Guideline

Chinese guidelines for the diagnosis and treatment of hospital-acquired pneumonia and ventilator-associated pneumonia in adults (2018 Edition)

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Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most common hospital-acquired infections in China. The difficulty in diagnosis and treatment of HAP/VAP leads to high mortality. In China, it has been nearly two decades since the initial "*Guideline for the Diagnosis and Treatment of Hospital-acquired Pneumonia (draft)*" was published in 1999 (1). Afterwards, a number of guidelines for HAP/VAP have been published or updated at home and abroad (2-10). The definitions of HAP/VAP have been changing as more and more relevant researches available highlighting greater details. Moreover, there are growing evidence in the epidemiology, etiology, clinical diagnosis and treatment of HAP/VAP, especially the accumulating evidence from the researches in China, which shows that the distribution and antibiotic resistance rate of HAP/VAP pathogens in China are largely different from the data reported in other countries. Therefore, it is necessary to amend the initial guideline in 1999 accordingly in order to better guide clinical practice.

The initial HAP guideline was updated by the Infection Study Group of Chinese Thoracic Society, Chinese Medical Association (CMA). The overall framework and main contents of the updated HAP/VAP guideline were finalized after multiple rounds of face-to-face workshops. After repeated discussions among all the members of the Infection Study Group and extensive consultations from domestic and

Table 1 Evidence level and grade of recommendation

Evidence level and grade of recommendation	Description
Evidence level	
Level I (high)	Evidence from well-designed, randomized, controlled trials (RCTs), authoritative guidelines, and high quality systematic reviews and meta-analyses
Level II (moderate)	Evidence from RCTs with some limitations (e.g., trials without allocation concealment, nonblinded, or loss to follow-up not reported), cohort studies, case series, and case-control studies
Level III (low)	Evidence from case reports, expert opinions and *in vitro* antimicrobial susceptibility studies without clinical data
Grade of recommendation	
A (strong)	Most patients, physicians, and policy makers will adopt the recommended action
B (moderate)	The recommendation will be adopted by the majority, but not by some individuals. Decisions should be made with consideration of the specific condition of the patient to reflect his/her values and willingness
C (weak)	Insufficient evidence; decisions must be made *via* mutual discussions involving the patients, physicians, and policy makers

foreign experts in related fields, the draft was revised several times. Finally, the consensus was reached on the basis of evidence-based medicine. The level of evidence and grading of recommendation are defined the same way as in "*Diagnosis and treatment of community-acquired pneumonia in adults: 2016 clinical practice guidelines by the Chinese Thoracic Society, Chinese Medical Association (2016 Edition)*" (11). The grading system classifies recommendations according to the balance of the benefits and downsides (harms, burden, and cost) on the basis of the quality of evidence. The quality of evidence reflects the confidence in estimates of the true effects of an intervention (*Table 1*). In general, the higher the quality of evidence is, the stronger the grade of recommendation. However, they do not fully correspond to each other. The source of evidence, willingness and values of patients, as well as resource consumption should also be considered when making a recommendation. We emphasize that under the premise of the same level of evidence, the evidence and research results in China should be adopted preferentially.

This guideline applies to the immunocompetent HAP/VAP patients aged 18 years or older. The main body of this document is composed of 8 sections and 1 annex. It is expected that the revision and popularization of this HAP/VAP guideline will further standardize the diagnosis and treatment of HAP/VAP in China.

Definitions

HAP is defined as a pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission in patients not receiving invasive mechanical ventilation during hospitalization. VAP is defined as a pneumonia occurring >48 hours after endotracheal intubation or tracheotomy to receive mechanical ventilation. A pneumonia occurring within 48 h after removing mechanical ventilation and extubation is also considered as VAP (2,3).

At early times, HAP was defined as any parenchymal lung infection occurring in hospital due to the pathogens existing in the hospital environment. In the Chinese "*Guideline for the Diagnosis and Treatment of Hospital-acquired Pneumonia (draft)*" published in 1999, the definition of HAP covered the pneumonia occurring after establishing artificial airway and mechanical ventilation (1). There are various confounding factors in the numerous HAP clinical studies previously conducted at home and abroad, including some patients undergoing mechanical ventilation. However, it is generally agreed that VAP is a special type of HAP. Considering the significant difference between HAP and VAP in terms of clinical features, empiric treatment, and prevention strategy, the *Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia* issued by the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) in 2005 (2005 IDSA/ATS HAP/VAP guideline) have classified HAP into HAP in narrow sense and VAP (2). The evidence in recent years further confirms that HAP is considerably different from VAP in empiric treatment and clinical prognosis. The updated IDSA/ATS

HAP/VAP guideline in 2016 specifically emphasizes that HAP only refers to the pneumonia occurring after hospital admission in the patients without endotracheal intubation and not associated with mechanical ventilation, while VAP represents the pneumonia occurring after endotracheal intubation and mechanical ventilation. HAP population is therefore totally different from VAP population (7). Nevertheless, there are geographic difference and different understandings about HAP/VAP. Currently, controversies exist among European and American countries regarding the definition of HAP/VAP. We still think that VAP is a special type of HAP. This Guideline will address HAP and VAP separately in sections of etiology, treatment and prevention due to the particularity of VAP. The HAP in patients who have to receive endotracheal intubation and mechanical ventilation due to disease progression still belongs to HAP, but such cases will be managed in the same way as VAP. A pneumonia occurring in the inpatients receiving non-invasive ventilation still belongs to narrowly defined HAP.

Epidemiology

HAP/VAP belongs to hospital-acquired infection. Large scale cross section survey of nosocomial infections in China showed that the incidence of hospital-acquired infection ranged from 3.22% to 5.22% in hospitalized patients, and the incidence of hospital-acquired lower respiratory tract infection was 1.76% to 1.94% (12,13). In the US, the incidence of hospital-acquired infection is 4.0% in inpatients, of which pneumonia accounts for 21.8% (14). The researches in China and other countries have demonstrated that lower respiratory tract infection, including HAP/VAP, accounts for the largest proportion of hospital-acquired infections.

The results of studies in other countries indicated that the incidence of HAP ranged from 5 to 10 cases per 1,000 hospitalized patients, and HAP accounted for 25.0% of the total number of infections in intensive care unit (ICU). HAP increases the average length of hospital stay by 7–10 days (15), and dramatically increases the in-hospital medical cost. HAP is also an important direct cause of death in critically ill patients, specifically associated with mortality of 15.5–38.2% (16,17).

A clinical HAP survey conducted in 13 large teaching hospitals in China has reported that the average incidence of HAP is 1.4% in Department of Respiratory Medicine and respiratory ICU (RICU) combined, specifically 15.3% in RICU and 0.9% in general wards. The all-cause mortality of HAP is 22.3% and 34.5% for VAP. HAP is associated with 23.8±20.5 days of hospital stay on average, 10 days longer than that of non-HAP patients. For HAP patients, the mean duration of antimicrobial therapy is 19±17 days. The in-hospital medical cost per HAP patient is at least 90,000 Yuan ($13,600) higher than that for a non-HAP inpatient, of which more than 66,000 Yuan ($10,000) is incurred after HAP. Every HAP patient spends up to 27,000 Yuan ($4,100) on antimicrobial agents (18).

Large scale studies worldwide have shown that the incidence of VAP is 2.5–40.0% (or 1.3 to 20.2 cases per 1,000 mechanical ventilation days) in ICU patients, associated with mortality of 13.0–25.2% (19-21). A survey conducted in China reports that among the 17,358 patients in ICU in 46 hospitals, the total days of endotracheal intubation is 91,448. The incidence of VAP is 8.9 cases per 1,000 mechanical ventilation days (22). The incidence of VAP is 9.7–48.4% (or 1.3 to 28.9 cases per 1,000 mechanical ventilation days in the patients receiving mechanical ventilation, associated with mortality of 21.2–43.2% (18,23-27). The results of relevant studies both at home and abroad indicate that the attributable mortality rate is up to 38.9–60.0% if VAP is caused by multi-drug resistant (MDR) or pan-drug resistant (PDR) pathogens. The mortality of VAP is associated with age, comorbidity diabetes mellitus or chronic obstructive pulmonary disease (COPD), septic shock, and highly resistant pathogens (27-31). VAP results in 5.4–21.8 days longer of mechanical ventilation, 6.1–20.5 days longer of ICU stay, and 11.0–32.6 days longer of hospital stay. In the US, VAP increases the hospital cost by $40,000 in each case on average (20,32-34). These clinical data are provided for reference only because the diagnostic criteria, study protocol, study subjects, and statistical method are inconsistent across the studies, and therefore the reported incidence and mortality of HAP/VAP vary greatly (15-36).

Risk factors and pathogenesis

Risk factors

The risk factors for incidence of HAP/VAP involve many aspects, which can be classified into patient-related factors and treatment-related factors as shown in *Table 2* (18,25,37-39). A patient usually has multiple risk factors simultaneously or other confounding factors, contributing to the occurrence and progression of HAP/VAP. For this reason, it is important to manage the underlying diseases, and strengthen

Table 2 Risk factors for incidence of HAP/VAP

Category	Risk factor
Patient-related	Advanced age
	Aspiration
	Underlying disease (chronic pulmonary disease, diabetes mellitus, malignancy, cardiac insufficiency, etc.)
	Immunocompromised state
	Disturbance of consciousness, mental disorder
	Craniocerebral injury or other serious trauma
	Electrolyte disturbance, anemia, malnutrition or hypoproteinemia
	Bedridden, obesity, smoking, alcohol abuse, etc.
Treatment-related	Length of ICU stay, duration of mechanical ventilation
	Invasive procedures, especially that involving respiratory tract
	Use of antacids (H2-receptor blocker, proton pump inhibitor)
	Use of sedatives, narcotics
	Surgery of head and neck, chest or upper abdomen
	Indwelling gastric tube
	Supine position
	Cross infection (contamination of respiratory devices and hands)

appropriate infection prevention and control measures.

Pathogenesis

HAP and VAP share the common pathogenesis that the responsible pathogen reaches the distal end of bronchi and alveoli, breaks through the defense mechanisms of the host, colonizes and multiplies in lung tissues, which causes invasive damage. Pathogenic microorganisms gain access to lower respiratory tract primarily via the following two ways: (I) aspiration: exposure to risk factors such as antimicrobial agents, antacids or indwelling gastric tube may change the normal oral flora of inpatients. The oropharyngeal secretion containing potentially pathogenic bacteria can enter lower respiratory tract through epiglottis or endotracheal intubation. This is the main route of infection caused by endogenous pathogenic microorganisms (38,39); (II) inhalation: the pathogenic microorganisms enter lower respiratory tract by inhalation in the form of aerosol or hydrogel microparticles. This is also an important cause resulting in outbreak of nosocomial infection. The inhaled pathogenic microorganisms are usually exogenous pathogens, such as *Mycobacterium tuberculosis*, *Aspergillus* and viruses. Additionally, HAP/VAP may result from other route of infection, for example, dissemination of the responsible pathogen from blood stream to lungs, direct dissemination from adjacent tissues or infection due to contaminated medical devices.

