Ten to 14 days** of therapy is recommended for those with a delayed response and in septic patients.

✓ **Colonized patients, without evidence of infection, do not require treatment**.

✓However, the indwelling catheter should be **changed or removed**.

✓**Treatment is not necessary for asymptomatic bacteriuria** and should be avoided due to concerns of increasing antimicrobial resistance.

✓**Routine screening is not recommended.**

- **Prevention –**

✓Indwelling catheters should be placed only when indicated,
✓Should be removed as soon as possible,
✓Sterility should be maintained.

VENTRICULITIS

- Bacterial ventriculitis (BV) is **inflammation of the ventricular drainage system** due to bacterial infection of the cerebrospinal fluid (CSF).

- BV is associated with **CSF shunts, EVD, or any other intracranial device.**

- **Hemorrhagic CSF** further contributes to the increased incidence of EVD-associated Infections.

- Infection risk increases significantly **after 5 days of placement and peaks at days 9–11** after placement.

- **CSF shunt-related** infection is reported in **8–40% of patients,** with most infections occurring within 1 month of implantation.

- The most common pathogens - **Gram-positive organisms and fungi followed by gram negative organisms.**

- **Diagnosis –**

✓Ventriculitis is diagnosed by the presence of **clinical symptoms and a positive CSF analysis**.

✓The clinical **symptoms** of ventriculitis include fever and signs of meningitis (nuchal rigidity, decreased mental status, seizures,etc.).

✓A **positive CSF culture** with absent symptoms should lead the clinician to suspect colonization or contamination.

✓In patients who have **already suffered a neurologic injury** that causes inflammation and breakdown of the blood–brain barrier, the **diagnosis of ventriculitis can be challenging.**

✓CSF may already contain blood with increased protein, inflammatory cells, and decreased glucose depending on the underlying pathology.

✓ Determination of a high lactate concentration can assist with diagnosis.

✓ Factors that may elevate CSF lactate include – cerebral hypoxia, vascular compromise.

✓ **Current guidelines recommend** that, in the postoperative neurosurgical patient, **initiation of empiric antimicrobial therapy should be considered if CSF lactate concentrations are 4.0 mmol/L**, pending results of additional studies.

✓ **Cranial sonography** is useful in diagnosing this condition in infants and young children. Findings include -

- Increased echogenicity of the ventricular wall,
- Increased thickness of the ventricular walls, and
- Presence of septations and debris in the ventricles.

✓ **Non-contrast CT –**

- Non-specific features,
- Hyperdense layering material may be seen dependently, particularly in the occipital horns of the lateral ventricles.
- Hydrocephalus and periventricular low density (represents reactive edema).

✓ In **contrast CT**, thin regular enhancement of the ependymal lining of the ventricles may be seen.

✓ **MRI findings include –**

- Ependymal enhancement and thickening,
- Dilated ventricles,
- Surrounding FLAIR signal hyperintensity, suggestive of parenchymal edema.
- Increased T2 hyperintensity in the ventricular wall, and
- Debris in the dependent portion of the ventricle (occipital horn) are other imaging findings.
- Restricted diffusion may be seen in the dependent purulent intraventricular fluid.

