ic Infection & Chemotherapy

Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

Mi Suk Lee[1*], Jee Youn Oh[2*], Cheol-In Kang[3], Eu Suk Kim[4], Sunghoon Park[5], Chin Kook Rhee[6], Ji Ye Jung[7], Kyung-Wook Jo[8], Eun Young Heo[9], Dong-Ah Park[10], Gee Young Suh[11], and Sungmin Kiem[12]

[1]Division of Infectious Diseases, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul; [2]Division of Respiratory, Allergy and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul; [3]Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [4]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam; [5]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang; [6]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [7]Division of Pulmonology, The Institute of Chest Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul; [8]Division of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul; [9]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul; [10]Division of Healthcare Technology Assessment Research, National Evidence-Based Healthcare Collaborating Agency, Seoul; [11]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Department of Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [12]Division of Infectious Diseases, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea

Community-acquired pneumonia is common and important infectious disease in adults. This work represents an update to 2009 treatment guideline for community-acquired pneumonia in Korea. The present clinical practice guideline provides revised recommendations on the appropriate diagnosis, treatment, and prevention of community-acquired pneumonia in adults aged 19 years or older, taking into account the current situation regarding community-acquired pneumonia in Korea. This guideline may help reduce the difference in the level of treatment between medical institutions and medical staff, and enable efficient treatment. It may also reduce antibiotic resistance by preventing antibiotic misuse against acute lower respiratory tract infection in Korea.

Key Words: Pneumonia; Community-acquired infections; Adults; Therapeutics; Guideline

Introduction

1. Background of guidelines

Clinical practice guidelines based on evidence-based medicine promote evidence-based, objective, and efficient medical practices. Numerous evidence-based clinical practice guidelines have also been developed, including the treatment guideline for community-acquired pneumonia developed in 2009. Additional data about the distribution of the causative bacteria of community-acquired pneumonia and antibiotic resistance have been obtained since then, and various guidelines about the diagnosis, treatment, and prevention of pneumonia have also been developed abroad. It has therefore become necessary to revise the current guideline on community-acquired pneumonia in Korea.

Antibiotic resistance has recently been raised as a serious public health issue worldwide. This is because whereas resistant bacteria that cannot be removed with existing antibiotics are increasing in number, less and less novel antibiotics are being developed. The issue of antibiotic resistance is much more serious in Korea than in other countries, with major causative bacteria having the highest antibiotic resistance in the former worldwide. Antibiotic resistance is proportional to the level of antibiotic misuse. The level of antibiotic use in Korea is higher than the average level of antibiotic use worldwide. The rate of prescribing antibiotics for infections that do not require antibiotic treatment is also higher in Korea than in other countries.

The present clinical practice guideline provides revised recommendations on the appropriate diagnosis, treatment, and prevention of community-acquired pneumonia. This guideline may help reduce the difference in the level of treatment between medical institutions and medical staff, and enable efficient treatment. It may also reduce antibiotic resistance by preventing antibiotic misuse against acute lower respiratory tract infection in Korea.

2. Development process of diagnosis and treatment guidelines

1) Guideline development committee

An antibiotic treatment guideline development committee for lower respiratory tract infection in adults was formed in November 2016. The committee included as many associated medical institutions as possible.

Committee members recommended by the Korean Society for Chemotherapy, the Korean Society of Infectious Diseases, the Korea Academy of Tuberculosis and Respiratory Diseases, the Korean Association of Family Medicine, the Korean Medical Practitioners Association, and the National Evidence-based Healthcare Collaborating Agency participated in the development of this guideline.

2) Guideline target and scope

This guideline sets forth fundamental principles of antibiotic use against community-acquired pneumonia in adults aged 19 years or older, taking into account the current situation regarding community-acquired pneumonia in Korea as of March 2017.

3) Method of literature search

Studies published in English in the last 10 years were searched. OVID-MEDLINE and OVID-EMBASE were used to search for foreign studies, and KMBase and KoreaMed were used to search domestic studies. Clinical practice guidelines were searched on NGC, G-I-N, and KoMGI. The search date is February 10th, 2017.

4) Recommendation and evidence levels

The level of recommendation was divided into "Strong, Weak", and the level of evidence was divided into "High, Moderate, Low, Very low". The level of recommendation and the level of evidence were determined using an unofficially agreed method. A consensus was deemed reached if over 70% of the participating committee members agreed.

(1) Level of recommendation

① Strong: Benefits evidently outweigh costs or loss, or costs and loss evidently outweigh benefits.
② Weak: Level of evidence is low, or there is no clear difference between benefits and loss.

(2) Level of evidence

① High: The possibility that the level of certainty about the estimated value of an effect will change in future studies is very low.
② Moderate: Future studies will have an important influence on the level of certainty about the estimated value of an effect, and the value may change.
③ Low: Future studies are highly likely to affect the level of certainty about the estimated value of an effect, and the value is highly likely to change.
④ Very low: An effect cannot be estimated with certainty.

162 Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

5) Guideline developmental process

This clinical practice guideline was developed using the adaptation method. First, 22 key questions (KQ) to be included in the guideline were selected. The key questions followed the population intervention, comparison, and outcome (PICO) principle. During the literature search process, experts used systematic search equations to search a total of 1,699 studies based on their contents. Experts reviewed the titles and abstracts of studies whose original copies were available, and selected 17 studies. Of these, a total of four clinical practice guidelines that addressed the key questions to be included in this guideline extensively were selected.

The qualities of these four domestic and foreign clinical practice guidelines were assessed using an assessment scale developed by the Clinical Practice Guideline Expert Committee of the Korean Academy of Medical Sciences, namely, the K-AGREE 2.0 (Korean version of AGREE 2.0). Twelve committee members who were educated on the assessment method through a workshop run by experts assessed the selected studies. Two guidelines which the British Thoracic Society (BTS) guidelines for the management of community acquired pneumonia in adults (updated in 2009) and the guidelinea for the management of adult lower respiratory tract infections (updated in 2011) by the Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases were selected for review. Ultimately a total of four clinical practice guidelines including a domestic guideline published in 2009 and a consensus guideline on the management of community-acquired pneumonia in adults published by the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) in 2007, which were the adaptation targets for domestic guidelines, were selected as adaptation targets.

The guideline developed by the Guideline Development Committee through internal meetings was presented in the spring academic conferences held by the Korean Society for Chemotherapy and the Korean Society of Infectious Diseases in 2017. The guideline was revised and improved based on what was discussed at the conferences. Further revisions were made based on expert opinions gathered during a public hearing participated in by experts from each related association to complete the guideline development.

6) Limitations and future to do's

This guideline has been developed using the adaptation method due to time limitations. Although some of the foreign clinical practice guidelines from which this guideline was adapted were scheduled for revisions in the near future, they were not presented during the developmental period, and could not be used in the development of this guideline. This guideline will undergo minor revisions as soon as the revised versions of these guidelines are published. This guideline will also be revised every 4-5 years to reflect recent study results both outside and inside Korea.

7) Support

This guideline has been developed with funds from the Government's Policy Research Projects of the Disease Control Centre in 2016. The committee members who participated in the guideline development were not influenced by any government branches, academic societies, pharmaceutical companies, or interest groups.

Current status regarding causative bacteria of pneumonia

1. Causative bacteria of community-acquired pneumonia

Most antibiotic treatments for pneumonia depend on the empirical method. Since the distribution of causative bacteria and antibiotic resistance vary between countries, it is necessary to develop an appropriate antibiotic treatment guideline based on domestic epidemiological data [1, 2]. This guideline summarizes domestic research findings on the causative bacteria of community-acquired pneumonia affecting Korean adults, and the current level of antibiotic resistance in Korea.

Community-acquired pneumonia is caused by various bacteria. Similar distributions of these bacteria are seen between Korea and other countries. Bacteria such as *Streptococcus pneumoniae,* and *Haemophilus influenzae*, and *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila,* which are classified as causative bacteria of atypical pneumonia, and respiratory bacteria can cause pneumonia. However, it is difficult to differentiate between these causative bacteria in the early period after hospital admission. Study findings about the major causative bacteria of community-acquired pneumonia in Korea are summarized in Table 1. The most important causative bacteria of bacterial pneumonia are *S. pneumoniae*. They account for 27-69% of all causative bacteria of bacterial pneumonia [3-10]. *Haemophilus* or *Moraxella,* which are respiratory pathogens, commonly cause pneumonia in patients with a lung disease. The prevalence of these bacteria varies greatly in domestic data

Summary of guidelines on antibiotic use for community-acquired pneumonia

Recommendation	Level of recommendation	Level of evidence
KQ 1. For adults who may have contracted community-acquired pneumonia, are the tests used to identify causative helpful for selecting therapeutic antibiotics?		
1-1. Use an appropriate testing method to identify the causative bacteria of pneumonia when a patient is diagnosed with moderate or severe community-acquired pneumonia.	Strong	Low
1-2. Selectively perform tests according to age, underlying diseases, severity markers, epidemiological factors, and current history of antibiotic use when treating outpatients with community-acquired pneumonia of low severity.	Strong	Low
1-3. It is advisable to perform blood culture, and sputum Gram smear and culture tests before antibiotic administration for patients with community-acquired pneumonia who require hospitalization.	Strong	Low
KQ 2. For adults who may have contracted community-acquired pneumonia, is the urinary *S. pneumoniae* antigen test useful for selecting therapeutic antibiotics?		
2-1. Perform a *S. pneumoniae* urinary antigen test for all patients with community-acquired pneumonia who require hospitalization.	Strong	Moderate
KQ 3. Is the *Legionella* urinary antigen test helpful for selecting therapeutic antibiotics for adults who may have contracted community-acquired pneumonia?		
3-1. A *Legionella* urinary antigen test is performed for patients with moderate or severe community-acquired pneumonia.	Strong	Moderate
KQ 4. Is a blood culture useful for choosing therapeutic antibiotics for adults who may have contracted community-acquired pneumonia?		
4-1. A blood culture test is performed before antibiotic administration for all patients with moderate or severe community-acquired pneumonia.	Strong	Low
KQ 5. For adults who may have contracted community-acquired pneumonia, does making a hospitalization decision according to hospitalization criteria produce good prognoses?		
5-1. Physicians must clinically decide whether a patient with community-acquired pneumonia should be hospitalized or not according to objective criteria.	Strong	Low
KQ 6. Of CURB-65 and PSI, which are hospital and intensive care unit (ICU) admission criteria, which one will lead to better prognoses for adults who may have contracted community-acquired pneumonia?		
6-1. It is recommended to use CRB-65 in clinics or outpatient clinics at the level of a hospital, and to use CURB-65 for patients who are in emergency departments or whose blood tests results are available.	Strong	Low
KQ 7. For adults who may have contracted community-acquired pneumonia, does making an ICU admission decision according to hospitalization criteria produce good prognoses?		
7-1. Patients with community-acquired pneumonia who require mechanical ventilation or have septic shock must be hospitalized in ICU.	Strong	Moderate
7-2. For patients who have CURB-65 ≥3, who exhibit ancillary signs of severe pneumonia as defined by the IDSA/ATS, who have developed pneumonia based on clinical findings, and whose underlying diseases have worsened, the need for ICU admission must be reassessed.	Weak	Low
KQ 8. What are the first choices of antibiotics in the outpatient treatment of patients who may have contracted community-acquired pneumonia?		
8-1. β-lactam is recommended to be used as an empirical antibiotic.	Strong	High
8-2. Respiratory fluoroquinolone is recommended to be used as an empirical antibiotic.	Strong	High
8-3. Use of respiratory fluoroquinolones as empirical antibiotics must be avoided in situations where tuberculosis cannot be excluded.	Weak	Low

164 Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

Recommendation	Level of recommendation	Level of evidence
KQ 9. For patients who may have contracted community-acquired pneumonia, does the β-lactam/macrolide (or respiratory fluoroquinolone) combination therapy produce better prognoses than the β-lactam monotherapy?		
9-1. Use of β-lactam antibiotics or respiratory fluoroquinolones is recommended in the empirical treatment of patients with mild to moderate pneumonia admitted to a general ward.	Weak	Moderate
9-2. β-lactam and macrolide antibiotics may be administered together in patients suspected of having atypical bacterial infection or in patients who have moderate pneumonia, under limited circumstances.	Weak	Moderate
KQ 10. What is the adequate duration of antibiotic treatment for patients who may have contracted community-acquired pneumonia?		
10-1. Antibiotics must be administered for at least five days.	Strong	Low
KQ 11. For patients who may have contracted community-acquired pneumonia, when is it appropriate to switch from intravenous antibiotics to oral antibiotics?		
11-1. A patient may switch from intravenous antibiotics to oral antibiotics once he/she is clinically stable, and can take oral medications.	Strong	High
KQ 12. For patients who may have contracted community-acquired pneumonia, when is the appropriate time to be discharged?		
12-1. If a patient can undergo oral treatment, does not require treatment or diagnostic tests for underlying diseases, and is in a social environment where he/she will be taken care of, discharge may be considered.	Strong	High
KQ 13. For patients who may have contracted community-acquired pneumonia, are oxygen therapy, low-molecular-weight heparin therapy, and early ambulation helpful?		
13-1. The level of oxygen is maintained at 94-98% via oxygen therapy in patients with hypoxemia.	Weak	Low
13-2. Low-molecular-weight heparin is injected into patients at high risk of venous thromboembolism.	Strong	High
13-3. Early ambulation is recommended.	Strong	High
KQ 14. For patients who may have contracted community-acquired pneumonia and are admitted to ICU for treatment, does the β-lactam/macrolide (or respiratory fluoroquinolone) combination therapy lead to better prognoses than the β-lactam monotherapy?		
14-1. For patients requiring ICU admission, the β-lactam + azithromycin/fluoroquinolone combination therapy is recommended over the β-lactam monotherapy.	Strong	Moderate
KQ 15. For patients who may have contracted community-acquired pneumonia and who are in admitted to ICU for treatment, does the β-lactam/macrolide (or respiratory fluoroquinolone) combination therapy lead to better prognoses than the respiratory fluoroquinolone monotherapy?		
15-1. For patients requiring ICU admission, the β-lactam + azithromycin/fluoroquinolone combination therapy is recommended over the respiratory fluoroquinolone monotherapy.	Strong	Moderate
15-2. For patients requiring ICU admission, the β-lactam + azithromycin/fluoroquinolone combination therapy is recommended over the respiratory fluoroquinolone monotherapy	Strong	Moderate
KQ 16. For patients who may have contracted community-acquired pneumonia and who are admitted to ICU for treatment, does a treatment against *Legionella* lead to better prognoses?		
16-1. For patients with severe community-acquired pneumonia who require ICU admission, it is necessary to perform treatment against *Legionella*	Strong	Low
KQ 17. For patients who may have contracted community-acquired pneumonia and who are admitted to ICU for treatment, does steroid therapy lead to good prognoses?		
17-1. Steroid therapy may be considered for patients who have severe community-acquired pneumonia accompanied by shock.	Weak	Low
KQ 18. For patients who may have contracted community-acquired pneumonia, are follow-up chest-X-rays useful for assessing treatment response?		
18-1. For patients with community-acquired pneumonia who do not show clear symptom improvements, or who are at high risk of lung cancer, it is recommended to take follow-up chest X-rays to examine the treatment response.	Strong	Low

Recommendation	Level of recommendation	Level of evidence
KQ 19. For patients who may have contracted community-acquired pneumonia, is the C-reactive protein (CRP) test useful for assessing therapeutic effects?		
19-1. CRP levels may be repeatedly measured to assess the risk of treatment failure and complications in patients who do not clinically show clear symptom improvements.	Weak	Low
KQ 20. For patients who may have contracted community-acquired pneumonia, is the procalcitonin test useful for assessing therapeutic effects?		
20-1. The procalcitonin test may be used in the process of deciding whether to continue antibiotic treatment or not for patients who show clinical improvements.	Weak	Moderate
KQ 21. For adults who have contracted community-acquired pneumonia, and have the risk factors of *S. pneumoniae* infection, can vaccination against *S. pneumoniae* prevent community-acquired pneumonia?		
21-1. Older adults, and adults who have the risk factors of *S. pneumoniae* infection are recommended to be vaccinated against *S. pneumoniae*.	Strong	High
KQ 22. Does smoking cessation education prevent community-acquired pneumonia among adults who have contracted community-acquired pneumonia?		
22-1. Smoking cessation education is necessary for current smokers who have pneumonia.	Strong	High

Table 1. The distribution of the major causative bacteria of community-acquired pneumonia in Korean adults

	Jeong et al. [7]	Seong et al. [4]	Chong et al. [10]	Choi et al. [9]	Yoo et al. [3]	Kim et al. [5]	Kang et al. [6]	Jeon et al. [8]
No. of patients	519	275	619	2,221	693	456	212	175
No. of causative bacteria isolated	122	105	131	568	191	250	62	63
Gram-positive bacteria								
Streptococcus pneumoniae	59 (48.4)	44 (41.9)	52 (39.7)	276 (48.6)	51 (26.7)	88 (35.2)	43 (69.4)	21 (33.3)
Staphylococcus aureus	13 (10.7)	10 (9.5)	8 (6.1)	109 (19.2)	21 (11.0)	5 (2.0)	8 (12.9)	9 (14.3)
Streptococcus species	8 (6.6)	5 (4.8)	1 (0.8)	9 (1.6)	5 (2.6)	5 (2.0)	-	-
Gram-negative bacteria								
Klebsiella pneumoniae	14 (11.5)	6 (5.7)	26 (19.8)	105 (18.5)	17 (8.9)	7 (2.8)	3 (4.8)	13 (20.6)
Pseudomonas aeruginosa	11 (9.0)	10 (9.5)	11 (8.4)	83 (14.6)	22 (11.5)	2 (0.8)	2 (3.2)	4 (6.3)
Hemophilus influenzae	7 (5.7)	1 (1.0)	1 (0.8)	105 (18.5)	10 (5.2)	5 (2.0)	7 (11.3)	7 (11.1)

Data are shown in percentage (%).

possibly because the separation and identification of these bacteria are difficult. *Staphylococcus aureus* are also relatively common causative bacteria. They commonly occur after an influenza epidemic. Enteric Gram negative bacilli or *Pseudomonas aeruginosa* pneumonia commonly occur in patients who have underlying lung diseases, who have alcohol addiction, or who have frequently undergone antibiotic treatment. Domestic data show the ratio of Gram-negative bacteria including *Klebsiella pneumoniae* and *P. aeruginosa*

to be relatively high. This may be because most domestic studies have been conducted in tertiary university hospitals, and therefore, a large number of patients who are frequently admitted to a hospital for chronic respiratory diseases were included. Studies have reported mixed infections caused by two or more microorganisms to be relatively common. These infections include mixed infections caused by atypical causative bacteria of pneumonia. Distributions of causative bacteria may change depending on underlying diseases and

risk factors.

