

Clinical Stability versus Clinical Failure in Patients with Community-Acquired Pneumonia

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Abstract

Once antibiotics have been started in patients with community-acquired pneumonia (CAP), the evaluation of clinical outcomes represents one of the essential steps in patient care. Among CAP patients who improve, recognition of clinical stability should be based on both subjective and objective parameters that are locally available in the everyday clinical practice. Different steps in the management of the pneumonia depend on this early outcome, including the switch from intravenous to oral antibiotics, patients' discharge from the hospital, and outcomes after hospitalization. When deterioration occurs in CAP patients, a "treatment failure" or a "clinical failure" should be identified. It is crucial to understand the etiology of failure so as to develop different measures at both international and local levels to prevent adverse outcomes. Finally, several efforts should be made to define incidence, timing, and risk factors for nonresolving pneumonia that, to date, remains one of the most indeterminate clinical outcomes in patients with CAP.

Keywords

- ▶ community-acquired pneumonia
- ▶ outcomes
- ▶ failure
- ▶ nonresolving pneumonia
- ▶ stability

After initiation of empirical antibiotic therapy, patients with community-acquired pneumonia (CAP) can experience different clinical outcomes that strictly depend on three main factors: (1) host characteristics, such as immune system, comorbidities, and performance status; (2) pathogen characteristics, such as virulence, susceptibility, and resistance to antimicrobials; (3) antibiotic characteristics, such as timing, adequacy of therapy, and pharmacokinetic factors (▶**Fig. 1**). The interaction between these factors is responsible for both type and timing of clinical outcomes. Once antibiotics have been started in patients with CAP, the severity of the disease can decrease, and patients can experience a clinical improvement; or it can increase, leading to patients' clinical deterioration; or it can remain at the same degree in comparison with baseline, and clinical improvement may not occur. The clinical response of CAP patients during the first week of hospitalization can, thus, be categorized into five possible outcomes, see ▶**Fig. 2**. CAP patients may have an early clinical improvement within the first 3 to 4 days after hospitalization

(▶**Fig. 2**, point 1), or a late clinical improvement (▶**Fig. 2**, point 2). Patients may also develop an early clinical deterioration within the first 3 days of hospitalization (▶**Fig. 2**, point 3), or a late clinical deterioration (▶**Fig. 2**, point 4). If after 7 days of therapy there is no evidence of clinical improvement or deterioration, the patient is categorized as having a non-resolving pneumonia (▶**Fig. 2**, point 5).¹

This review discusses the current understanding of clinical outcomes experienced during hospitalization by CAP patients after initiation of empirical antibiotic therapy.

A Model of Improvement in Patients with Community-Acquired Pneumonia

The clinical response to therapy in patients with CAP could be described in a model consisting of four different phases (▶**Fig. 3**). After the administration of appropriate empirical therapy, the bacterial counts in the alveoli decrease, and this produces the "microbiological resolution," the first phase of

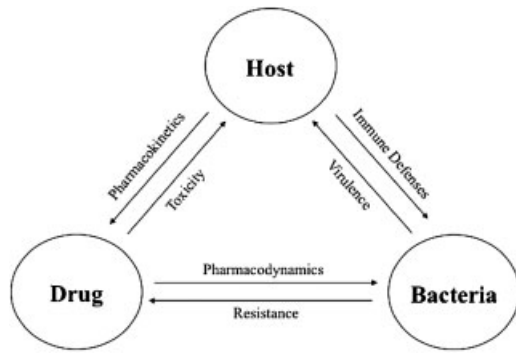


Figure 1 Determinants of clinical outcomes in patients with community-acquired pneumonia.

response to therapy. During the microbiological response to therapy, a significant decrease of the bacterial load in the lung parenchyma occurs. The decreased bacterial load produces the second phase of resolution characterized by a decrease of the local and systemic inflammatory response. The local production of proinflammatory mediators such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and IL-8

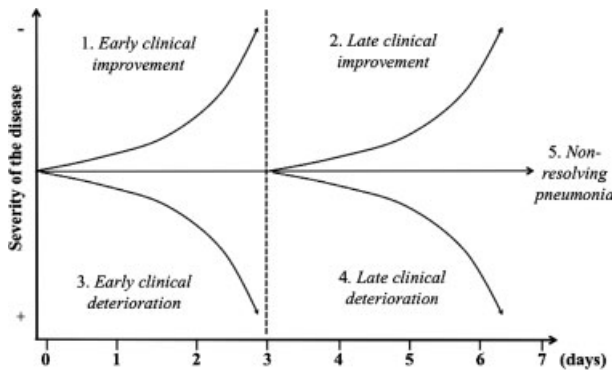


Figure 2 Type and timing of clinical outcomes in patients with community-acquired pneumonia.