The mechanism of VAP is slightly different from HAP in that endotracheal intubation makes the relatively bacteria-free lower respiratory tract expose directly to external environment, and therefore increases the difficulty of oral hygiene. The bacteria colonizing the oropharynx proliferate massively. The oral secretion containing massive amount of bacteria enters lower respiratory tract through the gap between balloon and tracheal wall in the presence of various factors (balloon deflation or underpressure, change of position) (40). The presence of endotracheal intubation makes the patient unable to cough effectively, which interferes with the function of mucociliary clearance, and reduces the protective ability of airway, and hence increases the risk of developing VAP. Biofilm may readily form on the internal and external surfaces of the tracheal cannula. Many factors (aspiration of sputum, for example) can cause exfoliation of the generated biofilm, which may obstruct small airways, and then lead to VAP (41). In addition,

Table 3 Proportion of common bacterial pathogens isolated from HAP patients in China (%)

Bacterial species	Tertiary hospital[a]		Secondary hospital (46)
	≥18 years[b] (18,28)	≥65 years[c] (45,47,48)	
Acinetobacter baumannii	20.6–25.7	7.9–14.6	18.0
Pseudomonas aeruginosa	18.7–20.0	23.8–28.3	11.0
Klebsiella pneumoniae	8.9–14.9	5.3–17.1	21.0
Staphylococcus aureus	9.8–12.0	8.6–15.0	11.0
Escherichia coli	3.8–7.4	9.2–11.8	8.0
Enterobacter cloacae	2.1–4.3	2.5	NA
Stenotrophomonas maltophilia	4.3–6.0	1.2–2.6	NA

All the studies cited are single center or local retrospective studies except (18,28), which are multi-center, nation-wide, prospective studies. [a], the data are mainly from tertiary hospitals, and mostly from retrospective studies. The specimens are mostly sputum. So there are some limitations about these data. [b], the population of ≥18 years also includes some people of 65 or older age. The patients were not stratified in terms of age in the original study. [c], few data are from secondary hospitals. Only one report on the cases in secondary hospitals was identified with high quality. The proportion of the bacterial pathogens in this study is rounded to the nearest integer. NA, not available.

analgesic agents and sedatives are usually used to alleviate patient's intolerance to endotracheal intubation. Such drugs will suppress the ability of the patient to cough, and so increase the risk of VAP (42).

HAP/VAP may progress gradually from localized infection to sepsis, or even septic shock. The main mechanism underlying this process is that the pathogenic microorganisms enter blood and induce systemic inflammation out of control, which results in multiple organ dysfunction (including respiratory system, as well as circulatory, urinary, nervous, and coagulation systems), and metabolic disorder (43,44).

Etiology

The HAP/VAP in immunocompetent patients is usually caused by bacteria, and infrequently by viruses or fungi. The distribution and antibiotic resistance profile of the common pathogens vary with geographic region, level of hospital, patient population and the extent of antibiotic exposure, and may change over time. The common pathogens of HAP/VAP in China include *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli*. It is more important to know the data of antimicrobial resistance surveillance in local hospitals. Empiric antimicrobial therapy should be based on the latest antimicrobial susceptibility data of the pathogens isolated from the region, the hospital, or even the specific department.

Pathogenic spectrum

Unlike the US and European countries, few large-scale epidemiological studies are available on HAP in China. Three survey studies on HAP etiology conducted in large general hospitals have shown that the pathogenic spectrum of HAP in China is highly different from that in the US and European countries, mainly evidenced by the proportion of the most common bacterial pathogens, including *A. baumannii* (16.2–35.8%), *P. aeruginosa* (16.9–22.0%), *S. aureus* (8.9–16.0%), and *K. pneumoniae* (8.3–15.4%) (28). The proportion of *P. aeruginosa* and *A. baumannii* in secondary hospitals is slightly lower than that in tertiary hospitals, while *K. pneumoniae* shows higher proportion in secondary hospitals than in tertiary hospitals (18,45,46). About 70% of the HAP patients were old people (≥65 years of age). As for these elderly patients, *P. aeruginosa* accounts for higher percentage, and *A. baumannii* relatively lower percentage (18,45,47,48) (*Table 3*).

VAP patients in China are mostly identified in ICU. The pathogenic spectrum of VAP is slightly different from that of HAP, evidenced by even higher proportion of *A. baumannii* (35.7–50.0%), followed by similar proportion of *P. aeruginosa* and *S. aureus* (*Table 4*). In addition, the proportion of *P. aeruginosa* is also higher in the elderly patients with VAP (≥65 years) than in other patient populations (18,49-54).

Currently, no high quality, prospective epidemiological

Table 4 Proportion of common bacterial pathogens isolated from VAP patients in China (%)

Bacterial species	≥18 years (28,49-52)	≥65 years (53,54)
Acinetobacter baumannii	12.1–50.5	10.3–18.5
Pseudomonas aeruginosa	12.5–27.5	27.7–34.6
Klebsiella pneumoniae	9.0–16.1	5.1–13.9
Staphylococcus aureus	6.9–21.4	5.8–15.4
Escherichia coli	4.0–11.5	1.3–6.2
Enterobacter cloacae	2.0–3.4	3.1
Stenotrophomonas maltophilia	1.8–8.6	4.6–9.6

All the studies cited are single center or local retrospective studies except (28), which is a multi-center, nation-wide, prospective study. These data are mainly from tertiary hospitals, and mostly from retrospective studies. The specimens are mostly sputum. So there are some limitations about these data.

study is conducted on HAP/VAP in secondary or lower level hospitals in China. Majority of the reports currently available are retrospective. The above data are provided for reference only.

Antibiotic resistance of common pathogens

Antimicrobial resistance poses a serious challenge to the treatment of HAP/VAP. In clinical practice, MDR is defined as resistance to 3 or more classes of antimicrobial agents (excluding constitutive resistance), while extensive drug resistance (XDR) is defined as resistance to all antimicrobial agents except only 1 to 2 classes. Pan-drug resistance (PDR) means that a pathogen is resistant to all the accessible antimicrobial agents and those available in the panel of antimicrobial agents included in routine susceptibility testing.

The common antibiotic-resistant bacteria identified in HAP/VAP patients include carbapenem-resistant *A. baumannii* (CRAB), carbapenem-resistant *P. aeruginosa* (CRPA), extended-spectrum β-lactamases (ESBLs)-producing *Enterobacteriaceae*, methicillin-resistant *S. aureus* (MRSA), and carbapenem-resistant *Enterobacteriaceae* (CRE), etc. According to the multi-center, bacterial resistance surveillance networks in China, i.e., China Surveillance Network for Bacterial Resistance (CHINET) and Chinese Antimicrobial Resistance Surveillance of Nosocomial Infection (CARES), the prevalence of CRAB is up to 60–70% in the strains isolated from various clinical specimens including blood, urine and sputum, while the corresponding prevalence of CRPA is 20–40%, and the prevalence of ESBLs-producing *K. pneumoniae* and *E. coli* is 25–35% and 45–60%, respectively. The prevalence of MRSA is 35–40% in the *S. aureus* isolates, and that of CRE is 5–18% in the *Enterobacteriaceae* isolates (55,56). Some antibiotic-resistant bacteria such as MRSA, show higher prevalence in the strains isolated from sputum.

The CARES data on antibiotic resistance in HAP/VAP pathogens during 2007–2013 indicated that the prevalence of MDR *A. baumannii* increased over time, while the prevalence of MDR *P. aeruginosa* decreased, from 23% in 2007 to 10.3% in 2013. The prevalence of MDR strains in VAP is generally higher than that in HAP except CRE strains (0.7% in VAP, 1.9% in HAP), specifically, CRAB (63.9%, 59.8%), CRPA (41.0%, 33.4%), ESBLs-producing *E. coli* (64.7%, 57.3%), ESBLs-producing *K. pneumoniae* (47.4%, 32.4%), and MRSA (85.7%, 74.3%). The prevalence of CRE, especially carbapenem-resistant *K. pneumoniae* (CRKP), is increasing. The data from China Antimicrobial Resistance Surveillance System (CARSS) in 2015 showed that the prevalence of CRKP was 4.9% and CRAB 52.1% in the corresponding pathogens isolated from lower respiratory tract in the Department of Respiratory Medicine in China. The prevalence of CRKP and CRAB was 5.2% and 53.5% in tertiary hospitals, higher than that in secondary hospitals (2.5% and 33.9% respectively). The prevalence of CRKP and CRAB in RICU is higher than that in general wards. The prevalence of ESBLs-producing *Enterobacteriaceae*, especially ESBLs-producing *E. coli*, in secondary hospitals is similar to or even higher than that in tertiary hospitals (63.9% versus 53.5%) (57).

The data from CHINET and CARES indicate that polymyxin B (97–100%) and tigecycline (85–100%) inhibit the highest percentage of *A. baumannii* isolates. More than

70% of the *P. aeruginosa* strains are still susceptible to polymyxin, amikacin, piperacillin/tazobactam, cefepime, ciprofloxacin, ceftazidime, meropenem, and imipenem. *E. coli* and *K. pneumoniae* are highly susceptible to carbapenems (82–98%), β-lactam/β-lactamase inhibitor combinations (80–96%), and amikacin (90–97%). *S. maltophilia* isolates are highly susceptible to minocycline (81–94%), levofloxacin (76–90%), and trimethoprim/sulfamethoxazole (67–92%). Vancomycin, teicoplanin, and linezolid remain highly active against MRSA strains (100% susceptible).

It should be noted that both the distribution and antibiotic resistance profile of HAP/VAP pathogens are very different between large (tertiary) hospitals and primary/secondary hospitals in urban area of China. The data from relevant high-quality studies in primary care hospitals are still lacking severely. Therefore, the empiric antimicrobial regimen prescribed in primary care hospitals should be based on local microbiological data as much as possible, rather than completely depending on the data from large urban hospitals.

Diagnosis and differential diagnosis

Clinical diagnostic criteria

HAP/VAP varies in clinical manifestation and disease severity, which may develop rapidly from uncomplicated typical pneumonia to severe pneumonia complicated with sepsis, or even septic shock. Currently, no single "gold standard" is available for clinical diagnosis of HAP/VAP. The clinical diagnosis of pneumonia is more accurate when more of the following relevant clinical conditions are satisfied.

Clinical diagnosis can be established when a new or progressive infiltrate, consolidation, or ground glass opacity is revealed on chest radiograph or CT scan (58,59), plus 2 or more of the following 3 criteria: (I) fever >38 ℃; (II) purulent airway secretions; (III) peripheral white blood cell count $>10\times10^9$/L or $<4\times10^9$/L (7).

Radiology is essential and important for diagnosing HAP/VAP. Chest X-ray film should be taken routinely, and chest CT scan should be considered if possible. For critically ill patients or other patients who are unable to receive chest CT scan, point-of-care lung ultrasound can be considered if possible (60,61). Lung ultrasound, performed by an experienced physician, is helpful to monitor lung aeration changes and differentiate pneumonia from pulmonary embolism, atelectasis, or other pulmonary diseases (62) (IB). In the process of clinical decision-making, one or more imaging techniques may be ordered when clinically indicated in order to improve the rate of early diagnosis.

Etiological diagnosis

The pathogenic microorganism can be identified on the basis of clinical diagnosis if any of the following condition is satisfied.

(I) Pathogen isolated from qualified sample of lower respiratory tract secretion (neutrophils >25 cells per low power field, epithelial cells <10 per low power field, or the ratio between neutrophils and epithelial cells >2.5:1), protected specimen brush (PSB), bronchoalveolar lavage fluid (BALF), lung tissues or sterile body fluid, AND consistent with clinical manifestations (5).

(II) Fungi presented in pathological, cytopathological or direct microscopic examination of lung tissues, associated with relevant evidence of tissue damage (63,64).

(III) Seroconversion is observed for IgM antibody against atypical pathogen or virus or a 4-fold or greater rise in specific IgG antibody titer between acute and convalescent sera. Viral antigen assay, nucleic acid test, or culture with respiratory tract secretion is positive for the target virus during epidemic of respiratory viruses, associated with a history of epidemiological exposure (5).