M. pneumoniae, C. pneumoniae, and *L. pneumophila* are the major causative bacteria of atypical pneumonia. Of the recently published studies on community-acquired pneumonia in Korea, very few have investigated the incidence of atypical pneumonia and its causative bacteria. A large number of published studies have been conducted at a single institution, or use a retrospective design. Therefore, the prevalence of atypical pneumonia in Korea and clinical significance can only be assessed with limited accuracy. In a domestic study on pneumonia, *Mycoplasma, C. pneumoniae,* and *Legionella* accounted for 6.3-9.2%, 7.1-13.2%, and 0.5-3% of all cases of pneumonia [11-13]. *Legionella* were especially more common for cases of moderate to severe pneumonia requiring ICU admission compared with other atypical pneumococcal bacteria.

Respiratory virus induces pneumonia in children, as well as community-acquired pneumonia in adults. Rapid antigen tests for influenzas and respiratory syncytial virus (RSV) have recently been introduced and used in clinical settings. Multi-plex reverse transcriptase polymerase chain reaction (RT-PCR) has also been used against various respiratory viruses. In a recent study involving 456 adults with community-acquired pneumonia, multiplex RT-PCR was performed for 327 patients. Respiratory viruses were detected in 60 patients (18.3%) [5]. Influenza virus was the most common (n = 23, 38%), followed by RSV (n = 9, 15%), rhinovirus (n = 7, 12%), coronavirus (n = 6, 10%), adenovirus (n = 6, 10%), metapneu-movirus (n = 5, 8%), parainfluenza virus (n = 3, 5%) [6]. When a respiratory virus test was performed on patients with community-acquired pneumonia hospitalized in ICU, more than one type of respiratory virus was detected in 72 of 198 patients (36.4%) for whom RT-PCR was performed [14]. Rhinovirus was the most common (n = 17, 23.6%), followed by parainflu-enza (n = 15, 20.8%), metapneumovirus (n = 13, 18.1%), influ-enza virus (n = 12, 16.7%), RSV (n = 10, 13.9%), coronavirus (n = 4, 5.6%), and adenovirus (n = 1, 1.4%) [14]. Other causative bacteria of atypical pneumonia in Korea include *Mycobacteri-um tuberculosis,* non-tuberculous mycobacteria, *Orientia tsutsugamushi, Leptospira, Coxiella burnetii.* Since the preva-

Table 2. Common causative bacteria of community-acquired pneumonia by epidemiological characteristics and risk factors

Risk factors and epidemiological characteristics	Common causative bacteria
Alcohol addiction	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae, Acineto-bacter* species, *Mycobacterium tuberculosis*
Chronic obstructive pulmonary disease, smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* species, *S. pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae*
Smoking	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	Oral anaerobes, *M. tuberculosis*, atypical mycobacteria
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Exposure to farm animals	*Coxiella burnetii* (Q fever)
Influenza epidemic	Influenza virus, *S. pneumoniae, Staphylococcus aureus, H. influenzae*
Long-term coughing or vomiting after coughing	*Bordetella pertussis*
Structural anomalies of the lung (*e.g.* bronchodilation)	*Pseudomonas aeruginosa, Burkholderia cepacia, Staphylococcus aureus*
Use of intravenous medications	*S. aureus*, anaerobes, *M. tuberculosis, S. pneumoniae*
Bronchial obstruction	Anaerobes, *S. pneumoniae, H. influenzae, S. aureus*

Table 3. Common clinical characteristics associated with specific causative bacteria

Causative bacteria	Common clinical characteristics
Streptococcus pneumoniae	Age, underlying diseases, acute progress, fever, pleuritic chest pain
Bacteremic *S. pneumoniae*	Female gender, alcohol addiction, diabetes, chronic obstructive pulmonary disease, dry cough
Legionella pneumophila	Relatively young female, smoker, having no underlying diseases, diarrhea, neurological symptoms, severe pneumonia, multiple organ dysfunctions (*e.g.* liver dysfunction, kidney dysfunction, *etc.*)
Mycoplasma pneumoniae	Young age, previous history of antibiotic use, multiple organ dysfunction is uncommon
Chlamydophila pneumoniae	Symptoms that persisted for a long period before hospital admission, headache

lence of tuberculosis is still quite high, the possibility of tuberculosis being one of the causes of pneumonia must always be considered. When a patient shows delayed response to antibiotic treatment, or has underlying diseases such as diabetes, chronic obstructive respiratory disease, chronic kidney diseases, and long-term steroid use, tuberculosis must be considered as a possible cause of pneumonia. In addition, pneumonia caused by *M. tuberculosis* can occur as typical bacterial pneumonia or atypical pneumonia. Since tsutsugamushi disease and leptospirosis, which are febrile illnesses that usually occur in the fall, are sometimes accompanied by atypical pneumonia, when a patient has a febrile illness accompanied by pneumonia in the fall, pneumonia must be differentiated with the possibility of febrile illnesses in mind. Furthermore, as there have been reports of pneumonia caused by *C. burnetii* in Korea, it is necessary to differentiate *C. burnetii,* which may possibly be the causative bacteria of pneumonia in persons who come in close direct or indirect contact with livestock. Table 2 lists common causative bacteria of community-acquired pneumonia by epidemiological characteristics and risk factors [15]. Table 3 summarizes common clinical characteristics associated with certain causative bacteria [16].

2. Antibiotic resistance of the major causative bacteria of community-acquired pneumonia in Korea

S. pneumoniae isolated in Korea have been reported to be highly resistant against penicillin. In an investigation on antibacterial resistance measured according to the antimicrobial susceptibility testing standards, *S. pneumoniae* were moderately or highly resistant to penicillin [17]. However, as experts claimed that there is no association between clinical outcomes of pneumonia caused by penicillin-resistant *S. pneumoniae* and antibiotic resistance against penicillin, the antimicrobial susceptibility testing standards by the Clinical and Laboratory Standards Institute (CLSI) of the United States were revised in January 2008. According to the previous standards, *S. pneumoniae* are deemed to be susceptible to penicillin if MIC ≤0.06 µg/mL, moderately resistant if MIC=0.1-1.0 µg/mL, and highly resistant if MIC ≥2.0 µg/mL. The revised standards deem the bacteria to be susceptible if MIC ≤2.0 µg/mL, moderately resistant if MIC=4.0 µg/mL, and highly resistant if MIC ≥8.0 µg/mL. When the revised standards are used, the antibacterial resistance against pencilling drops to below 10%. Table 4 summarizes the current antibiotic resistance of *S. pneumoniae* strains isolated in Korea. While then antibiotic resistance against penicillin and ceftriaxone is reported to be low at 10% or below, that against erythromycin and azithromycin are still high at 73-81% [18-22]. Antibiotic resistance against fluoroquinolones is still quite low, but gradually increasing. Antibiotic resistance against levofloxacin and moxifloxacin is reported at 0.8-8.2%, and 0.9-1.0%, respectively [18, 20].

Resistance against ampicillin due β-lactamase production is common in *H. influenzae*. In a domestic study that analysed 544 bacterial strains, the antibiotic resistance against ampicillin, cefuroxime, clarithromycin, cefaclor, and amoxicillin/clavulanate was 58.5%, 23.3%, 18.7%, 17.0%, and 10.4%, respectively [23]. This study did not identify bacterial strains that are resistant to levofloxacin and cefotaxime. In another study that analysed 229 bacterial strains, the antibiotic resistance against ampicillin high at 58.1%, and that against cefaclor,

Table 4. Antibiotic resistance of *Streptococcus pneumoniae* isolated in Korea

	Kim et al. [18]	Kim et al. [20]	Kim et al. [19]	Lee et al. [21]	Torumkuney et al. [22]
Research period	2008-2009	1997-2008	2013-2015	1996-2008	2012-2014
Number of strains	327	208	805	386	85
Antibiotic					
Penicillin (%)	0.3	3.4	8.3	3.6	3.5
Amoxicillin/clavulanate (%)	-	-	18.7	-	2.4
Ceftriaxone (%)	1.9	0.5	7.8	10.4	8.2
Erythromycin (%)	77.7	-	80.9	74.9	81.2
Azithromycin (%)	-	73.1	-	-	78.8
Levofloxacin (%)	4.6	1.9	9.2	0.8	8.2
Moxifloxacin (%)	0.9	1.0	-	-	-
Clindamycin (%)	68.2	-	68.2		67.1

168   Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

clarithromycin, amoxicillin/clavulanate, cefixime, and levo-floxacin was 41.4%, 25.8%, 13.5%, 10.9%, and 1.3%, respectively [24].

Not many studies have analysed the antibiotic susceptibility of *M. pneumoniae* in Korea. In a study that examined *M. pneumoniae* isolated from respiratory organ samples of pediatric patients in 2000-2011, genes related to macrolide resistance was detected in 31.4% of the samples, and this rate was reported to increase every year [25]. In another study using respiratory organ samples from pediatric patients, genes related to macrolide resistance were found in 17.6% of the samples of *M. pneumoniae* [26]. Although the ratio of methicillin-resistant *S. aureus* (MRSA) in community-acquired *S. aureus* infection has been increasing in Korea, systematic research on the role of MRSA in community-acquired pneumonia is lacking [27-29].

New method of diagnosing pneumonia

1. Respiratory virus PCR

Methods of respiratory virus testing include the culture test, rapid antigen test, immunofluorescence, enzyme immunoassay test, and PCR. PCR is more sensitive than the culture test, or the enzyme immunoassay test [30]. This strength of PCR makes it advantageous for adult patients with a smaller number of nasopharyngeal virus compared with pediatric patients [31, 32]. Multiplex RT-PCR is useful for simultaneously testing various respiratory viruses, and is frequently used today [33].

PCR can test various respiratory organ samples including nasopharyngeal samples, sputum, airway aspirates, and bronchoalveolar lavage fluid [31, 32]. In most studies on pneumonia caused by respiratory viruses, virus testing was performed using samples from the upper airway. Nasal swabs are the most commonly used method to detect viruses, and are more sensitive than throat swabs in adults [31].

In 20-40% of patients with community-acquired pneumonia, respiratory viruses are detected by PCR [34-37]. Rhinovirus is the most commonly detected, and other respiratory viruses such as influenza, metapneumovirus, RSV, parainfluenza virus, and coronavirus are also relatively commonly detected [38, 39].

However, positive results of upper airway samples do not necessarily indicate viral infection, and positive PCR results do not indicate that pneumonia was caused by a respiratory virus. Furthermore, although respiratory viruses can induce pneumonia by themselves, they may simple be a predisposing

factor of pneumonia [40]. Therefore, the possibility of bacterial pneumonia cannot be disregarded simply because respiratory bacteria were detected in the PCR test. In fact, respiratory viruses are detected in 20% of patients diagnosed with bacterial pneumonia [40].

It is unclear whether the use of antiviral agents is necessary or not when respiratory viruses aside from influenza are detected, and it is difficult to diagnose viral pneumonia based on positive results only [33]. With the costs of tests and various factors taken into consideration [33], it may be useful to perform the PCR test to detect respiratory viruses when a patient is suspected of having pneumonia caused by respiratory viruses based on clinical symptoms or radiographic findings.

2. *Legionella, Mycoplasma, Chlamydophila* PCR

1) *Legionella* PCR

Whereas the *Legionella* urinary antigen test can only diagnose the *L. pneumophila* serogroup 1, PCR can diagnose all serogroups, and thus has higher sensitivity for *Legionella* diagnosis. In a recent systematic review, the sensitivity of the *Legionella* PCR test using respiratory organ samples was 97.4%, and its specificity was 98.6% [41]. *Legionella* PCR may be performed using nasopharyngeal samples or nasal swabs when no sputum is secreted even in the induced sputum analysis, but this testing method has a lower diagnosis rate compared with when sputum samples are used [42, 43].

2) *Mycoplasma* PCR

Various serological tests have been traditionally used to diagnose *Mycoplasma*. These tests may fail to detect antibodies in the early period after infection [44, 45], and IgM antibody reactions may not occur in adults aged 40 years or older [46]. *Mycoplasma* PCR, which uses various respiratory organ samples has higher sensitivity, has higher sensitivity than serological tests [47], and has similar sensitivity to that of *Legionella* PCR [48]. Just as *Legionella* PCR, *Mycoplasma* PCR has a lower diagnosis rate with nasopharyngeal samples than with sputum samples [49].

3) *Chlamydophila* PCR

Serological tests for *Chlmydophila* have lower specificity compared with PCR [50], and may report false negative in the early period after infection as is the case with *Mycoplasma* infection [51]. For this reason, PCR may be more useful than serological tests for diagnosing *Chlmydophila* infection. Although the sensitivity of *Chlamydophila* PCR has not been

accurately measured, *Chlamydophila* PCR is reported to have high specificity [52].

3. Chest CT

Chest computed tomography (CT) is the most accurate test for assessing parenchymal anomalies. Radiographic findings indicative of pneumonia may be observed even when no anomalies are observed on chest X-rays [53]. Chest CT is more accurate than chest X-rays in the diagnosis of complications such as pleuritis and pulmonary necrosis [54, 55] and in the exclusive diagnosis and differential diagnosis of non-infectious lung diseases such as atelectasis, pulmonary infarction, tumor, and interstitial lung disease that may exhibit similar characteristics as those of pneumonia on X-rays [56-59]. Since CT findings can vary depending on the identity of the causative bacteria of pneumonia, CT is useful for identifying causative bacteria [56, 60-62]. CT findings suggestive of mycobacteria that must be differentiated from common pneumonia, and of fungal lung infection can also be obtained [56, 63, 64].

However, due to the relatively high cost and danger of irradiation compared with those of chest X-rays [65], CT must be selectively performed in cases where the differentiation of accompanying diseases such as pulmonary embolism is necessary, fungal infection is suspected, it is difficult to check for lung infiltration on chest X-rays due to other underlying lung diseases, and it is difficult to check for pneumonia complications due to lack of response to pneumonia treatment [33].

4. Chest ultrasounds

Chest ultrasounds are used in the diagnosis of various lung diseases such as pneumothorax, hydrothorax, and pulmonary enema, as well as pneumonia [66]. According to a recent systematic review and meta-analysis using the data of 1,172 patients diagnosed with pneumonia, chest ultrasounds had excellent sensitivity and specificity of 94% and 96%, respectively, in the diagnosis of pneumonia [67].

Compared to chest X-rays, chest ultrasounds do not pose the burden of radiation exposure, can be performed right next to the patient, can be performed on pregnant women, and can more accurately diagnose lung consolidation and hydrothorax [66-68]. It is also useful for evaluating hydrothorax, which can occur as a complication of pneumonia. It can diagnose septation within hydrothorax more accurately than CT [69]. Septation is indicative of birous strands between the parietal and visceral pleura, as well as inefficient drainage through the drainage tube [56].

A trained examiner must perform ultrasounds to obtain ac-

curate results. Although a problem of interexaminer reproducibility may arise [70], chest ultrasounds may be useful for diagnosing and assessing pneumonia in situations where it is impossible to take chest X-rays (*i.e.* it is difficult to transfer a patient to the examination room because the patient is pregnant or immobile).

Diagnosis of pneumonia

KQ 1. For adults who may have contracted community-acquired pneumonia, are the tests used to identify causative helpful for selecting therapeutic antibiotics?

Recommendation
- Use an appropriate testing method to identify the causative bacteria of pneumonia when a patient is diagnosed with moderate or severe community-acquired pneumonia (level of recommendation: strong, level of evidence: low).
- Selectively perform tests according to age, underlying diseases, severity markers, epidemiological factors, and current history of antibiotic use when treating outpatients with community-acquired pneumonia of low severity (level of recommendation: strong, level of evidence: low).
- It is advisable to perform blood culture, and sputum Gram smear and culture tests before antibiotic administration for patients with community-acquired pneumonia who require hospitalization (level of recommendation: strong, level of evidence: low).

Key points
- Although microbial tests have low sensitivity for community-acquired pneumonia, they are still required for reasons related to appropriate antibiotic use, public health and epidemiological importance, and provision of information about causative bacteria within communities.
- For outpatients who are suspected of having antibiotic-resistant bacteria or bacteria that are difficult to treat empirically using common antibiotics, perform sputum gram smear and culture.
- For all inpatients with pneumonia, it is recommended to perform blood culture, and sputum gram smear and culture tests before antibiotic treatment as long as they are clinically indicated.

<Summary of Evidence>

When a patient is diagnosed with moderate or severe community-acquired pneumonia, appropriate testing methods are used to identify the causative bacteria of pneumonia. The main reason for performing microbial tests for communi-

170 Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

ty-acquired pneumonia is that appropriate, individualized treatment can be performed based on the test results, and unnecessary use of wide-spectrum antibiotics can be avoided. Detection is necessary since some microorganisms hold epidemiological significance in public health and infection control. It is also important to obtain information about common causative microorganisms of pneumonia and their antibiotic sensitivity.

However, microbial tests lack sensitivity, and are often not very useful in early treatment [71]. Despite being prospective tests for diagnosing causative microorganisms, they fail to detect causative microorganisms in 25-60% of patients [72, 73]. They lack sensitivity especially for patients who have pneumonia of low severity, who have not contract any diseases, or who have already been treated. Although a study has demonstrated a correlation between the severity of community-acquired pneumonia and the rate of blood culture positivity [74], another has reported no such correlation [75].

1. Appropriate methods of causative bacteria detection in outpatients

When treating outpatients with community-acquired pneumonia of low severity, tests are selectively performed according to age, underlying diseases, severity markers, epidemiological factors, and current history of antibiotic use. Sputum gram smear and culture may be performed when antibiotic-resistant bacteria or bacteria that are difficult to treat with common empirical antibiotics are suspected. If tuberculosis is suspected based on clinical or radiographic findings, a sputum stain and tuberculosis test are performed. It is also recommended to perform diagnostic tests when *Legionella* infection or influenza are suspected based on clinical and epidemiological findings.

2. Appropriate methods of causative bacteria detection in inpatients

For inpatients with pneumonia, it is advisable to perform blood culture, and sputum gram smear and culture tests before antibiotic administration as long as they are indicated. Sputum tests must be done using sputum samples obtained before antibiotic administration, and should only be performed when sufficient amounts of sputum are released, collected, transferred, and treated [76]. For patients with moderate community-acquired pneumonia, a blood culture, *Legionella, S. pneumoniae* urinary antigen test, and sputum gram smear and culture must be performed [77-79]. For patients with airway intubation, a test using trans-tracheal aspi-

rate samples must be performed. For immunodeficient patients, or patients for whom common treatments have failed, invasive tests such as airway endoscopy and percutaneous pulmonary aspiration are useful [80, 81].

KQ 2. For adults who may have contracted community-acquired pneumonia, is the urinary *S. pneumoniae* antigen test useful for selecting therapeutic antibiotics?

Recommendations

- Perform a *S. pneumoniae* urinary antigen test for all patients with community-acquired pneumonia who require hospitalization (level of recommendation: strong, level of evidence: moderate).

