Guideline Interpretation

Causes and management of initial treatment failure in patients with community-acquired pneumonia

Xuehua Chen

Department of Respiratory Diseases, Zhongshan Hospital Affiliated to Fudan University, Shanghai 200032, China

The initial treatment of community-acquired pneumonia (CAP) is empirical. About 6-24% of the hospitalized CAP patients fail to respond to the initial antibiotic therapy, and the percentage of seriously ill patients may rise to 31%.[1-4] The causes of initial treatment failure are extremely complex, since it may arise from either improper treatment or initial misdiagnosis. Feinsilver *et al*.[5] reported that for 15% of CAP patients, the diagnosis needed correcting, and for 8% of CAP patients, the differential diagnosis should be made by tracheoscopy. CAP treatment failure is not defined by the same standards, and the definition varies with observation points and evaluation indicators. The most widely-used concept is the nonresponding pneumonia, which was proposed earlier in 1991. In 1998, the CAP guideline of Infectious Diseases Society of America (ISDA) sorted out the causes and management of CAP treatment failure, and in 2001, the CAP guideline of American Thoracic Society (ATS) elaborated it further. The CAP guideline well-known in China is the adult CAP guideline jointly issued by ISDA and ATS in 2007, in which nonresponding pneumonia is well defined and expounded, the causes are fully analyzed, and the management is recommended.

DEFINITION AND CLASSIFICATION OF COMMUNITY-ACQUIRED PNEUMONIA TREATMENT FAILURE

Three factors determine the success of CAP treatment. (1) The characteristics of the host, such as, immunologic functions, nutrition, underlying health problems and age; (2) pathogenic characteristics, like, toxicity and invasive ability, sensitivity to antibacterial agents; (3) the characteristics of antibacterial agents, for example, the course of treatment and pharmacokinetic properties. The causative agents of CAP are complicated, but in general, targeted at bacterial pneumonia, the CAP treatment also includes the treatment of atypical pathogens like *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella*, but not that of specific pathogens, such as virus, fungi and parasites. The ultimate aim of CAP antibacterial treatment is the absorption and dissipation of the newly-presented lung inflammation. The course often lasts for more than 4 weeks, though it is shorter in the treatment with effective antibacterial agents. Therefore, in clinical research, the efficacy of the treatment is measured not by imaging, but by simpler standards, such as changes in clinical symptoms, physical signs, and laboratory examinations.

The CAP initial treatment outcome includes success and failure. Treatment success is usually expressed in terms of clinical improvement and stability. The standards of clinical stability in the CAP guideline in 2007 are as follows:

1. Body temperature ≤37.8°C;
2. heart rate ≤100 times/min;
3. respiratory rate ≤24 times/min;
4. systolic pressure ≥90 mmHg (1 mmHg = 0.133 kPa);
5. in breathing room air, arterial oxygen saturation ≥90% or oxygen partial pressure ≥7.98 kPa;
6. oral administration maintenance;
7. mental competence.

These are easily-operated evaluation indicators, but the frequently-used indicators in reexamination, such as leukocytes, C-reactive protein, procalcitonin and so on are not recommended. Compared with clinical stability, treatment failure includes nonresponding and deterioration. The average time for CAP stability is 3 days. The early failure refers to the following cases: death within 3 days, septic shock, severe cases that need mechanical ventilation in intensive care unit and progressive pneumonia in which pulmonary shadow occupies over 50% of lungs when the conditions worsen. The failure in advanced stage usually

Address for correspondence:
Dr. Xuehua Chen, Department of Respiratory Diseases, Zhongshan Hospital Affiliated to Fudan University, Shanghai 200032, China.
E-mail: chen.xuehua@zs-hospital.sh.cn

Access this article online	
Quick Response Code:	Website: www.caijournal.com
	DOI: 10.4103/2225-6482.147665

includes nonresponding pneumonia (the failure to achieve the above-mentioned indicators of clinical stability after 3-7 days of hospitalization), nonresolving pneumonia (the existence of lung infiltration shadows or nonimprovement or deterioration of the clinical conditions after 10 days' antibiotic therapy, or no significant absorption in lung shadows 12 weeks after the onset of pneumonia) and slowly resolving pneumonia (the absorption rate is <50% within 4 weeks). Figure 1 is a good illustration of the prognosis after CAP initial treatment.[6]

