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Pneumonia

Kai Man Chan and Charles D Gomersall

The management of pneumonia is based on four findings and premises:

- Pneumonia is associated with a wide range of largely non-specific clinical features.[1]
- Pneumonia can be caused by over 100 organisms.
- The relationship between specific clinical features and aetiological organism is insufficiently strong to allow a clinical diagnosis of the causative organism.[2]
- Early administration of appropriate antibiotics is important.[2]

The net result is that the differential diagnosis is wide and treatment should be started before the aetiological agent is known. The differential diagnosis and the likely causative organisms can be narrowed by using epidemiological clues, the most important of which are whether the pneumonia is community-acquired or healthcare-associated and whether the patient is immunocompromised. Note that the flora and antibiotic resistance patterns vary from country to country, hospital to hospital and even ICU to ICU within a hospital and this must be taken into account.

COMMUNITY-ACQUIRED PNEUMONIA

Evidence-based guidelines have been issued by the British Thoracic Society,[3] the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS)[2] and the European Respiratory Society.[4] Links to these and other pneumonia-related guidelines can be found at the following 'link page': http://www.aic.cuhk.edu.hk/web8/Pneumonia%20guidelines.htm.

DEFINITION

An acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by an acute infiltrate on a chest radiograph (CXR), or auscultatory findings consistent with pneumonia (e.g. altered breath sounds, localised crackles) in a patient not hospitalised or residing in a long-term care facility for ≥14 days prior to the onset of symptoms.

The overall incidence is 3–40 per 1000 inhabitants per year, with 40–60% requiring hospital admission. Overall, 10% of patients are admitted to ICU. The overall mortality of hospitalised patient is approximately 10%.[5]

AETIOLOGY

Table 36.1 gives possible aetiological agents based on epidemiological clues. *Streptococcus pneumoniae* is the most commonly isolated organism. The next most common bacterial pathogens in patients admitted to ICU are: *Legionella* species, *Haemophilus influenzae,* Enterobacteriaceae species, *Staphylococcus aureus* and *Pseudomonas* species.[2]

CLINICAL PRESENTATION

Pneumonia produces both systemic and respiratory manifestations. Common clinical findings include fever, sweats, rigors, cough, sputum production, pleuritic chest pain, dyspnoea, tachypnoea, pleural rub and inspiratory crackles. Classic signs of consolidation occur in less than 25% of cases. Multi-organ dysfunction or failure may occur depending on the type and severity of pneumonia.

The diagnosis of pneumonia may be more difficult in the elderly. Although the vast majority of elderly patients with pneumonia have respiratory symptoms and signs, over 50% may also have non-respiratory symptoms and over a third may have no systemic signs of infection.

INVESTIGATIONS[2,4]

Investigations should not delay administration of antibiotics as delays are associated with an increase in mortality.[2] Important investigations include:

1. Chest X-ray (CXR)
2. Arterial blood gases or oximetry
3. Full blood count
4. Serum creatinine, urea and electrolytes
5. Liver function tests
6. Blood cultures (×2) prior to the administration of antimicrobials
7. Sputum (if immediately available) for urgent Gram stain and culture. The usefulness of sputum tests remains debatable because of contamination by upper respiratory tract commensals. However, a

Table 36.1 Possible aetiological agents based on epidemiological clues[2,3,9,7]

EXPOSURE	ORGANISM
EXPOSURE TO ANIMALS	
Handling turkeys, chickens, ducks or psittacine birds or their excreta	*Chlamydia psittaci*
Exposure to birds in countries in which avian flu has been identified in birds	Influenza A H5N1
Handling infected parturient cats, cattle, goats or sheep or their hides	*Coxiella burneti*
Handling infected wool	*Bacillus anthracis*
Handling infected cattle, pigs, goats or sheep or their milk	*Brucella* spp.
Insect bite. Transmission from rodents and wild animals (e.g. rabbits) to laboratory workers, farmers and hunters	*Francisella tularensis*
Insect bites or scratches; transmission from infected rodents or cats to laboratory workers and hunters	*Yersinia pestis*
Contact with infected horses (very rare)	*Pseudomonas mallei*
Exposure to mice or mice droppings	Hantavirus
GEOGRAPHICAL FACTORS	
Immigration from or residence in countries with high prevalence of TB	*Mycobacterium tuberculosis*
North America; contact with infected bats or birds or their excreta; excavation in endemic areas	*Histoplasma capsulatum*
South-west USA	*Coccidiodes* species, Hantavirus
USA; inhalation of spores from soil	*Blastomyces dermatitidis*
Asia, Pacific, Caribbean, north Australia. Contact with local animals or contaminated skin abrasions	*Burkholderia pseudomallei*
HOST FACTORS	
Diabetic ketoacidosis	*Streptococcus pneumoniae, Staphylococcus aureus*
Alcoholism	*Strep. pneumoniae, S. aureus, Klebsiella pneumoniae,* oral anaerobes, *M. tuberculosis, Acinetobacter* spp.
Chronic obstructive pulmonary disease or smoking	*Strep. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella* spp., *Pseudomonas aeruginosa*
Sickle cell disease	*Strep. pneumoniae*
Pneumonia complicating whooping cough	*Bordatella pertussis*
Pneumonia complicating influenza	*Strep. pneumoniae, S. aureus,* CA-MRSA
Pneumonia severe enough to necessitate artificial ventilation	*Strep. pneumoniae, Legionella* spp., *S. aureus, Haemophilus influenzae, Mycoplasma pneumoniae,* enteric Gram-negative bacilli, *Chlamydia pneumoniae, M. tuberculosis,* viral infection, endemic fungi
Nursing home residency	Treat as healthcare-associated pneumonia
Poor dental hygiene	Anaerobes
Suspected large-volume aspiration	Oral anaerobes, Gram-negative enteric bacteria
Structural disease of lung (e.g. bronchiectasis, cystic fibrosis)	*P. aeruginosa, Burkholderia cepacia, S. aureus*

Table 36.1 Possible aetiological agents based on epidemiological clues—cont'd

EXPOSURE	ORGANISM
Lung abscess	Community-acquired meticillin-resistant *S. aureus*, oral anaerobes, endemic fungi, *M. tuberculosis*, atypical mycobacteria
Endobronchial obstruction	Anaerobes, *Strep. pneumoniae, H. influenzae, S. aureus*
Intravenous drug addict	*S. aureus*, CA-MRSA, anaerobes, *M. tuberculosis, Strep. pneumoniae*
End-stage renal failure	CA-MRSA
OTHERS	
Epidemic	*M. pneumoniae,* influenza virus
Air-conditioning cooling towers, hot tubs or hotel or cruise ship stay in previous 2 weeks	*Legionella pneumophilia*
Presentation of a cluster of cases over a very short period of time	Bioterrorist agents: *B. anthracis, F. tularensis, Y. pestis*

single or predominant organism on a Gram stain of a fresh sample or a heavy growth on culture of purulent sputum is likely to be the organism responsible. The finding of many polymorphonuclear cells (PMN) with no bacteria in a patient who has not already received antibiotics can reliably exclude infection by most ordinary bacterial pathogens. Specimens should be obtained by deep cough and be grossly purulent. Ideally the specimen should be obtained before treatment with antimicrobials, if this does not delay administration of antibiotics, and be transported to the laboratory immediately for prompt processing to minimise the chance of missing fastidious organisms (e.g. *Strep. pneumoniae*). Acceptable specimens (in patients with normal or raised white blood cell counts) should contain >25 PMN per low-power field (LPF) and <10–25 squamous epithelial cells (SEC)/LPF or >10 PMN per SEC. These criteria should not be used for *Mycobacteria* and *Legionella* infection. Certain organisms are virtually always pathogens when recovered from respiratory secretions (**Box 36.1**). Patients with risk factors for tuberculosis (TB) (**Box 36.2**), and particularly those with cough for more than a month, other common symptoms of TB and suggestive radiographic changes, should have sputum examined for acid-fast bacilli. Sputum cannot be processed for culture for anaerobes owing to contamination by the endogenous anaerobic flora of the upper respiratory tract. In addition to the factors listed in Table 36.1, foul-smelling sputum, lung abscess and empyema should raise suspicion of anaerobic infection.