Summary

- The *S. pneumoniae* urinary antigen test produces results within 15 minutes, is simple to perform, can give positive results even when antibiotics are administered, and have 50-80% sensitivity and over 90% specificity for adults.

<Summary of Evidence>

A *S. pneumoniae* urinary antigen test is performed for all patients with community-acquired pneumonia who require hospitalization. The urinary antigen test for *S. pneumoniae* detection produces results within 15 minutes, and can give positive results even when antibiotics are administered. It is reported to have sensitivity of 50-80% and specificity of over 90% for adults [82-84]. The drawbacks of this test are that it is expensive to perform, and it does not assess antibiotic susceptibility. It can also produce false positive results in pediatric patients with chronic lung diseases characterized by *S. pneumoniae* colonization, and patients who suffered from community-acquired pneumonia in the last four months [85, 86]. The test is unaffected by the normal bacterial flora in patients with chronic obstructive pulmonary disease [78, 85]. The positivity rate of the *S. pneumoniae* urinary antigen test and the severity of pneumonia are reported to be correlated [87]. In 80-90% of patients who tested positive in the *S. pneumoniae* urinary antigen test, positivity continue until 7 days after treatment was begun [88], and the test can be performed using other bodily fluids such as pleural fluid [89]. Among studies on the effects of the results of *S. pneumoniae* urinary antigen test on treatment, a retrospective study has reported that pneumonia caused by *S. pneumoniae* was safely and effectively treated by high-dose penicillin administration in patients who tested positive in the *S. pneumoniae* urinary

antigen test [90].

KQ 3. Is the *Legionella* urinary antigen test helpful for selecting therapeutic antibiotics for adults who may have contracted community-acquired pneumonia?

Recommendations

- A *Legionella* urinary antigen test is performed for patients with moderate or severe community-acquired pneumonia (level of recommendation: strong, level of evidence: moderate).

Key points

- The *Legionella* urinary antigen test is an appropriate testing method for patients hospitalized for idiopathic pneumonia, and is recommended in cases of moderate pneumonia, in cases where epidemiological evidence of the disease is available, and in cases of no response to β-lactam antibiotics.

<Summary of Evidence>

A *Legionella* urinary antigen test is performed for patients with moderate or severe community-acquired pneumonia (level of recommendation: strong, level of evidence: moderate). The *Legionella* urinary antigen test is an appropriate testing method for patients hospitalized for idiopathic pneumonia, and is recommended in cases of moderate pneumonia, in cases where epidemiological evidence of the disease is available, and in cases of no response to β-lactam antibiotics [77-79]. The *Legionella* urinary antigen test has high sensitivity (~80%) and specificity (>95%) for diagnosing type 1 *L. pneumophila* infection [91]. The test gives positive results starting on the first day a disease occurs, and the positivity continues for several weeks [84-92]. The introduction of the *Legionella* urinary antigen test has enabled rapid diagnosis and treatment of *Legionella* in epidemic situations, and has improved treatment outcomes and fatality [93]. In another study, early diagnosis of *Legionella* infection using the *Legionella* urinary antigen test in patients with community-acquired pneumonia in non-epidemic situations, the test results positively affected the treatment of seven of nine patients who tested positive [94].

KQ 4. Is a blood culture useful for choosing therapeutic antibiotics for adults who may have contracted community-acquired pneumonia?

Recommendations

- A blood culture test is performed before antibiotic administration for all patients with moderate or severe community-acquired pneumonia (level of recommendation: strong, level of evidence: low).

Key points

- Although the bacterial detection rate of a blood culture for community-acquired pneumonia is low at 5-14%, it has a high diagnostic value compared with other culture testes once the bacteria grow, and provides important information about antibiotic resistance.
- For patients with severe community-acquired pneumonia, and immunodeficient patients, a blood culture test is especially important.

<Summary of Evidence>

A blood culture test is performed before antibiotic administration for all patients with moderate or severe community-acquired pneumonia. *S. pneumoniae* is the most commonly detected causative bacteria of community-acquired pneumonia in blood culture tests. It has a high diagnostic value compared with other culture testes once the bacteria grow, and provides important information about antibiotic resistance. However, it has low bacterial detection rates of 5-14% for community-acquired pneumonia [75, 95], and it has a limited influence on treatment even when positive results are obtained [74, 75]. In a systematic analysis using data of 3,898 patients with community-acquired pneumonia from 15 observational studies, blood culture results had almost no effect on the changes in the selection of empirical antibiotic, and even when they did, they did not significantly affect treatment outcomes [96]. However, since immunodeficient patients and other high-risk groups were excluded in this analysis, its results cannot be generalized to moderate community-acquired pneumonia. There is an overlap between the predictors of blood culture positivity and the risk factors of severe community-acquired pneumonia [97]. For this reason, a blood culture test is indicated and must be performed for patients with severe community-acquired pneumonia. The test is also recommended for patients with immunodeficiency disorders such as alienia and complement deficiencies, chronic liver disease, and leukopenia [74].

Hospitalization criteria for pnemonia

KQ 5. For adults who may have contracted community-ac-

quired pneumonia, does making a hospitalization decision according to hospitalization criteria produce good prognoses?

Recommendation
- Physicians must clinically decide whether a patient with community-acquired pneumonia should be hospitalized or not according to objective criteria (level of recommendation: strong, level of evidence: low).

Key points
- By using objective criteria, unnecessary hospitalization and its associated side effects can be minimized, and patients requiring hospitalization can be treated in a timely manner.

<Summary of Evidence>

One of the most important decisions in the treatment of community-acquired pneumonia is the one of hospitalization. Hospitalization of patients who do not require hospitalization causes an unnecessary increase in medical costs. Treating patients with mild pneumonia in outpatient clinics instead of hospitalizing them will allow these patients to return to their normal life and workplace faster [98]. Hospitalization increases the risk of thrombosis [99], and the risk of infection by more pathogenic or resistant bacteria. On the other hand, treating a patient requiring hospitalization in an outpatient clinic, and later hospitalizing him/her after symptoms have worsened can increase the risk of death [100]. Higher mortalities have been reported among moderate community-acquired pneumonia are treated in general wards and are later admitted to ICU than among those who are treated in ICU from the beginning [101]. Therefore, it is important to appropriate decide whether a patient needs outpatient care or hospitalization depending on the severity of the disease and risk of death, and if the patient is hospitalized, whether he/she should be treated in a general ward or ICU.

The rate of hospitalization of patients with community-acquired pneumonia largely varies between hospitals and physicians [15]. It has been reported that physicians generally tend to overestimate the severity of pneumonia, and cause unnecessary hospitalization [102]. In one study, 845 of 1,889 patients (44.7%) with low-risk pneumonia admitted to an emergency department required hospitalization, and at least 1/5 of these patients did not meet the criteria for hospitalization, and were hospitalized for unnecessary reasons [103]. In Korea, there are many patients with community-acquired pneumonia who have been hospitalized for no clear reasons

[104]. Objective markers that can be used by clinicians to predict the death of patients with community-acquired pneumonia, or the severity of pneumonia in outpatient clinics, outpatient departments of medical institutions at the level of a hospital, and emergency departments may be useful for deciding whether to request hospitalization in a medical institution or to hospitalize a patient or not.

KQ 6. Of CURB-65 and PSI, which are hospital and intensive care unit (ICU) admission criteria, which one will lead to better prognoses for adults who may have contracted community-acquired pneumonia?

Recommendation
- It is recommended to use CRB-65 in clinics or outpatient clinics at the level of a hospital, and to use CURB-65 for patients who are in emergency departments or whose blood tests results are available (level of recommendation: strong, level of evidence: low).

Key points
- The PSI and CURB-65/CRB-65 have equal predictive power. However, PSI is superior to CURB-65/CRB-65 in terms of applicability, and CRB-65 is the most appropriate in an outpatient environment in which blood tests are not performed.

<Summary of Evidence>

The two markers for assessing the severity of pneumonia that have been the most extensively studied and widely used include the pneumonia severity index developed in the United States using the data from Pneumonia Patient Outcome Research Team (PORT)'s research [105], and the CURB-65 and CRB-65 based on the death prediction model proposed by the British Thoracic Society (BTS) in 1987 [106].

The PSI is a scoring system developed to identify low-risk patients among patients with community-acquired pneumonia. It was derived from the data of 14,199 inpatients with community-acquired pneumonia. Its validity has been verified using data of 38,039 inpatients with community-acquired pneumonia, and in a prospective cohort involving 2,287 patients [15] (Table 5). The PSI scores 20 variables. The total scores are used to predict the 30-day mortality, with which patients are divided into five groups. The predicted mortality of each group is shown in Table 6. In general, outpatient treatment is recommended for PSI I-II groups, PSI III group is recommended outpatient treatment or hospitalization for short-

Table 5. Pneumonia severity index (PSI)

Factor	Score
Patient age	
Male	Age
Female	Age - 10
Long-term care facility resident	+10
Accompanying disease[a]	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Chronic kidney disease	+10
Symptoms at diagnosis	
Acute psychosis[b]	+20
Breathing rate ≥30/min	+20
Systolic pressure <90 mmHg	+15
Body temperature <35°C or ≥ 40°C	+15
Heart rate ≥125/min	+10
Laboratory measurements	
Arterial blood pH <7.35	+30
BUN ≥30 mg/dL	+20
Serum sodium <130 mEq/L	+20
Serum glucose >250 mg/dL	+10
Hb <9 gm/dL (hematocrit <30%)	+10
Atmospheric arterial blood gas (PaO$_2$)	+10
<60 mmHg (SaO$_2$ <90%)	
Hydrothorax on chest X-rays	+10

[a]Accompanying diseases (Neoplastic diseases: within one year, exclude cutaneous basal cell carcinoma and squamous cell carcinoma; liver disease: clinically or histologically diagnosed liver cirrhosis or chronic active hepatitis; congestive heart failure: medical history, examination, or tests; cerebrovascular diseases: stroke diagnosed based on clinical findings, CT or MRI).
[b]Psychosis: Disorientation related to people, places, and time; or recently reduced level of consciousness.

term monitoring depending on the situation, and IV-V groups are recommended hospitalization [15, 104].

The CURB-65 and CRB-65 are pneumonia severity scoring systems developed using data prospectively collected from four hospitals across England, New Zealand, and the Netherlands [106] (Table 7). The data of 80% of the 1,068 patients included in this study were used in the guideline development, and the remaining 20% were used for validating the indices. The CURB-65 assigns six scores. One point is given for satisfying each of the following conditions: C: Confusion; U: Urea >7 mmol/L (= BUN >19 mg/dL); R: Respiratory rate ≥30/min; B: Blood pressure, systolic pressure <90 mmHg or diastolic pressure ≤60 mmHg; and 65: age ≥65 years. The total resulting score ranges from 0 to 5 points. The CRB-65 is essentially the CURB-65 with the blood urea parameter requiring a blood test removed, and it assigns 0 to 4 points. The higher the CURB-65 and CRB-65 scores, the higher the mortality as

shown in Table 7. The CURB-65 and CRB-65 are reported to be on a par with one another in terms of their clinical usefulness [107-113], and discriminatory power [110, 113].

However, it is unclear whether the use of these pneumonia severity markers can improve treatment outcomes or not. Although treatment outcomes have been reported to improve in various aspects when guidelines that include patient characteristics and severity assessments as part of the hospitalization decision-making process such as the PSI is used [114], these guidelines also consider other factors that can affect not only the hospitalization decision, but also antibiotic recommendations and treatment outcomes, and it is difficult to determine the impact of these factors on hospitalization decisions using severity markers. However, using these objective standards can reduce the rate of hospitalization among patients with pneumonia [115-118].

It is unclear between the PSI and CURB-65 or CRB-65, which is superior. There have not been any randomized studies that compare these two scoring systems. In addition, studies that have compared the predictive power of the two scoring systems using identical patient groups have reported similar predictive power between the two systems [113, 119-122], and thus, one cannot say one is superior to the other. In some studies, the PSI showed more excellent results. According to a study in which the developer of the PSI participated as a co-researcher, the PSI classifies a larger number of patients as the low-risk group compared with the CURB-65 (PSI I-III, 68% *vs.* CURB-65 <2, 61%), similar mortality rates are observed between the two groups, and the CURB-65 had significantly higher predictive power measured in terms of AUC than the PSI [107].

However, the PSI measures 20 parameters, and many blood test results are included in the score calculation. This works as a serious disadvantage in outpatient or emergency departments in Korea where patients must be examined as quickly as possible. Therefore, for patients who have been diagnosed with pneumonia for the first time in an outpatient department of a medical institution at the level of a clinic or hospital, it is recommended to assess the patients with the CRB-65, and consider the transfer to another hospital that can accommodate inpatients, or hospitalization for those whose CRB-65 scores at not 0. However, outpatient treatment may be considered for patients who satisfy the age condition of the CRB-65 (65 years or older) and whose other physiological indices are stable. In addition, in the case of patients whose blood test results can be used in emergency or outpatient treatment, the CURB-65 can be used for the same purpose, and physicians

Table 6. Predicted mortality rates, risks, and recommendations according to the pneumonia severity index (PSI)

Class	PSI score	Predicted mortality rate (%)	Risk	Recommendation
I	Age <50 years, no accompanying diseases and clinical symptoms.	0.1 – 0.1	Low	Treat at home
II	1 - 70	0.6 – 0.7	Low	Treat at home
III	71 - 90	0.9 – 2.8	Low	Treat at home or hospitalize
IV	91 - 130	8.2 – 9.3	Moderate	Hospitalize
V	>130	27.0 – 31.1	High	Consider ICU admission

Table 7. Stratification of mortality rate using the CURB-65 and CRB-65

Mortality risk	CURB-65 score	Observed mortality rate[a] (%)	Recommendation	CRB-65	Observed mortality rate[a] (%)	Recommendation
Low	0 or 1	1.5	Home treatment	0	1.2	Can be treated at home
Moderate	2	9.2	Hospitalization	1 or 2	8.15	Must be referred to and assessed in a patient that can accommodate inpatients as soon as possible
High	3-5	22	Treatment for moderate pneumonia	3 or 4	31	Requires hospitalization as soon as possible

[a]Lim WS, et al. Thorax 2003;56;377-82 [106].

are recommended to refer to the CURB-65 results when making clinical decisions (Table 7).

A decision regarding a patient's need for hospitalization cannot always be perfect even when an objective severity scoring system with high predictive power is used. Severity scoring systems are mere tools to help clinicians make decisions, not absolute standards, and cannot replace health professionals' 'clinical decisions'. For instance, a patient may be placed in a low-risk group according to a severity scoring system, but may still require hospitalization in the following situations: 1) the patient developed complications of pneumonia; 2) the patient's underlying diseases have worsened due to pneumonia; 3) the patient cannot take oral medications; and 4) the patient has been placed in a low-risk group because he/she slightly did not meet the conditions for being classified as high-risk [15]. When determining a patient's need for hospitalization, the patient's social situations and his/her physician must be considered together. For instance, a patient of advanced age who lives alone, and has reduced mobility may require hospitalization until he/she recovers from pneumonia even if his/her severity scores are low.

KQ 7. For adults who may have contracted community-acquired pneumonia, does making an ICU admission decision according to hospitalization criteria produce good prognoses?

Recommendation
- Patients with community-acquired pneumonia who require mechanical ventilation or have septic shock must be hospitalized in ICU (level of recommendation: strong, level of evidence: moderate)
- For patients who have CURB-65 ≥3, who exhibit ancillary signs of severe pneumonia as defined by the IDSA/ATS, who have developed pneumonia based on clinical findings, and whose underlying diseases have worsened, the need for ICU admission must be reassessed (level of recommendation: weak, level of evidence: low).

Key points
- With an exception to patients requiring ICU admission who depend on mechanical ventilation or who have septic shock, it is difficult to decide whether to hospitalize patients or not according to specific criteria. This decision must be made after considering various situations.

<Summary of Evidence>

Patients who require mechanical ventilation or have septic shock require ICU admission.

Although the CURB-65 or the IDSA/ATS definition of severe pneumonia (2007) may be used, these standards do not have perfect predictive power, and their clinical usefulness has not been verified. Therefore, an ICU admission decision must be made after considering various situations.

It is traditionally accepted that patients who require mechanical ventilation due to respiratory failure, or have septic shock must be admitted and treated in an ICU. However, it is a challenge to determine whether to admit a patient who do not have such needs to an ICU or not.

The community-acquired pneumonia guideline developed by the ATS/IDSA in 2007 proposes the new definition of severe pneumonia that requires ICU admission modified from the earlier definition proposed by the ATS in 2001 [15, 123] (Table 8). This standard consists of main and minor standards. The main standard includes dependence on mechanical ventilation, and septic shock that requires vasopressors. The minor standard consists of seven conditions, which include the factors included in the 2001 ATS standard [123], plus clinical factors from the CURB-65. A patient is diagnosed with severe pneumonia if he/she satisfies one of the conditions from the main standard, or three of the seven conditions from the minor standard. This standard is reported to have higher predictive power than the PSI ≥4 or CURB-65 ≥3 [124]. However, although the predictive power of the standard is improved relative to that of the PSI or CURB-65 when only the minor conditions are used (excluding patients who satisfy the main conditions for ICU admission), and the standard has good specificity, it has moderate sensitivity [125]. It has also been reported that since some of the factors included in the minor standard (leukopenia, thrombocytopenia, and hypothermia) are rarely observed in patients, the predictive power of the minor standard does not change even after these factors are excluded, and that adding other factors can increase its predictive power [126]. There are other scoring systems such as the SMART-COP [127], and the SCAP [128] that are used to predict ICU admission, but they also have similar limitations.

Table 8. ISDA/ATS criteria for severe community-acquired pneumonia

Main criteria	Invasive mechanical ventilation Septic shock requiring vasopressors
Minor criteria	Breathing rate ≥30 breaths/min
	PaO_2/FiO_2 ratio ≤250
	Multilobar invasion
	Confusion/disorientation
	Uremia (BUN ≥20 mg/dL)
	Leukopenia (leukocyte count, <4,000/mm^3)
	Thrombocytopenia (platelet count, <100,000/mm^3)
	Hypothermia (core body temperature, <36°C)
	Hypotension requiring active fluid resuscitation

IDSA, Infectious Diseases Society of America; ATS, American Thoracic Society; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; BUN, blood urea nitrogen.

As there is not yet a tool that can be used to accurately predict a patient's need for ICU care, a patient must be considered for ICU admission if he/she has CURB-65 ≥3, exhibits ancillary signs of severe pneumonia as defined by the ATS/IDSA, has pneumonia based on clinical signs, and has had his/her underlying diseases worsen.

Treatment of pneumonia

1. Pneumonia treatment for outpatients

KQ 8. What are the first choices of antibiotics in the outpatient treatment of patients who may have contracted community-acquired pneumonia?