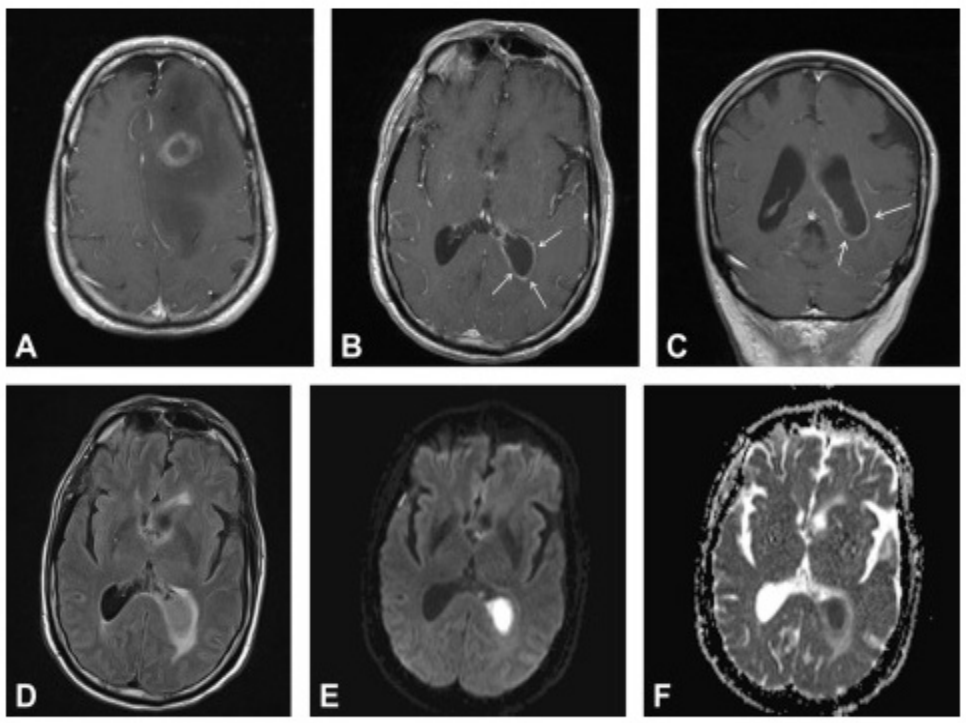


Fig. 19.5. A 70-year old man with known intracranial abscess with rupture into the left ventricle. (A) Axial T1-weighted postcontrast magnetic resonance (MR) image demonstrates a mass with thick and irregular ring enhancement in the medial left frontal lobe, just above the body of the left lateral ventricle, consistent with a brain abscess. T1-weighted postcontrast axial (B) and coronal (C), axial fluid-attenuated inversion recovery (FLAIR) (D) and axial diffusion (E) and apparent diffusion coefficient (F) MR images at the level of the atrium of the lateral ventricle demonstrate restricted diffusion within the dependent portion of the occipital horn of the left lateral ventricle with associated ependymal enhancement (arrows), consistent with ventriculitis. The adjacent brain parenchyma demonstrates significant FLAIR signal hyperintensity, consistent with vasogenic edema.

- **Treatment -**

✓ Recommended **empiric therapy** are combination of –
  - ➢ Vancomycin and cefepime for adults, or
  - ➢ Vancomycin plus ceftazidime, or
  - ➢ Vancomycin plus meropenem.

✓ In most cases treatment is continued for **10–14 days.**

✓ For aerobic Gram-negative bacilli, therapy may be continued for up to 21 days.

✓ A fungal infection with **Candida species** should be managed with voriconazole and the polyene amphotericin B for **2 weeks** since the last negative CSF culture.

- ✓ In addition to antimicrobial therapy, **infected hardware should be removed, replaced, or externalized when appropriate**.

- ✓ **Intraventricular (IVT) administration of antibiotics** may be effective in selected cases, although indications remain controversial.

- ✓ IVT antibiotics can lead to **rapid CSF sterilization** in post neurosurgical patients with meningitis and ventriculitis (**mean time 2.9- 2.7 days, range 1–12 days**).

- ✓ The **relapse rate of ventriculitis is also very low** among patients treated by IVT antibiotics.

- ✓ The typical indications for **intrathecal administration** are:
  - ➢ Failure to achieve adequate CSF antimicrobial concentrations with nontoxic drug doses, or
  - ➢ Persistently positive CSF cultures despite intravenous dosing with an appropriate antibiotic, and
  - ➢ Exhaustion of all appropriate means of source control.

- ✓ Drug concentrations at least **10 times the MIC are recommended** in CSF to achieve rapid bactericidal activity.

- ✓ Intrathecal antibiotics are administered at **24-hour intervals** and **for 48–72 hours** after sterilization of the CSF in most cases.

- **Prevention –**

✓ **Protocolized** EVD insertion and nursing care.

✓ A recent meta-analysis found that **both antibiotic- and silver-impregnated EVDs were more effective than standard EVDs** for the prevention of catheter-related infection.

✓ There is **no** conclusive evidence guiding **preference** of antibiotic or silver-impregnated EVDs.

✓ It is **not recommended to exchange EVDs** with the aim of preventing ventriculitis.