CAUSES OF COMMUNITY-ACQUIRED PNEUMONIA INITIAL TREATMENT

The causes of treatment failure are various at different stages since the time points and indicators of noneffective treatment are not the same. Table 1 is a summary of the causes by American CAP guideline in 2007.[3]

To put it simply, the causes of treatment failure can be classified into four types. The first type is the inadequate initial treatment mainly caused by the layered faults in initial treatment, which results in nontarget at pathogens or ignorance of the drug-resistant pathogens, such as drug-resistant *Streptococcus pneumoniae* (DRSP), drug-resistant *Pseudomonas aeruginosa*, enzyme-producing *Enterobacteriaceae* or methicillin-resistant *Staphylococcus aureus* (MRSA). The second type is the rare pathogen infections caused by *Mycobacterium tuberculosis*, fungi like *Cryptococcus* and *Aspergillus*, nocardiosis, *Pneumocystis carinii*, influenza virus, and hantavirus. The third type is the emergence of complications, like pyothorax, necrotizing pneumonia, or blood-borne dissemination. The fourth type is noninfectious diseases or parapneumonic diseases, like pulmonary embolism, tumor-induced obstructive pneumonia, lymphoma, cryptogenic organizing pneumonia, vasculitis, various interstitial lung diseases, allergic pneumonitis, drug-related lung diseases, eosinophilic pneumonia and so on.

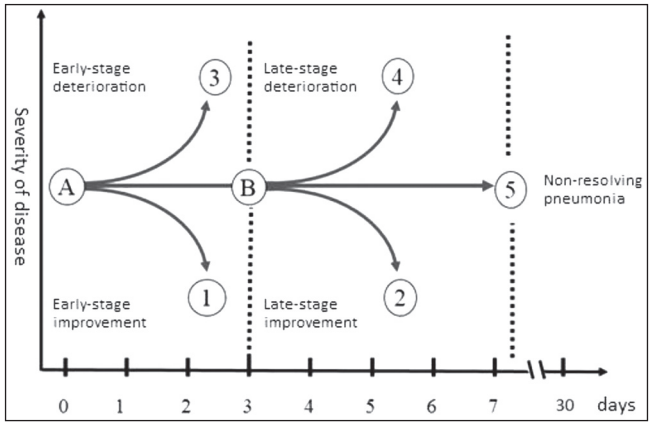

Figure 1: Clinical prognosis after CAP initial treatment. CAP: Community-acquired pneumonia

MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA TREATMENT FAILURE

In fact, for some patients, CAP treatment failure is not a failure in the real sense, but merely a misdiagnosis in the initial stage. The disease, similar to pneumonia, is treated with CAP therapy, so it is impossible to have an effect on antibacterial agents. Therefore, CAP treatment failure is a problem not only in the treatment but also in diagnose. During CAP initial treatment, the therapeutic effects should be observed daily. Diagnostic reevaluation should be conducted if there is no obvious improvement in clinical signs and symptoms [Figure 2]. During the reevaluation, the clinicians need examine every question in Table 2.

The questions in Table 2 boil down to the CAP diagnosis. If the treatment is effective, we have no doubt on the diagnosis; if not, we need to examine and modify the therapeutic plan, and observe the efficacy. The CAP treatment plays a diagnostic role. The CAP diagnosis can be confirmed when the treatment succeeds, indicated by the absorption of

Table 1: Types and etiology of the nonresponding pneumonia

No improvement
Early stage (treatment time <72 h)
Normal reaction
Delay
Drug-resistant microorganisms infections
Nontarget to pathogens
Poor drug susceptibility
Parapneumonic effusion or pulmonary abscess
Superinfection in hospital
Hospital-acquired pneumonia
Extrapulmonary infection
Noninfectious factors
Complications of pneumonia (e.g., organizing pneumonia)
Misdiagnosis: pulmonary embolism, cardiac insufficiency, vasculitis
Drug-induced fever
Deterioration or development
Early stage (treatment time <72 h)
Severe cases
Drug-resistant microorganisms
Nontarget to pathogens
Poor drug susceptibility
The spread of infection
Pulmonary abscess/parapneumonic effusion
Endocarditis, meningitis, arthritis
Inaccurate diagnosis
Pulmonary embolism, inhalation, ARDS
Vasculitis
Delay
Superinfection in hospital
Hospital-acquired pneumonia
Extrapulmonary infection
Acute exacerbation of complications
Concurrent noninfectious diseases
Pulmonary embolism
Myocardial infarction
Renal insufficiency

