Chapter 6
Lower Respiratory Tract Infections

Scenario

A 73 year old man with a 50 pack year smoking history is admitted with a 3 day history of shortness of breath and increasing confusion. He has a respiratory rate of 35/min and a blood pressure of 85/40 mmHg.

1. What is his expected clinical course?
2. What is the likelihood that if he has pneumonia his pneumonia is bacterial in origin?
3. Is there a place for non-invasive ventilatory support?

Introduction

Lower respiratory tract infections are common and are important in the intensive care setting either because they precipitate admission to the intensive care unit, e.g. severe viral pneumonia or because they complicate the course of a patient with significant underlying disease or following major surgery, e.g. after multiple trauma. Furthermore, respiratory failure requiring artifical ventialtion is a well recognised reason for intensive care support but it can be difficult to determine if this is due to an underlying non-infectious condition such as chronic obstructive pulmonary disease (COPD), infection or a combination of both. The early diagnosis and management of respiratory infection combined with appropriate ventilatory support aids prognosis and the efficient use of intensive care facilities given the number of patients affected.

Community-Acquired Pneumonia

Background

Community acquired pneumonia (CAP) is common with an estimated incidence of 2–12 cases/1,000 population annually [1] representing 5.9 % of UK ICU admissions [2]. Community acquired pneumonia requiring ICU admission has a high mortality (ICU). In a study of 17,869 cases of CAP admitted to UK intensive care units, ICU mortality was 34.9 % and ultimate hospital mortality 49.4 %. Mortality was 46.3 % in those admitted to the ICU within 2 days of hospital admission rising to 50.4 % in those admitted at 2–7 days and 57.6 % in those admitted after 7 days following hospital admission [2].

At presentation many patients with severe CAP will already be developing multiple organ failure. Identification of the critically ill pneumonia patient is essential to the early and effective management of this condition. Severity-of-illness scores, such as the CURB-65 (confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater), or prognostic models, such as the Pneumonia Severity Index (PSI), can be used to identify patients with CAP who might benefit from ICU admission. In some studies, significant numbers of patients with CAP are transferred to the ICU in the first 24–48 h after admission. Mortality and morbidity among these patients appears to be greater than those among patients admitted directly to the ICU.

The most recent modification of the British Thoracic Society (BTS) criteria includes five easily measurable factors [3]. Multivariate analysis of 1,068 patients identified the following factors as indicators of increased mortality: confusion (based on a specific mental test or disorientation to person, place, or time), BUN level 17 mmol/L (20 mg/dL), respiratory rate 30 breaths/min, low blood pressure (systolic, <90 mmHg; or diastolic, 60 mmHg), and age 65 years. This gave rise to the original acronym CURB- 65. In the derivation and validation cohorts, the 30-day mortality among patients with 0, 1, or 2 factors was 0.7, 2.1, and 9.2 %, respectively. Mortality was higher when 3, 4, or 5 factors were present and was reported as 14.5, 40, and 57 %, respectively. The authors suggested that patients with a CURB-65 score of 0–1 be treated as outpatients, those with a score of 2 be admitted to the wards, and that patients with a score of 3 often required ICU care.

Direct admission to an ICU is required for patients with septic shock requiring vasopressors or with acute respiratory failure requiring immediate intubation and mechanical ventilation. Decisions on direct admission to an ICU or high-level monitoring unit should be based on a number of parameters and is recommended for patients with three or more of the following [3]:

1. **Respiratory rate >30 breaths/min**
2. **PaO_2/FiO_2 ratio >250**
3. **Multilobar infiltrates on chest X-ray** (Fig. 6.1)
4. **Confusion/disorientation**
5. **Uremia**