8. Aspiration of pleural fluid for Gram stain, culture, pH and leucocyte count – all patients with a pleural effusion >1 cm thick on a lateral decubitus chest X-ray.

Box 36.1 Organisms that are virtually always pathogens when recovered from respiratory secretions

Legionella
Chlamydia
TB
Influenza, para-influenza virus, RSV, adenovirus, hantavirus, SARS coronavirus
Stronglyloides stercoralis
Toxoplasma gondi
Histoplasma capsulatum
Coccidiodes immitis
Blastomycoses dermatitidis
Cryptococcus neoformans

Box 36.2 Risk factors for pulmonary tuberculosis

Living in or originating from a developing country
Age (<5 years, middle-aged and elderly men)
Alcoholism and/or drug addiction
HIV infection
Diabetes mellitus
Lodging-house dwellers
Immunosuppression
Close contact with smear-positive patients
Silicosis
Poverty and/or malnutrition
Previous gastrectomy
Smoking

9. Urinary *Legionella* antigen. This test is specific (>95%). In patients with severe Legionnaires disease sensitivity is 88–100% for *L. pneumophilia* serogroup 1 (the most commonly reported cause of *Legionella* infection). Thus a positive result is virtually

diagnostic of *Legionella* infection but a negative result does not exclude it. In areas (e.g. South Australia) where other *Legionella* species are more common, this test is less helpful.

10. Urinary pneumococcal antigen has moderate sensitivity (50–80%) and high specificity (>90%).
11. Microimmunofluorescence serology for *Chlamydia pneumoniae* IgM. A titre ≥1:16 is significant.
12. HIV serological status.

Other investigations should be considered in patients with risk factors for infection with unusual organisms. Bronchoalveolar lavage may be useful in immunocompromised patients, those who fail to respond to antibiotics, or those in whom sputum samples cannot be obtained.[6]

Molecular diagnosis (e.g. PCR-based methods) has the advantages of quick results (within 3 hours), enhanced sensitivity, independence from organism viability and hence previous antibiotics, and theoretical possibility for determination of antimicrobial susceptibility.[7] Of note, it is important to test for genes specific for the organism in question[10] and the sampling site remains important. PCR is most useful when performed on specimens from a normally sterile site. For example, PCR for *Pneumococcus* is positive in 62% of blood samples from adult patients with confirmed or probable pneumococcal pneumonia,[8] whereas blood cultures are positive in only 37%. For respiratory specimens under most circumstances, interpretation remains problematic due to low specificity related to floral contamination and colonisation. PCR assays are more sensitive than culture for *Mycoplasma* and *Chlamydia* species and at least as sensitive for *Legionella*.[7] PCR assays also detect *Legionella* strains other than serogroup 1. The BTS guidelines[3] recommend PCR of lower respiratory tract sample or, if unavailable, throat swab for the diagnosis of *Mycoplasma* pneumonia. PCR for *Chlamydophilia* should be performed when invasive respiratory samples were collected from patients with severe community-acquired pneumonia. The role of PCR in diagnosing PCP is mainly limited to non-HIV patients, in whom conventional microscopy and staining of induced sputum and BAL have a lower sensitivity than in HIV patients.[9]

MANAGEMENT

GENERAL SUPPORTIVE MEASURES

Intravenous fluids may be required to correct dehydration and provide maintenance fluid. A general approach should be made to organ support with an emphasis on correcting hypoxia.

ANTIMICROBIAL REGIMENS

Increased mortality among those who do not receive empirical antibiotics that cover the infecting pathogen(s) is well documented.[11] Each unit should have its own regimens tailored to the local flora and antibiotic resistance patterns. In the absence of such regimens the regimen outlined in **Figure 36.1** may be helpful. This

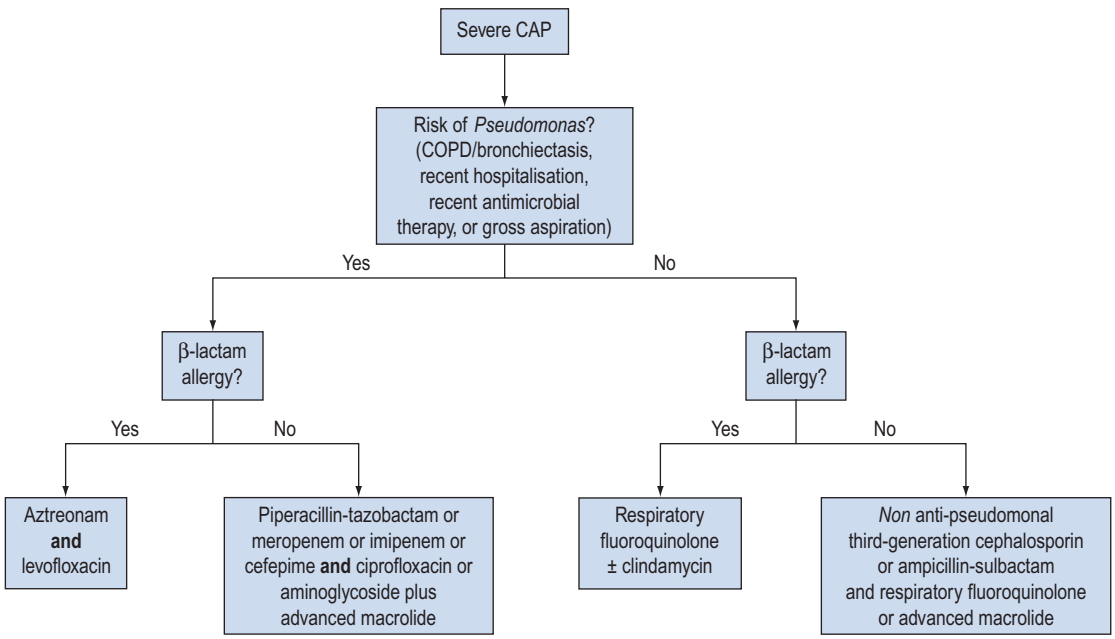

Figure 36.1 Antibiotic regimens for treatment of severe community-acquired pneumonia in critically ill patients.[2,4] Respiratory fluoroquinolones include moxifloxacin and levofloxacin. Advanced macrolides include azithromycin and clarithromycin. Non-antipseudomonal third-generation cephalosporins include cefotaxime and ceftriaxone.