Differential diagnosis

HAP/VAP is not specific in clinical manifestation and imaging results, which should be differentiated from other febrile diseases with concomitant pulmonary opacity, including infectious and non-infectious diseases (65).

(I) Other infectious diseases affecting lungs: (i) systemic infection involving lungs, for instance: catheter-related bloodstream infection, infective endocarditis, which may lead to multiple secondary pulmonary abscesses; (ii) focal infection involving lungs such as subdiaphragmatic abscess, liver abscess. The key points for differentiation include detailed history inquiry and physical examination, identification of extra-pulmonary site of infection, and pathogen-specific tests.

(II) Common non-infectious diseases easily confused with HAP: (i) acute pulmonary thromboembolism accompanied by pulmonary infarction (66); (ii) atelectasis; (iii) acute respiratory distress syndrome (ARDS) (67); (iv) pulmonary edema (68); (v) Other diseases, such as tumor, bronchiectasis, drug-induced lung disease, connective tissue disease, and neurogenic fever. The differentiation is primarily based on how well the underlying diseases are controlled, and meanwhile infective fever should be excluded.

Utility of laboratory techniques in the diagnosis and treatment of HAP/VAP

After clinical diagnosis of HAP/VAP is established, specimens should be collected actively for microbiological tests.

Collection of specimens: including the specimens from respiratory tract, blood, and pleural effusion

Respiratory tract specimens: mainly include sputum (airway aspirate), BALF, and lung tissue. The specimens should be firstly subjected to smear and microscopic examination as soon as possible (e.g., gram stain, acid-fast stain, as well as potassium hydroxide wet mounts preparation and methenamine silver stain if necessary), followed by culture, antigen assay, and nucleic acid quantification, etc. (IIIC).

Respiratory tract specimens can be obtained by non-invasive or invasive approaches. Non-invasive approach means collection of the following specimens, including coughed-up phlegm, nasopharyngeal swab, nasopharyngeal aspirates or endotracheal aspiration (ETA). Invasive approach refers to the fact that specimens (BALF or tissue samples) are obtained from the lower respiratory tract via a bronchoscope or percutaneous lung biopsy. Invasive sampling with quantitative cultures generally does not show advantages over non-invasive sampling with semiquantitative cultures in predicting the prognosis (69,70). Quantitative culture of airway secretions is a highly demanding technique and may not be able to improve patient outcome. It should be used only when necessary and accessible. For HAP patients, it is recommended to use non-invasive method to obtain the initial respiratory tract specimens for smear and semi-quantitative cultures. Invasive sampling with microbiological testing is necessary in patients failed to respond to empiric treatment or suspected to be infected by special pathogens, or routine respiratory tract culture failed to identify the pathogens (IIIB). ETA could be routinely sampled in VAP patients. Additionally, it is also convenient to collect invasive sample of respiratory tract for smear and semiquantitative cultures to identify the pathogen via artificial airway in VAP patients. Culture of airway secretions twice a week is helpful in predicting the etiology of VAP (71). The conversion from positive to negative result of quantitative culture is helpful for clinicians to determine whether it is appropriate to discontinue antimicrobial agents (72,73) (IIB).

Blood: blood culture is an important way for diagnosing bacteremia. For adults, 2 or 3 sets of blood samples should be collected from different body sites each time for blood culture. Blood samples (one set) collected from the same puncture site are usually injected into an aerobic bottle and an anaerobic bottle concurrently. And 8–10 mL of blood sample is needed in each bottle in order to increase positivity (58). Blood samples should be drawn at the onset of chills or initial fever, preferably before the use of antimicrobial agents (74).

Pleural effusion: thoracentetis is recommended for HAP/VAP patients with pleural effusion for routine tests, biochemical tests, smear (gram stain, acid-fast stain), and culture of microorganisms.

Interpretation of etiological testing results: including smear and microscopic examination, microbiological culture, antigen test, high throughput sequencing, and other molecular biological techniques

Smear/microscopic examination: smear and gram stain of ETA samples showing ≥2% of the leucocytes contain intracellular organisms per high-power field is valuable for etiological diagnosis of VAP patients (75), and is useful for the initial empiric antimicrobial therapy (76-81).

Microbiological culture: conventionally, the microorganism is highly suspected to be the culprit pathogen if it meets any of following conditions: $\geq 10^7$ cfu/mL of bacteria in quantitative sputum culture, $\geq 10^5$ cfu/mL in ETA microbiological culture, $\geq 10^4$ cfu/mL in BALF quantitative culture, $\geq 10^3$ cfu/mL in PSB sampl culture (82-84). *Acinetobacter* spp., *Pseudomonas* spp., and *Candida* may colonize the native and/or artificial airway in patients receiving mechanical ventilation. Such microorganisms revealed by culture should be clarified whether they are pathogenic microorganisms or not. It is recommended to evaluate the role of these microorganisms comprehensively in terms of the following three factors: (I) host: including immune status, underlying diseases and the current clinical manifestations; (II)

bacteria: such as whether there are leucocytes containing intracellular organisms in smear/microscopic examination of airway secretions, whether the result of smear/microscopic examination is consistent with microbiological culture findings or not, and how many bacteria colonies there are; (III) antimicrobial agent: for instance, recent use of antimicrobial agents, whether clinical symptoms improve after antimicrobial therapy against target pathogen. Microorganisms identified from airway secretions could be considered as colonization or contamination if the patient does not have pneumonia-related clinical manifestations or laboratory results. Blood culture is important for early diagnosis of infection and pathogen-specific antimicrobial therapy. However, conclusion that microorganism originates from lungs cannot be made from a positive blood culture, because lung is the source of infection in only 10–37% of bacteremic cases (83,85-89). Positive result of pleural effusion culture is helpful for clarifying etiological diagnosis, especially when the specimen is obtained by thoracentesis or at the time of initial placement of catheter in thoracic cavity. The positive result of the specimen directly sampled from the indwelling catheter should be interpreted cautiously because of the possibility of contamination (IIIC). Positive result of respiratory viruses culture confirms viral infection.

Pathogen-specific antigen test: urinary antigen detection targeting *S. pneumoniae* and *Legionella pneumophila*, and detection of serum cryptococcal capsular polysaccharide antigen are highly sensitive and specific. Two consecutive positive results of serum 1,3-β-D-glucan assay (G test), serum or BALF galactomannan (GM) antigen test (only once in case of BALF) support the diagnosis of invasive fungal infection.

High throughput sequencing and other molecular biological techniques: clinical metagenomics based on sequencing technique can help determine the potential pathogen by analyzing the content or abundance of microorganic DNA or RNA in clinical specimens. This technique can significantly increase the sensitivity of etiological test, and shorten the turnaround time of laboratory test. It is especially useful for the diagnosis of infections caused by pathogens rarely encountered. This technique can be used judiciously to identify pathogens which cannot be identified by established methods, or in patients who fail to respond to appropriate and standard anti-infective treatment. However, the results should be evaluated comprehensively in combination with epidemiological data and clinical features to determine whether it is true pathogen. There are many challenges in clinical application of this technique, including interference by human genome in specimen, bioinformatics analysis, result assessment and interpretation. In particular, respiratory tract is not germ-free, so the presence of the nucleic acid derived from a large number of colonizing bacteria poses challenge to clinical interpretation of testing results (90-92).

Infection-related biomarkers

Both C-reactive protein (CRP) and procalcitonin (PCT) are most commonly used biomarkers in clinical practice to determine the presence or absence of infection (93,94). CRP increases remarkably in case of infection, but with low specificity in detecting infection (95,96). It can be used as adjunctive test to support diagnosis (IIC). PCT responds quickly to bacterial infection and sepsis (97,98). It is a more specific biomarker of bacterial infection, when compared to CRP (93,99). Higher PCT value indicates more severe bacterial infection, and higher possibility of bacterial VAP and sepsis (97,100). The diagnostic efficiency of PCT is affected by prior exposure to antimicrobial agents, but not affected by the type of disease or onset time of VAP. Furthermore, PCT is also an important predictor of VAP mortality (100). Dynamic monitoring of PCT level in the course of disease is helpful for deciding the duration of antimicrobial treatment (101-104) (IIB). It should be emphasized that neither CRP nor PCT can replace microbiological testing. Any biomarker of infection should be combined with clinical manifestations to make comprehensive judgement. The dynamic change of biomarkers is usually more valuable than the absolute value (94). Early empiric antimicrobial therapy should not be delayed for waiting for the results of laboratory testing in order to increase treatment success rate.

Evaluation of disease severity

The severity evaluation of HAP/VAP is important for empiric selection of antimicrobial agents and prognosis estimation, but there is not a unified criterion currently. The commonly used scoring systems for evaluating disease severity include sequential organ failure assessment (SOFA) (*Table 5*) and acute physiology and chronic health evaluation (APACHE-II) score. These scoring systems are equal in predicting mortality. Mortality rate increases with the scores (105). SOFA score focuses on the evaluation of organ dysfunction or failure. It is associated with the relapse of VAP (106,107). While, APACHE-II score >16 is an independent predictor of death in VAP patients

Table 5 Sequential Organ Failure Assessment (SOFA) score

Organ/system	Predictor	Score				
		0	1	2	3	4
Respiration	PaO_2/FiO_2 (mmHg)	≥400	300–399	200–299	100–199 and mechanically ventilated	<100 and mechanically ventilated
Coagulation	Platelets ($\times 10^9$/L)	>150	101–150	51–100	21–50	<21
Liver	Bilirubin (μmol/L)	<20	20–32	33–101	102–204	>204
Cardiovascular system	Mean arterial pressure (mmHg)	≥70	<70			
	Administration of catecholamines ($\mu g \cdot kg^{-1} \cdot min^{-1}$)			Dopamine ≤5 or dobutamine (any dose)	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system	Glasgow coma score	15	13–14	10–12	6–9	<6
Kidneys	Serum creatinine (μmol/L)	<110	110–170	171–299	300–440	>440
	24 h urine output (mL)				201–500	<200

SOFA score is the sum of six different parameters, the worst value of which should be adopted on daily assessment.

(106-109). Some scholars suggest that SOFA score can be used as a criterion to assess the severity of disease. For non-ICU patients, quick SOFA (qSOFA) score is simpler, more convenient and efficient than SOFA score in predicting in-hospital mortality (110). qSOFA score is composed of altered mental status, systolic blood pressure ≤100 mmHg (1 mmHg =0.133 kPa), and respiratory rate ≥22 breaths/min. Clinicians should alert the occurrence of critical illness when qSOFA score ≥2.

In this guideline, HAP patients are considered critically ill and at high risk of death if satisfying any of the following criteria: (I) requiring endotracheal intubation and mechanical ventilation; (II) septic shock still requiring vasoactive agents after active fluid resuscitation. Unlike the narrowly defined HAP, VAP should be generally considered as critical illness. However, in some cases, underlying disease cannot be controlled adequately, and long term invasive mechanical ventilation is required. If VAP occurs (sometimes recurrent) in such cases, not all VAPs are critical illness. The severity of VAP can be evaluated according to qSOFA or APACHE-II score.

Procedures for clinical management

Step 1

Confirm the clinical diagnosis of HAP/VAP based on symptoms, signs, and imaging findings, AND differentiate it primarily from other febrile diseases accompanied by pulmonary opacities, AND assess the severity of disease (complicated with sepsis or not), possible pathogens and risk factors for antibiotic resistance.

Step 2

Collect lower respiratory tract secretions and blood samples for testing of pathogenic microorganisms and infection-related biomarkers as soon as possible, AND initiate empiric antimicrobial treatment immediately. The treatment regimen, including appropriate antimicrobial agents, monotherapy or combination therapy, loading dose and maintenance dose, should be determined according to physicochemical properties and pharmacokinetic/pharmacodynamics (PK/PD) parameters of each antimicrobial agent.