Recommendations
- β-lactam is recommended for use as an empirical antibiotic (level of recommendation: strong, level of evidence: high).
- Respiratory fluoroquinolones are recommended for use as empirical antibiotics (level of recommendation: strong, level of evidence: high).
- Use of respiratory fluoroquinolones as empirical antibiotics must be avoided in situations where tuberculosis cannot be excluded (level of recommendation: weak, level of evidence: low).

Key points
- The therapeutic effects of the β-lactam monotherapy are not inferior to those of the β-lactam + macrolide combination therapy.
- β-lactam + macrolide is recommended for suspected atypical pneumonia.
- Respiratory fluoroquinolones have excellent antibacterial activities against tuberculosis bacilli. They may thus delay the diagnosis of tuberculosis in patients for whom tuberculosis has been misdiagnosed as another kind of bacterial pneumonia, and may allow tuberculosis bacilli to develop resistance against fluoroquinolones.

<Summary of Evidence>

For patients who do not require hospitalization, the use of β-lactam alone, the combined use of β-lactam and macrolide, or the use of respiratory fluoroquinolones as empirical antibiotics is recommended. The following antibiotics are recommended (in alphabetical order).

- β-lactam: amoxicillin, amoxicillin-clavulanate, cefditoren, cefpodoxime
- Macrolide: azithromycin, clarithromycin, roxithromycin

- Respiratory fluoroquinolone: gemifloxacin, levofloxacin, moxifloxacin

Macrolide or tetracycline monotherapy is not recommended due to the high antibiotic resistance of *S. pneumoniae*. β-lactam and macrolide may be used together if atypical pneumonia is suspected. Macrolides such as azithromycin, clarithromycin, and roxithromycin are recommended.

There is a controversy regarding whether or not antibiotics that target the causative bacterial of atypical pneumonia should be used in the treatment of mild community-acquired pneumonia that does not require hospitalization. In a retrospective study secondarily conducted using the Community-Acquired Pneumonia Organization (CAPO) database registered at the multi-institutional phase-three clinical trial conducted in various countries, antibiotics that were effective against the causative bacteria of atypical pneumonia showed more excellent outcomes in terms of mortality rate and clinical progress [129]. The study reported that the antibiotic treatment of the causative bacteria of atypical pneumonia is advisable for all patients with community-acquired pneumonia in terms of their mortality rates and treatment outcome. In addition, the IDSA/ATS guideline on pneumonia treatment developed in the United States in 2007 also gives the same recommendation. However, in a meta-analysis of patients with mild community-acquired pneumonia, use of a single antibiotic targeting the causative bacteria of atypical pneumonia had poorer clinical results than the use of β-lactam alone [130], and similar results were also reported by the 2010 Cochrane review on patients hospitalized due to community-acquired pneumonia [131]. In a study published in 2015, the β-lactam monotherapy was not inferior to the β-lactam + macrolide combination therapy [132]. Therefore, this guideline recommends using macrolide in addition to β-lactam only in cases of suspected atypical pneumonia.

Of the β-lactams that are classified as penicillin, amoxicillin, and or amoxicillin/clavulanic acid are recommended. This recommendation is based on a research finding *S. pneumoniae* isolated in Korea have low penicillin resistance when the antibacterial susceptibility standard developed by the CLSI (revised in January 2008), which has stricter criteria for the penicillin antibiotics of *S. pneumoniae* for patients without meningitis, is used. The 2007 IDSA/ATS guideline, the 2009 BTS guideline, and the 2011 ERS/ESCMID guideline all recommended to use amoxicillin as the main antibiotic.

Of oral cephalosporins, cefpodoxime recommended by the 2007 IDSA/ATS guideline, and the 2011 ERS/ESCMID guideline, and cefditoren recommended by the 2011 ERS/ESCMID

guideline with available data regarding the antibiotic susceptibility of the causative bacteria of pneumonia in Korea have been included in this guideline [133]. On the other hand, cefuroxime has been excluded since *S. pneumoniae* isolated in Korea are highly resistant against the antibiotic. The 2011 ERS/ESCMID guideline has also mentioned a study that reported an association between increased mortality rates and cefuroxime use in patients with *S. pneumoniae* pneumonia accompanied by bacteremia [134].

The 2007 IDSA/ATS guideline, 2009 BTS guideline, and 2011 ERS/ESCMID guidelines recommend use of macrolide or tetracycline alone. However, this recommendation has not been included in this guideline. This is because *S. pneumoniae* isolated in Korea show high resistance against these antibiotics.

The fluoroquinolone monotherapy shows excellent antibacterial activities against tuberculosis bacilli. For this reason, it may delay the diagnosis of tuberculosis in patients with community-acquired pneumonia whose tuberculosis has been misdiagnosed as a type of bacterial pneumonia, and can allow tuberculosis bacilli to develop resistance against fluoroquinolones. Therefore, in cases where tuberculosis cannot be eliminated, it is recommended to avoid the empirical use of fluoroquinolones.

For levofloxacin, it has been reported that the once-daily administration of levofloxacin 750 mg is pharmacodynamically more ideal than the same therapy using 500 mg levofloxacin [135]. A clinical study reported that once-daily administration of levofloxacin 750 mg for five days has excellent therapeutic effects, and this therapy has settled as the standard method of treatment for pneumonia since then [136]. A study has also reported that the five-day gemifloxacin therapy is not inferior to its seven-day counterpart in terms of therapeutic effects [137].

2. Treatment of pneumonia in patients hospitalized in general wards

KQ 9. For patients who may have contracted community-acquired pneumonia, and are hospitalized in an ICU, does the β-lactam /macrolide (or respiratory fluoroquinolone) combination therapy produce better prognoses than the β-lactam monotherapy?

Recommendations
- Use of β-lactam antibiotics or respiratory fluoroquinolones is recommended in the empirical treatment of patients with mild to moderate pneumonia admitted to a general ward (level of recommendation: weak, level of evidence: moderate).

- β-lactam and macrolide antibiotics may be administered together in patients suspected of having atypical bacterial infection or in patients who have moderate pneumonia, under limited circumstances (level of recommendation: weak, level of evidence: moderate).

Key points
- There was no significant difference in treatment outcomes (cure rate, side effects, mortality rate, *etc.*) between the administration of β-lactams, and that of β-lactam + macrolide.
- The combined administration of β-lactam and macrolide led to a higher rate of reaching clinical stability compared with the administration of β-lactams only in patients with pneumonia caused by atypical bacteria or with severe pneumonia.

<Summary of Evidence>

Empirical antibiotics for patients admitted to general wards are selected based on the severity of the disease; in other words, they are selected based on whether the patient has mild pneumonia (CURB-65 0-1 points, PSI 1-2 points), moderate pneumonia (CURB-65 2 points, PSI 3-4 points), or severe pneumonia (CURB-65 3 points, PSI 5 points). Empirical antibiotics and the method of administration are chosen based on health professionals' judgment on the patient's clinical situations and the selected antibiotics, antibiotic resistance, medication allergy, compliance, previous antibiotic use (penicillin, macrolide, fluoroquinolone, *etc.*), cost, and potential side effects. Isolation and susceptibility results of causative bacteria that are later reported must be considered along with the clinical progress to readjust the antibiotic selection.

Use of β-lactams or respiratory fluoroquinolone alone is recommended for the empirical treatment of mild or moderate pneumonia. The 2007 IDSA/ATS guideline and the 2009 Korean guideline on community-acquired pneumonia recommend the administration of β-lactams alone or in conjunction with macrolide, or the administration of respiratory fluoroquinolones alone [15, 104]. Most of the studies on combined antibiotic administration included in these guidelines were either retrospective or observational studies [138-141]. In prospective comparative studies conducted after these studies, the β-lactam and macrolide combination therapy for mild-moderate pneumonia showed no difference from the β-lactam monotherapy in terms of treatment outcomes (cure rate, incidence of side effects, mortality rates, *etc.*) [130-132, 142, 143]. In a meta-analysis on 18 studies that compare the therapeutic effects of β-lactams, and those of macrolide or fluoroquinolone which have the effect to atypical pathogens, in

the treatment of mild-moderate pneumonia, there were no significant differences in the clinical progress between the two antibiotic groups (relative risk, 0.97; 95% confidence interval 0.87-1.07) [130]. In a prospective CAP-START study conducted by Postma et al., patients hospitalized in general wards were subjected to β-lactam administration (656 patients), β-lactam + macrolide administration (739 patients), and fluoroquinolone administration (888 patients), and therapeutic effects were compared among the groups. The 90-day mortality rate was 9.0% in the β-lactam group, 11.1% in the β-lactam + macrolide group, and 8.8% in the fluoroquinolone group. Therefore, the treatment outcomes observed in the β-lactam group were on a par with those observed in the other groups [144]. In a study by Grain et al. that prospectively compares β-lactam administration, and β-lactam + macrolide administration in the treatment of patients with severe pneumonia, 41.2% and 33.6% of the patients in the β-lactam group, and the β-lactam + macrolide group did not reach a clinically stable state after seven days, respectively (P = 0.07). Although there was no difference in the rate of reaching clinical stability between the patients without atypical bacterial infection (relative risk, 0.99; 95% CI, 0.80-1.22) and with pneumonia corresponding to PSI 1-3 points in the β-lactam, and β-lactam + macrolide groups, when patients with atypical pneumonia (relative risk, 0.33; 95% confidence interval, 0.13-0.85) or severe pneumonia corresponding to PSI 5 points (relative risk, 0.81; 95% confidence interval, 0.59-1.10) were considered, the rate of reaching clinical stability was lower in the β-lactam group. The rate of readmission within 30 days was higher in the β-lactam group (7.9%, 3.1%, P = 0.01), and there were no significant differences in other clinical markers including the 90-day mortality rate, rate of ICU admission, incidence of complications, duration of hospital stay, and rate of pneumonia recurrence between the two administration groups [142].

Therefore, the present revised guideline on the treatment of community-acquired pneumonia in Korea recommends the administration of β-lactam or respiratory fluoroquinolone alone for patients with mild-moderate pneumonia who are hospitalized in general wards. In addition, considering inpatients' characteristics, the guideline recommends intravenous injections of β-lactams including amoxicillin/clavulanic acid, ampicillin/sulbactam, cefotaxime, and ceftriaxone, or respiratory fluoroquinolones including gemifloxacin, levofloxacin, and moxifloxacin over oral antibiotics [expert opinion] [143, 144]. Combined administration of β-lactams and macrolides is recommended for treating atypical bacterial infections (*Mycoplasma* spp., *Chlamydophila* spp., *Legionella* spp.), for

which the antibiotics have been reported to reduce the mortality rates of the infections, and for treating severe pneumonia [143, 144]. Oral macrolides must be used with care as they are associated with increased cardiovascular risks in patients of advanced age. These antibiotics are not recommended as there have been reports of low oral bioavailability of erythromycin, increased QT interval, and increased cardiovascular risks associated with macrolides [145, 146].

For patients who show severe adverse reactions to penicillin, and cannot use β-lactams, respiratory fluoroquinolones such as gemifloxacin, levofloxacin, and moxifloxacin are recommended. As studies have reported that use of fluoroquinolones is associated with delayed tuberculosis diagnosis, and increased drug tolerance, fluoroquinolones must be used with caution in Korea where the prevalence of tuberculosis is not low [147-149]. A prospective randomized controlled clinical report has reported that the therapeutic effects of the moxifloxacin monotherapy are not inferior to those of the ceftriaxone and levofloxacin combination therapy [150]. It has also been reported that similar results were observed between a group that was orally administered gemifloxacin, and another that was administered cefuroxime followed by ceftriaxone, and that gemifloxacin was better in terms of costs [151].

KQ 10. What is the adequate duration of antibiotic treatment for patients who may have contracted community-acquired pneumonia?

Recommendations
- Antibiotics must be administered for at least five days (level of recommendation: strong, level of evidence: low).

Key points
- Antibiotics must be administered for at least five days. The adequate duration of antibiotic administration may change depending on the causative bacteria, patient's conditions, type of antibiotics, treatment response, accompanying diseases, and pneumonia complication status.

<Summary of Evidence>

Although antibiotics are generally administered for 7-10 days, the adequate duration of the administration period may change depending on the causative bacteria, patient's conditions, types of antibiotics, treatment response, accompanying diseases and complications of pneumonia the patient has [15, 152]. In general, antibiotics are administered for at least five days. For a treatment to be terminated, a patient must not

Table 9. Criteria for clinical stability

Reduced fever >24 hours
Heart rate <100 beats/min
Reduced hyperventilation
Reduced hypotension and stable blood pressure
Reduced hypoxemia
Improved leukocyte count

have a fever for 48-72 hours, and must show one or more of the signs of clinical stable shown in Table 9 before the treatment completion [15]. A study has reported that for gemifloxaicn and levofloxacin (750 mg/d), five-day administration is sufficient [138, 153]. Antibiotics with long half-lives (*e.g.* azithromycin) may be used for 3-5 days [153-155]. In the cases of *S. aureus* pneumonia accompanied by bacteremia, enteric Gram-negative bacilli pneumonia, pneumonia accompanied by infections of other organs, and early treatment failures, short-term antibiotic treatment may be insufficient [15]. Patients who have formed cavities, or show signs of tissue necrosis may require long-term treatment [15]. *Legionella* pneumonia must be treated for at least 14 days [152].

KQ 11. For patients who may have contracted community-acquired pneumonia, when is it appropriate to switch from intravenous antibiotics to oral antibiotics?

Recommendations
- A patient may switch from intravenous antibiotics to oral antibiotics once he/she is clinically stable, and can take oral medications (level of recommendation: strong, level of evidence: high).

<Summary of Evidence>

Patients hospitalized in an ICU, who do not have severe pneumonia, show clinical improvements, are hemodynamically stable, can perform normal oral ingestion, and have normal digestive functions, maybe switch to oral treatment (Table 10). The criteria for switching to oral treatment are: 1) reduced cough and dyspnea; 2) fever: body temperature in the last eight hours <37.8°C; 3) normal leukocyte count in a blood test; and 4) sufficient oral ingestion and normal gastrointestinal absorption [156, 157]. In a prospective study that used these criteria, 133 of 200 patients (67%) hospitalized due to pneumonia satisfied these criteria within three days, and could switch to oral treatment [157]. Only one patient had a clinical treatment failure [157]. These criteria may also be ap-

plied to pneumonia caused by *S. pneumoniae* accompanied by bacteremia, which is known to have poor prognoses [158].

Another method to reduce the duration of antibiotic administration for inpatients is to start with oral treatment from the beginning, or to perform intravenous treatment for a certain period, and then switch to oral treatment. The latter has been reported to produce the same treatment outcomes as existing methods, while shortening the duration of hospital stay [159]. However, more detailed research is needed to investigate which patient groups may benefit from this approach, and what the most appropriate duration of administration is.

It is not necessary to monitor a hospitalized patient's conditions after he/she switches to oral antibiotics. In a retrospective study on 5,248 patients of advanced age who had pneumonia, there was no difference in the 14-day readmission rate, and the 30-day mortality rate between the patients who were discharged on the day that they switched to oral antibiotics, and those who were monitored for one more day after the switch [160].

Generally, it is recommended to use identical antibiotics when switching from intravenous to oral treatment. If the same antibiotics are not available, it is recommended to use antibiotics of the same class. In areas such as the United States where the rate of high-level macrolide resistance is low in *S. pneumoniae*, oral administration of macrolide is recommended if 1) there are no isolated bacteria or the causative bacteria are *S. pneumoniae*; and 2) β-lactam and macrolide have been intravenously injected as empirical antibiotics [15]. However, in areas where the rate of high-level macrolide resistance is high in *S. pneumoniae* such as Korea, there is insufficient evidence to accept these principles as they are. For this reason, it is recommended to use oral antibiotics that are of the same class as that of the starting intravenous antibiotics for a sufficient period.

KQ 12. For patients who may have contracted community-acquired pneumonia, when is the appropriate time to be discharged?

Recommendations
- If a patient can undergo oral treatment, does not require treatment or diagnostic tests for underlying diseases, and is in a social environment where he/she will be taken care of, discharge may be considered (level of recommendation: strong, level of evidence: high).

<Summary of Evidence>

If patient does not require treatment for underlying diseases, and does not require diagnostic tests, and a social environment in which the patient can be taken care of is established, discharge may be considered [136, 157, 161] (Table 11). However, a discharge decision cannot be made solely based on objective criteria. Ultimately, the clinician in charge must make the decision after considering the patient's clinical and social situations. There is a controversy regarding whether or not a patient must satisfy all conditions of clinical stability in the PSI before discharge. However, the more conditions the patient does not satisfy, the more likely he/she is likely to have poor prognoses [162, 163]. According to a prospective study that monitored 680 inpatients with pneumonia, the rate of mortality or readmission was 10.5% when a patient satisfied all conditions of clinical stability shown in Table 9 in the last 24 hours before discharge, but it increased to 13.7% with the odds ratio at 1.6 when the patient did not meet one of the conditions, and to 46.2% with the odds ratio at 5.4 if the patient did not satisfy two or more conditions [162]. A recently published prospective study has also reported that as the number of unsatisfied conditions increases, the 30-day mortality rate increases, and that fever is the most highly associated with prognosis [163].

As the PSI increases, the time until clinical stability increases [104], and this leads to longer recovery time required for elderly patients who have various accompanying diseases [164]. In addition, underlying diseases are the most common cause of readmission for patients who are discharged after undergoing treatment for pneumonia. Therefore, when determining the timing for discharge in elderly patients with various underlying diseases, it is advisable to assess whether or not the

Table 10. Criteria for switching to oral antibiotics

Patient satisfies all criteria for clinical stability shown in Table 9
Pneumonia without bacteremia
Other etiology of pneumonia, than *Legionella* spp., *Staphylococcus aureus* or *Enterobacteriaceae*
Normal gastrointestinal absorption

Table 11. Discharge criteria

Patient satisfies all conditions for switching to oral medications listed in Table 10
Patient does not require treatment for underlying diseases
Patient not require additional diagnostic tests
A social environment in which the patient can be taken care of has been established.

patients require additional interventions including early rehabilitative therapy.

KQ 13. For patients who may have contracted community-acquired pneumonia, are oxygen therapy, low-molecular-weight heparin therapy, and early ambulation helpful?

> **Recommendations**
> - The level of oxygen is maintained at 94-98% via oxygen therapy in patients with hypoxemia (level of recommendation:
> - weak, level of evidence: low).
> - Low-molecular-weight heparin is injected into patients at high risk of venous thromboembolism (level of recommendation: strong, level of evidence: high).
> - Early ambulation is recommended (level of recommendation: strong, level of evidence: high).

<Summary of Evidence>

Oxygen therapy: High concentrations of oxygen may be safely applied if a patient requires oxygen therapy to maintain the arterial partial oxygen pressure at over 8 kPa, and oxygen saturation level at 94-98%, and the risk of hypercapnic respiratory failure is not high. For patients at high risk of hypercapnic respiratory failure, treatment must begin with 24-28% low concentration oxygen therapy, followed by oxygen infusion with the oxygen saturation maintained at 88-92% and pH ≥7.35 while the arterial blood gas test results are being repeatedly checked [165].