should be modified in the light of risk factors (see Table 36.1). Quinolones may be less appropriate in areas with a high prevalence of TB as their use may mask concurrent TB infection. Appropriate antimicrobial therapy should be administered within 1 hour of diagnosis.[4,12] There is controversy regarding the appropriate change to empirical therapy based on microbiological findings.[2,4] Changing to narrower-spectrum antimicrobial cover may result in inadequate treatment of the 5–38% of patients with polymicrobial infection. Increasing evidence demonstrates improved outcome with combination antimicrobial as compared with monotherapy, particularly in severely ill patients with bacteraemic pneumococcal pneumonia.[5] Odds ratio of death was 1.5 to 6 for monotherapy as compared with combination therapy. Benefits were seen only in combination therapy with macrolide as part of the regimen, but not in combination with fluroquinolone regimen.[13] For the treatment of drug-resistant *Strep. pneumoniae* (DRSP) the regimens in Figure 36.1 are probably suitable for isolates with a penicillin MIC<4 mg/L.[2] If the MIC is ≥4 mg/L an antipneumococcal fluoroquinolone, vancomycin, teicoplanin or linezolid should be given.[4]

DURATION OF THERAPY

No clinical trial has specifically addressed this issue. Courses as short as 5 days may be sufficient.[14] IDSA/ATS guidelines recommend stopping after a minimum of 5 days if the patient is afebrile for 48–72 hours and organ dysfunction has largely resolved.[2] Short courses may be suboptimal for patients with bacteraemic *S. aureus* pneumonia, meningitis or endocarditis complicating pneumonia or infection with less common organisms (e.g. *Burkholderia pseudomallei* or fungi) or *Pseudomonas aeruginosa*. Procalcitonin may be useful to guide antibiotic therapy, but not all studies have demonstrated a benefit.[15]

RESPONSE TO THERAPY[2]

This can be assessed subjectively (a response is usually seen within 1–3 days of starting therapy) or objectively on the basis of respiratory symptoms, fever, oxygenation, WBC count, bacteriology, CXR changes, C-reactive protein reduction and procalcitonin reduction of 80–90% from peak value. The average time to defervescence varies with organism, severity and patient age (7 days in elderly patients, 2.5 days in young patients with pneumococcal pneumonia, 6–7 days in bacteraemic patients with pneumococcal pneumonia, 1–2 days in patients with *M. pneumoniae* pneumonia and 5 days in patients with *Legionella* pneumonia). Both blood and sputum cultures are usually negative within 24–48 hours of treatment although *P. aeruginosa* and *M. pneumoniae* may persist in the sputum despite effective therapy. CXR changes lag behind clinical changes with the speed of change depending on the organism, the age of the patient and the presence or absence of comorbid illnesses. The CXR of most young or middle-aged patients with bacteraemic pneumococcal pneumonia is clear by 4 weeks, but resolution is slower in elderly patients and patients with underlying illness, extensive pneumonia on presentation or *Legionella pneumophilia* pneumonia.

If the patient fails to respond consider the following questions:

- Has the patient got pneumonia?
- Are there host factors that explain the failure (e.g. obstruction of bronchus by a foreign body or tumour, inadequate host response)?
- Has a complication developed (e.g. empyema, superinfection, bronchiolitis obliterans organising pneumonia, metastatic abscess)?
- Is the right drug being given in an adequate dose by the right route?
- Is the organism resistant to the drug being given?
- Are there other organisms?
- Is the fever a drug fever?

Useful investigations include computerised tomography (CT) of the chest, thoracocentesis, bronchoalveolar lavage (**Table 36.2**) and transbronchial or open-lung biopsy.

PREDICTION OF ADVERSE OUTCOME AND ADMISSION TO ICU

Scoring systems have been developed to predict adverse outcome and ICU admission including pneumonia severity index (PSI), CURB-65, CRB-65, modified ATS major and minor criteria, SCAP prediction rule, SMART-COP, REA-ICU index and CAP-PIRO.[16] Although they may help identify the sicker patients they should not be used as a sole determinant of ICU admission as local admission criteria will be affected by local facilities, both in and outside ICU. It should be noted that none of the criteria has been prospectively demonstrated to avoid late transfers or lower mortality.

INFLUENZA PNEUMONIA

Influenza pneumonia may present with severe respiratory failure and multi-organ failure. However the pattern of organ failure appears to vary between strains with H5N1 being associated with a much higher mortality and a higher incidence of multi-organ failure than pandemic H1N1,[17] which itself presented differently to seasonal influenza. In particular, trophism for lower respiratory tract, a higher rate of ICU admission[18] and a higher rate of extrapulmonary complications[19] were observed.

Early initiation of oseltamivir is recommended for critically ill patients although there is no direct evidence of outcome benefit. Glucocorticoids do not appear to be useful and may prolong viral replication.[20] Bacterial superinfection should be considered, with Gram-positive cocci being most frequently isolated.[21]

Table 36.2 Procedure for obtaining microbiological samples using bronchoscopy and protected specimen brushing and/or bronchoalveolar lavage[35,49]

Infection control	In patients suspected of having a disease that is transmitted by the airborne route (e.g. tuberculosis): • the risk of transmission should be carefully weighed against the benefits of bronchoscopy, which may generate large numbers of airborne particles • perform bronchoscopy in a negative-pressure isolation room • consider the use of a muscle relaxant in ventilated patients, to prevent coughing • staff should wear personal protective equipment, which should include a fit-tested negative-pressure respirator (N95, FFP2 or above) as a minimum; use of a powered air-purifying respirator should be considered
General recommendations	Suction through the endotracheal tube should be performed before bronchoscopy Avoid suction or injection through the working channel of the bronchoscope Perform protected specimen brushing before bronchoalveolar lavage
Ventilated patients	Set Fi_{O_2} at 1.0 Set peak pressure alarm at a level that allows adequate ventilation Titrate ventilator settings against exhaled tidal volume Consider neuromuscular blockade in addition to sedation in patients at high risk of complications who are undergoing prolonged bronchoscopy
Protected specimen brushing (PSB)	Sample the consolidated segment of lung at subsegmental level If purulent secretions are not seen advance the brush until it can no longer be seen, but avoid wedging it in a peripheral position Move brush back and forth and rotate it several times
Bronchoalveolar lavage (BAL)	Wedge tip of bronchoscope into a subsegment of the consolidated segment of lung Inject, aspirate and collect 20 mL of sterile isotonic saline. Do not use this sample for quantitative microbiology or identification of intracellular organisms. It can be used for other microbiological analysis Inject, aspirate and collect additional aliquots of 20–60 mL The total volume of saline injected should be 60–200 mL
Complications	Hypoxaemia (possibly less with smaller BAL volumes) Arrhythmia Transient worsening in pulmonary infiltrates Bleeding (particularly following PSB) Fever (more common after BAL)
Positive results	>5% of cells in cytocentrifuge preparations of BAL fluid contain intracellular bacteria OR $\geq 10^3$ colony-forming units/mL in PSB specimen OR $\geq 10^4$ colony-forming units/mL in BAL fluid

Although there are data demonstrating that surgical masks are as effective as N95 (FFP 2) masks in preventing transmission of seasonal influenza in non-ICU settings it is important to note that the capacity for airborne transmission (and hence the need for N95 masks) is dependent on the exact characteristics of the organism and the frequency of aerosol-generating procedures so these data should not be extrapolated to other influenza viruses and ICU settings.