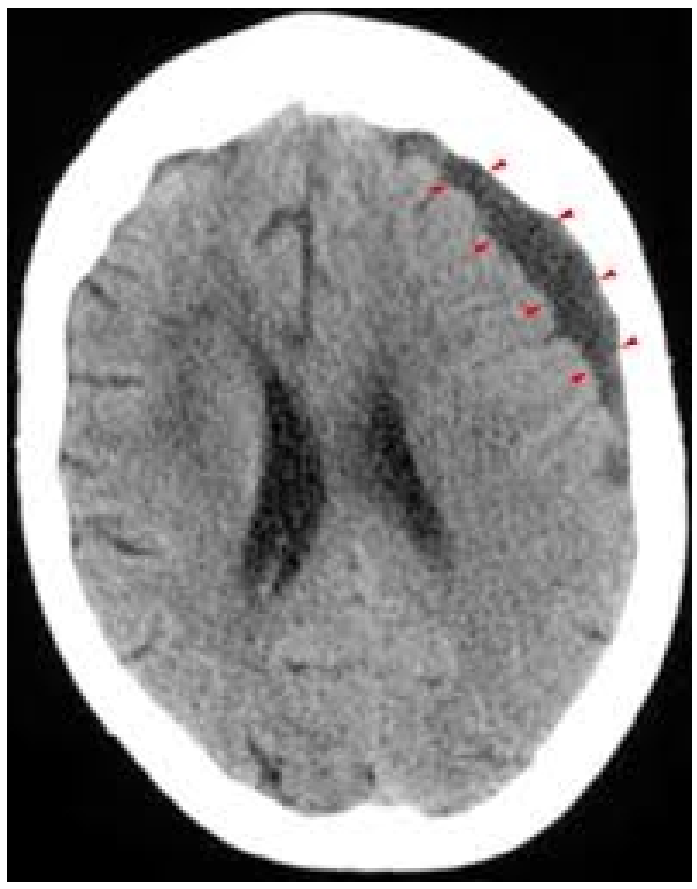
✓ **Systemic antibiotic prophylaxis** should be **avoided** in patients treated with antibiotic coated EVD.

✓ **Prolonged systemic antibiotic therapy** should be **avoided** in after placement of EVD.

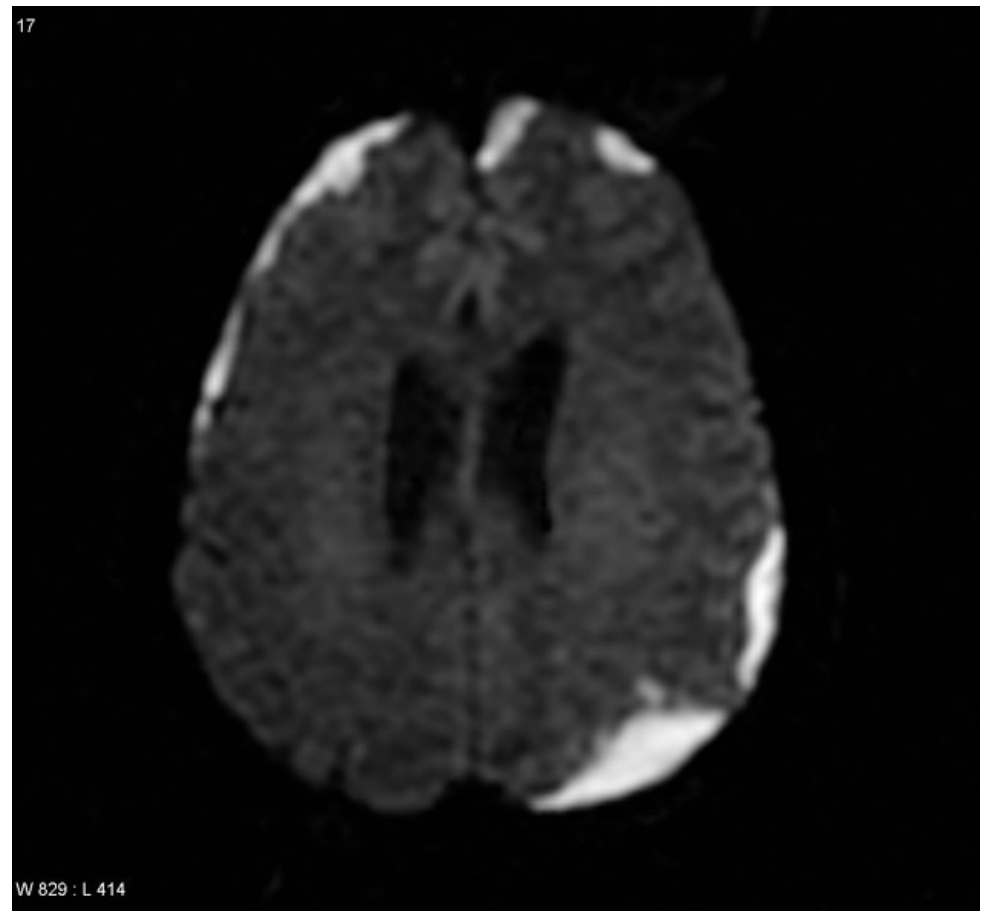
SUBDURAL EMPYEMA

- SDE occurs after neurosurgery in **4% of cases**.
- Signs and symptoms of SDE usually present within **1–8 weeks** (mean 2 weeks).
- Staphylococci and Gram-negative bacilli are the most common pathogens.
- Pus can be found over the **convexities**, layering along the **tentorium cerebelli**, or in the **interhemispheric fissure,** with 1–10% of SDEs located in the **posterior fossa.**
- Lumbar puncture is **not recommended** due to increased risk for cerebral herniation.
- The recommended management for SDEs includes **surgical drainage and antibiotic therapy.**