Low-molecular-weight heparin therapy: Patients with pneumonia accompanied by acute respiratory failure are classified into the high-risk group, and must be administered low-molecular-weight heparin [166, 167]. Administration of appropriate antibiotics at appropriate time, and use of a guideline on heparin administration for the prevention of thromboembolism have been observed to reduce mortality rates [168].

Early ambulation: Early ambulation show good clinical prognoses. In a prospective study involving 458 subjects, the duration of hospital stay was shorter by 1.1 days for patients who came out of bed and maintained an upright posture for at least 20 minutes in the first 24 hours after their hospital admission, and gradually increased the level of physical activity [169].

3. Treatment of patients with pneumonia in ICU

KQ 14. For patients who may have contracted community-acquired pneumonia and are admitted to ICU for treatment, does the β-lactam/macrolide (or respiratory fluoroquinolone) combination therapy lead to better prognoses than the β-lactam monotherapy?

> **Recommendations**
> - For patients requiring ICU admission, the β-lactam + azithromycin/fluoroquinolone combination therapy is recommended over the β-lactam monotherapy. (level of recommendation: strong, level of evidence: moderate).

KQ 15. For patients who may have contracted community-acquired pneumonia and who are in admitted to ICU for treatment, does the β-lactam/macrolide (or respiratory fluoroquinolone) combination therapy lead to better prognoses than the respiratory fluoroquinolone monotherapy?

> **Recommendations**
> - For patients requiring ICU admission, the β-lactam + azithromycin/fluoroquinolone combination therapy is recommended over the β-lactam monotherapy (level of recommendation: strong, level of evidence: moderate).
> - For patients requiring ICU admission, the β-lactam + azithromycin/fluoroquinolone combination therapy is recommended over the respiratory fluoroquinolone monotherapy (level of recommendation: strong, level of evidence: moderate).

> **Key points**
> - For patients with community-acquired pneumonia who require ICU admission, combination therapy is recommended over monotherapy.
> - If pneumonia caused by *P. aeruginosa* is suspected, a combination therapy using two antibiotics with antipseudomonal effects is performed to prevent inappropriate treatments.
> - If community-acquired pneumonia caused by MRSA is suspected, vancomycin, teicoplanin, or linezolid may be used, and clindamycin or rifampin may be added.

<Summary of Evidence>

There are not many domestic clinical studies on the causative bacteria of antibiotic treatment of severe community-acquired pneumonia. According to foreign research, *S. pneumoniae, Legionella* spp. *H. influenzae, Enterbacteriaceae* spp., *S. aureus,* and *Pseudomonas* spp. are the major causative bacteria of community-acquired pneumonia, and about 20% cases of community-acquired pneumonia are due to atypical bacteria [170, 171]. Because *Legionella* are especially important in severe pneumonia caused by atypical bacteria, antibiotics that have antibacterial activities against these bacteria must be included in the early empirical treatment [172]. In clinical stud-

ies that have been conducted up to date, combination therapy has been not more beneficial than monotherapy for treating mild pneumonia; however, combination therapy has produced better results for patients with severe pneumonia [142, 173, 174].

1) *P. aeruginosa* infection is not suspected

(a) β-lactam + azithromycin or

(b) β-lactam + fluoroquinolone combination therapy is performed. The following antibiotics are recommended (in alphabetical order)

- β-lactam: ampicillin/sulbactam, cefotaxime, ceftriaxone
- Macrolide: azithromycin
- Respiratory fluoroquinolone: gemifloxacin, levofloxacin, moxifloxacin
  (Respiratory fluoroquinolone + aztreonam are recommended if a patient is hypersensitive to penicillin.)

In a randomized controlled clinical trial involving patients with community-acquired pneumonia not accompanied by shock, combination therapy had no significant effects; however, the combination therapy showed better outcomes than the fluoroquinolone monotherapy for patients who were on mechanical ventilation [173]. In another retrospective study, the β-lactam + macrolide combination therapy led to higher survival rates than the fluoroquinolone monotherapy for patients with severe pneumonia [175]. Most patients who are admitted to an ICU experience shock, or require mechanical ventilation. Therefore, combination therapy is recommended over the fluoroquinolone monotherapy for these patients. The effectiveness of the fluoroquinolone monotherapy in pneumonia accompanied by meningitis caused by *S. pneumoniae* is unclear. In a recent noninferiority trial, the β-lactam + macrolide combination therapy produced better outcomes than the β-lactam monotherapy in severe pneumonia or pneumonia caused by atypical bacteria [142]. In a prospective observational study involving patients with *S. pneumoniae* bacteremia, the combination therapy (β-lactam + macrolide or β-lactam + fluoroquinolone) also led to higher survival rates compared with the β-lactam monotherapy, and this result was observed not in patients with mild pneumonia, but patients with severe pneumonia [176]. Some studies have also reported better treatment outcomes from combination therapy than from monotherapy even in patients treated with effective antibiotics [177-179]. Therefore, for the empirical antibiotic treatment of patients with severe community-acquired pneumonia requiring ICU admission, combination therapy is recommended over monotherapy.

2) Suspected *P. aeruginosa* infection

The following combination therapies may be performed. Anti-pneumococcal, anti-pseudomonal β-lactams, such as cefepime, piperacillin/tazobactam, imipenem, and meropenem may be used.

(a) Anti-pneumococcal, anti-pseudomonal β-lactam + ciprofloxacin or levofloxacin

(b) Anti-pneumococcal, anti-pseudomonal β-lactam + aminoglycoside + azithromycin

(c) Anti-pneumococcal, anti-pseudomonal β-lactam + aminoglycoside + anti-pneumococcal fluoroquinolone (gemifloxacin, levofloxacin, moxifloxacin)

The risk factors of *P. aeruginosa* infection include alcohol consumption, structural lung diseases such as bronchodilation, frequent use of steroids due to acute worsening of chronic obstructive pulmonary disease, and use of antibiotics in the last three months. If there is a possibility that a patient has pneumonia caused by *P. aeruginosa,* antibiotics that are effective against and highly sensitive to *S. pneumoniae* must be selected. Examples of these antibiotics include cefepime, piperacillin/tazobactam, imipenem, and meropenem. In a prospective observational study, gram-negative bacillus infections including those caused by *P. aeruginosa* were associated with high mortality rates [180]. In a multi-institutional study conducted in Asian, gram-negative bacilli accounted for 10.1% of all cases of deaths, were the most common causative bacteria of severe pneumonia, and were a risk factor of death [181]. Of these bacteria, *P. aeruginosa* may exhibit various levels of antibiotic resistance. Therefore, more than two empirical combination therapies are needed against these bacteria, and it is recommended to readjust the antibiotic selection once the bacteria are isolated and their susceptibility results are obtained [180].

3) Suspected MRSA infection

Although community-acquired MRSA have been usually detected in skin and soft tissue infections, they are rarely a cause of severe community-acquired pneumonia [182]. They occur in healthy adults who are not associated with the common risk factors of hospital-acquired infection, and have been reported to occur in association with new influenza viruses [183]. They produce Panton-Valentine Leucocidin (PVL) toxins, cause necrotic pneumonia and are associated with high mortality rates.

182 Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

Unlike in the case of hospital-acquired MRSA, community-acquired MRSA may be susceptible to sulfamethoxazole (TMP-SMX) or clindamycin. Vancomycin cannot reduce toxin production, and it is not yet clear if TMP-SMX and fluoroquinolones can reduce toxin production. Although there is no established method of treatment, clindamycin, which can reduce toxin production, and rifampin, which has bactericidal activities against *S. aureus* may be used [184, 185]. Among novel antibiotics, daptomycin is effective for soft tissue infection caused by MRSA or bacteremia. However, its effectiveness may be reduced due to surfactants of the lungs, and are therefore not recommended [186]. There is not enough evidence regarding the effectiveness of tigecycline in pneumonia [187].

KQ 16. For patients who may have contracted community-acquired pneumonia and who are admitted to ICU for treatment, does a treatment against Legionella lead to better prognoses?

Recommendations
- For patients with severe community-acquired pneumonia who require ICU admission, it is necessary to perform treatment against *Legionella* (level of recommendation: strong, level of evidence: low).

Key points
- Community-acquired pneumonia caused by *Legionella* is often severe, and treatment against these bacteria must be included in the empirical antibiotic treatment.

\<Summary of Evidence\>

All patients admitted to an ICU must be subjected to treatment against *S. pneumoniea* and *Legionella* spp. [171, 188]. According to foreign studies, infections caused by atypical bacteria account for over 20% of all cases of severe community-acquired pneumonia, and of these, *Legionella* plays the main role [170-172]. In domestic studies, *Legionella* accounted for 0-5.3% of the causative bacteria of pneumonia, but they were more common compared with other atypical pathogens in patients with severe pneumonia requiring ICU admission [11-13].

KQ 17. For patients who may have contracted community-acquired pneumonia and who are admitted to ICU for treatment, does steroid therapy lead to good prognoses?

Recommendations
- Steroid therapy may be considered for patients with severe community-acquired pneumonia accompanied by shock (level of recommendation: weak, level of evidence: low).

Key points
- Although use of steroids to treat severe community-acquired pneumonia shortened the time until reaching clinical stability in some studies, it did not lead to any changes in the mortality rate.
- However, in studies involving patients with septic shock and adrenal insufficiency, steroid use lead to a decrease in the mortality rate.

\<Summary of Evidence\>

Study results regarding the use of steroids for severe community-acquired pneumonia vary greatly. In a recently-conducted large-scale study, use of steroids in addition to pneumonia treatment led to faster bacteriological conversion, shortened the time until clinical stability, and shortened the duration of hospital stay [189-192]. In a small-scale randomized study involving patients admitted to an ICU, seven-day use of hydrocortisone reduced the duration of hospital stay and mortality rate [193]. In two small-scale studies, use of steroids produced better treatment outcomes as opposed to when they were not used [194, 195]. However, these studies are small in scale, and differ in the characteristics of their patient groups. In a relatively recently conducted randomized controlled study, the duration of hospital stay was reduced by 1-1.5 days in the steroid group, but no difference in the mortality rate was observed [190, 193]. In addition, when steroids were additionally used for patients with pneumonia, no significant differences in symptom improvements, overall cure rate, complications, rate of ICU admission, and mortality rate were observed compared with the other group that was not subjected to steroid administration, and the rates of hyperglycemia and side effects were higher in the steroid group [189-192]. However, in a randomized controlled study involving patients with septic shock, seven-day use of low-dose hydrocortisone reduced mortality rates in patients who had hypoadrenalism [196], and reduced mortality rates and the number of days on mechanical ventilation in patients with acute respiratory failure in addition to hypoadrenalism [197]. Therefore, patients with severe community-acquired pneumonia accompanied by shock that requires vasopressors, use of steroids may be considered.

Assessment of effectiveness of pneumonia treatment

KQ 18. For patients who may have contracted community-acquired pneumonia, are follow-up chest-X-rays useful for assessing treatment response?

Recommendations
- For patients with community-acquired pneumonia who do not show clear symptom improvements, or who are at high risk of lung cancer, it is recommended to take follow-up chest X-rays to examine the treatment response (level of recommendation: strong, level of evidence: low).

Key points
- Lesion improvements manifest themselves more slowly than clinical symptoms on chest-X-rays of patients with pneumonia.
- Lesion loss may radiologically manifest slowly even after 12 weeks after treatment in patients who are aged 50 years or older, who have multilobar pneumonia, and have underlying diseases.
- For patients who are aged 50 years or older, are male, and are smokers, chest X-rays must be performed to differentiate between underlying lung diseases such as pneumonia 7-12 weeks after treatment, and to confirm complete lesion loss.

<Summary of Evidence>

In general, radiological anomalies of pneumonia manifest more slowly than clinical symptoms.

In a study that prospectively observed 288 inpatients with severe pneumonia, 56% of the patients showed clinical improvements at seven days, but only 25% radiologically showed improvements. At 28 days, 78% patients completely recovered based on clinical findings, but only 53% had complete lesion loss based on chest X-rays [198]. In a study that monitored chest X-rays of 81 patients with community-acquired pneumonia in emergency and outpatient departments for 24 weeks, 50.6% of the patients had complete lesion loss at two weeks, and only 66.7% had complete lesion loss at four weeks [199]. Radiological improvements were usually observed slowly in multilobar pneumonia, and the rate of improvement in chest X-rays changed depending on the patient's age and underlying lung diseases [199, 200]. Most patients who were 50 years old or younger, and had no underlying lung diseases show lesion improvement on chest X-rays within four weeks; however, patients who are 50 years or older, and have under-

lying lung diseases may not show radiological improvements until after 12 weeks [200]. In addition, treatment outcome of pneumonia is not associated with signs of worsening on chest X-rays taken during a follow-up period [198]. Therefore, repeatedly taking chest X-rays from patients with pneumonia who have shown clinical improvements may not have any additional benefits.

However, it is necessary to take follow-up chest X-rays to eliminate the possibility of underlying diseases such as pneumonia for patients who are 50 years old or older, male, and smokers. In a large-scale cohort study involving 3,000 patients, 1.1% patients diagnosed with community-acquired pneumonia were newly diagnosed with pneumonia within 90 days, and age of 50 years or older (adjusted HR 19.0, 95% CI 5.7-63.6), male gender (adjusted HR 1.8, 95% CI 1.1-2.9), and smoking (adjusted HR 1.7, 95% CI 1.0-3.0) were significant risk factors of pneumonia [201]. Of 236 patients with community-acquired pneumonia, 10 were diagnosed with pneumonia, and high proportion (17%) of these patients was aged 60 years or older. Therefore, it is necessary to take follow-up chest X-rays from patients with community-acquired pneumonia [72]. In addition, to eliminate the possibility of pneumonia and underlying diseases in patients who do not show sufficient clinical improvements at 4-5 weeks after treatment, chest X-rays may be repeatedly obtained [202].

KQ 19. For patients who may have contracted community-acquired pneumonia, is the C-reactive protein (CRP) test useful for assessing therapeutic effects?

Recommendations
- CRP levels may be repeatedly measured to assess the risk of treatment failure and complications in patients who do not clinically show clear symptom improvements (level of recommendation: weak, level of evidence: low).

Key points
- Repeated CRP measurement after three or four days of treatment can help identify patients who are at risk of treatment failure or who are at increased risk of complications.
- Patients whose CRP has not decreased by over 50% after four days of treatment tend to have higher a 30-day mortality rate, higher risk of ventilator and vasopressor use, and risk of complications of pneumonia such as pyothorax.

<Summary of Evidence>
Based on the findings of prospective studies that have ana-

lyzed inpatients with community-acquired pneumonia, repeated CRP measurement at three or four days of treatment helped identify patients at risk of treatment failure or at increased risk of complications [203-206]. CRP levels >10 mg/dL at four days of treatment were significantly associated with the incidence of complications [207]. On the other hand, patients with CRP levels <3 mg/dL at three days after treatment were at low risk of complications [205]. In addition, patients whose CRP levels did not decrease by over 50% at four days of treatment had a higher 30-day mortality rate, higher risk of ventilator and vasopressor use, and higher risk of complications of pneumonia such as pyothorax [204]. Therefore, although repeated CRP measurement is not significantly beneficial in clinical aspects for patients whose symptoms are worsening, CRP monitoring may help identify patients at risk of treatment failure or complications among those who do not show clear signs of clinical improvements or worsening in the early period of hospitalization.

KQ 20. For patients who may have contracted community-acquired pneumonia, is the procalcitonin test useful for assessing therapeutic effects?

Recommendations
- The procalcitonin test may be used in the process of deciding whether to continue antibiotic treatment or not for patients who show clinical improvements (level of evidence: moderate, level of recommendation: weak).

Key points
- Repeated procalcitonin measurement may be used as an auxiliary method to predict the prognoses of patients with pneumonia
- Antibiotic use or cessation of antibiotic use based on procalcitonin levels helps reduce the doses and duration of antibiotic use without increasing the risk of treatment failure and complications

<Summary of Evidence>
Repeated procalcitonin measurement may help predict a patient's prognosis. When procalcitonin levels of 100 patients admitted to an ICU due to severe community-acquired pneumonia were measured at one and three days of hospitalization, an increase in procalcitonin levels at three days was identified as a significant prognostic factor indicative of poor prognoses [208]. In another study, of 394 patients hospitalized due to community-acquired pneumonia, those who clinically

stabilized within 72 hours, and whose procalcitonin levels repeatedly measured at 72 hours were below 0.25 ng/mL did not develop serious complications [205]. When procalcitonin, CRP, mild regional pro-atrial natriuretic peptide (MR pro-ANP) levels were continuously measured in 75 patients with pneumonia, high levels of MR pro-ANP and procalcitonin levels were consistently observed in patients who developed complications or died [209].

Numerous randomized controlled clinical studies have been conducted to determine whether or not procalcitonin can be used as criteria for beginning or ceasing antibiotic use. According to a meta-analysis that analysed 4,221 patients 14 different acute respiratory infections, using procalcitonin as the criteria for antibiotic use did not lead to significant differences in the risk of treatment failure and mortality rate compared with when existing treatment guidelines were used, but significantly reduced the number of days of antibiotic use [210]. When the meta-analysis analysed patients with community-acquired pneumonia separately, there was no significant difference in the mortality rate between the procalcitonin and control groups (9.2% and 10.8%, respectively; adjusted odds ratio (OR) 0.89 (95% CI 0.64-1.23). However, the rate of treatment failure was lower in the procalcitonin group compared with the existing treatment group (19.0% and 23.4%, respectively; adjusted OR 0.77 [95% CI 0.62-0.96, P <0.05]), and the median number of days of antibiotic use decreased by 3.9 days from 10 to 6 days (P <0.01) [211]. A prospective multi-institutional randomized controlled clinical study has recently published its findings regarding the use of the procalcitonin test as the criteria for cessation of antibiotic use in patients who are administered antibiotics within 24 hours after ICU admission due to an infection [212]. Of the 1,575 patients included in this study, 792 (50.3%) had community-acquired pneumonia. In the procalcitonin group, cessation of antibiotic use was recommended if the procalcitonin level has decreased by over 80% relative to the level at the time of admission, or if the level is below 0.5 µg/L. Consistent with previous studies, the doses of antibiotics used and the duration of antibiotic use significantly decreased in the procalcitonin group compared with the control group. The mortality rate at 28 days decreased by 5.4% (P = 0.0122), and the one-year mortality rate decreased by 6.1% (P = 0.0158) in the procalcitonin group compared with the control group. However, most of studies have been published in Europe, and the patient groups included in the studies are heterogeneous in terms of diseases. In addition, the ratio of patients in the procalcitonin group varied depending on the research

algorithm (47-81%). Further studies are needed to investigate the cost-effectiveness of the procalcitonin test in reducing the cost of antibiotic prescriptions, and it is yet too early to recommend antibiotic treatment according to procalcitonin test results in an actual clinical practice guideline.