HEALTHCARE-ASSOCIATED PNEUMONIA

Nosocomial pneumonia occurs in 0.5–5% of hospital patients, with a higher incidence in certain groups (e.g. postoperative patients and patients in ICU). Diagnosis may be difficult: the clinical features of pneumonia are non-specific and many non-infectious conditions (e.g. atelectasis, pulmonary embolus, aspiration, heart failure and cancer) can cause infiltrates on a chest X-ray. Identification of the organism responsible is even more difficult than in patients with community-acquired pneumonia owing to the high incidence of oropharyngeal colonisation by Gram-negative bacteria. Blood cultures are positive in only about 6% of cases of nosocomial pneumonia. Ventilator-associated pneumonia (VAP) is nosocomial pneumonia arising >48–72 hours after intubation. Reported incidence of VAP is between 10 and 20% for those receiving mechanical ventilation for more than 48 hours.[22] It is associated with a higher incidence of multi-drug-resistant organisms.[1]

PATHOGENESIS

Nosocomial pneumonia is thought to result from microaspiration of bacteria colonising the upper respiratory tract. Other routes of infection include macroaspiration

of gastric contents, inhaled aerosols, haematogenous spread, spread from pleural space and direct inoculation from ICU personnel.

CLINICAL DIAGNOSIS

Diagnosis is based on time of onset (>48 hours after admission to a healthcare facility[1]), CXR changes (new or progressive infiltrates) and either clinical features and simple laboratory investigations or the results of quantitative microbiology. Using a clinical approach, pneumonia is diagnosed by the finding of a new infiltrate or a change in an infiltrate on chest radiograph and growth of pathogenic organisms from sputum plus one of the following: white-blood-cell (WBC) count greater than 12×10^5/L, core temperature ≥38.3°C, sputum Gram stain with scores of more than two on a scale of four of polymorphonuclear leucocytes and bacteria.

INVESTIGATIONS

These are broadly similar to those required in community-acquired pneumonia:

- *Chest X-ray:* although studies using a histological diagnosis as the gold standard have demonstrated that pneumonia may be present despite a normal CXR, most definitions of nosocomial pneumonia require the presence of new persistent infiltrates on a CXR.
- *Respiratory secretions:* considerable controversy surrounds the issue of whether invasive bronchoscopic sampling (Table 36.2) of respiratory secretions is necessary. Whether invasive sampling is employed or tracheal aspirates are used, empirical broad-spectrum antibiotics should be started while results are awaited. The results of microbiological analysis of respiratory secretions are used to either stop antibiotics or narrow the spectrum.[1] Although the use of an invasive strategy is associated with a higher likelihood of modification of initial antimicrobials,[23] the effect on important clinical outcome such as mortality, antibiotic-free days, and organ dysfunction is variable.[1] Although tracheal aspirates may predominantly reflect the organisms colonising the upper airway, they may be useful in indicating which organisms are not responsible for the pneumonia, thus allowing the antimicrobial cover to be narrowed.[1] This interpretation is based on the premise that the predominant route of infection is via the upper respiratory tract. From this it can be assumed that if the organism is not present in the upper respiratory tract the probability of it being present in the lung parenchyma is low. Certain organisms are virtually always pathogens when recovered from respiratory secretions (see Box 36.1).
- *Blood cultures:* identify the aetiological agent in 8–20% of patients. Bacteraemia is associated with a worse prognosis. In 50% of patients with severe hospital-acquired pneumonia and positive blood cultures there is another source of sepsis.

MANAGEMENT

Management is based on the finding that early treatment with antimicrobials that cover all likely pathogens results in a reduction in morbidity and mortality.[2] The initial selection of antimicrobials is made on the basis of epidemiological clues (**Fig. 36.2**, **Table 36.3**). Antimicrobials should be administered within 1 hour of diagnosis.[12] The results of microbiological investigations are used to narrow antimicrobial cover later. Treatment should be reassessed after 2–3 days or sooner if the patient deteriorates (**Fig. 36.3**). An outline of management based on an invasive approach is given in **Figure 36.4**.

DURATION OF THERAPY

Current ATS guidelines recommend 7 days' treatment provided the aetiological agent is not *P. aeruginosa* or other non-lactose fermenter and the patient has a good clinical response with resolution of clinical features of infection.[1] The outcome of patients who receive appropriate initial empirical therapy for ventilator-associated pneumonia for 8 days is similar to those who receive treatment for 15 days.[1]

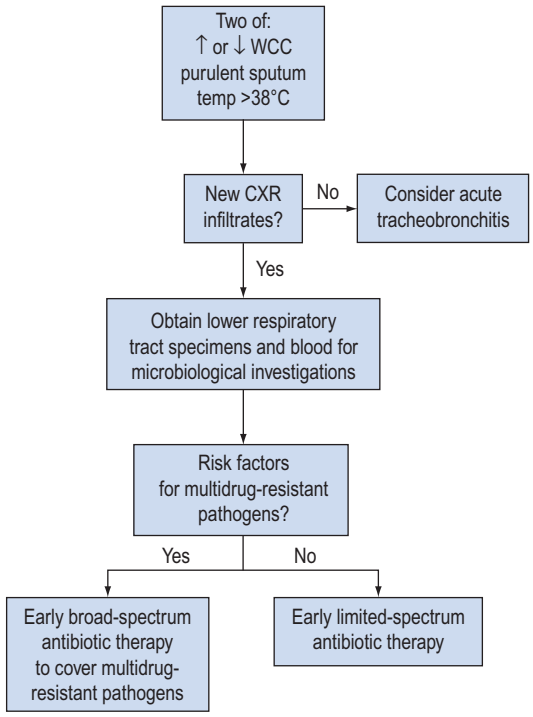

Figure 36.2 An outline of initial management of nosocomial pneumonia based on a non-invasive clinical approach.[1]

Table 36.3 Recommended initial empirical treatment for nosocomial pneumonia[1]

SITUATION	ANTIBIOTICS
No risk factors for multidrug-resistant pathogens	Ceftriaxone *or* Levofloxacin, moxifloxacin or ciprofloxacin *or* Ampicillin/sulbactam *or* Ertapenem
Antimicrobial therapy in previous 90 days *or* Current hospitalization for ≥5 days *or* High frequency of antibiotic resistance in the specific hospital unit *or* Hospitalisation for 2 days or more in previous 90 days *or* Residence in nursing home or extended care facility *or* Home infusion therapy (including antibiotics) *or* Chronic dialysis within 30 days *or* Home wound care *or* Family member with multidrug-resistant pathogen *or* Immunosuppression *or* Bronchiectasis	One of: Antipseudomonal cephalosporin (cefepime or ceftazidime) *or* Antipseudomonal carbapenem (meropenem or imipenem–cilastin) *or* ß-lactam/ß-lactamase inhibitor (e.g. piperacillin–tazobactam *or* cefaperazone–sulbactam) *plus* one of: Aminoglycoside *or* Antipseudomonal quinolone (levofloxacin or ciprofloxacin) *plus* one of the following for patients at high risk of meticillin-resistant *Staphylococcus aureus* (MRSA) infection: Linezolid *or* Vancomycin *or* Teicoplanin

The use of dual therapy is not well supported by evidence but it does reduce the probability that the pathogen is resistant to the drugs being given. If an extended spectrum β-lactamase-producing strain or an *Acinetobacter* sp. is suspected a carbapenem should be given. If *Legionella pneumophilia* is suspected use a quinolone. Risk factors for MRSA infection in areas with a high incidence of MRSA include diabetes mellitus, head trauma, coma and renal failure.