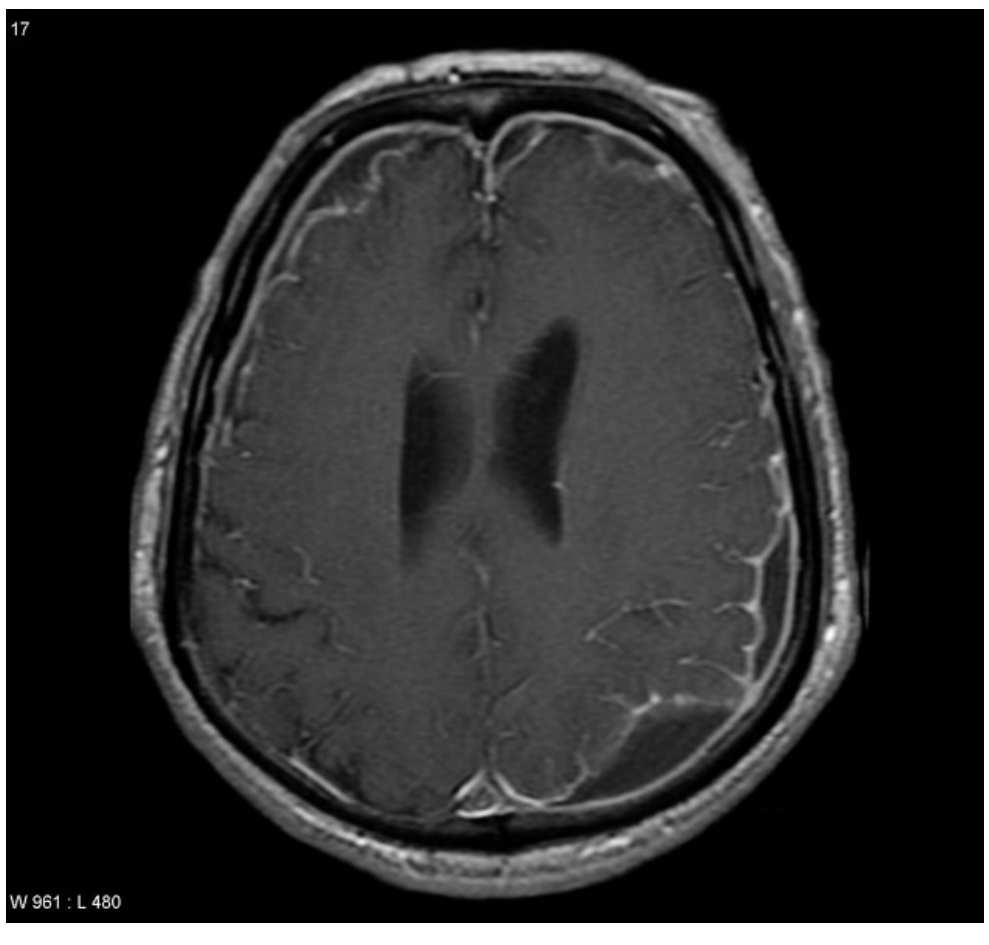
- **Empiric treatment -** Vancomycin plus a fourth generation cephalosporin (i.e., cefepime).
- **Cultures** should be sent from the surgical drainage.
- Appropriate antibiotic therapy should be tailored accordingly.
- Duration of treatment – **3 – 6 weeks.**