Adjuvant treatment and prevention of pneumonia

KQ 21. For adults who have contracted community-acquired pneumonia, and have the risk factors of *S. pneumoniae* infection, can vaccination against *S. pneumoniae* prevent community-acquired pneumonia?

Recommendations
- Old adults, and adults who have the risk factors of *S. pneumoniae* infection are recommended to be vaccinated against *S. pneumonia*e (level of recommendation: strong, level of evidence: high).

Key points
- A polysaccharide pneumococcal vaccine has recently shown to prevent invasive pneumococcal diseases in patients of advanced age, or those with the risk factors of *S. pneumoniae* infection.
- A protein conjugate pneumococcal vaccine has recently shown to prevent pneumonia and invasive pneumococcal diseases.
- For patients of advanced age, and patients with the risk factors of *S. pneumoniae* infection, a combined injection of protein conjugate and polysaccharide pneumococcal vaccines is recommended.

<Summary of Evidence>

The risk factors of invasive pneumococcal diseases caused include age of 65 years or older, residence in long-term care facilities, dementia, convulsive diseases, congestive heart failure, cardiovascular diseases, chronic obstructive pulmonary diseases, previous history of pneumonia, chronic liver diseases, diabetes, alienia, and chronic cerebrospinal fluid leakage.

According to previous literatures, the 23-valent polysaccharide pneumococcal vaccine prevented invasive pneumococcal diseases in 44-47% of older adults aged 65 years or older [213, 214], and its effectiveness was slightly reduced in patients with chronic diseases [215]. Numerous cohort studies have recently demonstrated that the vaccine can reduce the incidence of pneumonia, pneumococcal pneumonia, hospitalization due to pneumonia, and deaths by pneumonia [216-

221]. However, some have reported that the vaccine has no preventive effects against pneumonia, or hospitalization due to pneumonia [222, 223]. Patients who have asplenia, who are of advanced age, or who are in a high-risk group must be revaccinated after five years. The safety and immunogenicity of the vaccine have been verified in numerous studies [224-226].

In a recent large-scale study, the 13-valent protein conjugate pneumococcal vaccine prevented 45% of pneumococcal pneumonia, and 75% of invasive pneumococcal diseases. However, the vaccine had no preventive effects against other types of pneumonia [222].

The preventive effects of the polysaccharide pneumococcal vaccine against invasive pneumococcal diseases, as well as those of the protein conjugate pneumococcal vaccine against pneumococcal infections have been verified. Accordingly, a domestic pneumococcal vaccination guideline recommends performing a combined injection of the protein conjugate and polysaccharide vaccines in patients who are of advanced age, or who have the risk factors of pneumococcal infections.

KQ 22. Does smoking cessation education prevent community-acquired pneumonia among adults who have contracted community-acquired pneumonia?

Recommendations
- Smoking cessation education is necessary for current smokers who have pneumonia (level of recommendation: strong, level of evidence: high).

Key points
- Smoking is an important risk factor of pneumonia even for healthy adults. Therefore, smoking cessation is important for preventing pneumonia.

<Summary of Evidence>

Smoking is known to be a risk factor of invasive pneumococcal diseases even in young people who are not immunosuppressed [227]. Both direct and indirect smoking is a risk factor of community-acquired pneumonia [228, 229]. In addition, smoking is a risk factor of *Legionella* infections [230]. Smoking cessation education is needed to prevent pneumonia, and for smokers who are hospitalized due to pneumonia, the education must begin during the hospitalization [231].

186 Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

Acknowledgement

Supplementary material

Guideline Korean version.

Supplementary material can be found with this article online http://www.icjournal.org/src/sm/ic-50-160-s001.pdf.

Conflicts of Interests

No conflicts of interest.

ORCID

Mi Suk Lee   https://orcid.org/0000-0001-8951-5032
Cheol-In Kang   https://orcid.org/0000-0002-1741-4459
Eu Suk Kim   https://orcid.org/0000-0001-7132-0157
Eun Young Heo   https://orcid.org/0000-0003-3803-4903
Kyung-Wook Jo   https://orcid.org/0000-0002-5949-248X
Sunghoon Park   https://orcid.org/0000-0001-7004-6985
Dong-Ah Park   https://orcid.org/0000-0001-7225-3152
Gee Young Suh   https://orcid.org/0000-0001-5473-1712
Sungmin Kiem   https://orcid.org/0000-0003-3518-966X

References

1. Song JH, Huh K, Chung DR. Community-acquired pneumonia in the Asia-Pacific region. Semin Respir Crit Care Med 2016;37:839-54.

2. Yoon HK. Changes in the epidemiology and burden of community-acquired pneumonia in Korea. Korean J Intern Med 2014;29:735-7.

3. Yoo KH, Yoo CG, Kim SK, Jung JY, Lee MG, Uh ST, Shim TS, Jeon K, Shim JJ, Lee HB, Chung CR, Kang KW, Jung KS. Economic burden and epidemiology of pneumonia in Korean adults aged over 50 years. J Korean Med Sci 2013;28:888-95.

4. Seong GM, Kim M, Lee J, Lee JH, Jeong SY, Choi Y, Kim WJ. Healthcare-associated pneumonia among hospitalized patients: Is it different from community acquired pneumonia? Tuberc Respir Dis (Seoul) 2014;76:66-74.

5. Kim JE, Kim UJ, Kim HK, Cho SK, An JH, Kang SJ, Park

KH, Jung SI, Jang HC. Predictors of viral pneumonia in patients with community-acquired pneumonia. PLoS One 2014;9:e114710.

6. Kang YS, Ryoo SR, Byun SJ, Jeong YJ, Oh JY, Yoon YS. Antimicrobial resistance and clinical outcomes in nursing home-acquired pneumonia, compared to community-acquired pneumonia. Yonsei Med J 2017;58:180-6.

7. Jeong BH, Koh WJ, Yoo H, Um SW, Suh GY, Chung MP, Kim H, Kwon OJ, Jeon K. Performances of prognostic scoring systems in patients with healthcare-associated pneumonia. Clin Infect Dis 2013;56:625-32.

8. Jeon EJ, Cho SG, Shin JW, Kim JY, Park IW, Choi BW, Choi JC. The difference in clinical presentations between healthcare-associated and community-acquired pneumonia in university-affiliated hospital in Korea. Yonsei Med J 2011;52:282-7.

9. Choi MJ, Song JY, Cheong HJ, Jeon JH, Kang SH, Jung EJ, Noh JY, Kim WJ. Clinical usefulness of pneumococcal urinary antigen test, stratified by disease severity and serotypes. J Infect Chemother 2015;21:672-9.

10. Chong YP, Jung KS, Lee KH, Kim MN, Moon SM, Park S, Hur J, Kim DM, Jeon MH, Woo JH. The bacterial etiology of community-acquired pneumonia in Korea: A nationwide prospective multicenter study. Infect Chemother 2010;42:397-403.

11. Song JH, Oh WS, Kang CI, Chung DR, Peck KR, Ko KS, Yeom JS, Kim CK, Kim SW, Chang HH, Kim YS, Jung SI, Tong Z, Wang Q, Huang SG, Liu JW, Lalitha MK, Tan BH, Van PH, Carlos CC, So T; Asian Network for Surveillance of Resistant Pathogens Study Group. Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens. Int J Antimicrob Agents 2008;31:107-14.

12. Sohn JW, Park SC, Choi YH, Woo HJ, Cho YK, Lee JS, Sim HS, Kim MJ. Atypical pathogens as etiologic agents in hospitalized patients with community-acquired pneumonia in Korea: a prospective multi-center study. J Korean Med Sci 2006;21:602-7.

13. Lee SJ, Lee MG, Jeon MJ, Jung KS, Lee HK, Kishimoto T. Atypical pathogens in adult patients admitted with community-acquired pneumonia in Korea. Jpn J Infect Dis 2002;55:157-9.

14. Choi SH, Hong SB, Ko GB, Lee Y, Park HJ, Park SY, Moon SM, Cho OH, Park KH, Chong YP, Kim SH, Huh JW, Sung H, Do KH, Lee SO, Kim MN, Jeong JY, Lim CM, Kim YS, Woo JH, Koh Y. Viral infection in patients with severe

pneumonia requiring intensive care unit admission. Am J Respir Crit Care Med 2012;186:325-32.

15. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 (Suppl 2):S27-72.

16. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA; Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax 2009;64 (Suppl 3):iii1-55.

17. Song JH, Jung SI, Ki HK, Shin MH, Ko KS, Son JS, Chang HH, Kim SW, Lee H, Kim YS, Oh WS, Peck KR, Chongthaleong A, Lalitha MK, Perera J, Yee TT, Jamal F, Kamarulzaman A, Carlos CC, So T; Asian Network for Surveillance of Resistant Pathogens Study Group. Clinical outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains in Asian countries: a study by the Asian Network for Surveillance of Resistant Pathogens. Clin Infect Dis 2004;38:1570-8.

18. Kim SH, Song JH, Chung DR, Thamlikitkul V, Yang Y, Wang H, Lu M, So TM, Hsueh PR, Yasin RM, Carlos CC, Pham HV, Lalitha MK, Shimono N, Perera J, Shibl AM, Baek JY, Kang CI, Ko KS, Peck KR; ANSORP Study Group. Changing trends in antimicrobial resistance and serotypes of Streptococcus pneumoniae isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. Antimicrob Agents Chemother 2012;56:1418-26.

19. Kim SH, Song SA, Yi J, Song D, Chang CL, Park DC, Urm SH, Kim HR, Shin JH. Distribution and antimicrobial resistance of Streptococcus pneumoniae at four university hospitals in Busan and Gyeongnam. Ann Clin Microbiol 2016;19:48-53.

20. Kim T, Park SJ, Chong YP, Park KH, Lee YM, Hong HL, Kim HS, Kim ES, Lee S, Choi DR, Kim SH, Jeong JY, Lee SO, Choi SH, Woo JH, Kim YS. Fluoroquinolone resistance of Streptococcus pneumoniae isolates causing invasive disease: special focus on zabofloxacin. Diagn Microbiol Infect Dis 2016;86:181-3.

21. Lee S, Bae S, Lee KJ, Yu JY, Kang Y. Changes in serotype prevalence and antimicrobial resistance among invasive Streptococcus pneumoniae isolates in Korea, 1996-2008. J Med Microbiol 2013;62:1204-10.

22. Torumkuney D, Chaiwarith R, Reechaipichitkul W, Malatham K, Chareonphaibul V, Rodrigues C, Chitins DS, Dias M, Anandan S, Kanakapura S, Park YJ, Lee K, Lee H, Kim JY, Lee Y, Lee HK, Kim JH, Tan TY, Heng YX, Mukherjee P, Morrissey I. Results from the survey of antibiotic resistance (SOAR) 2012-14 in Thailand, India, South Korea and Singapore. J Antimicrob Chemother 2016;71 (Suppl 1):i3-19.

23. Bae S, Lee J, Lee J, Kim E, Lee S, Yu J, Kang Y. Antimicrobial resistance in Haemophilus influenzae respiratory tract isolates in Korea: results of a nationwide acute respiratory infections surveillance. Antimicrob Agents Chemother 2010;54:65-71.

24. Kim IS, Ki CS, Kim S, Oh WS, Peck KR, Song JH, Lee K, Lee NY. Diversity of ampicillin resistance genes and antimicrobial susceptibility patterns in Haemophilus influenzae strains isolated in Korea. Antimicrob Agents Chemother 2007;51:453-60.

25. Hong KB, Choi EH, Lee HJ, Lee SY, Cho EY, Choi JH, Kang HM, Lee J, Ahn YM, Kang YH, Lee JH. Macrolide resistance of Mycoplasma pneumoniae, South Korea, 2000-2011. Emerg Infect Dis 2013;19:1281-4.

26. Uh Y, Hong JH, Oh KJ, Cho HM, Park SD, Kim J, Yoon KJ. Macrolide resistance of Mycoplasma pneumoniae and its detection rate by real-time PCR in primary and tertiary care hospitals. Ann Lab Med 2013;33:410-4.

27. Sohn KM, Chung DR, Baek JY, Kim SH, Joo EJ, Ha YE, Ko KS, Kang CI, Peck KR, Song JH. Post-influenza pneumonia caused by the USA300 community-associated methicillin-resistant Staphylococcus aureus in Korea. J Korean Med Sci 2012;27:313-6.

28. Leem AY, Jung WJ, Kang YA, Park SC, Kim YJ, Hwang ED, Kim EY, Jung KS, Park MS, Kim SY, Kim YS, Kim SK, Chang J, Jung JY. Comparison of methicillin-resistant Staphylococcus aureus community-acquired and healthcare-associated pneumonia. Yonsei Med J 2014;55:967-74.

29. Hwang JW, Joo EJ, Ha JM, Lee W, Kim E, Yune S, Chung DR, Jeon K. Community-acquired necrotizing pneumonia caused by ST72-SCCmec type IV-methicillin-resistant Staphylococcus aureus in Korea. Tuberc Respir Dis (Seoul) 2013;75:75-8.

30. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet 2011;377:1264-75.

188 Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

31. Lieberman D, Lieberman D, Shimoni A, Keren-Naus A, Steinberg R, Shemer-Avni Y. Identification of respiratory viruses in adults: nasopharyngeal versus oropharyngeal sampling. J Clin Microbiol 2009;47:3439-43.

32. Loens K, Van Heirstraeten L, Malhotra-Kumar S, Goossens H, Ieven M. Optimal sampling sites and methods for detection of pathogens possibly causing community-acquired lower respiratory tract infections. J Clin Microbiol 2009;47:21-31.

33. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. Lancet 2015;386:1097-108.

34. Musher DM, Roig IL, Cazares G, Stager CE, Logan N, Safar H. Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. J Infect 2013;67:11-8.

35. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis 2010;50:202-9.

36. Johnstone J, Majumdar SR, Fox JD, Marrie TJ. Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. Chest 2008;134:1141-8.

37. Falsey AR, Becker KL, Swinburne AJ, Nylen ES, Formica MA, Hennessey PA, Criddle MM, Peterson DR, Baran A, Walsh EE. Bacterial complications of respiratory tract viral illness: a comprehensive evaluation. J Infect Dis 2013;208:432-41.

38. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney DM, Chappell JD, Qi C, Hart EM, Carroll F, Trabue C, Donnelly HK, Williams DJ, Zhu Y, Arnold SR, Ampofo K, Waterer GW, Levine M, Lindstrom S, Winchell JM, Katz JM, Erdman D, Schneider E, Hicks LA, McCullers JA, Pavia AT, Edwards KM, Finelli L; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015;373:415-27.

39. Karhu J, Ala-Kokko TI, Vuorinen T, Ohtonen P, Syrjälä H. Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. Clin Infect Dis 2014;59:62-70.

40. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med 2014;371:1619-28.

41. Avni T, Bieber A, Green H, Steinmetz T, Leibovici L, Paul M. Diagnostic accuracy of PCR alone and compared to urinary antigen testing for detection of Legionella spp.: a systematic review. Clin Microbiol 2016;54:401-11.

42. Maze MJ, Slow S, Cumins AM, Boon K, Goulter P, Podmore RG, Anderson TP, Barratt K, Young SA, Pithie AD, Epton MJ, Werno AM, Chambers ST, Murdoch DR. Enhanced detection of Legionnaires' disease by PCR testing of induced sputum and throat swabs. Eur Respir J 2014;43:644-6.

43. Cho MC, Kim H, An D, Lee M, Noh SA, Kim MN, Chong YP, Woo JH. Comparison of sputum and nasopharyngeal swab specimens for molecular diagnosis of Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella pneumophila. Ann Lab Med 2012;32:133-8.

44. Vikerfors T, Brodin G, Grandien M, Hirschberg L, Krook A, Pettersson CA. Detection of specific IgM antibodies for the diagnosis of Mycoplasma pneumoniae infections: a clinical evaluation. Scand J Infect Dis 1988;20:601-10.

45. Nilsson A, Björkman P, Persson K. Polymerase chain reaction is superior to serology for the diagnosis of acute Mycoplasma pneumoniae infection and reveals a high rate of persistent infection. BMC Microbiol 2008;8:93.

46. Uldum SA, Jensen JS, Søndergård-Andersen J, Lind K. Enzyme immunoassay for detection of immunoglobulin M (IgM) and IgG antibodies to Mycoplasma pneumoniae. J Clin Microbiol 1992;30:1198-204.

47. Parrott GL, Kinjo T, Fujita J. A compendium for Mycoplasma pneumoniae. Front Microbiol 2016;7:513.

48. Loens K, Beck T, Ursi D, Overdijk M, Sillekens P, Goossens H, Ieven M. Evaluation of different nucleic acid amplification techniques for the detection of M. pneumoniae, C. pneumoniae and Legionella spp. in respiratory specimens from patients with community-acquired pneumonia. J Microbiol Methods 2008;73:257-62.

49. Herrera M, Aguilar YA, Rueda ZV, Muskus C, Vélez LA. Comparison of serological methods with PCR-based methods for the diagnosis of community-acquired pneumonia caused by atypical bacteria. J Negat Results Biomed 2016;15:3.

50. Villegas E, Sorlózano A, Gutiérrez J. Serological diagnosis of Chlamydia pneumoniae infection: limitations and perspectives. J Med Microbiol 2010;59:1267-74.

51. Benitez AJ, Thurman KA, Diaz MH, Conklin L, Kendig NE, Winchell JM. Comparison of real-time PCR and a microimmunofluorescence serological assay for detection of Chlamydophila pneumoniae infection in an outbreak investigation. J Clin Microbiol 2012;50:151-3.

52. Waterer GW. Diagnosing viral and atypical pathogens in the setting of community-acquired pneumonia. Clin Chest Med 2017;38:21-8.

53. Syrjst H, Broas M, Suramo I, Ojala A, Lähde S. High-reso-lution computed tomography for the diagnosis of community-acquired pneumonia. Clin Infect Dis 1998;27:358-63.

54. Heffner JE, Klein JS, Hampson C. Diagnostic utility and clinical application of imaging for pleural space infections. Chest 2010;137:467-79.

55. Arenas-Jiménez J, Alonso-Charterina S, Sánchez-Payá J, Fernández-Latorre F, Gil-Sánchez S, Lloret-Llorens M. Evaluation of CT findings for diagnosis of pleural effusions. Eur Radiol 2000;10:681-90.

56. Ketai L, Jordan K, Busby KH. Imaging infection. Clin Chest Med 2015;36:197-217.

57. Raoof S, Amchentsev A, Vlahos I, Goud A, Naidich DP. Pictorial essay: multinodular disease: a high-resolution CT scan diagnostic algorithm. Chest 2006;129:805-15.

58. Revel MP, Triki R, Chatellier G, Couchon S, Haddad N, Hernigou A, Danel C, Frija G. Is it possible to recognize pulmonary infarction on multisection CT images? Radiology 2007;244:875-82.