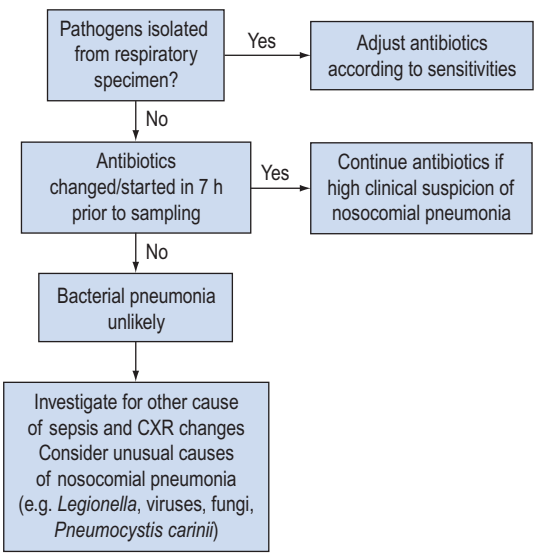

Figure 36.3 Subsequent management of nosocomial pneumonia based on a non-invasive clinical approach.[1]

RESPONSE TO THERAPY

Clinical improvement is usually not apparent for 48–72 hours and therapy should not be changed during this time. The CXR is of limited value for assessing response; initial deterioration is common and improvement often lags behind clinical response. However, a rapidly deteriorating CXR pattern with a >50% increase in size of infiltrate in 48 hours, new cavitation or a significant new pleural effusion should raise concern. If the patient fails to respond consider the diagnosis, host factors (e.g. immunosuppressed, debilitated), bacterial factors (e.g. virulent organism) and therapeutic factors (e.g. wrong drug, inadequate dose). Review the antibiotics and repeat cultures. It may be useful to broaden the antimicrobial cover while waiting for the results of investigations. Consider invasive sampling of respiratory secretions, computerised tomography or ultrasound of the chest (to look for an empyema or abscess), another source of infection, open-lung biopsy to establish diagnosis and aetiology, or administration of steroids.

MORTALITY AND MORBIDITY ATTRIBUTABLE TO VAP

Substantial morbidity and mortality associated with VAP have previously been reported.[22] However, a causal relationship is difficult to establish. It should be noted that patients who developed VAP tend to be more severely ill and at higher risk of death not only on ICU admission, but throughout the course of their illness. Most of the relevant studies were observational and failed to adequately control confounders like disease severity, evolution of disease progression, and ICU length of stay with mortality. In addition, significant heterogeneity exists among these studies. Although the presence of VAP is associated with a significantly longer ICU length of stay (mean of 6.1 days; 95% CI: 5.32–6.87) and increased healthcare cost,[22] more recent studies reported that mortality attributable to VAP tends to be small, if any.[24,25] The attributable mortality has been reported to be 1% on the 30th day of ICU and

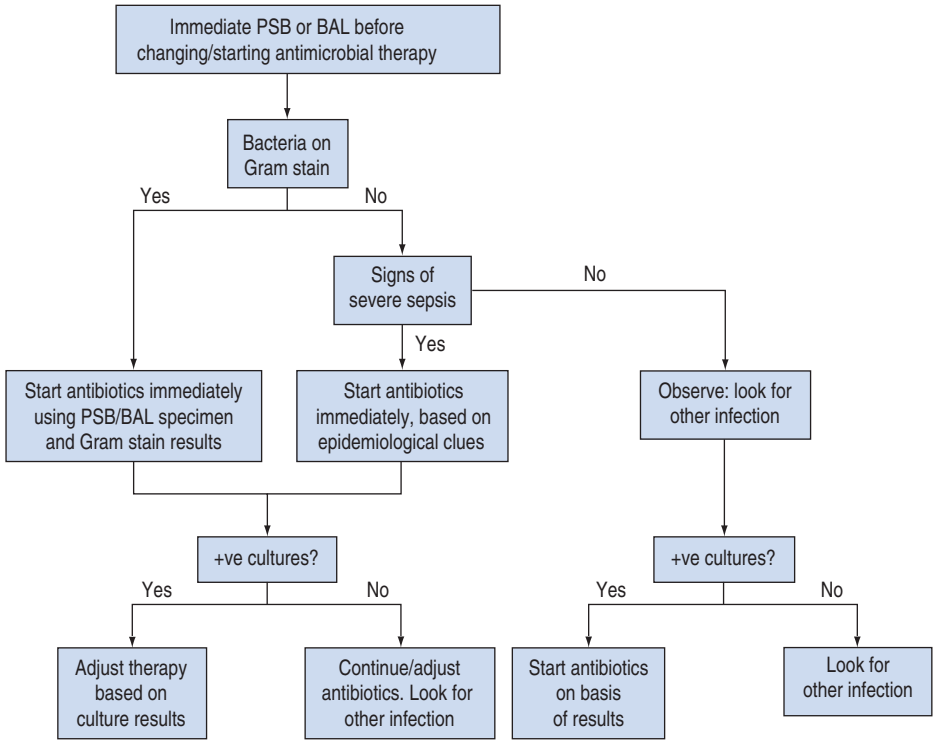

Figure 36.4 Management of suspected nosocomial pneumonia based on invasive sampling of respiratory secretions.

1.5% on the 60th day of ICU in a recent study using a multicentre high-quality database and incorporating novel statistical methodology to control evolution of severity of illness.[25]

PREVENTION

Several guidelines for prevention of ventilator-associated pneumonia and hospital-acquired pneumonia have been published.[26–30] Interventions can be divided into general infection control measures and specific measures. General measures include alcohol-based hand disinfection, hospital education programme on infection control, the use of microbiological surveillance and a programme to reduce antibiotic prescription. The major specific recommendations are summarised in **Table 36.4**. There is no evidence that 'bundles' of recommendations are more effective than the sum of the individual components.

TUBERCULOSIS

The main risk factors are listed in Box 36.2. Typical clinical features include fever, sweating, weight loss, lassitude, anorexia, cough productive of mucoid or purulent sputum, haemoptysis, chest wall pain, dyspnoea, localised wheeze and apical crackles. Patients may also present with unresolved pneumonia, pleural effusions, spontaneous pneumothorax and hoarseness or with enlarged cervical nodes or other manifestations of extrapulmonary disease. Clinical disease is seldom found in asymptomatic individuals, even those with strongly positive tuberculin test (Heaf grade III or IV). The outlook for patients with tuberculosis who require ICU admission is poor. In one retrospective study the in-hospital mortality for all patients with tuberculosis requiring ICU admission was 67% but in those with acute respiratory failure it rose to 81%.[31] The presentation and management of TB in HIV-positive patients are different (see below).