Step 3

Re-evaluate results of laboratory tests and response to the initial antimicrobial therapy 48–72 hours later, and manage the patient specifically as follows: (I) switch to targeted therapy (de-escalation or step-down) when early favorable treatment response is observed clinically, and meaningful positive result is obtained from microbiological tests; (II) make an attempt to discontinue antimicrobial agents when clinical condition is stable without sepsis or without positive microbiological cultural result; (III) carefully evaluate the

Table 6 Risk factors for MDR pathogens of HAP and VAP

Category	Risk factors for MDR pathogens (113-120)
Evidence-based risk factors HAP	Prior intravenous antibiotic use within 90 d
Evidence-based risk factors VAP	Prior intravenous antibiotic use within 90 d
	Five or more days of hospitalization before the occurrence of VAP
	Critical illness, septic shock at time of VAP
	ARDS preceding VAP
	Continuous renal replacement therapy before VAP onset
	Prior intravenous antibiotic use within 90 d
Potential risk factors HAP/VAP	History of MDR infection or colonization
	Recurrent or chronic hospitalization
	ICU stay
	Presence of structural pulmonary disease
	Severe pulmonary dysfunction
	Receiving glucocorticoids, immunosuppressants, or presence of immunocompromised status
	Stay in a medical facility with high prevalence of resistant pathogens
	The skin mucosal barrier is damaged (trachea cannula, indwelling gastric tube or deep venous catheter, etc.)

MDR, multi-drug resistant; HAP, Hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

clinical implication of positive results of microbiological culture when the patient is not improved clinically in order to clarify whether the identified microorganism is pathogenic, or if there is mixed bacterial infection, any complications or infection in sites other than lung. The antimicrobial regimen should be adjusted accordingly based on relevant factors such as coverage of pathogens, antibiotic resistance profile, the consistency between *in vivo* efficacy and *in vitro* antimicrobial activity, and PK/PD parameters of antimicrobial agents; (IV) further clarify the diagnosis with additional etiological tests and identify non-infectious causes when the patient is not improved clinically and microbiological culture shows negative results.

Step 4

Monitor clinical presentations and systemic levels of infection-related biomarkers dynamically. Assess the response to the measures in step 3, and decide the duration of antimicrobial therapy and other subsequent management.

Treatment

HAP/VAP is usually managed by an integrated approach including antimicrobial therapy, respiratory support technique, multiple organ support therapy, and non-antimicrobial pharmacotherapy. Antimicrobial therapy is the fundamental treatment modality, including empiric antimicrobial therapy and pathogen-specific (targeted) treatment.

Empiric antimicrobial treatment

Principles of empiric antimicrobial therapy

(I) Timing of antimicrobial therapy: empiric antimicrobial therapy should be administered as soon as possible after the clinical diagnosis of HAP/VAP is established and etiological testing is submitted. Appropriate antimicrobial therapy, if delayed, is still associated with increased mortality and longer length of hospital stay (111,112). Therefore, HAP/VAP patients should be managed empirically with antimicrobial agents as soon as possible (IIIA). (II) Properly evaluate the risk factors for MDR pathogens: the risk factors for common antibiotic-resistant pathogens of HAP/VAP are listed in *Table 6*. Additionally, *Table* 7 lists the risk factors for several specific common MDR pathogens.

Selection of antimicrobial agents for initial empiric therapy

The strategy of initial empiric antimicrobial therapy for

Table 7 Risk factors for specific common MDR pathogens

MDR pathogen	Specific risk factors
ESBLs-producing *Enterobacteriaceae*	History of infection or colonization due to ESBLs-producing bacteria, prior use of third-generation cephalosporins within 90 d (121-124)
MRSA	MRSA colonization in respiratory tract (125), high prevalence of MRSA in the healthcare unit
P. aeruginosa	Destruction of skin and mucosa barrier, immunocompromised status, chronic structural pulmonary disease, severe pulmonary dysfunction, etc. (115,116)
A. baumannii	Severe underlying disease, *A. baumannii* colonization
CRE	CRE colonization, prior use of carbapenems within 90 d, advanced age, critical illness, surgical procedure, etc. (121)

ESBLs, extended spectrum β-lactamases; MRSA, methicillin-resistant *S. aureus*; CRE, carbapenem-resistant *Enterobacteriaceae.*

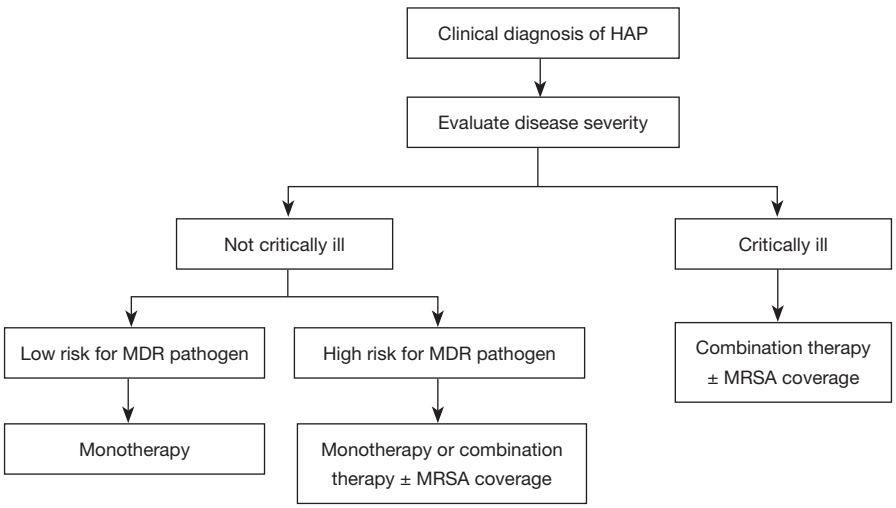

Figure 1 Recommended empiric antibiotic therapy for hospital-acquired pneumonia. HAP, hospital-acquired pneumonia; MDR, multi-drug resistant; MRSA, methicillin-resistant *S. aureus.*

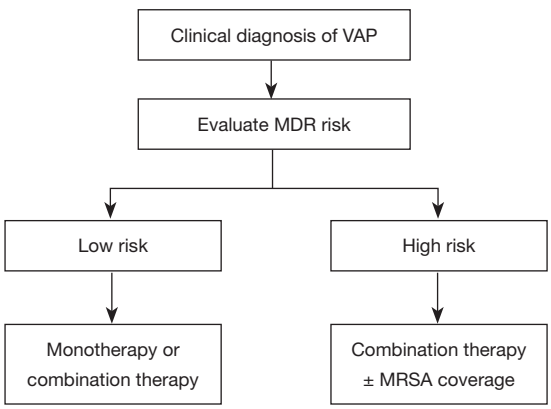

Figure 2 Recommended empiric antibiotic therapy for ventilator-associated pneumonia. VAP, ventilator-associated pneumonia; MDR, multi-drug resistant; MRSA: methicillin-resistant *S. aureus.*

HAP/VAP is described in *Figures 1* and *2*. Appropriate antimicrobial agents should be selected in terms of disease severity, pathogen distribution in local hospital, antibiotic resistance profile, and risk factors for resistant pathogens, meanwhile taking the clinical characteristics, underlying diseases, and organ function of patients, PK/PD properties of antimicrobial agents, prior antibiotic use, and history of drug allergy into account (*Tables 8* and *9*) (126). The etiological spectrum and antibiotic resistance profile vary greatly with geographical region and hospital grade in China. Therefore, the recommended treatment in this guideline is fundamental only. The specific regimen should be provided according to the following conditions: (I) periodically prepare and release the distribution and antibiogram data of HAP/

Table 8 Recommended initial empiric antibiotic therapy for hospital-acquired pneumonia (non-ventilator-associated pneumonia)

Not critically ill		Critically ill[a]
Low risk for MDR pathogens	High risk for MDR pathogens	
Monotherapy:	Monotherapy or combination therapy[b,c]:	Combination therapy[b,c]:
Anti-*P. aeruginosa* penicillins (piperacillin, etc.)	Anti-*P. aeruginosa* β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam, cefoperazone/sulbactam, etc.)	Anti-*P. aeruginosa* β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam, cefoperazone/sulbactam, etc.)
Or β-lactam/β-lactamase inhibitor combinations (amoxicillin/clavulanic acid, piperacillin/tazobactam, cefoperazone/sulbactam, etc.)	Or anti-*P. aeruginosa* cephalosporins (ceftazidime, cefepime, cefoselis, etc.)	Or anti-*P. aeruginosa* carbapenems (imipenem, meropenem, biapenem, etc.)
Or third-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, etc.)	Or anti-*P. aeruginosa* carbapenems (imipenem, meropenem, biapenem, etc.)	Above drugs combine with any one of the following:
Or fourth generation cephalosporins (cefepime, cefoselis, etc.)	Above drugs monotherapy or combine with any one of the following:	Anti-*P. aeruginosa* quinolones (ciprofloxacin, levofloxacin)
Or oxacephems (latamoxef, flomoxef, etc.)	Anti-*P. aeruginosa* quinolones (ciprofloxacin, levofloxacin, etc.)	Or aminoglycosides (amikacin, isepamicin, etc.)
Or quinolones (ciprofloxacin, levofloxacin, moxifloxacin, etc.)	Or aminoglycosides (amikacin, isepamicin, etc.)	Combine with the following when at risk of XDR gram negative infection:
	Or Combine with the following when at risk of MRSA infection: lycopeptides (vancomycin, norvancomycin, teicoplanin, etc.)	Polymyxin (polymyxin B, polymyxin E)
	Or linezolid	Or tigecycline
		Combine with the following when at risk of MRSA infection:
		Glycopeptides (vancomycin, norvancomycin, teicoplanin, etc.)
		Or linezolid

[a], critically ill patients include those requiring mechanical ventilation and those with septic shock; [b], the combination of two β-lactams is usually inappropriate; [c], aminoglycosides are used only in combination therapy. MDR, multi-drug resistant; XDR, extensively drug-resistant.

VAP pathogens in local hospital (127-129). The specific empiric treatment regimen should be based on the pathogens distribution of HAP/VAP and susceptibility testing results in local hospital (115,130,131) (IIIA). (II) For the patients with MRSA colonization in respiratory tract or treated in a healthcare unit with high prevalence of MRSA, it is recommended to cover MRSA empirically (IIIC). (III) For the HAP/VAP patients with risk factors for MDR *P. aeruginosa* or other MDR gram negative bacilli or at high risk of death, it is recommended to combine two different classes of antimicrobial agents. For the HAP/VAP patients not critically ill and without risk factors for MDR pathogens, antimicrobial monotherapy is appropriate for empiric treatment (IIIA). (IV) It is recommended to reserve polymyxin and tigecycline only for the patients with risk factors for XDR gram negative pathogens. (V) In the HAP/VAP patients complicated with sepsis, the loading dose and maintenance dose of antimicrobial agents should be adjusted according to the physicochemical properties, PK/PD profiles of antimicrobial agents and severity of organ dysfunction (especially kidneys and liver).