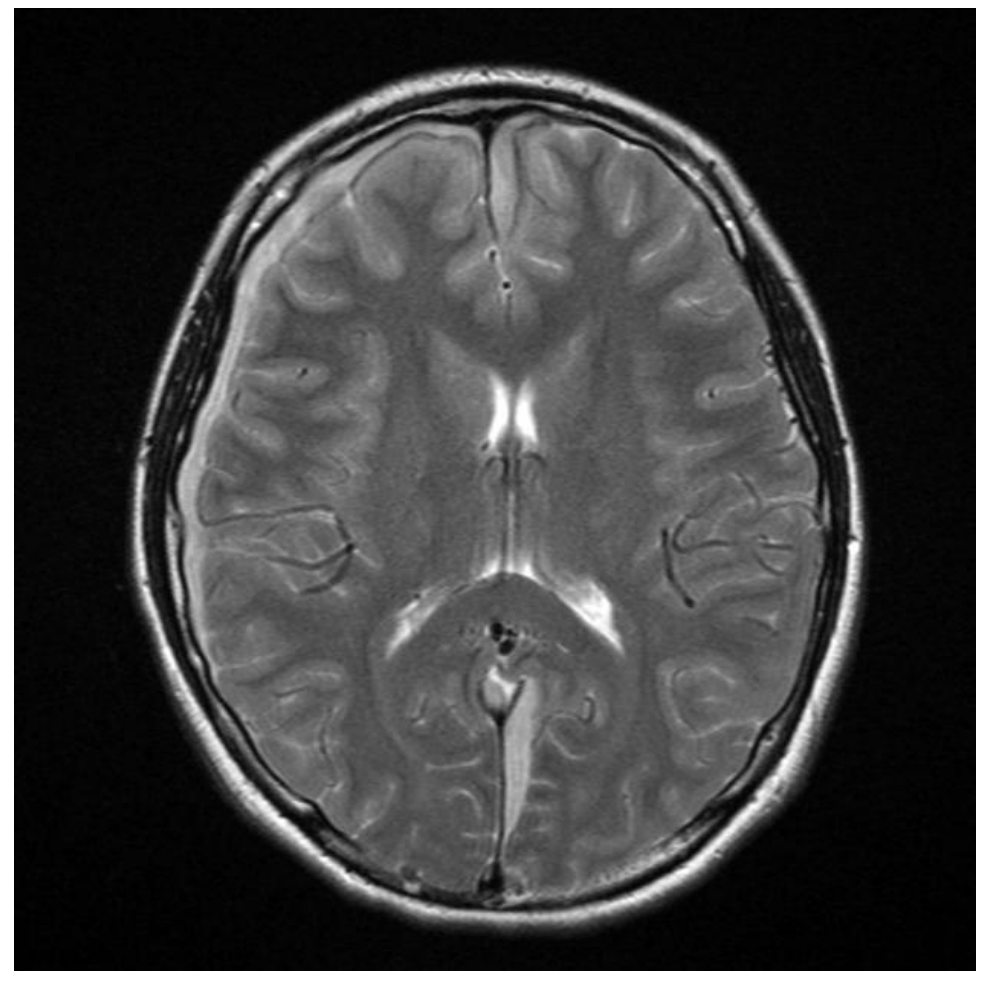
CT Scan



DWI



MRI – T1



MRI – T2

BRAIN ABSCESS

- Abscess formation is an **uncommon but serious** complication after neurosurgical procedures.

- **Risk factors** include -
  - ✓Immunocompromised patients,
  - ✓Head trauma patients with penetrating brain injury are at higher risk.

- Patients typically present **2 weeks post surgery** with –
  - ✓Headache,
  - ✓Low-grade fevers (present in over 50% of cases),
  - ✓Seizures and signs of increased intracranial pressure may be present.
  - ✓Focal neurologic deficit or altered level of consciousness (over 60% of cases).

- The **most common pathogens** - Staphylococcus aureus and S. epidermidis, or Gram-negative bacilli.

- **Lumbar puncture** should be performed only when there is clinical suspicion of meningitis or abscess rupture into the ventricular system.

- **Herniation** is estimated to occur in **15–20%** of patients who have a lumbar puncture with cerebral abscess.

- When CSF analysis fails to identify a causative pathogen, **surgical aspiration** should be considered to isolate the organism and to reduce the abscess diameter.

- **CT -**

✓ Outer hypodense and inner hyperdense rim (double rim sign) in most cases.