INVESTIGATION OF PULMONARY TUBERCULOSIS

IDENTIFICATION OF MYCOBACTERIA

Multiple[32,33] sputum samples should be collected, preferably on different days, for microscopy for acid-fast bacilli and culture. If sputum is not available bronchial washings taken at bronchoscopy and gastric lavage or aspirate samples should be obtained. Gastric aspirates need to be neutralised immediately on collection. Bronchoscopy and transbronchial biopsy may be useful in patients with suspected TB but negative sputum smear. Pleural biopsy is often helpful and mediastinoscopy is occasionally needed in patients with mediastinal lymphadenopathy. Part of any biopsy specimen should always be sent for culture. Nucleic acid amplification tests on sputum have sensitivity similar to culture in

Table 36.4 Strategies for prevention of ventilator-associated pneumonia

LEVELS OF RECOMMENDATIONS	SPECIFIC INTERVENTIONS	REMARKS
Universally recommended by all guidelines[27–30]	1. Semirecumbent position to 45° 2. Avoidance of endotracheal intubation 3. Preference of oral tracheal route 4. New circuit for a new patient and no schedule change unless soiled or damaged 5. Avoidance of flushing of condensate into lower airway or in-line medication 6. HME changes no more frequently than 5–7 days	At least 30–45°
	7. Continuous aspiration of subglottic suctioning	For patients expected to require mechanical ventilation for >72 hours
Generally recommended by most guidelines	1. Preferential use of non-invasive ventilation[27,28,30] 2. Avoidance of unplanned re-intubation[27,28,30] 3. Maintenance of endotracheal cuff pressure of about 20 mmHg (2.66 kPa)[27,28,30]	
	4. Closed suctioning[28,29]	No effect on VAP, mainly for staff safety
	5. Chlorhexidine oral decontamination[27,29,30] 6. Sedation vacation and weaning protocol[27,28] 7. Judicious use of stress ulcer prophylaxis[27,28,30] 8. Restrictive blood transfusion[28]	
Benefits less clear	1. Preference of HME over heated humidifier[28,30] 2. Silver-sulfadiazine-coated endotracheal tube[27,28,30] 3. Early tracheostomy (within 7 days of mechanical ventilation)[29]	HME associated with reduction in VAP in patients ventilated for >7 days, lower cost
	4. Selective decontamination of digestive tract (SDD)[27,28,30]	Mortality reduction demonstrated when topical antimicrobials combined with short-course systemic antibiotics, BSAC recommended SDD in patients expected to require mechanical ventilation for >48 hours, ETF discourage routine use due to concern of emergence of resistant organisms
Not yet reviewed by guidelines[50]	1. High-volume low-pressure ultrathin membrane endotracheal tube cuff with SSD 2. Ultrathin membrane cuff with tapered shape and SSD 3. Low-volume low-pressure endotracheal tube cuff with SSD 4. Balloon device for biofilm removal 5. Saline instillation before tracheal suctioning	

HME=heat moist exchanger; SSD=subglottic secretion drainage.

smear-negative patients with pulmonary tuberculosis but have the advantage of a much more rapid result. There is, however, a significant false-negative rate.[32]

CHEST X-RAY (CXR)

A normal CXR almost excludes TB (except in HIV-infected patients) but endobronchial lesions may not be apparent and early apical lesions can be missed. Common appearances include patchy/nodular shadowing in the upper zones (often bilateral), cavitation, calcification, hilar or mediastinal lymphadenopathy (may cause segmental or lobar collapse), pleural effusion, tuberculomas (dense round or oval shadows) and diffuse fine nodular shadowing throughout the lung fields in miliary TB. Inactivity of disease cannot be inferred from the CXR alone. This requires three negative sputum samples *and* failure of any lesion seen on CXR to progress. CXR appearances in HIV-positive

patients with TB differ from those in non-HIV-infected patients.

TREATMENT OF PULMONARY TB[32–34]

The decision to initiate anti-TB treatment should be based on level of clinical suspicion, results of AFB smear and sometimes mycobacterial culture. If the initial clinical suspicion is strong and the patient is seriously ill attributable to possible TB, treatment should be initiated promptly, sometimes before the result of AFB smear. Subsequent positivity of AFB smear or nucleic acid amplification test provides support to the continuation of treatment. Combination chemotherapy consisting of four drugs is necessary for maximal efficacy. Treatment is divided into initial phase and continuation phase. The most commonly used initial regimen consists of 8 weeks of rifampicin 600 mg daily (450 mg for patients <50 kg), isoniazid 300 mg daily, pyrazinamide 2 g daily (1.5 g for patients <50 kg) and ethambutol 15 mg/kg daily as initial phase treatment. Ethambutol should be used only in patients who have reasonable visual acuity and who are able to appreciate and report visual disturbances. This mandates careful consideration in patients who require heavy sedation. Visual acuity and colour perception must be assessed (if ethambutol is to be used) and liver and renal function checked before treatment is started. Steroids are recommended for children with endobronchial disease and, possibly, for patients with tuberculous pleural effusions. Pyridoxine 10 mg daily should be given to prevent isoniazid-induced neuropathy to those at increased risk (e.g. patients with diabetes mellitus, chronic renal failure or malnutrition or alcoholic or HIV-positive patients). Negative AFB smear should not delay initial treatment if clinical suspicion remains high. Supporting features included chronic cough, weight loss, characteristic chest X-ray findings, emigration from a high-incidence country, no other immediate diagnosis, and positive tuberculin test.

INFECTION CONTROL

Patients admitted to an ICU with infectious TB or suspected of having active pulmonary TB should be managed in an isolation room with special ventilation characteristics, including negative pressure. Patients should be considered infectious if they are coughing or undergoing cough-inducing procedures or if they have positive AFB smears and they are not on or have just started chemotherapy, or have a poor clinical or bacteriological response to chemotherapy.[32,35] Patients with non-drug-resistant TB should be non-infectious after 2 weeks of treatment which includes rifampicin and isoniazid.[32] As TB spreads through aerosols it is probably appropriate to isolate patients who are intubated even if only their bronchial washings are smear-positive. Staff caring for patients who are smear-positive should wear personal protective equipment including a fit-tested negative-pressure respirator (N95, FFP2 or higher). Use of a powered air-purifying respirator should be considered when bronchoscopy is being performed.[35] Detailed infection control advice can be obtained via the 'link page' (http://www.aic.cuhk.edu.hk/web8/Pneumonia%20guidelines.htm.).

PNEUMONIA IN THE IMMUNOCOMPROMISED

The lungs are amongst the most frequent target organs for infectious complications in the immunocompromised. The incidence of pneumonia is highest amongst patients with haematological malignancies, bone marrow transplant (BMT) recipients and patients with AIDS.