ARDS: Acute respiratory distress syndrome

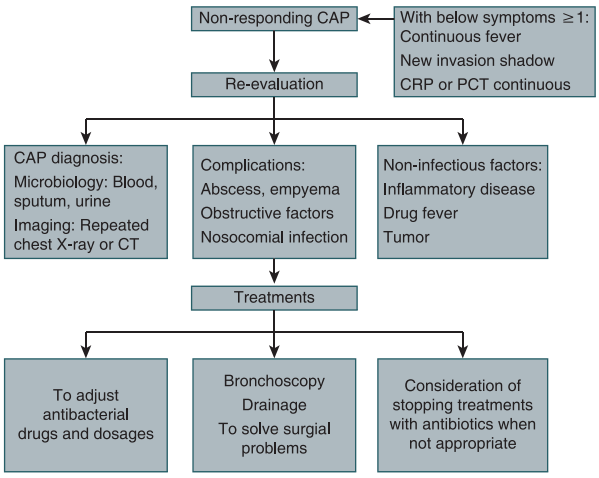

Figure 2: Management strategies for CAP treatment failure. CRP: C-reactive protein, PCT: Procalcitonin, CT: computed tomography, CAP: Community-acquired pneumonia

Table 2: Questions for CAP treatment failure

The confirmation of treatment failure
Is the time enough for observation? <72 h
Are some indicators improved? CRP and PCT are decreasing
The confirmation of medicine administration under the CAP guideline
Are *Streptococcus pneumoniae* and atypical pathogens targeted?
Is the drug-resistance of *Streptococcus pneumoniae* taken into account? And is the dosage proper?
Is medicine taken in layers according to the guideline? Are the modified factors taken into account?
The existence of immunosuppression
HIV infections, tumor chemotherapy, organ transplantation
Are they specific pathogens?
Virus, tuberculosis, fungi, PCP
Are there any mechanical factors?
Is there obstructive pneumonia, like tumor or an obstruction and oppression of foreign bodies?
Is drainage or focal infection in other distant locations neglected?
Pulmonary abscess, brain abscess, endocarditis, osteomyelitis, and hepatapostema
Are there any noninfectious causes similar to pneumonia?

CAP: Community-acquired pneumonia, CRP: C-reactive protein, PCT: procalcitonin, CT: computed tomography

inflammation. Therefore, the initial antimicrobial therapy is of vital importance. Correct initial treatment can avoid changing the therapy and reevaluating the therapeutic effects. For patients with specific pathogens or parapneumonic diseases, it can shorten the time for revising diagnosis.

Then what is adequate initial treatment for CAP? Foreign researches on the etiology of CAP suggest that the most common CAP pathogens are *S. pneumoniae* and atypical pathogens including *M. pneumoniae*, *C. pneumoniae*, and *Legionella pneumophilia*.[3] The CAP epidemiological survey led by Liu *et al*.[7] in China reveal that *M. pneumoniae* showed the highest positivity rate, accounting for 20.7%, followed by *S. pneumoniae* (10.3%), *Haemophilus influenza* (9.2%), *C. pneumoniae* (6.6%), *Klebsiella pneumoniae* (6.1%), and *L. pneumophilia* (5.1%). Another CAP epidemiological survey led by Tao *et al*.[8] show that *S. pneumoniae* was the No. 1 pathogen (32.6%), followed by *H. influenza* (22.7%), and in serological tests, the positivity rate of *M. pneumoniae* was 38.9%, and that of the *C. pneumoniae* was 11.4%. Both surveys reveal the coexistence of *S. pneumoniae* and atypical pathogens. Hence, in CAP initial treatment, the major targeted pathogens in the guideline at home and abroad is *S. pneumoniae*, and atypical pathogens are also included in North American guidelines. *Enterobacteriaceae* or *Pseudomonas* is targeted only for people who have specific risk factors, especially those who are constantly exposed to medical institutions or patients with chronic pulmonary diseases and need antibacterial agents repeatedly. Specific pathogens like *M. tuberculosis*, *Cryptococcus* and pneumocystis need not be targeted by CAP initial treatment in normal hosts.