HAP/VAP pathogen-specific treatment

Pathogen-specific treatment is also known as targeted

Table 9 Recommended initial empiric antibiotic therapy for ventilator-associated pneumonia

Low risk for MDR pathogens	High risk for MDR pathogens
Monotherapy or combination therapy[a]:	Combination therapy[a]:
Anti-*P. aeruginosa* penicillins (piperacillin, etc.)	Anti-*P. aeruginosa* β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam, cefoperazone/sulbactam, etc.)
Or anti-*P. aeruginosa* third-, fourth generation cephalosporins (ceftazidime, cefepime, cefoselis, etc.)	Or anti-*P. aeruginosa* third-, fourth generation cephalosporins (ceftazidime, cefepime, cefoselis, etc.)
Or β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam, cefoperazone/sulbactam, etc.)	Or aztreonam
Or anti-*P. aeruginosa* carbapenems (imipenem, meropenem, biapenem, etc.)	Or anti-*P. aeruginosa* carbapenems (imipenem, meropenem, biapenem, etc.)
Or quinolones (ciprofloxacin, levofloxacin, etc.)	Or antipseudomonal quinolones (ciprofloxacin, levofloxacin, etc.)
Or aminoglycosides (amikacin, isepamicin, etc.)[b]	Or aminoglycosides (amikacin, isepamicin, etc.)
	Combine with the following when at risk of XDR gram negative infection:
	Polymyxins (polymyxin B, polymyxin E)
	Or tigecycline
	Combine with the following when at risk of MRSA infection:
	Glycopeptides (vancomycin, norvancomycin, teicoplanin)
	OR linezolid

[a], the combination of two β-lactams is used only in special cases; [b], aminoglycosides are used only in combination therapy. MDR, multi-drug resistant; XDR, extensively drug-resistant.

antimicrobial therapy, which means to prepare specific antimicrobial treatment regimen (narrow spectrum or broad spectrum, monotherapy or combination therapy) targeting the identified pathogenic microorganisms based on the results of *in vitro* antimicrobial susceptibility testing. Attention should be paid to the following points when prescribing HAP/VAP pathogen-specific antimicrobial therapy.

(I) Before initiation of an empirical antimicrobial treatment, qualified specimens should be submitted for microbiological testing, and evaluating the results of microbiological testing to rule out possible contamination or colonization.

(II) Adjust antimicrobial regimen appropriately according to the results of microbiological studies and susceptibility testing, as well as the efficacy of initial empiric therapy.

(III) XDR or PDR pathogens are usually found in HAP/VAP. In such cases, antimicrobial therapy should be given as early as possible, at adequate dosage, and in combination. The regimen, including specific dosage, mode and frequency of administration, should be prescribed based upon the minimum inhibitory concentration (MIC) value and PK/PD theory to optimize the effectiveness of antimicrobial treatment (132,133).

The recommended treatment regimen targeting the common drug-resistant pathogens of HAP/VAP is presented in *Table 10*.

Assessment of treatment efficacy and length of therapy

The length of antimicrobial therapy for HAP/VAP patients is generally 7 days or longer.

(I) Preliminary assessment of treatment efficacy: treatment response should be assessed 48–72 hours after initiation of empiric therapy. Treatment efficacy should be assessed comprehensively in terms of clinical symptoms and signs, imaging findings, and laboratory tests including infection-related markers. The treatment should be switched to pathogen-specific therapy or de-escalation (switching from combination therapy to monotherapy, or from broad spectrum to narrow spectrum antimicrobial agents) as soon as possible

Table 10 Recommended antimicrobial treatment regimen targeting common drug-resistant pathogens of HAP/VAP

Pathogen category	Pathogen	Recommended therapy	Comment
Gram positive cocci	MRSA	Glycopeptides (vancomycin, norvancomycin, teicoplanin) or linezolid	Vancomycin (and other glycopeptides) is comparable to linezolid in treatment efficacy (7). Trough concentration of vancomycin should be maintained at 10–15 mg/L (134). Loading dose of 25–30 mg/kg should be used in severe patients (135), and trough concentration maintained at 10–20 mg/L (134,136). Teicoplanin should be administered at dose of 6–12 mg/kg (or 400–800 mg), q12h, as loading dose for 3 consecutive times, followed by 400 mg, once daily as maintenance dose (137-140)
	VRE	Linezolid, teicoplanin	VRE is infrequently associated with pulmonary infection. Colonization and contamination should be ruled out at first (141). VRE strains are constitutively resistant to multiple classes of antibiotics including cephalosporins. The treatment option should be based on the results of susceptibility testing (141-143). Teicoplanin is used only for VanB type VRE infection (141,144)
Enterobacteriaceae	ESBLs-producing *Enterobacteriaceae*	Mild to moderate infection: cephamycins (cefoxitin, cefmetazole, cefminox), oxacephems (latamoxef, flomoxef), β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam, cefoperazone/sulbactam). Moderate to severe infection: carbapenems (imipenem, meropenem, biapenem), or combination therapy. Combination regimen: carbapenems + quinolones or aminoglycosides, β-lactam/β-lactamase inhibitor combinations + quinolones or aminoglycosides	Treatment option should be based on the results of susceptibility testing and individual factors (7). Monotherapy is adequate for majority of patients. Combination therapy is required only for a few patients with severe infection (145)
	CRE	Principal treatment: polymyxins (polymyxin B, polymyxin E), tigecycline, ceftazidime/avibactam. Combination therapy: fosfomycin, aminoglycosides (amikacin, isepamicin), carbapenems (imipenem, meropenem, biapenem). Combine with other drugs, increase dosing frequency or dosage, and/or prolong the duration of IV infusion when carbapenems MIC is 4–16 mg/L (121,146-148). Avoided if carbapenems MIC >16 mg/L (121). The use is appropriate when polymyxin B or polymyxin E MIC ≤2 mg/L. Concomitant inhaled polymyxin E is acceptable in case of XDR or PDR infection (149,150). Combination with drugs to which the isolate is susceptible (e.g., fosfomycin, tigecycline) is appropriate when polymyxin B or polymyxin E MIC >2 mg/L (151,152). Polymyxins should be used cautiously when MIC >8 mg/L because no evidence is available. Combination therapy: carbapenems-containing regimens: carbapenems + polymyxin or tigecycline; carbapenems + polymyxin + tigecycline; regimens without carbapenems: tigecycline + aminoglycosides or fosfomycin; polymyxin + tigecycline or fosfomycin; aminoglycosides + fosfomycin or aztreonam	As early as possible, at adequate dosage, and in combination (153-157). For the prevalent carbapenemases in China (most are KPC-type): ceftazidime/avibactam is appropriate (158-160). The dose of polymyxin B can be increased to 300 mg/d (161,162). The dose of meropenem can be increased to 2 g, q8h. The dose of biapenem is up to 0.3–0.6 g, q6h to q8h. All these antibiotics should be infused intravenously over 3 h (163-165). Combination of two carbapenems: ertapenem + doripenem, or imipenem, or meropenem (166-169). Such combinations should be used cautiously because there is little evidence *in vivo* (166,170,171)

Table 10 (*continued*)

Table 10 (*continued*)

Pathogen category	Pathogen	Recommended therapy	Comment
Non-fermenting bacteria	*P. aeruginosa*	Antibiotics with anti-*P. aeruginosa* activity: cephalosporins (ceftazidime, cefepime, cefoselis), carbapenems (imipenem, meropenem, biapenem), β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam, cefoperazone/sulbactam), fluoroquinolones (ciprofloxacin, levofloxacin), aminoglycosides (amikacin, tobramycin, isepamicin), aztreonam, polymyxins (polymyxin B, polymyxin E). Monotherapy: For mild cases without MDR pathogen or significant underlying disease, antibiotics (except aminoglycosides) with anti-*P. aeruginosa* activity can be used as monotherapy. Combination therapy: MDR pathogens: Anti-*P. aeruginosa* β-lactams + aminoglycosides, fluoroquinolones, fosfomycin; polymyxin + β-lactams, ciprofloxacin, fosfomycin; aminoglycosides + ciprofloxacin, levofloxacin. XDR pathogens: polymyxin + β-lactams + ciprofloxacin, fosfomycin; pneumonia caused by XDR or PDR: in addition to IV infusion, aminoglycosides (tobramycin, amikacin) (172,173) or polymyxin E can be given via aerosol inhalation (174). Combination of two β-lactams: ceftazidime or aztreonam + piperacillin/tazobactam, ceftazidime + cefoperazone/sulbactam; ceftazidime or cefepime + aztreonam (175,176). Carbapenem-resistant *P. aeruginosa*: polymyxins; polymyxin + β-lactams, or ciprofloxacin, or fosfomycin, or carbapenems; β-lactams + aminoglycosides, or fosfomycin; aminoglycosides + ciprofloxacin, or levofloxacin	Adequate dose: dose of piperacillin/tazobactam up to 4.5 g, q6h, IV infusion over 3 h (177). For severe cases, the treatment can be enhanced by increasing dosage, longer duration of IV infusion or persistent infusion (178). Combination of two β-lactams may be effective, but such regimens should be used cautiously
	A. baumannii	Treatment options: sulbactam or sulbactam-based combinations (cefoperazone/sulbactam, ampicillin/sulbactam), carbapenems (imipenem/cilastatin, meropenem, biapenem), polymyxins (B or E), tigecycline, tetracyclines (minocycline, doxycycline), aminoglycosides (amikacin, isepamicin) or quinolones (ciprofloxacin, levofloxacin, moxifloxacin). For non-MDR pathogens, β-lactams can be used according to the results of susceptibility testing. Combination therapies for XDR or PDR pathogens: sulbactam or sulbactam-based combinations + polymyxin, or tigecycline, or doxycycline, or carbapenems; polymyxin + carbapenems; tigecycline + carbapenems, or polymyxin; sulbactam or sulbactam-based combinations + doxycycline + carbapenems; sulbactam or sulbactam-based combinations + tigecycline + carbapenems; imipenem/cilastatin + rifampicin + polymyxin or tobramycin. For carbapenem-resistant *A. baumannii*: polymyxin, sulbactam or sulbactam-based combinations, tigecycline. Commonly used combination therapies: polymyxin + sulbactam or sulbactam-based combinations, carbapenems, rifampicin, aminoglycosides, or tigecycline	For MDR pathogens, the dose of sulbactam is up to 6–8 g/d (179-182). Carbapenems can be used at higher dosage, and/or longer duration of IV infusion (183,184)

Table 10 (*continued*)

Table 10 (*continued*)

Pathogen category	Pathogen	Recommended therapy	Comment
	S. maltophilia	Treatment options: SMZ/TMP, β-lactam/β-lactamase inhibitor combinations (cefoperazone/sulbactam, ticarcillin/clavulanic acid), fluoroquinolones (levofloxacin, ciprofloxacin, moxifloxacin), tigecycline, tetracyclines (minocycline, doxycycline), cephalosporins (ceftazidime, cefepime). Combination therapy: SMZ/TMP + ticarcillin/clavulanic acid, or cefoperazone/sulbactam, or fluoroquinolones, or tetracyclines, or ceftazidime, or polymyxin; fluoroquinolones, or polymyxin + ticarcillin/clavulanic acid, or cefoperazone/sulbactam, or ceftazidime	Combination therapy is indicated for severe infections, XDR or PDR pathogens (185,186). Constitutively resistant to carbapenems. Limited clinical experience is available for tigecycline

MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant *Enterococcus*; HAP, Hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; ESBL, extended-spectrum β-lactamases; CRE, carbapenem-resistant *Enterobacteriaceae*; PDR, pan-drug resistant; MDR, multi-drug resistant; XDR, extensively drug-resistant.

after learning the true pathogens (187-189) (IIIC). If empiric therapy fails and pathogen is unknown, additional microbiological tests are required to re-evaluate the probable pathogens, and adjust treatment regimen.