The speed of progression of pneumonia, the CXR changes (**Table 36.5**) and the type of immune defect provide clues to the aetiology. Bacterial pneumonias progress rapidly (1–2 days) whereas fungal and protozoal pneumonias are less fulminant (several days to a week or more). Viral pneumonias are usually not fulminant, but on occasions may develop quite rapidly. Bronchoscopy is a major component of the investigation of these patients. Empirical management based on CXR appearances is outlined in Table 36.5. Early non-invasive ventilation may improve outcome amongst immunocompromised patients with fever and bilateral infiltrates.[36]

PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP)[37]

The incidence of this common opportunistic infection has fallen substantially in patients with AIDS who are receiving prophylaxis and effective antiretroviral therapy, with most cases occurring in patients who are not receiving HIV care or among patients with advanced immunosuppression. The onset is usually insidious with dry cough, dyspnoea and fever on a background of fatigue and weight loss. Crackles in the chest are rare. Approximately 15% of patients have a concurrent cause for respiratory failure (e.g. Kaposi sarcoma, TB, bacterial pneumonia). Useful investigations are:

1. *CXR:* classical appearance is diffuse bilateral perihilar interstitial shadowing, but in the early stages this is very subtle and easily missed. The initial CXR is normal in 10%. In a further 10% the changes are atypical with focal consolidation or coarse patchy shadowing. None of the changes are specific for PCP and may be seen in other lung diseases associated with AIDS. Pleural effusions, hilar or mediastinal lymphadenopathy are unusual in PCP but common in mycobacterial infection or Kaposi's sarcoma or lymphoma.
2. *Induced sputum:* in this technique the patient inhales nebulised hypertonic saline from an ultrasonic nebuliser. This provokes bronchorrhoea and the patient

Table 36.5 Causes of CXR changes and empirical treatment of pneumonia in the immunocompromised

CHEST X-RAY APPEARANCE	CAUSES	EMPIRICAL TREATMENT FOR SUSPECTED PNEUMONIA
Diffuse infiltrate	CMV and other herpes viruses *Pneumocystis carinii* Bacteria *Aspergillus* (advanced) *Cryptococcus* (uncommon) Non-infectious causes, e.g. drug reaction, non-specific interstitial pneumonitis, radiation pneumonitis (uncommon), malignancy, leucoagglutinin reaction	Broad-spectrum antibiotics for at least 48 h (e.g. 3rd-generation cephalosporin and aminoglycoside) Co-trimoxazole Lung biopsy or lavage within 48 h or full 2-week course of co-trimoxazole (depends on patient tolerance of invasive procedure)
Focal infiltrate	Gram-negative rods *S. aureus* *Aspergillus* *Cryptococcus* *Nocardia* *Mucor.* *P. carinii* (uncommon) Tuberculosis Legionella Non-infectious causes (e.g. malignancy, non-specific interstitial pneumonitis, radiation pneumonitis)	Broad-spectrum antibiotics If response seen continue treatment for 2 weeks If disease progresses lung biopsy/aspirate within 48–72 hours or empirical trial of antifungal ± macrolide

coughs up material containing cysts and trophozoites. The technique is time-consuming and requires meticulous technique and is less sensitive than bronchoscopy but less invasive. The possibility of concurrent tuberculosis should be considered and steps taken to minimise the risk of spread of infection.

3. Bronchoscopy with bronchoalveolar lavage leads to the diagnosis in over 90% of cases. Specimens should be sent for cytology. Transbronchial biopsy is not necessary in most cases. PCR using bronchial lavage specimens may be useful in non-HIV patients with suspected PCP.

Antipneumocystis treatment should be started as soon as the diagnosis is suspected. Treatment of choice is trimethoprim plus sulfamethoxazole (co-trimoxazole) 20 mg/kg/day+100 mg/kg/day for 3 weeks plus prednisolone 40 mg orally twice daily for 5 days followed by 20 mg twice daily for 5 days and then 20 mg per day until the end of PCP treatment. Side-effects of co-trimoxazole are common in HIV patients (nausea, vomiting, skin rash, myelotoxicity). The dose should be reduced by 25% if the WBC count falls. Patients who are intolerant of co-trimoxazole should be treated with:

- pentamidine 4 mg/kg/day i.v. or
- primaquine with clindamycin or
- trimetrexate with leucovorin (±oral dapsone).

Response to treatment is usually excellent, with a response time of 4–7 days. If the patient deteriorates or fails to improve: consider (re-)bronchoscopy (is the diagnosis correct?), treat co-pathogens and consider a short course of high-dose i.v. methylprednisolone and/or diuretics (patients often fluid-overloaded). Approximately 40% of patients with HIV-related PCP who require mechanical ventilation survive to hospital discharge.[38]

Initiation of antiretroviral therapy in patients presenting with HIV-related PCP is controversial. The Centers for Disease Control and Prevention (CDC) recommend against doing so in the acute phase, but recent data suggest that the outcome may be improved by initiation within the first 4 days of ICU admission.[39]

BACTERIAL PNEUMONIA[37]

This is the most common cause of acute respiratory failure in HIV-positive patients. Bacterial pneumonia is more common in HIV-infected patients than in the general population and tends to be more severe. *Strep. pneumoniae, H. influenza, Pseudomonas aeruginosa* and *S. aureus* are the commonest organisms. *Nocardia* and Gram negatives should also be considered. Atypical pathogens (e.g. *Legionella*) are rare. Response to appropriate antibiotics is usually good but may require protracted courses of antibiotics because of high tendency to relapse. Patients with severe immunodeficiency ($CD4^+$ T lymphocyte count <100/μL) and a history of *Pseudomonas* infection or bronchiectasis or neutropenia should receive antibiotics that cover *P. aeruginosa* as well as other Gram negatives. The possibility of concurrent PCP or tuberculosis should be excluded.

TUBERCULOSIS

TB may be the initial presentation of AIDS, particularly in sub-Saharan Africa. The pattern of TB in HIV patients

depends on the degree of immunosuppression. In patients with $CD4^+$ T lymphocytes >350 cells/μL the clinical presentation is similar to TB in non-HIV-infected patients, although extrapulmonary disease is more common. In patients with $CD4^+$ T lymphocytes <350 cells/μL extrapulmonary disease (pleuritis, pericarditis, meningitis) is common. Severely immunocompromised patients ($CD4^+$ T lymphocytes <100 cells/μL) may present with severe systemic disease with high fever, rapid progression and systemic sepsis. In these patients lower and middle lobe disease is more common, miliary disease is common and cavitation is less common. Sputum smears and culture may be positive even with a normal CXR.