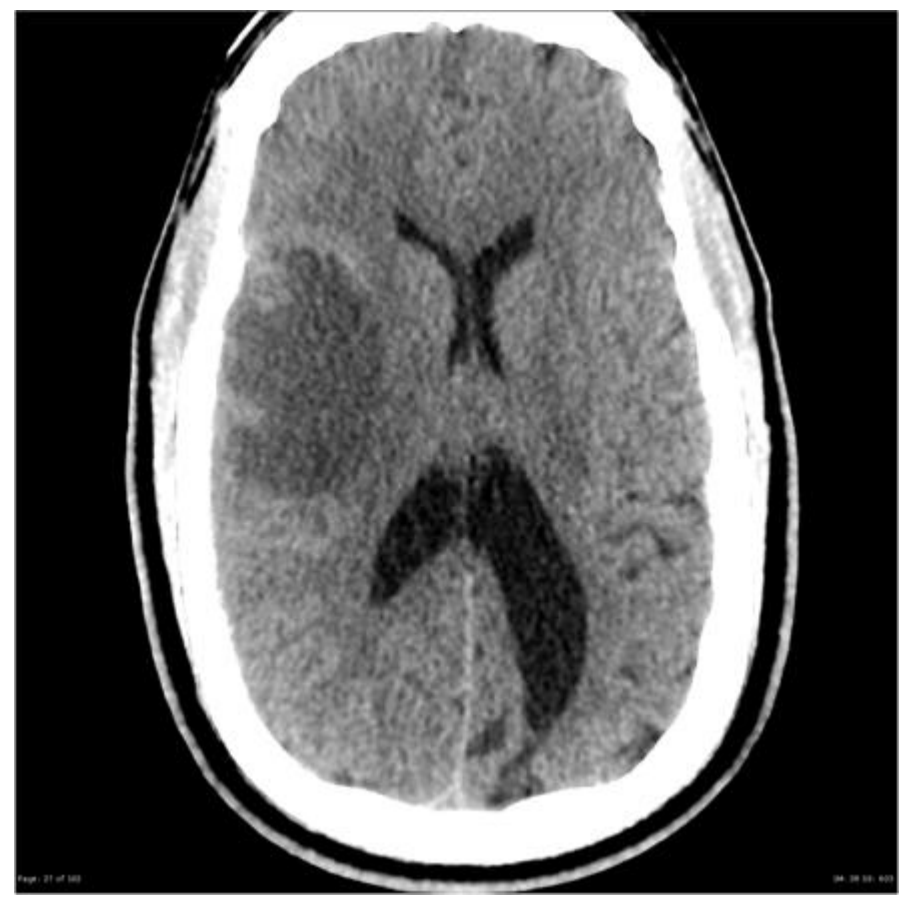
✓ Ring of iso- or hyperdense tissue, typically of uniform thickness.

✓ Central low attenuation (fluid/pus).

✓ Surrounding low density (vasogenic edema).

✓ Ventriculitis may be present, seen as enhancement of the ependyma.

✓ Obstructive hydrocephalus will commonly be seen when intraventricular spread has occurred.