(II) Length of antimicrobial therapy: it should be determined according to multiple factors including severity of infection, specific pathogens and their resistance profiles, and clinical efficacy. The length of therapy is generally 7–8 days for the immunocompetent patients who receive appropriate initial empiric antimicrobial therapy with good clinical treatment response if the infection is caused by single pathogen without pulmonary emphysema, cystic fibrosis, cavity, necrotizing pneumonia, or lung abscess (8). For the patients failing to respond to initial antimicrobial therapy, and associated with critical illness, XDR or PDR pathogen, and lung abscess or necrotizing pneumonia, the length of therapy should be prolonged appropriately.

(III) Indications for stopping antimicrobial agents: discontinuation of antimicrobial therapy should be decided according to clinical symptoms and signs, imaging findings, and the results of laboratory tests (especially PCT) (IIIB).

Inhaled antimicrobial therapy

Inhaled antimicrobial therapy can be used in combination with systemic antimicrobial therapy when the following conditions are satisfied simultaneously: (I) HAP/VAP is caused by MDR GNB such as *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*; (II) systemic antimicrobial therapy alone cannot provide adequate therapeutic concentration in the site of infection, and thus have poor efficacy; (III) the inhaled antimicrobial agent to be used is active against the target pathogens (7,190,191) (IC). The inhaled antimicrobial agents are mainly aminoglycosides (including tobramycin and amikacin) and polymyxins (7,190-193).

Most of the clinical studies evaluating inhaled antimicrobial agents have major limitations, including small sample size, remarkable heterogeneity in study populations and dosing regimens. The clinical evidence of outcome improvement achieved by intravenous therapy in combination with inhaled antimicrobial agents is mainly seen in polymyxins. Therefore, the efficacy and safety of inhaled antimicrobial therapy require further evaluation

(149,150,194,195).

No optimal regimen is available for inhaled antimicrobial agents currently. It is recommended to use polymyxin E at dose of 30–60 mg colistin base activity (CBA, equivalent to 1,000,000–2,000,000 IU), in 2–4 mL normal saline for IV administration, q8h-q12h (196,197). The recommended regimen of amikacin is 400 mg, bid or 25 mg/kg, once daily (198-200). The recommended regimen of tobramycin is 300 mg, q12h (172). The inhaled antimicrobial agents (especially polymyxin E) should be prepared immediately before use (197). The length of inhaled therapy is generally 14 d or until ventilator withdrawal. For the patients receiving mechanical ventilation, suitable atomization device/nebulizer should be selected, and appropriate oxygen concentration and preferred mode of ventilation is set properly according to the pathophysiological features of the patient (191,201).

Respiratory side effect of inhaled therapy is mainly airway spasm, which is characteristic of cough, wheezing, and dyspnea. The patient should be monitored for respiratory symptoms and oxygen saturation in the course of atomization. Atomization can be suspended in case of mild airway spasm, and bronchodilator should be given to alleviate the spasm. If airway spasm is persistent or severe, inhaled therapy should be stopped. The patients receiving nebulized aminoglycosides and polymyxin should be monitored for renal function, and therapeutic drug monitoring should be performed if possible. The patients under mechanical ventilation should be monitored for: (I) peak airway pressure, which will increase due to filter obstruction or airway spasm; (II) mental status. Low-dose sedatives can reduce patient-ventilator asynchrony, which should be discontinued timely at the end of atomization.

Adjuvant and supportive therapy

In addition to empiric and pathogen-specific antimicrobial therapies, it is also important for HAP/VAP patients to receive comprehensive management, including drainage of airway secretions, rational oxygen therapy, mechanical ventilation, fluid management, glycemic control, and nutritional support. Especially for critically ill patients, such adjuvant therapy usually can influence patient outcomes. Patients can benefit from reasonable use of adjuvant therapies.

Respiratory support techniques

(I) Drainage of airway secretions: airway secretions must be drained out timely and effectively so as to keep patency of the airway. This is the primary measures to support successful antimicrobial therapy of HAP/VAP, especially in critically ill patients complicated with lung abscess, empyema or poor airway clearance. Bedridden patients should be managed with regular body-turning and backslap, and active postural drainage in order to prevent aspiration. The patients are encouraged to take active respiratory function exercises (202). Extrasomatic vibration sputum discharge machine is appropriate for the patients with poor airway clearance and inadequate expectoration, to directly stimulate cough and sputum aspiration through nose/mouth or artificial airway, and sputum suction by bronchofibroscope if necessary. Bronchofibroscopic sputum suction should be implemented as early as possible for the patients receiving non-invasive mechanical ventilation with high output of sputum. This is helpful to reduce the rate of endotracheal intubation (203). (II) Rational oxygen therapy: oxygen therapy should be provided timely to the hypoxemic and severe HAP patients in order to keep arterial oxygen saturation (SaO_2) >90%. Continuous oxygen therapy is required in the following cases: respiratory rate >24 breaths/min, PaO_2 <60 mmHg, presence of shock or severe metabolic acidosis, and tissue hypoxia. High concentration oxygen therapy is appropriate for the patients with type I respiratory failure. Fraction of inspired oxygen (FiO_2) ≥35% can increase PaO_2 to above 60 mmHg or finger pulse oxygen saturation (SpO_2) to above 90%. Low concentration continuous oxygen therapy (FiO_2 <35%) should be administered routinely to the patients with type II respiratory failure to maintain PaO_2 ≥60 mmHg or SpO_2 ≥90%, and avoid significant increase of $PaCO_2$. Other way of delivering oxygen therapy should be considered when $PaCO_2$ increases significantly or PaO_2 cannot be improved. There are many methods to deliver oxygen therapy, including traditional oxygen therapy (inhalation via nasal cannula or face mask), and high-flow nasal oxygen (HFNO). For critically ill HAP patients, HFNO may produce certain level of positive end-expiratory pressure (PEEP) because of inhalation of high oxygen flow, and associated with adequate humidification. It has gradually become an important way of oxygen therapy, and also as sequential treatment for patients after ventilator withdrawal and extubation, which has shown good efficacy and safety (204-206). (III) Mechanical ventilation: for the HAP patients with abnormal respiratory frequency (>30 breaths/min or <12 breaths/min), weak or absence of spontaneous breathing, seriously abnormal respiratory rhythm associated with disturbance of

consciousness, use of accessory muscle with breathing or paradoxical breathing, mechanical ventilation should be considered timely when hypoxemia cannot be corrected even after HFNO therapy (207). Mechanical ventilation includes non-invasive and invasive mechanical ventilation. Non-invasive approaches assist ventilation primarily via oronasal mask or nasal mask, which are suitable for the conscious patients with stable vital signs and hemodynamics, and low volume of sputum, or the patients who can expectorate soberly. Pressure support ventilation (PSV) and bilevel positive airway pressure (BiPAP) are the frequently used non-invasive approaches of ventilation. The effect of ventilatory treatment can be evaluated in terms of the change of symptoms and signs, patient-ventilator synchrony, results of blood gas analysis, and other parameters. Appropriate use of non-invasive mechanical ventilation can reduce endotracheal intubation and the incidence of related complications, shorten the length of ICU stay (208). When the patient develops apparent abnormality of consciousness, poor drainage of sputum, abnormal hemodynamics, or respiratory failure indicated by blood gas analysis, the ventilation support should be switched to invasive mechanical ventilation in time. Invasive mechanical ventilation works mainly by endotracheal intubation (via mouth or nose) or tracheotomy, which is indicated for the HAP patients complicated with severe respiratory failure and/or abnormal vital signs, and meeting the following conditions: (i) Not indicated for non-invasive mechanical ventilation, and with severe life-threatening hypoxemia and/or hypercapnia (PaO_2/FiO_2 <150 mmHg); (ii) Inadequate clearance of airway secretions associated with high risk of aspiration (e.g., bulbar paralysis or abdominal distension, vomiting), disturbance of consciousness; (iii) hemodynamic instability, multiple organ failure; (iv) proper use of non-invasive mechanical ventilation fails to achieve the expected effect or even makes the condition worse. Non-invasive methods should not be used to replace invasive mechanical ventilation in the patients with clear indications for invasive mechanical ventilation, unless they refuse endotracheal intubation or tracheotomy. (IV) Extracorporeal membrane oxygenation (ECMO): if adequate conventional mechanical ventilation still cannot effectively improve the condition and reverse hypoxemia, ECMO should be considered as early as possible (209).

Multiple organ support therapy

(I) Hemodynamic monitoring and fluid management: critically ill HAP/VAP patients may experience insufficiency of effective circulating volume, and even septic shock at early stage due to fever, eating less, inflammatory response, and other factors. Their hemodynamic status should be evaluated dynamically as clinically indicated, and fluid resuscitation provided in time. Vasoactive drugs should be administered if necessary to maintain mean arterial pressure >65 mmHg. When large volume of crystalloid solution is required for fluid resuscitation, infusion of albumin can be considered as appropriate. (II) Glycemic control: blood glucose should be managed with reference to standard protocol. The target glucose level is ≤10 mmol/L. (III) Prevention of stress ulcer: in general, routine use of antacids is not recommended for prevention of stress ulcer. If patients have the risk factors for stress ulcer and gastrointestinal hemorrhage, they should be managed with gastric mucosal protective agents (e.g., sucralfate) and antacids, preferably proton pump inhibitors (PPIs), or H2 receptor antagonists (210). However, antacids may increase the incidence of HAP/VAP (211). (IV) Continuous renal replacement therapy (CRRT): currently, no consensus is reached in the timing, operating mode, parameter setting, and effect on patient outcomes for HAP/VAP patients to use CRRT. It is recommended to consider CRRT when HAP/VAP patients are complicated with septic shock and acute renal dysfunction. CRRT is helpful in eliminating metabolites in the body, managing liquid volume, correcting the disturbance of water, electrolytes, and acid-base balance, nutritional support, and clearance of some inflammatory mediators (212).

Non-antimicrobial pharmacotherapy

(I) Glucocorticoids: so far, no consensus is available for the timing, types, dosage, and duration of treatment regarding use of glucocorticoids in HAP/VAP patients. With reference to China CAP guideline (2016 Edition), it is recommended to use glucocorticoids only in critically ill HAP/VAP patients associated with hemodynamic instability. (II) Nutritional support: the HAP/VAP patients complicated with sepsis or septic shock should be supported with enteral nutrition as early as possible. If energy and protein intake don't reach 60% of the target after enteral nutrition support for 7–10 days, parenteral nutrition supplements must be provided no matter what is the risk of malnutrition. If it is impossible to provide early (within 7 days since disease onset) enteral nutrition, and there is not risk of malnutrition, nutritional risk screening 2002 (NRS-2002) score ≤3, or nutrition risk in critically ill (NUTRIC) score

≤5, the patients should be supported by parenteral nutrition 7 days after disease onset. If there is risk of malnutrition or severe malnutrition, parenteral nutrition support should be initiated as early as possible (213,214). (III) Immunotherapy: there is controversy about the immunotherapy for HAP/VAP patients because we still lack clinical data from evidence-based medicine. In addition to antimicrobial therapy, critically ill HAP/VAP patients can be treated with immunoglobulin (0.5–1.0 $g \cdot kg^{-1} \cdot d^{-1}$) as appropriate, which may be helpful for controlling inflammatory reaction. Thymosin α1, an immunomodulator, may play a role in sepsis to improve immune paralysis (215).

Prevention

The overall strategy for HAP/VAP prevention is to minimize and control various risk factors. All healthcare activities must be consistent with the fundamental requirements and principles regarding disinfection, sterilization, and infection control in medical facilities. Medical staffs must be educated to improve their awareness of infection control, increase their compliance to hand hygiene, ensure careful disinfection and sterilization of medical devices and tools, strictly practise aseptic procedures, put target monitoring into place, and implement optimal use of antimicrobial agents.