Fig. 6.1 Left-sided multi-lobar infiltrates in a patient with community-acquired pneumonia
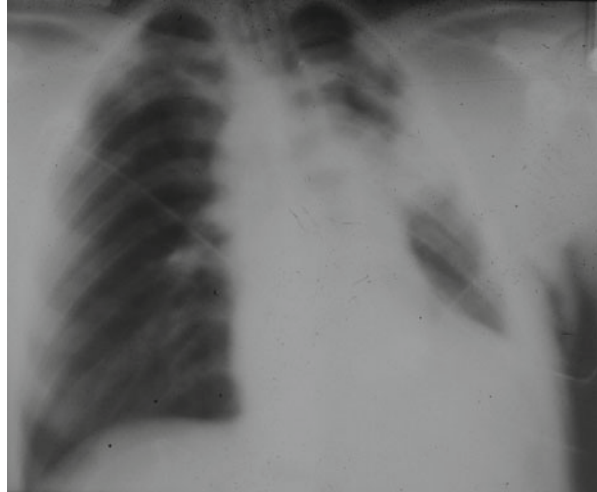
6. **Leukopenia (WBC count, <4,000 cells/mm³)**
7. **Thrombocytopenia (platelet count, <100,000 cells/mm³)**
8. **Hypothermia (core temperature, <36 °C)**
9. **Hypotension requiring aggressive fluid resuscitation**

Diagnosis

A relatively small number of pathogens account for the majority of cases of CAP with *Streptococcus pneumoniae* consistently shown to be the commonest pathogen in Europe and North America although in at least one third of cases no definite caus-ative organism is isolated [4]. A survey of 16 studies of severe CAP found the fol-lowing pathogens: *S. pneumoniae* 12–38 %; *Legionella* spp., 0–30 %; *Staphylococcus aureus* 1–18 %; and Gram negative enteric bacilli 2–34 % [1].

Historically, CAP was divided into so-called 'typical' and 'atypical' and was said to produce different presentations. 'Typical' pneumonia was caused by pneumococci and was said to present with fever of greater than 39 °C, pleuritic chest pain, lobar consolidation, and a left shift of granulocytes. 'Atypical' pneumonia had a more gradual onset with diffuse interstitial or alveolar pattern on the plain chest X-ray. Studies, however, have shown that clinical overlap between the different pathogens is great and that symptoms and plain chest radiology can not reliably differentiate between the different pathogens [1]. In severe CAP the situation is even more difficult. In the UK Intensive Care National Audit and Research Centre (www.icnarc.org) case mix database viral pneumonia accounted for 2 % of cases admitted to criti-cal care units with CAP accounting for 39 % of cases. However, no organism was isolated in 59 % of cases where the primary admission diagnosis was pneumonia.

The BTS recommends the following investigations for all severe cases of CAP [3]:

- **Blood cultures**
- **Sputum or lower respiratory tract sample** for Gram stain, routine culture, and antibiotic susceptibility tests
- **Pleural fluid analysis**, if a pleural effusion/empyema is present
- **Pneumococcal antigen test** on sputum, blood, or urine
- **Investigations for legionella** including

  - Urine for legionella antigen
  - Sputum or lower respiratory tract samples for legionella culture and direct immunofluorescence
  - Initial and follow up legionella serology

- **Direct immunofluorescence** on appropriate samples, e.g. bronchoscopy sample or equivalent for respiratory viruses (e.g. influenza in season, adenovirus, respiratory synctial virus, etc), *Chlamydia* species, and possibly *Pneumocystis jirovecii* (*carinii*)
- **Initial and follow up serology** for pathogens difficult to culture such as *Mycoplasma pneumoniae*

However, there is no good evidence that this strategy alters the outcome of severe CAP and studies disagree about the impact of microbiological testing on outcome [5].

Management

The American Thoracic Society recommendations for inpatient, ICU antibiotic treatment are a beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone. For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended. For community-acquired methicillin-resistant *Staphylococcus aureus* infection, vancomycin or linezolid are suggested [6]. The BTS guidelines recommend the combination of amoxicillin/clavulanate with clarithromycin and the optional addition of rifampicin, which provides additional cover, especially against *Staphylococcus aureus* and *Legionella* spp.