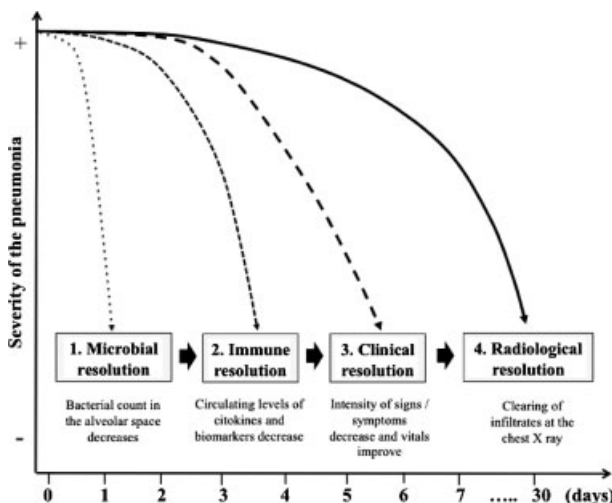


Figure 3 Model of clinical response in patients with community-acquired pneumonia.

significantly diminishes. At this time the large numbers of neutrophils recruited into the alveoli undergo programmed cell death, or apoptosis, and alveolar macrophages start clearing the apoptotic neutrophils and producing antiinflammatory cytokines such as IL-4 and IL-10. This phase results in tissue repair that is defined as “immunological resolution.” Following the immunological response, patients’ signs and symptoms begin to improve, and the third phase of response to therapy, the “clinical resolution,” starts. During this phase, the patient begins to show evidence of clinical improvement. Finally, after several days from the onset of the pneumonia, a “radiological resolution” of the pulmonary infiltrates ends the cure of the pneumonia.

Different parameters could be used to identify patients’ improvement along these four phases. To evaluate when a significant decrease in bacterial colony counts occurs, patients with CAP will need to have serial invasive procedures (ie, bronchoalveolar lavages with quantitative cultures). Daily determinations are required to evaluate when inflammatory cytokines or other biomarkers decrease in the systemic circulation. However, detection of both microbiological and immunological resolutions is not performed during routine clinical practice, and most of the immunological tests are for research purposes only. Finally, the evaluation of a patient’s improvement based on the radiological clearance of the pulmonary infiltrates could be possible only in a late stage of the pneumonia course.

In view of all these considerations, the “clinical resolution” represents the phase of patients’ improvement that is more easily detectable. Its recognition, in fact, is based on parameters that are readily available in the everyday clinical practice, such as patient’s symptoms, vitals, respiratory signs, and simple blood tests.

Definition of Clinical Improvement

During the past 2 decades, several studies evaluated clinical improvement of hospitalized patients with CAP, using clinical or laboratory parameters.^{2,3} Different efforts have been made by international societies to recommend criteria for clinical improvement in hospitalized patients with CAP (→ **Table 1**).⁴⁻⁷

The two set of criteria suggested by the American Thoracic Society (ATS) in the 2001 and 2007 guidelines show some differences. The ATS 2001 set of criteria is based on both subjective and objective parameters and seems to be simpler to obtain. On the other hand, more criteria were incorporated in the ATS 2007 guidelines, only focused on objective criteria (ie, normalization of different vital signs as well as pulmonary gas exchange). More parameters are added as criteria for clinical improvement and more physicians are confident that their CAP patients are clinically improved. However, this could lead to a delay in defining clinical improvement with an increase of time to switch from intravenous to oral antibiotics and to discharge the patient. We could speculate that the two sets of criteria proposed by the ATS in 2001 and 2007 look at two different phases of the patient’s improvement. ATS 2001 criteria seem to identify an initial phase of a patient’s improvement, or early clinical stability, whereas

Table 1 Definition of Clinical Improvement in Patients with Community-Acquired Pneumonia as Suggested by International Societies

American Thoracic Society 2001 Guidelines ⁴	American Thoracic Society/ IDSA (Infectious Diseases Society of America) 2007 Guidelines ⁵	European Respiratory Society Guidelines 2005 ⁶	British Thoracic Society Guidelines 2009 ⁷
Improvement of cough and dyspnea Temperature < 100°F on two occasions 8 hours apart White blood cell count decreasing	Temperature ≤ 37.8°C Heart rate ≤ 100 bpm Respiratory rate ≤ 24 bpm Systolic blood pressure ≥ 90 mm Hg Arterial oxygen saturation ≥ 90% or pO ₂ ≥ 60 mm Hg on room air Normal mental status	Body temperature Parameters of respiration (preferably respiratory rate and partial oxygen tension or oxygen saturation) Hemodynamics (arterial blood pressure and heart rate) Mental state	Resolution of fever for > 24 hours Pulse rate < 100 bpm Resolution of tachypnea Clinically hydrated and taking oral fluids Resolution of hypotension Absence of hypoxia Improving white cell count Nonbacteremic infection No microbiological evidence of <i>Legionella</i> , staphylococcal, or gram-negative enteric bacilli infection

ATS 2007, by adding more criteria, detect a more advanced phase of improvement, or late clinical stability.