Prevention of HAP

(I) Prevent aspiration: patients should be in semi-recumbent position (head-of-bed elevation 30–45°). The head of bed should not be too high to increase the risk of pressure sore. Feeding must be proper and reasonable.

(II) Reduce bacterial colonization in upper respiratory tract and/or gastrointestinal tract (216,217): oral care with chlorhexidine (Hibitane), chlorhexidine sponge bath, selective oropharyngeal decontamination (SOD), and use of probiotics.

(III) Actively treat underlying diseases: for critically ill patients, reinforce the nutritional support, promptly manage water, electrolytes, and acid-base imbalance, and control infection-related risk factors such as hypoproteinemia and hyperglycemia; active treatment and rehabilitation of cardiac and pulmonary diseases, adoption of airway clearance therapy (ACT) techniques, including breathing exercises, postural drainage, external manipulation or mechanical devices (218). More attention should be paid to the airway management of perioperative patients (especially those receiving thoracic and upper abdominal surgery). The respiratory tract must be kept humid and patent. Postoperative patients are encouraged to get out of bed as early as possible. Sedatives should be avoided if possible (219).

(IV) Strengthen patient management: protective isolation should be provided to seriously immunocompromised patients such as organ transplant recipients and neutropenic patients. Contact precautions should be adopted for the patients infected or colonized with antibiotic-resistant microorganisms (e.g., MRSA, CRAB, CRPA, CRE) (143).

Prevention of VAP

There are specific risk factors and pathogenesis for VAP. Hence, in addition to the above-stated common preventive measures, the following specific precautions are necessary for prevention of VAP.

Prevent aspiration

The patients receiving invasive mechanical ventilation are recommended to raise the head of bed to 30–45° unless contraindicated (3,217,220) (IIA). Efforts should be made to help patients with sputum excretion by body-turning, machine vibration and percussion on back.

The subglottic cumulated secretions are the main source leading to aspiration in patients with artificial airway. The endotracheal tube with subglottic suction can reduce the incidence of VAP, and decrease the length of ICU stay (221-224). It is recommended to use such an endotracheal tube in the patients who are expected to undergo invasive ventilation for more than 48 or 72 hours (3,217) (IA). The cuff pressure should be kept at 25 cmH2O or higher (40,217,225) (IA). The subglottic secretions should be removed as clean as possible before balloon deflation or extubation.

Condensed fluid is usually formed in the pipelines of ventilator, which may facilitate bacterial growth and proliferation. Every effort should be made to avoid the condensate containing bacteria flowing directly into lower respiratory tract and so causing VAP, and also avoid its backflow into humidifier to allow the humidified bacteria-containing aerosol to be inhaled into lower respiratory tract. Condensate collecting bottle must be put at the lowest point of the pipelines, always kept upright, and made clean

in time. Sterilized water should be used in the humidifier and nebulizer, and completely replaced every 24 hours. The circuit and accessories of ventilator should be patient-specific, and disinfected and sterilized every time after use. The patients receiving long-term mechanical ventilation are recommended to change ventilator circuit every week in general, but change immediately in case of visible filth or malfunction (217) (IIA).

The patients under mechanical ventilation should be supported by enteral nutrition as possible (3,217) (IIB). Enteral nutrition at early stage can promote intestinal movement, stimulate secretion of gastrointestinal hormones, improve intestinal blood perfusion, help maintain the structural integrity and barrier function of intestinal mucosa, and so reduce colonization and translocation of pathogens. It is better than parenteral nutrition. Post-pyloric feeding can reduce the incidence of VAP compared to gastric tube feeding, especially in the patients at high risk of aspiration. However, the mortality rate does not show significant difference between these two approaches of nutrition (226). Intermittent feeding and feeding with minimal gastric residual volume can reduce gastroesophageal reflux, decrease the risk and mortality of pneumonia. Gastrostomy can also reduce VAP incidence. Regular monitoring of gastric residual volume is not recommended for the patients who are asymptomatic and receiving enteral nutrition (217,227) (IIA).

Reduce colonization

Regular oral care is recommended for the patients who are receiving mechanical ventilation (217) (IIA), including oral rinse with gargles such as normal saline, chlorhexidine or povidone iodine solution, cleaning teeth and lingual surface with a toothbrush, q6h–q8h.

SOD means application of nonabsorbable antimicrobial agents to oropharynx, while selective digestive tract decontamination (SDD) indicates that nonabsorbable antimicrobial agents are used by application to oropharynx and oral administration, combined with parenteral antimicrobial agents or not. The aim of SOD and SDD is to eliminate the potential pathogens in oropharynx and gastrointestinal tract, which may cause secondary infection. Studies have shown that (228) either SOD (229) or SDD can reduce the incidence of HAP/VAP, and colonization of resistant pathoegns in respiratory tract. However, insufficient evidence is available to support its effect on decreasing the duration of mechanical ventilation, length of ICU stay, or reducing mortality. SDD may increase the risk of infection due to antibiotic-resistant bacteria, including *Clostridium difficile* infection. However, no study is available on the risk of long term use. SOD or SDD should be used cautiously in the patients under mechanical ventilation while considering the risk/benefit balance (3,217) (IIB).

Silver-coated endotracheal tube can reduce the incidence of VAP, but has no effect on the duration of mechanical ventilation, length of ICU stay, or mortality (230). At present, silver-coated endotracheal tube is not recommended for routine use (217) (IIB).

Oral administration of probiotics can reduce the incidence of VAP (231), but not mortality. Probiotics should be avoided in immunocompromised patients or the patients with gastrointestinal disorder at increased risk of bacterial translocation. In general, probiotics are not recommended for routine use to prevent VAP (3,217) (IIB).

Prevention of stress ulcer is one of the important measures to manage the patients under mechanical ventilation in ICU. The medicine commonly used in clinical practice include gastric mucosal protective agents (e.g., sucralfate) and antacids such as H_2 receptor antagonists (H_2RA), and PPIs. Gastric mucosal protective agents can reduce the risk of VAP compared to antacids, but only play a minor role in preventing gastrointestinal hemorrhage. It is currently considered that the use of antacids to prevent stress ulcer may increase bacterial colonization in gastrointestinal tract and airway, but do not have effect on the mortality of VAP. So antacids should be used as clinically indicated (232) (IIB).

Reduce the use of invasive ventilation

Establishment of artificial airway and use of mechanical ventilation are the most important risk factors for developing VAP, and endotracheal intubation makes the risk of pneumonia increase by 6–21 fold (233), especially repeated or prolonged intubation. Frequent replacing ventilator pipelines can further increase the risk of VAP (216,234,235). It is crucial to prevent VAP by minimizing the use of invasive ventilation, and reducing the duration of invasive ventilation (217) (IA).

The indications for endotracheal intubation or tracheotomy should be adhered to strictly. Non-invasive ventilation is preferred for the patients requiring ventilator-assisted ventilation. Non-invasive positive-pressure ventilation (NIPPV) should be used as early as possible in the patients with chronic obstructive pulmonary disease or congestive heart failure and complicated with hypercapnia or hypoxemia, which can reduce the use of endotracheal

intubation (236,237), and thus reduce the incidence of VAP (IA). HFNO can be used in the patients with type I respiratory failure due to various causes (238,239), and some patients with mild type II respiratory failure to reduce the rate of endotracheal intubation and reintubation (240) (IA). It is important to note that the use of the respiratory support measures mentioned above should not delay the necessary endotracheal intubation and make the condition worse.

The use of sedatives should be reduced or avoided if possible during invasive ventilation. The patient should be evaluated on a daily basis to see if the sedatives in-use are necessary, and they should be discontinued as early as possible (IA). It is especially important to avoid the use of benzodiazepines (241). The patients should be aroused every day if indicated to administer spontaneous breathing trial, and evaluate whether the ventilator and endotracheal tube can be removed. The duration of mechanical ventilation should be minimized if possible in order to reduce the risk of VAP (242) (IA).

Bundle interventions

Current researches have shown that the following core interventions can reduce the mean duration of mechanical ventilation and days of hospital stay, incidence and mortality of VAP, and/or cost (217,243-252) (IA). The primary interventions are: (I) use non-invasive respiratory support techniques preferably if possible; (II) evaluate the necessity of invasive mechanical ventilation and endotracheal intubation every day, and remove ventilator or endotracheal tube as early as possible; (III) deep sedation should be avoided if possible in the patients who are receiving mechanical ventilation. If the use of sedatives is necessary, the patients should be aroused regularly to administer spontaneous breathing trial. The patients should be evaluated on a daily basis to see if the sedatives in-use are necessary, and they should be discontinued as early as possible; (IV) use endotracheal tube with subglottic suction in the patients who are expected to undergo mechanical ventilation for more than 48 or 72 hours; (V) Cuff pressure should be kept at 25 cmH2O or higher; (VI) the head of bed should be raised to 30–45° unless contraindicated; (VII) Strengthen oral care, preferably with chlorhexidine gargle; (VIII) ventilator circuit should be cleaned and disinfected appropriately. It is recommended to replace ventilator circuit every week in general, but replace immediately in case of visible filth or malfunction; (IX) strictly follow the aseptic techniques during airway-related procedures; (X) encourage and help the patients under mechanical ventilation to get out of bed and receive rehabilitation training as early as possible.

In addition to implementation of the above core interventions, the following precautions can be adopted selectively according to the characteristics of patient population and specific conditions in local ICU. Clinicians should collect evidence-based data and health economic information to support relevant preventive interventions, such as early tracheotomy for the patients under endotracheal intubation, prevention of stress ulcer, SOD/SDD, prophylactic use of probiotics, use of endotracheal tube made of special material (e.g., antibiotic-coated, silver-coated, or ultrathin polyurethane cuff). Closed endotracheal suction system has no effect on VAP incidence or other outcomes of patient (217), but it is useful for the control of respiratory infectious diseases which are disseminated via aerosol/air in hospitals.

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Footnote

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Comments and recommendations regarding other issues related to HAP/VAP in this guideline

Healthcare-associated pneumonia (HCAP)

IDSA/ATS first proposed the concept of healthcare-associated pneumonia (HCAP) in 2005 (2), the aim of which is to timely identify infections caused by MDR pathogens from community-acquired pneumonia, and improve the outcome of this kind of pneumonia by empirically covering MDR microorganisms with broad spectrum antimicrobial agents. The clinical utility of this concept was supported by the data from large scale clinical studies in the US in the early days (253). However, as relevant studies are conducted extensively worldwide, controversies about the concept of HCAP are growing. European guidelines for the management of adult lower respiratory tract infections in 2011 state that the data currently available from evidence-based medicine don't support the adoption of HCAP concept in Europe (254).

The controversy mainly focuses on the following two aspects: (I) there is great difference in the results of various HCAP etiological studies, and the results of most studies have shown that the concept of HCAP cannot exactly identify MDR infections (255). The prevalence of antibiotic-resistant pathogens in HCAP is generally lower in European and Asian countries than the level reported in the US (256-261). The meta-analysis recently published indicates that the sensitivity and specificity of using HCAP definition to screen antimicrobial-resistant infections don't reach the threshold for its use in clinical practice (255). In fact, in addition to the risk factors mentioned in the definition of HCAP, there are still at least 10 additional risk factors which may increase the risk of antibiotic-resistant pneumonia. In specific study population, the combination of several of these risk factors usually performs better than HCAP in screening antibiotic-resistant infections (262). (II) The empiric, broad spectrum antimicrobial regimen recommended in 2005 IDSA/ATS guidelines cannot effectively improve the outcome of HCAP patients. Although the results of early studies suggested that the higher mortality of HCAP may be associated with inadequate coverage of antibiotic-resistant pathogens by initial treatment (263,264), most of the studies in recent years have indicated that the higher mortality rate of HCAP is primarily associated with advanced age, complications, severe underlying diseases, and organ dysfunction, but not necessarily with antibiotic-resistant pathogens. The broad spectrum antimicrobial treatment regimen recommended in 2005 IDSA/ATS guidelines could not shorten the length of hospital stay and stable duration of disease in HCAP patients (265). When the IDSA/ATS updated their HAP/VAP guidelines in 2016, all authors agreed unanimously that the concept of HCAP would no longer be accepted (7).