In recent two decades, the resistance of *S. pneumoniae* to penicillin and erythromycin is on rise year by year. The resistance analysis of respiratory pathogens in Asian community, led by Wang *et al*. in the years 2009-2010,[9] shows that the resistance rate of *S. pneumoniae* to penicillin in mainland China was 24.5%, medium 27.1%, and minimal inhibitory concentration 90 (MIC90) 4 mg/L; the resistance rate of *S. pneumoniae* to ceftriaxoneis 10.2%, medium was 5%, and MIC90 was 4 mg/L; macrolides displays high levels of drug-resistance, and the resistance rate of azithromycin was up to 88.1% with 32 mg/L in MIC50 and MIC90, and that of the clarithromycin was 87.4%. Other studies also show that macrolides is a highly resistant erm-mediated drug in mainland China, and respiratory fluoroquinolone remains sensitive basically, among which moxifloxacin has the highest sensitivity (99.1%) with MIC90 0.125 mg/L, and the drug-resistance rate of levofloxacin is 2.6% with MIC90 1 mg/L. Multivariate analysis shows that clinically DRSP infections mostly affects the elderly (>65), people who have taken β-lactams in the past 3 months, people who have a habit of excessive drinking or a variety of medical complications, or receive immunosuppressive therapy, or children in kindergarten. Therefore, the use of macrolides in treating *S. pneumoniae* is being challenged. In 2007, the American CAP guideline had no recommendations on the single use of macrolides in the area where high-level (MIC ≥16 mg/L) macrolides-resistant pneumococci is highly prevalent (≥25%). The surveys in large and medium-sized cities of China are consistent with it.

With the adjustment of breakpoints for nonmeningitis *S. pneumoniae* by the Clinical and Laboratory Standards Institute, the proportion of penicillin-resistant strains of pneumococci has declined. Theoretically, penicillin can be used as a goal-directed therapy of pneumococci, but the half-life of penicillin is <1 h, and the effective PK/PD parameter (over 40% T > MIC) needs 4 h administration at intervals, so the clinical application is limited.

In 1999, Gleason *et al.*[10] discovered three initial CAP therapeutic plans (the combination of second-generation cephalosporins and macrolides, the combination of third-generation cephalosporins of nonresistant *Pseudomonas* and macrolides and the single use of respiratory fluoroquinolones), which can reduce the mortality of CAP elderly patients within 30 days' hospitalization. Therefore, in North America, two basic therapeutic plans, the single use of fluoroquinolones and the combination of β-lactams and macrolides were established. However, as for the choice of β-lactams, not all the third-generation cephalosporins, like cefoperazone and ceftazidime, is appropriate, and ceftriaxone and cefotaxime, highly active to *S. pneumonia*, should be chosen.

There are many controversies on the advantages and disadvantages of two therapeutic plans: The espiratory fluoroquinolones and the combination of β-lactams and macrolides. The respiratory fluoroquinolones have many merits in theory, for example, sensitivity to DRSP, no resistance by *Mycoplasma*, once in daily drug use and relevant sequential drugs. Yet, in 2007, American CAP guideline recommended the two therapeutic plans and suggested the use of a group of drugs without exposure for almost 3 months to decrease the risk of drug-resistance. However, Menéndez *et al.*[4] found that the initial treatment with fluoroquinolones was an independent correlative factor in the low failure rate of CAP treatment recently, Ott *et al.*[11] also discovered that patients who have received moxifloxacin had lower treatment failure rate (10.9% *vs.* 20.6%, $P < 0.001$); compared with the single use of β-lactams, moxifloxacin was an independent factor in reducing treatment failure, shown by multivariate analysis (odds ratio [OR]: 0.43, 95% confidence interval [CI]: 0.27-0.68), while the group treated by the combination of β-lactams and macrolides showed no such difference (OR: 0.68, 95% CI: 0.38-1.21).