59. Shah RM, Friedman AC. CT angiogram sign: incidence and significance in lobar consolidations evaluated by contrast-enhanced CT. AJR Am J Roentgenol 1998;170:719-21.

60. Okada F, Ando Y, Tanoue S, Ishii R, Matsushita S, Ono A, Maeda T, Mori H. Radiological findings in acute *Haemophilus influenzae* pulmonary infection. Br J Radiol 2012;85:121-6.

61. Miller WT Jr, Mickus TJ, Barbosa E Jr, Mullin C, Van Deerlin VM, Shiley KT. CT of viral lower respiratory tract infections in adults: comparison among viral organisms and between viral and bacterial infections. Am J Roentgenol 2011;197:1088-95.

62. Nambu A, Saito A, Araki T, Ozawa K, Hiejima Y, Akao M, Ohki Z, Yamaguchi H. *Chlamydia pneumoniae*: comparison with findings of *Mycoplasma pneumoniae* and *Streptococcus pneumoniae* at thin-section CT. Radiology 2006;238:330-8.

63. Ors F, Deniz O, Bozlar U, Gumus S, Tasar M, Tozkoparan E, Tayfun C, Bilgic H, Grant BJ. High-resolution CT findings in patients with pulmonary tuberculosis: correlation with the degree of smear positivity. J Thorac Imaging 2007;22:154-9.

64. Koh WJ, Lee KS, Kwon OJ, Jeong YJ, Kwak SH, Kim TS. Bilateral bronchiectasis and bronchiolitis at thin-section CT: diagnostic implications in nontuberculous mycobacterial pulmonary infection. Radiology 2005;235:282-8.

65. Brenner DJ, Hall EJ. Computed tomography--an increas-ing source of radiation exposure. N Engl J Med 2007;357:2277-84.

66. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, Melniker L, Gargani L, Noble VE, Via G, Dean A, Tsung JW, Soldati G, Copetti R, Bouhemad B, Reissig A, Agricola E, Rouby JJ, Arbelot C, Liteplo A, Sargsyan A, Silva F, Hoppmann R, Breitkreutz R, Seibel A, Neri L, Storti E, Petrovic T; International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 2012;38:577-91.

67. Chavez MA, Shams N, Ellington LE, Naithani N, Gilman RH, Steinhoff MC, Santosham M, Black RE, Price C, Gross M, Checkley W. Lung ultrasound for the diagnosis of pneumonia in adults: a systematic review and meta-analysis. Respir Res 2014;15:50.

68. Reissig A, Copetti R, Mathis G, Mempel C, Schuler A, Zechner P, Aliberti S, Neumann R, Kroegel C, Hoyer H. Lung ultrasound in the diagnosis and follow-up of community-acquired pneumonia: a prospective, multicenter, diagnostic accuracy study. Chest 2012;142:965-72.

69. Kearney SE, Davies CW, Davies RJ, Gleeson FV. Computed tomography and ultrasound in parapneumonic effusions and empyema. Clin Radiol 2000;55:542-7.

70. Ramirez P, Torres A. Should ultrasound be included in the initial assessment of respiratory patients? Lancet Respir Med 2014;2:599-600.

71. Sanyal S, Smith PR, Saha AC, Gupta S, Berkowitz L, Homel P. Initial microbiologic studies did not affect outcome in adults hospitalized with community-acquired pneumonia. Am J Respir Crit Care Med 1999;160:346-8.

72. Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet 1987;1:671-4.

73. Menéndez R, Córdoba J, de La Cuadra P, Cremades MJ, López-Hontagas JL, Salavert M, Gobernado M. Value of the polymerase chain reaction assay in noninvasive respiratory samples for diagnosis of community-acquired pneumonia. Am J Respir Crit Care Med 1999;159:1868-73.

74. Waterer GW, Wunderink RG. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. Respir Med 2001;95:78-82.

75. Campbell SG, Marrie TJ, Anstey R, Dickinson G, Ack-

190   Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

royd-Stolarz S. The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia: a prospective observational study. Chest 2003;123:1142-50.

76. Jefferson H, Dalton HP, Escobar MR, Allison MJ. Transportation delay and the microbiological quality of clinical specimens. Am J Clin Pathol 1975;64:689-93.

77. Kim S, Sung H, Kim DJ, Kim MN. Clinical relevance of positive NOW(TM) legionella urinary antigen test in a tertiary-care hospital in Korea. Korean J Lab Med 2006;26:93-7.

78. Rosón B, Fernández-Sabé N, Carratalà J, Verdaguer R, Dorca J, Manresa F, Gudiol F. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis 2004;38:222-6.

79. Yzerman EP, den Boer JW, Lettinga KD, Schellekens J, Dankert J, Peeters M. Sensitivity of three urinary antigen tests associated with clinical severity in a large outbreak of Legionnaires' disease in The Netherlands. J Clin Microbiol 2002;40:3232-6.

80. Arancibia F, Ewig S, Martinez JA, Ruiz M, Bauer T, Marcos MA, Mensa J, Torres A. Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. Am J Respir Crit Care Med 2000;162:154-60.

81. van der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Jansen HM, Boersma WG. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2005;24:241-9.

82. Domínguez J, Galí N, Blanco S, Pedroso P, Prat C, Matas L, Ausina V. Detection of *Streptococcus pneumoniae* antigen by a rapid immunochromatographic assay in urine samples. Chest 2001;119:243-9.

83. Gutiérrez F, Masiá M, Rodríguez JC, Ayelo A, Soldán B, Cebrián L, Mirete C, Royo G, Hidalgo AM. Evaluation of the immunochromatographic Binax NOW assay for detection of *Streptococcus pneumoniae* urinary antigen in a prospective study of community-acquired pneumonia in Spain. Clin Infect Dis 2003;36:286-92.

84. Murdoch DR, Laing RT, Mills GD, Karalus NC, Town GI, Mirrett S, Reller LB. Evaluation of a rapid immunochromatographic test for detection of *Streptococcus pneumoniae* antigen in urine samples from adults with community-acquired pneumonia. J Clin Microbiol 2001;39:3495-8.

85. Murdoch DR, Laing RT, Cook JM. The NOW S. pneumoniae urinary antigen test positivity rate 6 weeks after pneumonia onset and among patients with COPD. Clin Infect Dis 2003;37:153-4.

86. Navarro D, García-Maset L, Gimeno C, Escribano A, García-de-Lomas J; Spanish Pneumococcal Infection Study Network. Performance of the Binax NOW *Streptococcus pneumoniae* urinary antigen assay for diagnosis of pneumonia in children with underlying pulmonary diseases in the absence of acute pneumococcal infection. J Clin Microbiol 2004;42:4853-5.

87. Ortega L, Sierra M, Domínguez J, Martínez J, Matas L, Bastart F, Galí N, Ausina V. Utility of a pneumonia severity index in the optimization of the diagnostic and therapeutic effort for community-acquired pneumonia. Scand J Infect Dis 2005;37:657-63.

88. Smith MD, Derrington P, Evans R, Creek M, Morris R, Dance DA, Cartwright K. Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW *Streptococcus pneumoniae* urinary antigen test: a prospective, controlled clinical evaluation. J Clin Microbiol 2003;41:2810-3.

89. Porcel JM, Ruiz-González A, Falguera M, Nogués A, Galindo C, Carratalá J, Esquerda A. Contribution of a pleural antigen assay (Binax NOW) to the diagnosis of pneumococcal pneumonia. Chest 2007;131:1442-7.

90. Oka H, Ueda A, Watanuki Y, Tsukiji J, Kuroda H, Akashi S, Hirai Y, Fuyuki T, Kaneko T, Ishigatsubo Y. The efficacy of high-dose penicillin for community-acquired pneumonia diagnosed by pneumococcal urine antigen test. J Infect Chemother 2009;15:108-12.

91. Birtles RJ, Harrison TG, Samuel D, Taylor AG. Evaluation of urinary antigen ELISA for diagnosing Legionella pneumophila serogroup 1 infection. J Clin Pathol 1990;43:685-90.

92. Helbig JH, Uldum SA, Lück PC, Harrison TG. Detection of *Legionella pneumophila* antigen in urine samples by the BinaxNOW immunochromatographic assay and comparison with both Binax *Legionella* urinary enzyme immunoassay (EIA) and Biotest *Legionella* urin antigen EIA. J Med Microbiol 2001;50:509-16.

93. Alvarez J, Domínguez A, Sabrià M, Ruiz L, Torner N, Cayla J, Barrabeig I, Sala MR, Godoy P, Camps N, Minguell S. Impact of the *Legionella* urinary antigen test on epidemiological trends in community outbreaks of legionellosis in Catalonia, Spain, 1990-2004. Int J Infect Dis 2009;13:e365-70.

94. Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, Saikku P. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 2001;56:296-301.

95. Lee JS, Kritchevsky SB, Harris TB, Tylavsky F, Rubin SM, Newman AB. Short-term weight changes in community-dwelling older adults: the health, aging, and body composition weight change substudy. Am J Clin Nutr 2005;82:644-50.

96. Afshar N, Tabas J, Afshar K, Silbergleit R. Blood cultures for community-acquired pneumonia: are they worthy of two quality measures? A systematic review. J Hosp Med 2009;4:112-23.

97. Metersky ML, Ma A, Bratzler DW, Houck PM. Predicting bacteremia in patients with community-acquired pneumonia. Am J Respir Crit Care Med 2004;169:342-7.

98. Labarere J, Stone RA, Obrosky DS, Yealy DM, Meehan TP, Fine JM, Graff LG, Fine MJ. Comparison of outcomes for low-risk outpatients and inpatients with pneumonia: a propensity-adjusted analysis. Chest 2007;131:480-8.

99. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Olsson CG, Turpie AG; MEDENOX Study. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med 2004;164:963-8.

100. Minogue MF, Coley CM, Fine MJ, Marrie TJ, Kapoor WN, Singer DE. Patients hospitalized after initial outpatient treatment for community-acquired pneumonia. Ann Emerg Med 1998;31:376-80.

101. Neill AM, Martin IR, Weir R, Anderson R, Chereshsky A, Epton MJ, Jackson R, Schousboe M, Frampton C, Hutton S, Chambers ST, Town GI. Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. Thorax 1996;51:1010-6.

102. McMahon LF Jr, Wolfe RA, Tedeschi PJ. Variation in hospital admissions among small areas. A comparison of Maine and Michigan. Med Care 1989;27:623-31.

103. Labarere J, Stone RA, Scott Obrosky D, Yealy DM, Meehan TP, Auble TE, Fine JM, Graff LG, Fine MJ. Factors associated with the hospitalization of low-risk patients with community-acquired pneumonia in a cluster-randomized trial. J Gen Intern Med 2006;21:745-52.

104. Song JH, Jung KS, Kang MW, Kim DJ, Pai H, Suh GY, Shim TS, Ahn JH, Ahn CM, Woo JH, Lee NY, Lee DG, Lee MS, Lee SM, Lee YS, Lee H, Chung DR; A Joint Committee for CAP Treatment Guideline. Treatment guidelines for community-acquired pneumonia in Korea: An evidence-based approach to appropriate antimicrobial therapy. Tuberc Respir Dis 2009;67:281-301.

105. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243-50.

106. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58:377-82.

107. Aujesky D, Auble TE, Yealy DM, Stone RA, Obrosky DS, Meehan TP, Graff LG, Fine JM, Fine MJ. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. Am J Med 2005; 118:384-92.

108. Bauer TT, Ewig S, Marre R, Suttorp N, Welte T; CAPNETZ Study Group. CRB-65 predicts death from community-acquired pneumonia. J Intern Med 2006;260:93-101.

109. Capelastegui A, España PP, Quintana JM, Areitio I, Gorordo I, Egurrola M, Bilbao A. Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 2006;27:151-7.

110. España PP, Capelastegui A, Gorordo I, Esteban C, Oribe M, Ortega M, Bilbao A, Quintana JM. Development and validation of a clinical prediction rule for severe community-acquired pneumonia. Am J Respir Crit Care Med 2006;174:1249-56.

111. Barlow G, Nathwani D, Davey P. The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia. Thorax 2007;62:253-9.

112. Bont JE, Hak E, Hoes AW, Schipper M, Schellevis FG, Verheij TJ. A prediction rule for elderly primary-care patients with lower respiratory tract infections. Eur Respir J 2007;29:969-75.

113. Man SY, Lee N, Ip M, Antonio GE, Chau SS, Mak P, Graham CA, Zhang M, Lui G, Chan PK, Ahuja AT, Hui DS, Sung JJ, Rainer TH. Prospective comparison of three predictive rules for assessing severity of community-acquired pneumonia in Hong Kong. Thorax 2007;62:348-53.

114. Yealy DM, Auble TE, Stone RA, Lave JR, Meehan TP, Graff LG, Fine JM, Obrosky DS, Mor MK, Whittle J, Fine MJ. Effect of increasing the intensity of implementing pneumo-

nia guidelines: a randomized, controlled trial. Ann Intern Med 2005;143:881-94.

115. Atlas SJ, Benzer TI, Borowsky LH, Chang Y, Burnham DC, Metlay JP, Halm EA, Singer DE. Safely increasing the proportion of patients with community-acquired pneumonia treated as outpatients: an interventional trial. Arch Intern Med 1998;158:1350-6.

116. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL study investigators. Community-acquired pneumonia intervention trial assessing levofloxacin. JAMA 2000;283:749-55.

117. Suchyta MR, Dean NC, Narus S, Hadlock CJ. Effects of a practice guideline for community-acquired pneumonia in an outpatient setting. Am J Med 2001;110:306-9.

118. España PP, Capelastegui A, Quintana JM, Soto A, Gorordo I, García-Urbaneja M, Bilbao A. A prediction rule to identify allocation of inpatient care in community-acquired pneumonia. Eur Respir J 2003;21:695-701.

119. Ananda-Rajah MR, Charles PG, Melvani S, Burrell LL, Johnson PD, Grayson ML. Comparing the pneumonia severity index with CURB-65 in patients admitted with community acquired pneumonia. Scand J Infect Dis 2008;40:293-300.

120. Abisheganaden J, Ding YY, Chong WF, Heng BH, Lim TK. Predicting mortality among older adults hospitalized for community-acquired pneumonia: an enhanced confusion, urea, respiratory rate and blood pressure score compared with pneumonia severity index. Respirology 2012;17:969-75.

121. Kim HI, Kim SW, Chang HH, Cha SI, Lee JH, Ki HK, Cheong HS, Yoo KH, Ryu SY, Kwon KT, Lee BK, Choo EJ, Kim DJ, Kang CI, Chung DR, Peck KR, Song JH, Suh GY, Shim TS, Kim YK, Kim HY, Moon CS, Lee HK, Park SY, Oh JY, Jung SI, Park KH, Yun NR, Yoon SH, Sohn KM, Kim YS, Jung KS. Mortality of community-acquired pneumonia in Korea: assessed with the pneumonia severity index and the CURB-65 score. J Korean Med Sci 2013;28:1276-82.

122. Lee JC, Hwang HJ, Park YH, Joe JH, Chung JH, Kim SH. Comparison of severity predictive rules for hospitalised nursing home-acquired pneumonia in Korea: a retrospective observational study. Prim Care Respir J 2013;22:149-54.

123. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, Dean N, File T, Fine MJ, Gross PA, Martinez F, Marrie TJ, Plouffe JF, Ramirez J, Sarosi GA, Torres A, Wilson R, Yu VL; American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730-54.

124. Chalmers JD, Taylor JK, Mandal P, Choudhury G, Singanayagam A, Akram AR, Hill AT. Validation of the Infectious Diseases Society of America/American Thoratic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. Clin Infect Dis 2011;53:503-11.

125. Marti C, Garin N, Grosgurin O, Poncet A, Combescure C, Carballo S, Perrier A. Prediction of severe community-acquired pneumonia: a systematic review and meta-analysis. Crit Care 2012;16:R141.

126. Salih W, Schembri S, Chalmers JD. Simplification of the IDSA/ATS criteria for severe CAP using meta-analysis and observational data. Eur Respir J 2014;43:842-51.

127. Charles PG, Wolfe R, Whitby M, Fine MJ, Fuller AJ, Stirling R, Wright AA, Ramirez JA, Christiansen KJ, Waterer GW, Pierce RJ, Armstrong JG, Korman TM, Holmes P, Obrosky DS, Peyrani P, Johnson B, Hooy M; Australian Community-Acquired Pneumonia Study Collaboration, Grayson ML. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis 2008;47:375-84.

128. Yandiola PPE, Capelastegui A, Quintana J, Diez R, Gorordo I, Bilbao A, Zalacain R, Menendez R, Torres A. Prospective comparison of severity scores for predicting clinically relevant outcomes for patients hospitalized with community-acquired pneumonia. Chest 2009;135:1572-9.

129. Arnold FW, Summersgill JT, Lajoie AS, Peyrani P, Marrie TJ, Rossi P, Blasi F, Fernandez P, File TM Jr, Rello J, Menendez R, Marzoratti L, Luna CM, Ramirez JA; Community-Acquired Pneumonia Organization (CAPO) Investigators. A worldwide perspective of atypical pathogens in community-acquired pneumonia. Am J Respir Crit Care Med 2007;175:1086-93.

130. Mills GD, Oehley MR, Arrol B. Effectiveness of beta lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. BMJ 2005;330:456.

131. Eliakim-Raz N, Robenshtok E, Shefet D, Gafter-Gvili A,

Vidal L, Paul M, Leibovici L. Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. Cochrane Database Syst Rev 2012;(9):CD004418.

132. Postma DF, van Werkhoven CH, van Elden LJ, Thijsen SF, Hoepelman AI, Kluytmans JA, Boersma WG, Compaijen CJ, van der Wall E, Prins JM, Oosterheert JJ, Bonten MJ; CAP-START Study Group. Antibiotic treatment strategies for community-acquired pneumonia in adults. N Engl J Med 2015;372:1312-23.

133. Lee MY, Ko KS, Oh WS, Park S, Lee JY, Baek JY, Suh JY, Peck KR, Lee NY, Song JH. In vitro activity of cefditoren: antimicrobial efficacy against major respiratory pathogens from Asian countries. Int J Antimicrob Agents 2006;28:14-8.

134. Yu VL, Chiou CC, Feldman C, Ortqvist A, Rello J, Morris AJ, Baddour LM, Luna CM, Snydman DR, Ip M, Ko WC, Chedid MB, Andremont A, Klugman KP; International Pneumococcal Study Group. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. Clin Infect Dis 2003;37:230-7.

135. Noreddin AM, Marras TK, Sanders K, Chan CK, Hoban DJ, Zhanel GG. Pharmacodynamic target attainment analysis against *Streptococcus pneumoniae* using levofloxacin 500 mg, 750 mg and 1000 mg once daily in plasma (P) and epithelial lining fluid (ELF) of hospitalized patients with community acquired pneumonia (CAP). Int J Antimicrob Agents 2004;24:479-84.