The structure of medical institutions in China is very different from that in the US. Even when the idea of HCAP is most popular, we did not follow the fashion to adopt this concept in China. The guidelines do not recommend the use of HCAP concept in China. The antibiotic resistance profile of local pathogens should be highly valued in the treatment of pneumonia patients. It is important to comprehensively analyze all the risk factors for antibiotic-resistant pathogens, rather than simply identify whether the pneumonia in a patient is HCAP or not (7) (IA).

Ventilator-associated tracheobronchitis (VAT)

It is generally considered that VAT is an intermediate step in the course of VAP pathogenesis when the microorganisms colonizing in lower respiratory tract become pathogens of VAP (266-269). At present, there is still controversy about whether VAT is an independent disease, and no uniform diagnostic criteria are available. It is still required to further clarify the exact boundary between microbial colonization, VAT, and VAP. Theoretically, in contrast to VAP, VAT is not associated with pulmonary parenchymal infiltration, and infrequently associated with decreased oxygenation capacity. Quantitative culture of the specimens from distal airway (PSB or BAL) also results in lower concentration of bacteria than that in VAP (267,268,270).

The pathogens and incidence of VAT, as well as the proportion of VAT progression to VAP vary with studies, medical institutions, and the different units in the same medical institution (266-268,270-275). The adverse effects of VAT include longer duration of mechanical ventilation (268,272-277), longer time of ICU stay (268,272-277) and total hospital stay (272,273), but the mortality is not affected significantly (266,271,273). Recently, several relevant studies and meta-analysis indicate that VAT is not an independent risk factor for increased mortality in the patients under mechanical ventilation (273). VAT also has no significant effect on the attributable mortality of the patients under mechanical ventilation (266). It is controversial about whether antimicrobial treatment is required for VAT (266,273,278). Studies have revealed that appropriate systemic antimicrobial treatment can reduce the proportion of VAT progression to VAP (266,270,273), but

cannot reduce VAT mortality (266,273). Few clinical studies are available on the effect of inhaled antimicrobial agents in treatment of VAT. The quality of these studies is poor. The clinical significance of antimicrobial therapy on VAT still cannot be evaluated accurately based on the study data currently available (279,280).

The recommendations of 2016 IDSA/ATS HAP/VAP guidelines state that antimicrobial therapy is not required for VAT (7). This, to some extent, makes the diagnosis of VAT meaningless in clinical practice. Since no uniform and critically feasible diagnostic criteria are available for VAT, and the high quality evidence to support antimicrobial therapy for VAT is not enough yet, we also suggest not adopting VAT as a diagnosis in clinical practice and not providing antimicrobial therapy for VAT (IIB). Before the well-accepted diagnostic criteria and high quality evidence are available, considering VAT as an independent disease and prescribing antibiotics for patients with VAT may further increase the consumption of antimicrobial agents in ICU, which is unfavorable for curbing the spread of antimicrobial resistant pathogens, and may also increase the incidence of antibiotic-related adverse effects.

For the critically ill patients, among which chest CT scan cannot be performed and point-of-care chest X-ray film often cannot exclude pneumonia, if there are new respiratory signs and systemic signs suggesting VAP, empiric antimicrobial therapy may be administered prudently even in the absence of enough radiographic evidence to confirm VAP. It is not necessary to deliberately differentiate whether the patients are suffering VAT or VAP.

Early-onset and late-onset HAP/VAP

The results of early studies have shown that the airway-colonizing microorganisms in the hospitalized patients gradually transform from community-acquired pattern to hospital-acquired pattern 3–4 days after hospital admission (281). Corresponding to such a shift, it was considered that the pathogenic spectrum of HAP/VAP and their antibiotic resistance profile would vary with the onset time of pneumonia after admission (2). Traditionally, HAP/VAP is usually classified into early-onset (≤4 d) and late-onset HAP/VAP (≥5 d) in terms of the onset time since hospital admission (2). It was previously considered that as for early-onset HAP/VAP, if the patient doesn't have other risk factors for MDR infection, the pathogen pattern is very similar to that isolated in CAP, while late-onset HAP/VAP are mostly caused by antibiotic-resistant pathogens, including *P. aeruginosa*, *Acinetobacter* spp., MDR *Enterobacteriaceae* or MRSA (2). In recent years, a series of clinical studies based on large sample size at home and abroad have reported that the composition of pathogens and prevalence of core pathogens are very similar between early-onset and late-onset HAP/VAP (18,282). It is not uncommon to isolate MDR pathogens in early-onset HAP/VAP (120,283,284).

In 2005 IDSA/ATS HAP/VAP guidelines, the onset time of pneumonia since hospital admission was set as one of the important criteria for patient stratification or formulation of empiric antimicrobial regimen (2). However, new evidence from clinical studies suggests that inappropriately emphasizing the effects of hospital stay length on HAP/VAP etiology may have unfavorable consequences on clinical outcomes. On the one hand, under-estimating the risk of antibiotic-resistant pathogens in the so-called early-onset HAP/VAP may lead to inadequate therapy, and so higher risk of failure of initial empiric antimicrobial therapy. On the other hand, for late-onset HAP/VAP, unnecessary overtreatment may be possible if only emphasizing the effects of onset time but neglecting detailed analysis of other true risk factors for antibiotic-resistant pathogens (250). Currently, it is widely accepted in China and abroad that prior intravenous antibiotic use 90 days before HAP/VAP onset is the most important risk factor for antibiotic-resistant pathogens, while the onset time since hospital admission only has relatively less effect on the risk of antibiotic-resistant infections.

In the Chinese "*Guidelines for Diagnosis and Treatment of Hospital-acquired Pneumonia* (draft)" released in 1999, the onset time was listed as one of the criteria for evaluating HAP with reference to the study results of foreign countries because the HAP/VAP survey data of our country were not available at that time (1). Subsequently, the results of our epidemiological survey didn't show significant difference between the overall prevalence of various pathogens in early-onset HAP/VAP and that in late-onset HAP/VAP (18). For these reasons, this guideline recommends that empiric antimicrobial treatment should be based on the comprehensive analysis of risk factors for antibiotic-resistant pathogens, rather than the onset time of pneumonia alone (IIB).

HAP/VAP in immunocompromised host

HAP/VAP varies greatly between immunocompromised and immunocompetent subjects in spectrum of pathogens, clinical manifestations, and radiological signs. In addition to length of hospital stay, ICU stay, mechanical ventilation, antibiotic use, the prognosis of immunocompromised

patients with HAP/VAP is also affected by type, severity, and duration of immunodeficiency (285-288).

Immunodeficiency can be classified into three types according to the impaired part of immune system, including neutropenia or neutrophils dysfunction, humoral immune defect, and cellular immune deficiency (286). Combined immunodeficiency may exist in some patients (286). In addition to the common HAP/VAP pathogens, opportunistic pathogens such as fungi (*Aspergillus*, *Pneumocystis*, *Cryptococcus*, *Zygomycete*, etc.), viruses (cytomegalovirus, herpes simplex virus, respiratory syncytial virus, etc.), *Legionella* and *Nocardia* are frequently found in HAP/VAP patients with severe neutropenia, or neutrophils dysfunction, serious cellular immune deficiency or combined immunodeficiency (285-291). HAP/VAP in immunocompromised patients is usually characterized by the following clinical features (285-288): insidious onset but rapid progression with poor outcomes and high mortality; earlier emergence and high incidence of dyspnea and respiratory failure; multiple lesions, sometimes diffuse lesion in the lungs; and high incidence of extrapulmonary breakthrough infections. In the patients with humoral immune defect alone, recurrent pyogenic infection caused by *S. aureus*, *K. pneumoniae*, *Haemophilus influenzae*, or *P. aeruginosa* are common. In the patients with cellular immunodeficiency, the pulmonary infections caused by *M. tuberculosis*, nontuberculous *Mycobacteria*, *Nocardia*, *Aspergillus*, or *Cryptococcus* are usually subacute or chronic disease, associated with single or multiple localized lesions in the lungs. Such infections are mostly community-acquired, and relatively fewer in HAP/VAP.

Clinical diagnosis of pneumonia is very challenging in immunocompromised patients due to the interference by underlying diseases and various treatment measures. It usually requires to be differentiated from some non-infectious pulmonary diseases (290,292). Chest CT scan can not only discover the occult lesions invisible on chest X ray film, but also reveal the imaging details of pulmonary lesions. CT scan can provide clues for estimating the possible pathogens, and guide the implementation of invasive procedures for etiological diagnosis (290,292-294). Therefore, when HAP/VAP is suspected in immunocompromised patients, it is recommended to perform chest CT scan instead of plain chest X film if possible (IIIC).

The etiology of pneumonia in immunocompromised patients is more diverse and complex than that in immunocompetent patients (285-291), so early and accurate etiological diagnosis is especially more important (285-288,290,292) (IIB). Routine smear, gram stain, and conventional bacterial culture of respiratory tract specimens are usually unable to allow accurate etiological diagnosis of pneumonia. So, additional etiological tests are required to identify fungi, viruses, *Nocardia*, *Legionella*, *M. tuberculosis*, and nontuberculous *Mycobacteria*, etc. according to the type of immunodeficiency and pulmonary imaging features (286,290,292). Bronchoalveolar lavage or TBLB (295), or percutaneous lung biopsy may be performed if necessary (296) to confirm diagnosis. Since the pathogens of infection secondary to immunodeficiency are required to be identified more quickly, and some opportunistic pathogens are difficult to be isolated, various special stains of respiratory tract specimens (smears), quick pathogen-specific antigen assay, and nucleic acid detection have more important diagnostic utility (286,292,297-302) (IIB). Detection of specific antibody in serum cannot allow early diagnosis, and false negative result is more frequent in immunocompromised patients, so its value is limited for immunocompromised patients (298,302) (IIIC).

The initial empiric antimicrobial therapy for HAP/VAP in immunocompromised patients should be based on the accurate assessment of the severity of pneumonia and immune deficiency. Efforts should be made to avoid both inadequate and delayed treatment due to under-estimation of the bad outcome of severe infection and/or serious immunodeficiency, and overtreatment due to indiscriminate "full coverage of pathogens". When speculating the possible pathogens and selecting antimicrobial agents for initial empiric treatment, in addition to the factors conventionally considered in pneumonia patients such as local epidemiological data of HAP/VAP pathogens, the type, severity, and duration of immunodeficiency, as well as imaging features of pulmonary lesions should be also taken into account (285-288,290,292,299). Etiological tests should be promptly performed before initiation of antimicrobial therapy. Treatment efficacy should be evaluated timely. The initial treatment regimen should be adjusted appropriately according to the results of etiological tests.

In the treatment of the HAP/VAP secondary to immunodeficiency, immune reconstitution is an important measure and should be addressed seriously (286,290,292). The specific measures include facilitating recovery of neutrophil count, stopping or reducing the use of drugs which may result in immunosuppression, supplementing exogenous immune active agents, improving or controlling the diseases which may result in immunodeficiency (IIIC).