Patients with hypoxemia or respiratory distress should receive a cautious trial of non-invasive ventilation (NIV) unless they require immediate intubation because of severe hypoxemia (arterial oxygen pressure/fraction of inspired oxygen [PaO_2/FiO_2] ratio, <150 mmHg or 20 kPa) and bilateral alveolar infiltrates [7]. Patients with underlying COPD are most likely to benefit from NIV [8]. Patients with CAP who were randomized to receive NIV had more than a 25 % absolute risk reduction for intubation [9]. Inability to cough may limit the use of NIV, but intermittent application of NIV may allow for its use in patients with productive cough without excessive sputum production. Prompt recognition of a failed NIV trial is important, as patients who require intubation after a prolonged NIV trial have a worse outcome. Within the first

1–2 h of NIV, failure to improve respiratory rate and oxygenation or failure to decrease carbon dioxide partial pressure (pCO_2) in patients with initial hypercarbia predicts NIV failure and warrants prompt intubation. NIV provides no benefit for patients with adult respiratory distress syndrome (ARDS), which may be indistinguishable from CAP among patients with bilateral alveolar infiltrates. Patients with CAP who have severe hypoxemia (PaO_2/FiO_2 ratio, <150) are also poor candidates for NIV [10].

The optimal ventilator strategy for patients with severe CAP has not been established. Both volume controlled and pressure controlled modes have been used with varying levels of positive end expiratory pressure (PEEP). Although there is a significant incidence of ARDS in patients with CAP it is unclear whether the ARDSnet lung protective strategy should be applied in all patients [11].

In patients with CAP who fail to respond to initial treatment, broncho-alveolar lavage identifies pathogens in 12–30 %. Although the yield is relatively low, it is recommended that bronchoscopy is performed in severe CAP where the diagnosis is not established or where treatment is failing [12]. Once the patient is intubated and ventilated this is relatively easy to perform although often associated with transient deterioration in oxygenation. The diagnosis should be reviewed and other conditions presenting with X-ray infiltrates such as cardiac failure and pulmonary infarction excluded. Culture results may be available by this stage and may necessitate a change in therapy. The possibility of immunosuppression should be considered with the consequent possibility of an opportunist pathogen, e.g. *Pneumocystis jirovecii* (*carinii*) and a history of recent foreign travel excluded which might impact on the choice of empirical antibiotic therapy. Pathogens may vary from country to country and tuberculosis does occasionally present as severe CAP. Therefore this diagnosis should be considered in the relevant settings or geographical areas.

Influenza

Most cases of influenza are self-limiting and are characterized by the sudden abrupt onset of fever, malaise, headache and a non-productive cough. This syndrome is usually easily distinguishable from the common cold caused by coronaviruses, rhinoviruses, para-influenza viruses, etc. The elderly and those with chronic underlying diseases such as ischemic heart disease are more at risk of complications from influenza, including death. However, when a pandemic occurs, as in 2009 with H1N1, other groups of patients were at risk of more severe disease as they had not been exposed to a radically new virus, different to those viral strains that circulated previously. Early diagnosis is important and the threshold for suspicion should fall during the influenza season or during a pandemic. Then every patient requiring critical care support with respiratory failure should have a throat swab in viral transport medium or nasopharyngeal aspirate, and a good quality lower respiratory sample, e.g. broncholaveloar lavage (BAL) or equivalent, sent for viral studies, i.e. immunofluorescence or the polymerase chain reaction (PCR).

Influenza- related pneumonia is similar to other forms of viral pneumonia although the recent pandemic H1N1 strain originating from Mexico had some different features. The Australasian experience was published by the Australia New Zealand Intensive Care Society Group [13]. A total of 722 patients with confirmed infection with H1N1 infection (28.7 cases per million inhabitants; 95 % confidence interval [CI], 26.5–30.8) required admission to an ICU in Australia or New Zealand. Of the 722, 92.7 % were under 65 and 9.1 % were pregnant. The obese were also adversely affected; 28.6 % of ICU patients had a body-mass index of more than 35. The median ICU stay was 7.0 days, 64.6 % required mechanical ventilation for a median of 8 days and 14.3 % had died within a month of presentation.