136. File TM Jr, Milkovich G, Tennenberg AM, Xiang JX, Khashab MM, Zadeikis N. Clinical implications of 750 mg, 5-day levofloxacin for the treatment of community-acquired pneumonia. Curr Med Res Opin 2004;20:1473-81.

137. File TM Jr, Mandell LA, Tillotson G, Kostov K, Georgiev O. Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. J Antimicrob Chemother 2007;60:112-20.

138. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med 1999;159:2562-72.

139. Houck PM, MacLehose RF, Niederman MS, Lowery JK. Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 western states: 1993, 1995, and 1997. Chest 2001;119:1420-6.

140. Dudas V, Hopefl A, Jacobs R, Guqlielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: a survey of nonteaching US community hospitals. Ann Pharmacother 2000;34:446-52.

141. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest 2003;123:1503-11.

142. Garin N, Genné D, Carballo S, Chuard C, Eich G, Hugli O, Lamy O, Nendaz M, Petignat PA, Perneger T, Rutschmann O, Seravalli L, Harbarth S, Perrier A. β-lactam monotherapy vs β-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. JAMA Intern Med 2014;174:1894-901.

143. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Read R, Verheij TJ; Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections--full version. Clin Microbiol Infect 2011;17 (Suppl 6):E1-59.

144. Paul M, Nielsen AD, Gafter-Gvili A, Tacconelli E, Andreassen S, Almanasreh N, Goldberg E, Cauda R, Frank U, Leibovici L. The need for macrolides in hospitalised community-acquired pneumonia: propensity analysis. Eur Respir J 2007;30:525-31.

145. Ray WA, Murray KT, Hall K, Arboqast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881-90.

146. Trac MH, McArthur E, Jandoc R, Dixon SN, Nash DM, Hackam DG, Garg AX. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. CMAJ 2016; 188:E120-9.

147. Chang KC, Leung CC, Yew WW, Lau TY, Leung WM, Tam CM, Lam HC, Tse PS, Wong MY, Lee SN, Wat KI, Ma YH. Newer fluoroquinolones for treating respiratory infection: do they mask tuberculosis? Eur Respir J 2010;35:606-13.

148. Chen TC, Lu PL, Lin CY, Lin WR, Chen YH. Fluoroquinolones are associated with delayed treatment and resistance in tuberculosis: a systematic review and meta-analysis. Int J Infect Dis 2011;15:e211-6.

149. Wang JY, Hsueh PR, Jan IS, Lee LN, Liaw YS, Yang PC, Luh KT. Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas. Thorax 2006;61:903-8.

150. Torres A, Garau J, Arvis P, Carlet J, Choudhri S, Kureishi A, Le Berre MA, Lode H, Winter J, Read RC; MOTIV (MOxifloxacin Treatment IV) Study Group. Moxifloxacin monotherapy is effective in hospitalized patients with community-acquired pneumonia: the MOTIV study--a randomized clinical trial. Clin Infect Dis 2008;46:1499-509.

151. Bhavnani SM, Ambrose PG. Cost-effectiveness of oral gemifloxacin versus intravenous ceftriaxone followed by oral cefuroxime with/without a macrolide for the treatment of hospitalized patients with community-acquired pneumonia. Diagn Microbiol Infect Dis 2008;60:59-64.

152. Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Verheij TJ; European Respiratory Society; European Society of Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections. Eur respir J 2005;26:1138-80.

153. Rizzato G, Montemurro L, Fraioli P, Montanari G, Fanti D, Pozzoli R, Magliano E. Efficacy of a three day course of azithromycin in moderately severe community-acquired pneumonia. Eur respir J 1995;8:398-402.

154. Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, Wiesinger BA, Xiang JX, Zadeikis N, Kahn JB. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 2003;37:752-60.

155. Schönwald S, Skerk V, Petricevic I, Car V, Majerus-Misic L, Gunjaca M. Comparison of three-day and five-day courses of azithromycin in the treatment of atypical pneumonia. Eur J Clin Microbiol Infect Dis 1991;10:877-80.

156. Ramirez JA. Switch therapy in community-acquired pneumonia. Diagn Microbiol Infect Dis 1995;22:219-23.

157. Ramirez JA, Vargas S, Ritter GW, Brier ME, Wright A, Smith S, Newman D, Burke J, Mushtaq M, Huang A. Early switch from intravenous to oral antibiotics and early hospital discharge: a prospective observational study of 200 consecutive patients with community-acquired pneumonia. Arch Intern Med 1999;159:2449-54.

158. Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired *Streptococcus pneumoniae* pneumonia. Arch Intern Med 2001;161:848-50.

159. Castro-Guardiola A, Viejo-Rodríguez AL, Soler-Simon S, Armengou-Arxé A, Bisbe-Company V, Peñarroja-Matutano G, Bisbe-Company J, García-Bragado F. Efficacy and safety of oral and early-switch therapy for communi-ty-acquired pneumonia: a randomized controlled trial. Am J Med 2001;111:367-74.

160. Nathan RV, Rhew DC, Murray C, Bratzler DW, Houck PM, Weingarten SR. In-hospital observation after antibiotic switch in pneumonia: a national evaluation. Am J Med 2006;119:512.e1-7.

161. Rhew DC, Riedinger MS, Sandhu M, Bowers C, Greengold N, Weingarten SR. A prospective, multicenter study of a pneumonia practice guideline. Chest 1998;114:115-9.

162. Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. Arch Intern Medicine 2002;162:1278-84.

163. Capelastegui A, España PP, Bilbao A, Martinez-Vazquez M, Gorordo I, Oribe M, Urrutia I, Quintana JM. Pneumonia: criteria for patient instability on hospital discharge. Chest 2008;134:595-600.

164. Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, Singer DE. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA 1998;279:1452-7.

165. O'Driscoll BR, Howard LS, Davison AG. BTS guideline for emergency oxygen use in adult patients. Thorax 2008;63 (Suppl 6):vi1-68.

166. Siempos II, Vardakas KZ, Kopterides P, Falagas ME. Adjunctive therapies for community-acquired pneumonia: a systematic review. J Antimicrob Chemother 2008;62:661-8.

167. Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmüller A, Juillard-Delsart D, Decousus H. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. Thromb Haemost 2000;83:14-9.

168. Dean NC, Silver MP, Bateman KA, James B, Hadlock CJ, Hale D. Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. Am J Med 2001;110:451-7.

169. Mundy LM, Leet TL, Darst K, Schnitzler MA, Dunagan WC. Early mobilization of patients hospitalized with community-acquired pneumonia. Chest 2003;124:883-9.

170. File TM. Community-acquired pneumonia. Lancet 2003;362:1991-2001.

171. Torres A, Serra-Batlles J, Ferrer A, Jiménez P, Celis R, Cobo E, Rodriguez-Roisin R. Severe community-acquired pneumonia. Epidemiology and prognostic factors.

Am Rev Respir Dis 1991;144:312-8.

172. Briones ML, Blanquer J, Ferrando D, Blasco ML, Gimeno C, Marín J. Assessment of analysis of urinary pneumococcal antigen by immunochromatography for etiologic diagnosis of community-acquired pneumonia in adults. Clin Vaccine Immunol 2006;13:1092-7.

173. Leroy O, Saux P, Bédos JP, Caulin E. Comparison of levofloxacin and cefotaxime combined with ofloxacin for ICU patients with community-acquired pneumonia who do not require vasopressors. Chest 2005;128:172-83.

174. Raz-Pasteur A, Shasha D, Paul M. Fluoroquinolones or macrolides alone versus combined with beta-lactams for adults with community-acquired pneumonia: systematic review and meta-analysis. Int J Antimicrob Agents 2015;46:242-8.

175. Lodise TP, Kwa A, Cosler L, Gupta R, Smith RP. Comparison of beta-lactam and macrolide combination therapy versus fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. Antimicrob Agents Chemother 2007;51:3977-82.

176. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortqvist A, Rello J, Morris AJ, Luna CM, Snydman DR, Ko WC, Chedid MB, Hui DS, Andremont A, Chiou CC; International Pneumococcal Study Group. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004;170:440-4.

177. Martínez JA, Horcajada JP, Almela M, Marco F, Soriano A, García E, Marco MA, Torres A, Mensa J. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003;36:389-95.

178. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001;161:1837-42.

179. Weiss K, Low DE, Cortes L, Beaupre A, Gauthier R, Gregoire P, Legare M, Nepveu F, Thibert D, Tremblay C, Tremblay J. Clinical characteristics at initial presentation and impact of dual therapy on the outcome of bacteremic *Streptococcus pneumoniae* pneumonia in adults. Can Respir J 2004;11:589-93.

180. Arancibia F, Bauer TT, Ewig S, Mensa J, Gonzalez J, Niederman MS, Torres A. Community-acquired pneumonia due to gram-negative bacteria and Pseudomonas aeruginosa: incidence, risk, and prognosis. Arch Intern Med 2002;162:1849-58.

181. Kang CI, Song JH, Oh WS, Ko KS, Chung DR, Peck KR; Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study Group. Clinical outcomes and risk factors of community-acquired pneumonia caused by gram-negative bacilli. Eur J Clin Microbiol Infect Dis 2008;27:657-61.

182. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462-74.

183. Murray RJ, Robinson JO, White JN, Hughes F, Coombs GW, Pearson JC, Tan HL, Chidlow G, Williams S, Christiansen KJ, Smith DW. Community-acquired pneumonia due to pandemic A(H1N1)2009 influenza virus and methicillin resistant *Staphylococcus aureus* co-infection. PLoS One 2010;5:e8705.

184. Bernardo K, Pakulat N, Fleer S, Schnaith A, Utermöhlen O, Krut O, Müller S, Krönke M. Subinhibitory concentrations of linezolid reduce *Staphylococcus aureus* virulence factor expression. Antimicrob Agents Chemother 2004;48:546-55.

185. Micek ST, Dunne M, Kollef MH. Pleuropulmonary complications of Panton-Valentine leukocidin-positive community-acquired methicillin-resistant *Staphylococcus aureus*: importance of treatment with antimicrobials inhibiting exotoxin production. Chest 2005;128:2732-8.

186. Carpenter CF, Chambers HF. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. Clin Infect Dis 2004;38:994-1000.

187. Falagas ME, Karageorgopoulos DE, Dimopoulos G. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of tigecycline. Curr Drug Metab 2009;10:13-21.

188. Ruiz M, Ewig S, Torres A, Arancibia F, Marco F, Mensa J, Sanchez M, Martinez JA. Severe community-acquired pneumonia. Risk factors and follow-up epidemiology. Am J Respir Crit Care Med 1999;160:923-9.

189. Snijders D, Daniels JM, de Graaff CS, van der Werf TS, Boersma WG. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med 2010;181:975-82.

190. Meijvis SC, Hardeman H, Remmelts HH, Heijligenberg R, Rijkers GT, van Velzen-Blad H, Voorn GP, van de Garde EM, Endeman H, Grutters JC, Bos WJ, Biesma DH. Dexamethasone and length of hospital stay in patients with

196   Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet 2011;377:2023-30.

191. Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, Gabarrús A, Sellarés J, Restrepo MI, Anzueto A, Niederman MS, Agustí C. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA 2015;313:677-86.

192. Blum CA, Nigro N, Briel M, Schuetz P, Ullmer E, Suter-Widmer I, Winzeler B, Bingisser R, Elsaesser H, Drozdov D, Arici B, Urwyler SA, Refardt J, Tarr P, Wirz S, Thomann R, Baumgartner C, Duplain H, Burki D, Zimmerli W, Rodondi N, Mueller B, Christ-Crain M. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2015;385:1511-8.

193. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della Porta R, Giorgio C, Blasi F, Umberger R, Meduri GU. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 2005;171:242-8.

194. Marik P, Kraus P, Sribante J, Havlik I, Lipman J, Johnson DW. Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia. A randomized controlled study. Chest 1993;104:389-92.

195. Montón C, Ewig S, Torres A, El-Ebiary M, Filella X, Rañó A, Xaubet A. Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. Eur Respir J 1999;14:218-20.

196. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaud P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288:862-71.

197. Annane D, Sébille V, Bellissant E; Ger-Inf-05 Study G. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. Crit Care Med 2006;34:22-30.

198. Bruns AH, Oosterheert JJ, Prokop M, Lammers JW, Hak E, Hoepelman AI. Patterns of resolution of chest radiograph abnormalities in adults hospitalized with severe community-acquired pneumonia. Clin Infec Dis 2007;45:983-91.

199. Mittl RL Jr, Schwab RJ, Duchin JS, Goin JE, Albeida SM,

Miller WT. Radiographic resolution of community-acquired pneumonia. Am J Respir Crit Care Med 1994;149:630-5.

200. El Solh AA, Aquilina AT, Gunen H, Ramadan F. Radiographic resolution of community-acquired bacterial pneumonia in the elderly. J Am Geriatr Soc 2004;52:224-9.

201. Tang KL, Eurich DT, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Incidence, correlates, and chest radiographic yield of new lung cancer diagnosis in 3398 patients with pneumonia. Arch Intern Med 2011;171:1193-8.

202. Holmberg H, Kragsbjerg P. Association of pneumonia and lung cancer: the value of convalescent chest radiography and follow-up. Scand J Infect Dis 1993;25:93-100.

203. Menéndez R, Cavalcanti M, Reyes S, Mensa J, Martinez R, Marcos MA, Filella X, Niederman M, Torres A. Markers of treatment failure in hospitalised community acquired pneumonia. Thorax 2008;63:447-52.

204. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. Am J Med 2008;121:219-25.

205. Menéndez R, Martinez R, Reyes S, Mensa J, Polverino E, Filella X, Esquinas C, Martinez A, Ramirez P, Torres A. Stability in community-acquired pneumonia: one step forward with markers? Thorax 2009;64:987-92.

206. Coelho LM, Salluh JI, Soares M, Bozza FA, Verdeal JC, Castro-Faria-Neto HC, Lapa e Silva JR, Bozza PT, Póvoa P. Patterns of c-reactive protein RATIO response in severe community-acquired pneumonia: a cohort study. Crit Care 2012;16:R53.

207. Hohenthal U, Hurme S, Helenius H, Heiro M, Meurman O, Nikoskelainen J, Kotilainen P. Utility of C-reactive protein in assessing the disease severity and complications of community-acquired pneumonia. Clin Microbiol Infect 2009;15:1026-32.

208. Boussekey N, Leroy O, Alfandari S, Devos P, Georges H, Guery B. Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. Intensive Care Med 2006;32:469-72.

209. Lacoma A, Rodríguez N, Prat C, Ruiz-Manzano J, Andreo F, Ramírez A, Bas A, Pérez M, Ausina V, Domínguez J. Usefulness of consecutive biomarkers measurement in the management of community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2012;31:825-33.

210. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Bhatnagar N, Annane D, Rein-

hart K, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Lima SS, Maravić-Stojković V, Verduri A, Cao B, Shehabi Y, Beishuizen A, Jensen JS, Corti C, Van Oers JA, Falsey AR, de Jong E, Oliveira CF, Beghe B, Briel M, Mueller B. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev 2017:CD007498.

211. Schuetz P, Briel M, Mueller B. Clinical outcomes associated with procalcitonin algorithms to guide antibiotic therapy in respiratory tract infections. JAMA 2013;309:717-8.

212. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loef BG, Dormans T, van Melsen GC, Kluiters YC, Kemperman H, van den Elsen MJ, Schouten JA, Streefkerk JO, Krabbe HG, Kieft H, Kluge GH, van Dam VC, van Pelt J, Bormans L, Otten MB, Reidinga AC, Endeman H, Twisk JW, van de Garde EMW, de Smet AMGA, Kesecioglu J, Girbes AR, Nijsten MW, de Lange DW. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis 2016;16:819-27.

213. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy: an evaluation of current recommendations. JAMA 1993;270:1826-31.

214. Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, Adair RK, Clemens JD. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med 1991;325:1453-60.

215. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 2008;(1):CD000422.

216. Maruyama T, Taguchi O, Niederman MS, Morser J, Kobayashi H, Kobayashi T, D'Alessandro-Gabazza C, Nakayama S, Nishikubo K, Noguchi T, Takei Y, Gabazza EC. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. BMJ 2010;340:c1004.

217. Christenson B, Hedlund J, Lundbergh P, Ortqvist A. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. Eur Respir J 2004;23:363-8.

218. Vila-Córcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodríguez T, Llor C; EVAN Study Group. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis 2006;43:860-8.

219. Christenson B, Pauksen K, Sylvan SP. Effect of influenza and pneumococcal vaccines in elderly persons in years of low influenza activity. Virol J 2008;5:52.

220. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. Clin Infect Dis 2006;42:1093-101.

221. Mykietiuk A, Carratalà J, Domínguez A, Manzur A, Fernández-Sabé N, Dorca J, Tubau F, Manresa F, Gudiol F. Effect of prior pneumococcal vaccination on clinical outcome of hospitalized adults with community-acquired pneumococcal pneumonia. Eur J Clin Microbiol Infect Dis 2006;25:457-62.

222. Jackson LA, Neuzil KM, Yu O, Benson P, Barlow WE, Adams AL, Hanson CA, Mahoney LD, Shay DK, Thompson WW; Vaccine Safety Datalink. Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med 2003;348:1747-55.

223. Skull SA, Andrews RM, Byrnes GB, Kelly HA, Nolan TM, Brown GV, Campbell DA. Prevention of community-acquired pneumonia among a cohort of hospitalized elderly: benefit due to influenza and pneumococcal vaccination not demonstrated. Vaccine 2007;25:4631-40.

224. Jackson LA, Neuzil KM, Whitney CG, Starkovich P, Dunstan M, Yu O, Nelson JC, Feikin DR, Shay DK, Baggs J, Carste B, Nahm MH, Carlone G. Safety of varying dosages of 7-valent pneumococcal protein conjugate vaccine in seniors previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine 2005;23:3697-703.

225. Törling J, Hedlund J, Konradsen HB, Ortqvist A. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. Vaccine 2003;22:96-103.

226. Waites KB, Canupp KC, Chen YY, DeVivo MJ, Nahm MH. Revaccination of adults with spinal cord injury using the 23-valent pneumococcal polysaccharide vaccine. J Spinal Cord Med 2008;31:53-9.

227. Nuorti JP, Butler JC, Farley MM, Harrison LH, McGeer A, Kolczak MS, Breiman RF. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med 2000;342:681-9.

228. Almirall J, Bolíbar I, Serra-Prat M, Roig J, Hospital I, Carandell E, Agustí M, Ayuso P, Estela A, Torres A; Community-Acquired Pneumonia in Catalan Countries (PACAP) Study Group. New evidence of risk factors for communi-

198 Lee MS, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia

www.icjournal.org

ty-acquired pneumonia: a population-based study. Eur Respira J 2008;31:1274-84.

229. Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med 2000;160:3082-8.

230. Marston BJ, Lipman HB, Breiman RF. Surveillance for Legionnaires' disease: risk factors for morbidity and mortality. Arch Intern Med 1994;154:2417-22.

231. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. Thorax 2000;55:987-99.