- **MRI -**

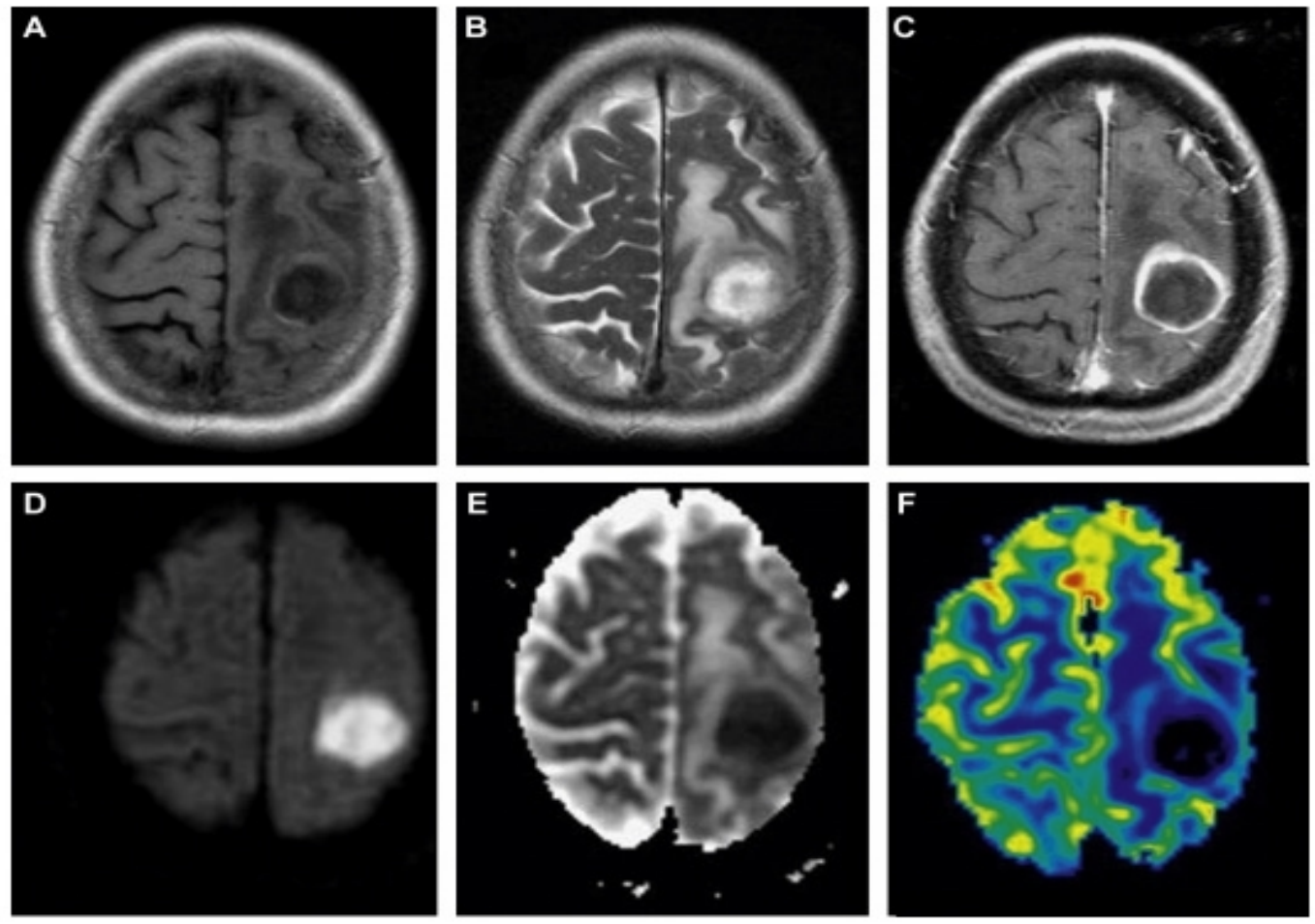


Figure 1 A–F: supratentorial pyogenic abscess in the gray-white junction: T1-weighted (A), T2-weighted (B), gadolinium-enhanced T1-weighted (Gd-MR) (C), DWI ($b = 1000$) (D), ADC (E) and PWI map of CBV (F) MR images. The capsule of the abscess is hyperintense in T1-weighted image (A), partially hypointense in T2-weighted image (B) with surrounding vasogenic oedema. Gd-MR image shows a ring-enhancing mass. The central component of the lesion shows high signal intensity in DWI image (D), and hypointense signal in ADC map, findings that are consistent with restricted diffusion (ADC = 0.440×10^{-3} mm^2/s). At PWI, the CBV map (F) does not show evidence of increased perfusion in the gadolinium-enhancing rim (rCBV = 0.85).

- **D/D –** Metastasis, haemorrhage, infarction, demyelination lesion, radiation necrosis.

- **Medical therapy alone** may be appropriate in following conditions –

✓ If the causative pathogen has been identified,

✓ Abscess measure less than 2.5 in diameter,

✓ When the abscess is located in deep or eloquent brai,

✓ Poor surgical candidacy,

✓ Concurrent meningitis, ventriculitis, or

✓ Concurrent hydrocephalus that requires CSF shunting which may become infected at the time of abscess drainage.

- **Empiric treatment -** vancomycin plus a fourth-generation cephalosporin (i.e., cefepime) and metronidazole for **6–8 weeks.**

MENINGITIS AND ENCEPHALITIS

- Meningitis and encephalitis are **pathologically distinct syndromes but have extensive clinical overlap.**

Causes of Meningitis

- Neonatal (< 1 month)

1. **Bacterial causes:**

Organism	*E. coli* >	*Gp B streptococci* >	Other gram-negative bacilli >	L. monocytogenes
Frequency	34%	30%	8%	6%

Other bacterias are: Staph, other Streptococci, *Pneumococcus, Pseudomonas, Haemophilus, Meningococcus.*

2. **Viral and protozoal infections:** TORCH, Varicella zoster and HIV.
3. **Spirochetal and fungal infections**

- **1-11 months:** *N. meningitidis* > *Strep pneumoniae* > *H. influenza*
- **1-20 years:** *N. meningitidis* > *Strep pneumoniae* > *H. influenza*
- More than 20 years : Strep pneumoniae (MC)

..... *Harrison 18/e, p 341*

- **Diagnostic tools include –** general signs, imaging, CSF analysis, blood cultures.

- **Differential diagnosis** – intracranial bleed, neuroinflammatory, and vasculitis disorders, post-ictal patients.