Higher numbers than usual for viral pneumonia received treatment with extra-corporeal membrane oxygenation (ECMO). Of patients who required mechanical ventilation, 11.6 % were subsequently treated with ECMO. This parallels the situation in UK (Richard Firmin, personal communication). A recent paper [14] matched 80 patients referred for ECMO in the UK with patients from a pool of 1,756 patients from the ICNARC casemix program using three different techniques and found a mortality of around 24 % in patients who were referred for ECMO and around 50 % for the matched controls.

During the 2009–2010 H1N1 influenza A pandemic, the United States Centers for Disease Control and Prevention and other agencies around the world released guidelines for the use of antivirals for patients with confirmed or suspected infection [15]. For most patients a neuraminidase inhibitor (e.g. oseltamivir) is recommended and this should be started as soon as possible to improve patient outcome and assist in reducing transmission.

Healthcare-Acquired Pneumonia

Background

Healthcare-associated pneumonia is defined as new onset of pneumonia more than 48 h after admission to a healthcare facility and may occur in either the open ward environment or in association with mechanical ventilation, i.e. associated pneumonia (VAP). Infection acquired in an acute hospital compared to that acquired in a long stay institution is more likely to be antibiotic-resistant and due cognisance needs to be taken of this when treating empirically.

Etiology

VAP was historically associated with the overgrowth of aerobic Gram negative bacilli but is now increasingly characterized by infection with Gram positive organisms such as *Staph aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA)

as well as resistant strains of *Acinetobacter* spp and Enterobacteriaceae resistant to extended-spectrum beta-lactam agents such as third generation cephalosporins.

Diagnosis

There is a lack of a clear and clinically accepted definition for VAP. There is also a difference between research definitions including the need for invasive lung sampling such as protected specimen brushing (PSB) or BAL, and clinical definitions stressing increased oxygen requirements, new infiltrates on chest X-ray, purulent tracheal aspirates etc.

The presence of new chest X-ray infiltrates plus one of the three clinical variables (fever, i.e. ≥ 38 °C, leucocytosis or leucopenia and purulent secretions) is useful for clinical screening and has high sensitivity but should where possible be followed by invasive respiratory sampling ideally before commencing antibiotics. Protected specimen brushing with a threshold on quantitative culture of 10^3 cfu/ml, or bronchoalveolar lavage with threshold of 10^4 cfu/ml have been said to be equivalent for the diagnosis of ventilator associated pneumonia [16]. However, 40–60 % of patients meeting the above clinical criteria for VAP will not have the diagnosis confirmed by alternate objective methods such as quantitative cultures of PSB or BAL samples [17].

In some studies VAP appears to be an independent risk factor for death, with a doubling of the mortality rate directly attributable to VAP [18]. This is, however, dependent on the patient population and the infecting organism [19]. Critical care length of stay is increased by a mean of 6.1 days, and the excess costs can be as high as $40,000 per patient with VAP [18].

Prevention

Recent attempts to limit VAP include the use of ventilator care bundles which include a number of the following, avoidance of endotracheal intubation and reintubation, a preference for NIV, semi-recumbent positioning, continuous aspiration of subglottic secretions and oral decontamination [20]. These interventions have been shown to reduce ventilator days and length of stay in a number of studies such as that by Crunden and colleagues [21].

Despite showing a reduction in mortality in some studies and critical care unit-acquired respiratory infections in many others, selective decontamination of the digestive tract (SDD) has failed to make the jump into mainstream practise outside the Netherlands [22, 23]. This is partly due to the perceived additional costs of the topical regimens and microbiological surveillance (although offset by the reduced need for therapeutic antibiotics to treat infections) and concerns about antibiotic resistance. Many of the larger studies have taken place in the Netherlands, a country characterized by admirably low levels of antibiotic consumption and antibiotic resis-

tance, e.g. MRSA but in settings where antibiotic resistance is more common, there is understandable concern about the long-term implications on the spread and dissemination of difficult to treat pathogens. SDD is also discussed in Chaps. 3 and 5.