A recent effort has been made to increase the performance of criteria for clinical stability adding biomarkers, such as C-reactive protein (CRP) and procalcitonin (PCT).⁸ The use of biological information provided by CRP and PCT together with clinical criteria of stability improved the safety of that prediction.

So far, it is difficult to identify the best set of criteria for clinical improvement. From a research point of view, most of them are valid and could be used to compare findings along different studies. From a clinical point of view, physicians need to look at CAP patients to define their improvement using both subjective and objective approaches. Outside strict and pre-defined sets of criteria, the evaluation of clinical improvement in CAP patients should be individualized on every single patient based on parameters (ie, signs, symptoms, biomarkers, temperature, hemodynamic or respiratory impairment) that are used in local settings and that are abnormal on admission and can be, thus, followed up during hospitalization.

Timing of Clinical Improvement

Clinical improvement is usually considered to have been attained on the first day that different parameters are normalized or have reached a predefined cutoff. In the immunocompetent host who shows a favorable interaction between the immune system, the microorganism, and the antibiotic, a clinical improvement is usually reached around day 3 or day 4 after hospitalization.^{3,9}

A delay in reaching clinical stability could be noted among CAP patients, and several factors seem to be associated with this delay. Patient characteristics, including age, alcoholism, multiple coexisting illnesses, and chronic bronchitis could be associated with delayed resolution.⁴ A longer time to clinical stability could also be experienced by CAP patients with a pneumonia that is complicated by multilobar infiltrates, pleural effusion, empyema, cavitation, or

cardiac and respiratory impairment.⁹ Viale and coworkers studied clinical stability in human immunodeficiency virus (HIV) infected patients with CAP.¹⁰ In this population of patients, time to clinical stability ranged from 3 to 6 days and, after improvement was attained, relapses were unlikely. As reported by other researchers, the presence of HIV infection seems not to influence time to clinical stability in hospitalized patients with CAP, after adjusting for significant confounders.¹¹

Some pathogen characteristics are also correlated with a delay in clinical improvement, including the presence of bacteremia as well as *Pneumocystis jiroveci* infection in HIV-infected patients.^{4,10} A remarkable correlation exists between the severity of the pneumonia on admission and the time to clinical stability. Based on some experiences, the initial severity of the disease, measured by the pneumonia severity index, the CRB-65 (confusion, respiratory rate >30 bpm, systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg; age ≥65 years) the presence of confusion, or admission to an intensive care unit, is correlated with the number of days needed until stability is reached.^{3,12} Finally, a positive influence of adherence to treatment guideline on the stability of CAP patients has been recently demonstrated.⁹

The Importance of Clinical Stability

Time to clinical stability (TCS) is considered a crucial outcome that can direct physicians' steps in the further management of patients with CAP.

TCS has been widely accepted as a tool to guide the switch from intravenous (IV) to oral antibiotic therapy during hospitalization, as well as to judge appropriateness for hospital discharge. An early switch to oral antibiotic therapy for patients with respiratory infections is often recommended to reduce the risk of side effects, the risk of antibiotic resistance, and costs. According to recent guidelines, the presence of clinical stability together with the ability to eat and drink is the major consideration for switching from IV to

oral antibiotic therapy in CAP patients.⁵ Originally, Ramirez and coworkers tested a set of criteria of clinical stability for an early switch from IV to oral therapy, lately adopted in the ATS guidelines published in 2001.² As many as two thirds of all patients in this study had clinical improvement and met criteria for a therapy switch in the first 3 days. A further study showed that, once a hospitalized patient with CAP reaches clinical stability, it is safe to switch from IV to oral even if bacteremia caused by *Streptococcus pneumoniae* is initially documented.¹³ A systematic review evaluating early switch to oral treatment in patients with moderate to severe CAP, comprising six randomized, controlled trials enrolling more than 1200 patients, was published in 2008.¹⁴ The authors found that an early switch from IV to oral antibacterial therapy seems to be as effective as continuous IV with a substantial reduction in duration of hospitalization.

Time to clinical stability also plays a role in the hospital discharge of patients with CAP. Guidelines recommend that discharge should be considered when a CAP patient is a candidate for oral therapy and when there is no need to treat any comorbid illness, no need for further diagnostic testing, and no unmet social need.⁵

A recent paper showed that the time in which patients with CAP reach clinical stability during the hospital course could impact outcomes after hospital discharge.¹⁵ In this study, patients with a time to clinical stability more than 3 days showed a significantly higher rate of adverse outcomes after discharge compared with those with a TCS equal to or less than 3 days. A propensity-adjusted analysis confirmed that a delay in reaching clinical stability during hospitalization is associated with a significant increased risk of adverse outcomes within 30 days after discharge.