In empiric CAP therapy, improper selection of initial treatment may lead to the expansion of infection toward periphery or distant areas, for example, pulmonary abscess and pyothorax, or result in delayed correctness of diagnosis, which will prolong the duration of hospital stays and increase mortality. For patients without underlying health problems and correction factors, respiratory fluoroquinolone drugs like moxifloxacin display apparent advantages in CAP initial treatment; meanwhile, they target at the DRSP and atypical pathogens so as to reduce the treatment failure rate and shorten the time to achieve clinical stability, and the duration of hospital stays by early sequential therapy. A wrong clinical tendency is to equate severe pneumonia with the infections of drug-resistance bacteria or specific pathogens, which leads to the blind targeting at multidrug-resistant Gram-negative bacilli, MRSA and *Aspergillus* when the CAP treatment is ineffective. In fact, the basic pathogens needed to be targeted in severe CAP are still *S. pneumoniae* and *L. pneumophila*. For severe CAP patients without immune impairments and correction factors, the probability of drug-resistant Gram-negative bacilli and specific pathogens is low, and moxifloxacin is still a good choice. Influenza virus infections should be considered during flu season.

CONCLUSION

Community-acquired pneumonia initial treatment failure is caused by incorrect initial diagnosis as well as the inappropriate therapies. The appropriate initial therapy contributes to the early confirmation of the diagnosis. The effective treatment is based on a full understanding of the basic pathogens and drug-resistance instead of the usage of new superspectrum drugs; thus, blind upgrading of antibacterial agents and excessive drug combinations can be avoided, and the abuse of antibacterial agents can be limited.

REFERENCES

1. Arancibia F, Ewig S, Martinez JA, Ruiz M, Bauer T, Marcos MA, *et al.* Antimicrobial treatment failures in patients with community-acquired pneumonia: Causes and prognostic implications. Am J Respir Crit Care Med 2000;162:154-60.
2. Aliberti S, Amir A, Peyrani P, Mirsaeidi M, Allen M, Moffett BK, *et al.* Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia. Chest 2008;134:955-62.
3. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, *et al.* 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.
4. Menéndez R, Torres A, Zalacaín R, Aspa J, Martín Villasclaras JJ, Borderías L, *et al.* Risk factors of treatment failure in community acquired pneumonia: Implications for disease outcome. Thorax 2004;59:960-5.
5. Feinsilver SH, Fein AM, Niederman MS, Schultz DE, Faegenburg DH. Utility of fiberoptic bronchoscopy in nonresolving pneumonia. Chest 1990;98:1322-6.
6. Aliberti S, Blasi F. Clinical stability versus clinical failure in patients with community-acquired pneumonia. Semin Respir Crit Care Med 2012;33:284-91.
7. Liu YN, Chen MJ, Zhao TM, Wang H, Wang R, Liu QF, *et al.* A multicentre study on the pathogenic agents in 665 adult patients with community-acquired pneumonia in cities of China. Zhonghua Jie He He Hu Xi Za Zhi 2006;29:3-8.
8. Tao LL, Hu BJ, He LX, Wei L, Xie HM, Wang BQ, *et al.* Etiology and antimicrobial resistance of community-acquired pneumonia in adult patients in China. Chin Med J (Engl) 2012;125:2967-72.
9. Wang H, Chen M, Xu Y, Sun H, Yang Q, Hu Y, *et al*. Antimicrobial susceptibility of bacterial pathogens associated with community-acquired respiratory tract infections in Asia: Report from the Community-Acquired Respiratory Tract Infection Pathogen Surveillance (CARTIPS) study, 2009-2010. Int J Antimicrob Agents 2011;38:376-83.
10. 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.
11. Ott SR, Hauptmeier BM, Ernen C, Lepper PM, Nüesch E, Pletz MW, *et al.* Treatment failure in pneumonia: Impact of antibiotic treatment and cost analysis. Eur Respir J 2012;39:611-8.

How to cite this article: Chen X. Causes and management of initial treatment failure in patients with community-acquired pneumonia. Community Acquir Infect 2014;1:65-8.

Source of Support: Nil, **Conflict of Interest:** None declared