Treatment

Prompt initiation of appropriate antibiotic therapy is the cornerstone of VAP management and requires knowledge of the local likely flora and antibiotic resistance patterns. Iregui et al. found a higher mortality rate in patients in whom administration of adequate antibiotic therapy was delayed by approximately 16 h (69.7 % vs. 28.4 % mortality, P<0.001) after meeting criteria for the diagnosis of VAP [24].

Because of the importance of adequate initial antibiotic therapy in reducing the mortality from VAP, especially when patients are at risk from drug resistant organisms, initial therapy should be broad and known to be effective against pathogens such as *Pseudomonas aeruginosa* and MRSA, and tailored using local knowledge. Recent North American guidelines suggest that the use of three antibiotics: two drugs of different classes active against Pseudomonas, and a third for MRSA [6].

Chronic Obstructive Pulmonary Disease

As previously mentioned COPD is a significant complicating factor in CAP. COPD is one of the most frequent comorbidities in patients admitted to hospital for CAP with respiratory failure [24]. A prospective study of CAP in 529 patients in 33 intensive care units in Spain showed that COPD was the most frequent comorbidity encountered [25]. COPD patients also fare badly compared with non-COPD patients [26]. Another Spanish study compared COPD patients with non-COPD patients and showed that ICU mortality (odds ratio (OR) 1.58; 95 % confidence interval (CI) 1.01–1.43) and mechanical ventilation (OR 2.78; 95 % CI 1.63–4.74) rates were higher than in non-COPD patients. The ICU mortality was 39 % for COPD patients initially intubated and 50 % for those who failed non-invasive ventilation [27]. COPD patients also present more frequently with organisms such as *Pseudomonas aeruginosa* and strains of *Moraxella catarrhalis* resistant to first-line therapy, e.g. co-amoxycalv, and empiric antibiotic therapy may need to account for this.

Noninvasive ventilation (Fig. 6.2) is routinely used in the management of hypercarbic respiratory failure in COPD and guidance was produced by the Royal College of Physicians (UK) in conjunction with the BTS and the Intensive Care Society recently [28]. NIV in a number of settings has been shown in a number of randomized controlled trials to reduce the rate of intubation and mortality in COPD patients with decompensated respiratory acidosis (pH <7.35 and $PaCO_2$ >6 kPa) despite maximal medical therapy. All units admitting such patients should have local protocols and training in place to offer NIV to patients presenting in respiratory failure in the context of COPD.

Fig. 6.2 A patient being
supported with non invasive
ventilation

Sinusitis

Infection of the paranasal sinuses is more common in critically ill patients than often realised by clinicians working in the area. It occurs in 25–75 % of all critically ill patients and 18–32 % of endotracheally intubated patients may develop sinusitis, the variation largely being accounted for by differences in diagnostic criteria [29].

Nasotracheal rather than orotracheal intubation appears to be a risk factor although nasogastric intubation may be a confounding factor. Plain radiographs of adequate diagnostic quality are often difficult to obtain in critical care patients and CT scanning is often required to make a radiological diagnosis which should be supplemented with microbiological samples to confirm the aetiology [30].

Nosocomial sinusitis is usually caused by gram-negative bacilli or is polymicrobial. *Pseudomonas aeruginosa* represents 15.9 % of isolates, with the most common gram-positive isolate being *Staph. aureus* (10.6 %); fungi represent 8.5 % of isolates [29]. Treatment usually involves a combination of appropriate antibiotics, removal of intranasal foreign bodies and drainage [30].

Answers to Case Scenario

1. If he has severe community-acquired pneumonia by any criteria, he has an estimated mortality of 40–60 % depending on the results of further investigations. He is highly likely to require intensive care admission.
2. Bacterial pneumonia is the most common and the pneumococcus accounts for 60–70 % of cases in most series but a substantial proportion will have no organism isolated

3. If he is known or suspected of having COPD then NIV may reduce the morbidity and mortality associated with intubation. Its place in routine pneumonia management is less well defined.