Response to treatment is usually rapid. Management of TB in HIV is complex owing to numerous drug interactions; consultation with an expert in treatment of HIV-related TB should be strongly considered. Complex interactions occur between rifamycins (e.g. rifampicin and rifabutin) and protease inhibitors and non-nucleoside reverse transcriptase inhibitors used to treat patients infected with HIV. The choice of rifampicin or rifabutin depends on a number of factors including the unique and synergistic adverse effects for each individual combination of rifampicin and anti-HIV drugs, and consultation with a physician with experience in treating both TB and HIV is advised.[40] IDSA-recommended dosage adjustment for patients receiving antiretrovirals and rifabutin[37] can be obtained via the 'link page' (http://www.aic.cuhk.edu.hk/web8/Pneumonia%20guidelines.htm.). The optimal time for initiating antiretroviral therapy in patients with TB is controversial. Early therapy may decrease HIV disease progression but may be associated with a high incidence of adverse effects and an immune reconstitution reaction.[37]

CMV PNEUMONITIS[41,42]

Risk of infection is highest following allogeneic stem cell transplantation, followed by lung transplantation, pancreas transplantation and then liver, heart and renal transplantation and advanced AIDS. If both the recipient and the donor are seronegative then the risk of both infection and disease are negligible. If the recipient is seropositive the risk of infection is approximately 70% but the risk of disease is only 20%, regardless of the serostatus of the donor. However if the recipient is seronegative and the donor is seropositive the risk of disease is 70%. If steroid pulses and antilymphocyte globulin are given for treatment of acute rejection the risk of developing disease is markedly increased. Infection may be the result of primary infection or reactivation of latent infection. It is clinically important, but often difficult to distinguish between CMV infection and CMV disease and a definitive diagnosis can be made only histologically. Detection of CMV-pp65 antigen in peripheral WBC and detection of CMV DNA or RNA in the blood by quantitative polymerase chain reaction are the most useful tests for demonstrating CMV disease. Using thresholds of 10/300 000–50/200 000 positive circulating peripheral WBC, the positive predictive value for CMV-pp65 ranges from 64% to 82% and the negative predictive value from 70% to 95%[43,44] Treatment consists of intravenous ganciclovir for at least 14 days. Foscarnet can be used if ganciclovir fails.

FUNGAL PNEUMONIA

Fungi are rare but important causes of pneumonia. They can be divided into two main groups based on the immune response required to combat infection with these organisms. Histoplasma, blastomycosis, coccidioidomycosis, paracoccidioidomycosis and *Cryptococcus* require specific cell-mediated immunity for their control and thus, in contrast to infections that are controlled by phagocytic activity, the diseases caused by these organisms can occur in otherwise healthy individuals although they cause much more severe illness in patients with impaired cell-mediated immunity (e.g. patients infected with HIV and organ transplant recipients). With the exception of *Cryptococcus* these organisms are rarely seen outside North America. *Aspergillus* and *Mucor* spores are killed by non-immune phagocytes and as a result these fungi rarely result in clinical illness in patients with normal neutrophil numbers and function.

CANDIDIASIS

This is effectively a combination of the two types of fungal infection in which impaired cell-mediated immunity predisposes to mucosal overgrowth with *Candida* but impaired phagocytic function or numbers is usually required before deep invasion of tissues occurs. Primary *Candida* pneumonia (i.e. isolated lung infection) is uncommon[41,45] and more commonly pulmonary lesions are only one manifestation of disseminated candidiasis. Even more common is benign colonisation of the airway with *Candida*. In most reported cases of primary *Candida* pneumonia amphotericin B has been used. In disseminated candidiasis treatment should be directed to treatment of disseminated disease rather than *Candida* pneumonia per se.[45]

INVASIVE ASPERGILLOSIS[46]

This is a highly lethal condition in the immunocompromised despite treatment and therefore investigation and treatment should be prompt and aggressive. It is associated with exposure to construction work. Definitive diagnosis requires both histological evidence of acute-angle branching, septated non-pigmented hyphae measuring 2–4 μm in width, and cultures yielding *Aspergillus* species from biopsy specimens of involved organs. Recovery of *Aspergillus* species from respiratory secretions in immunocompromised, but not immunocompetent, patients may indicate invasive disease with a positive predictive value as high as

80–90% in patients with leukaemia or bone marrow transplant recipients. Bronchoalveolar lavage with smear, culture and antigen detection has excellent specificity and reasonably good positive predictive value for invasive aspergillosis in immunocompromised patients. Although radiological features may give a clue to the diagnosis they are not sufficiently specific to be diagnostic.

In acutely ill immunocompromised patients intravenous therapy should be initiated if there is suggestive evidence of invasive aspergillosis while further investigations to confirm or refute the diagnosis are carried out. First-line therapy is voriconazole.[47] Echinocandins and amphotericin are alternatives.

PARAPNEUMONIC EFFUSION

This may be an uncomplicated effusion that resolves with appropriate treatment of the underlying pneumonia or a complicated effusion that develops into an empyema unless drained. Complicated effusions tend to develop 7–14 days after initial fluid formation. They are characterised by increasing pleural fluid volume, continued fever and pleural fluid of low pH (<7.3) that contains a large number of neutrophils and may reveal organisms on Gram staining or culture. An outline of management is given in **Figure 36.5**.

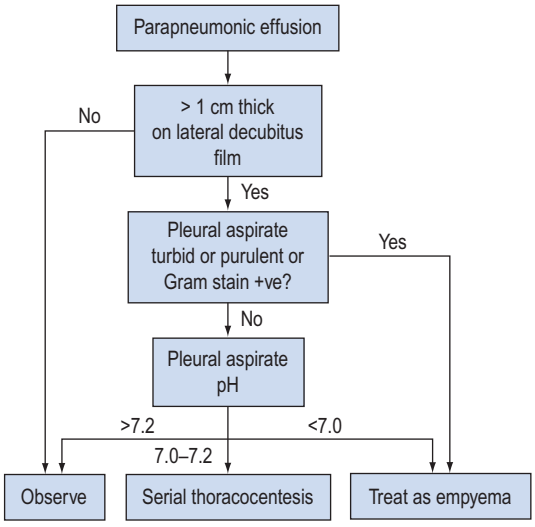

Figure 36.5 An approach to the management of parapneumonic effusions.

EMPYEMA[48]

DEFINITION

Collection of pus in the pleural space.

AETIOLOGY

Follows infection of the structures surrounding the pleural space, including subdiaphragmatic structures, and chest trauma, or may be associated with malignancy. Anaerobic bacteria, usually streptococci or Gram-negative rods, are responsible for 76% of cases.

DIAGNOSIS

The diagnosis is usually simple. The patient is usually septic and may have a productive cough and chest pain. The chest X-ray may show features suggestive of a pleural effusion and underlying consolidation but may also show an abscess cavity with a fluid level, in which case CT scanning will be required to distinguish between an abscess and an empyema. Ultrasound can be useful to confirm the presence of fluid in the pleural space and to determine whether it can be drained by needle aspiration or, if there is debris within the fluid, drainage using an intercostal drain. The diagnosis is confirmed by aspiration of pus.

TREATMENT

The mainstay of treatment is drainage either by intercostal drain or by surgical intervention. Patients who present before the pus is loculated and a fibrinous peel has formed on the lung can usually be treated by simple drainage. The combination with intrapleural fibrinolysis may be beneficial. Optimal surgical management, which consists of decortication (open or thoracoscopic), is indicated if the empyema is more advanced or if simple drainage fails. This is a major procedure and many patients with cardiac or chronic respiratory disease will not tolerate it. Alternatives for these patients are instillation of thrombolytics into the pleural space or thoracostomy. Antibiotics have only an adjunctive role. Broad-spectrum antibiotic regimens with anaerobic cover should be used until the results of microbiological analysis of the aspirated pus are available.

Acknowledgements

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