Table 2 CSF interpretation. Adapted from Koski and Loo 2010 [10] and Seehusen et al. 2003 [9]

CSF characteristic	Normal	Bacterial	Viral	Mycobacterial	Fungal
Opening pressure	< 10 mm H_2O	200–500 mm H_2O	Normal or elevated	Elevated	Elevated (>250 mm H_2O in cryptococcal meningitis)
WBC count	0–5 cells/ mm^3	100–20,000 cells/mm^3	5–500 cells/mm^3 cells/uL	5–2000 cells/mm^3	20–2000 cells/mm^3
Differential	N/A	>80% PMN	Early: neutrophil predominant Late: Lymphocytes	>80% lymphocytes	>50% lymphocytes
Protein	15–50 mg/ dL	100–500 mg/dL	30–150 mg/dL	>50 mg/dL	40–150 mg/dL
Glucose*	45–100 mg/ dL	<40 mg/dL	30–70 mg/dL	<40 mg/dL	30–70 mg/dL
Additional testing of note	N/A	Gram's stain and bacterial cultures, blood cultures	PCR for HSV	Mycobacterial culture and AFB staining	Fungal culture Fungal smear

Normal findings, common findings for untreated infectious syndromes described, as well as a common noninfectious syndrome (subarachnoid hemorrhage) for reference for an infection mimic. * Glucose assumes normal serum glucose

AFB Acid-fast bacilli, *CSF* cerebrospinal fluid, *PMN* polymorphonuclear cell, *RBC* red blood cell, *WBC* white blood cell

Table 3 Additional testing on CSF for CNS infection

Test	Utility
Cryptococcal antigen	High in immunosuppressed patients; recommended in suspected cases
Pneumococcal antigen	High; recommended when Gram's stain/culture not available or when antibiotics have been administered prior to culture. Urinary pneumococcal antigen testing is an alternative when CSF examination cannot be performed
Herpes simplex virus (HSV) PCR	High; common, treatable cause of viral meningoencephalitis
West Nile virus (WNV) IgM	High in appropriate clinical setting: viral encephalitis, WNV endemic area, appropriate season
HHV-6 PCR	High in appropriate clinical setting: viral encephalitis in an immunocompromised host
Cytomegalovirus (CMV) PCR	Low; not routinely recommended even in immunocompromised patients
Epstein–Barr virus (EBV) PCR	Low; false positives common, not routinely recommended even in immunocompromised patients

CMV Cytomegalovirus, *CNS* central nervous system, *CSF* cerebrospinal fluid, *EBV* epstein–barr virus, *HHV* Human herpesvirus, *HSV* herpes simplex virus, *PCR* polymerase chain reaction, *WNV* West Nile virus

- **Treatment –**

  - ✓ In **adult patients <50 years old**, the most common pathogens are **Neisseria meningitidis and Streptococcus pneumoniae**, and thus, recommended empiric therapy is **vancomycin plus a third-generation cephalosporin.**
  - ✓ **Age >50 years**, the risk of **Listeria monocytogenes** increases and prompts the **addition of ampicillin**.
  - ✓ In patients with suspected or confirmed **pneumococcal meningitis, adjunctive dexamethasone** is recommended.
  - ✓ The only commonly encountered **viral meningoencephalitis** with effective treatment is **HSV**, and empiric **acyclovir** should be administered.

TABLE 164-1 ANTIBIOTICS USED IN EMPIRICAL THERAPY OF BACTERIAL MENINGITIS AND FOCAL CENTRAL NERVOUS SYSTEM INFECTIONS[a]

Indication	Antibiotic
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 months	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 months and adults <55	Cefotaxime, ceftriaxone, or cefepime + vancomycin
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone or cefepime + vancomycin
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin

	Total Daily Dose and Dosing Interval	
Antimicrobial Agent	Child (>1 month)	Adult
Ampicillin	300 (mg/kg)/d, q6h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	225-300 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8h[b]	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	6 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	100–200 (mg/kg)/d, q6h	9–12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	45-60 (mg/kg)/d, q6h	45-60 (mg/kg)d, q6–12h[b]

[a]All antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function. [b]Doses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 µg/mL; trough: <2 µg/mL; vancomycin therapeutic level: peak: 25–40 µg/mL; trough: 5–15 µg/mL.

- **Antimicrobial prophylaxis for N.Meningitidis** is recommended only for **‘‘close contacts’’.**

  ✓**Chemoprophylaxis** include ciprofloxacin, rifampicin, and ceftriaxone.

  ✓Administered as **soon as possible** after exposure.

  ✓Not effective after 14 days.