References

1. Ewig S, Torres A. Severe community-acquired pneumonia. Clin Chest Med. 1999;20:575–87.
2. Woodhead M, Welch CA, Harrison DA, Bellingan G, Ayres JG. Community-acquired pneumonia on the intensive care unit: secondary analysis of 17,869 cases in the ICNARC Case Mix Programme Database. Crit Care. 2006;10:S1.
3. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377–82.
4. Brown PD, Lerner SA. Community-acquired pneumonia. Lancet. 1998;352:1295–302.
5. Leroy O, Santre C, Beuscart C, et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. Intensive Care Med. 1995;21:24–31.
6. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388–416.
7. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med. 2003;168:1438–44.
8. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
9. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Meduri GU. Acute respiratory failure in patients with severe communityacquired pneumonia: a prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med. 1999;160:1585–91.
10. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med. 2001;27:1718–28.
11. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
12. Feinsilver SH, Fein AM, Niederman MS, et al. Utility of fiberoptic bronchoscopy in nonresolving pneumonia. Chest. 1990;98:1322–6.
13. The ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med. 2009;361:1925–34.
14. Noah MA, Peek GJ, Finney SJ, Griffiths GJ, Harrison DA. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 Influenza A(H1N1). J Am Med Assoc. 2011;306:1659–68.
15. United States Centers for Disease Control and Prevention. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. http://www.cdc.gov/h1n1flu/recommendations.htm. Accessed on Jan 2012.
16. Woske HJ, Röding T, Schulz I, Lode H. Ventilator-associated pneumonia in a surgical intensive care unit: epidemiology, etiology and comparison of three bronchoscopic methods for microbiological specimen sampling. Crit Care. 2001;5:167–73.
17. Jourdain B, Novara A, Joly-Guillou ML, et al. Role of quantitative cultures of endotracheal aspirates in the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med. 1995;152:241–6.

18. Safdar N, Dezfulian C, Collard HR, et al. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med. 2005;33:2184–93.
19. Heyland DK, Cook DJ, Griffith L, et al. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. Am J Respir Crit Care Med. 1999;159: 1249–56.
20. Koeman M, van der Ven AJ, Hak E, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med. 2006;173: 1348–55.
21. Crunden E, Boyce C, Woodman H, Bray B. An evaluation of the impact of the ventilator care bundle. Nurs Crit Care. 2005;10:242–6.
22. ESICM systematic review group. Selective decontamination of the digestive tract clinical evidence in intensive care. MWV. 2011; 187–90.
23. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev. 2009;(4):CD000022.
24. Iregui M, Ward S, Sherman G, et al. Clinical importance of delays in the initiation of appropriate antibiotic therapy. Chest. 2002;122:262–8.
25. Boersma WG, Sportel JH, Lowenberg A, Koeter GH. High prevalence of obstructive airways disease in hospitalized patients with community-acquired pneumonia: comparison of four etiologies. Clin Pulm Med. 2005;12:291–6.
26. Bodi M, Rodriguez A, Solé-Violán A, et al. Antibiotic prescription for community-acquired pneumonia in the intensive care unit. Impact of adherence to IDSA guidelines on survival. Clin Infect Dis. 2005;41:1709–16.
27. Rello J, Rodriguez A, Torres A, for the CAPUCI study investigators, et al. Implications of COPD in patients admitted to the intensive care unit by community acquired pneumonia. Eur Respir J. 2006;27:1210–6.
28. Royal College of Physicians, British Thoracic Society, Intensive Care Society. Chronic obstructive pulmonary disease: non-invasive ventilation with bi-phasic positive airways pressure in the management of patients with acute type 2 respiratory failure. Concise Guidance to Good Practice series, No. 11. London: RCP; 2008.
29. Zanten ARH, Dixon JM, Nipshagen MD, et al. Hospital-acquired sinusitis is a common cause of fever of unknown origin in orotracheally intubated critically ill patients. Crit Care. 2005;9:R583–90.
30. Talmor M, Li P, Barie PS. Acute pranasal sinusitis in critically ill patients: guidelines for prevention, diagnosis and treatment. Clin Infect Dis. 1997;25:1441–6.