Finally, time to clinical stability could also play a role in determining duration of antibiotic therapy in CAP patients. Based on guidelines recommendations, duration of therapy should vary by individual patient, disease severity, and speed of resolution of the disease.⁵ However, these recommendations are mainly based on expert opinions. Recent data demonstrated that physicians worldwide do not use clinical response in determining the duration of antibiotic therapy and that total duration of therapy is generally much longer than the time needed to reach clinical stability.¹⁶ Further research should thus be, focused on the evaluation of duration of antibiotic therapy with an individualized approach based on each patient's clinical improvement during hospitalization.

Clinical Deterioration and Failure in CAP Patients

Among CAP patients who experience a lack of response, some patients may deteriorate and fail (progressive pneumonia). The incidence of failure in patients with CAP ranges from 6 to 24%^{9,17-22} and can reach up to 31% in patients with severe CAP.²³ When failure occurs in patients with CAP, it significantly increases the risk of complications, length of stay, and death, especially in patients with severe CAP.^{21,23} Finally, in hospitalized patients, failure contributes to a significant

increase in direct treatment costs, mainly because of a significant prolonged length of stay.²²

Definition of Failure

Different parameters have been reported in the literature and used in clinical practice to define failure in hospitalized patients with CAP. Among those, symptoms (ie, dyspnea, altered mental status), vital signs (ie, fever, respiratory rate, oxygen saturation), laboratory parameters (ie, white blood cells, partial oxygen pressure in arterial blood), radiological findings, and the need for invasive procedures or changes in treatment are the most commonly used. Based on these parameters, several definitions for failure in hospitalized patients with CAP have been adopted in the literature, mainly depending on the topic evaluated by different investigators (► **Table 2**).

A "treatment failure" definition has been adopted by investigators interested in analyzing the response of patients with CAP to a particular antibiotic treatment.^{9,19,20,22,24-28} When evaluating the effect of the antibiotic, patients that deteriorated within 48 hours of treatment initiation were usually excluded from the evaluation to allow the antibiotic time to take effect. Furthermore, immunocompromised patients or those who were likely to have poor outcomes were usually excluded from treatment trials.

In an attempt to include all patients who deteriorated in the analysis of failures, a definition of "clinical failure" was adopted by other investigators.^{20,21} In a recent experience, a clinical definition for failure, easily available in clinical practice, has been used, including pulmonary or hemodynamic deterioration as well as in-hospital death.²¹

Another decisive step in understanding clinical failure in hospitalized patients with CAP is to define its direct relationship with the inflammatory process. During the past decades, outcomes of CAP patients have been analyzed from a pathophysiological point of view, giving more weight to the role directly played by the infection and the inflammatory response. Using this approach, the etiology of mortality has been classified as CAP related or CAP unrelated, with significant differences in terms of timing and risk factors.²⁹ Following this approach, clinical failure during hospitalization has been evaluated as directly related or not related to the pulmonary infection and the systemic inflammatory response due to the pneumonia.²¹ More than 80% of clinical failures seem to be directly related to the pneumonia and occur primarily during the first 72 hours after hospital admission.

Etiology of Failure

The identification of the etiology of clinical failure is important to implement general clinical practice as well as local standard operating procedures. Some approaches identified infectious versus noninfectious causes of failure by microbiological evaluation.^{9,19} Other classifications were mainly based on signs and symptoms recorded during the hospitalization, such as fever, respiratory rate, and oxygen saturation.²³ A more comprehensive approach has been developed in which causes of failure were divided into host-related,

Table 2 Definitions of Failure in Patients with Community-Acquired Pneumonia

Study	Definition	Parameter
Arancibia et al, 2000 ¹⁸	Nonresponding pneumonia	Persisting fever >38°C and/or clinical symptoms after at least 72 hours of antimicrobial treatment
	Progressive pneumonia	Acute respiratory failure requiring ventilatory support and/or septic shock after at least 72 hours of antibiotic therapy
Menéndez et al, 2004 ²⁸	Late treatment failure	Persistence or reappearance of fever and symptoms or hemodynamic instability, development or impairment of respiratory failure, radiographic progression, or appearance of new infectious foci after 72 hours of antimicrobial treatment
	Early treatment failure	Clinical deterioration within 72 hours of treatment resulting from one or more of the following causes: hemodynamic instability, appearance or impairment of respiratory failure, need for mechanical ventilation, radiographic progression, or the appearance of new metastatic infectious foci
Rosón et al, 2004 ²³	Early failure	Lack of response or worsening of clinical and/or radiological status at 48 to 72 hours, requiring either changes in antibiotic therapy or performance of invasive procedures for diagnostic and therapeutic purposes
	Progressive respiratory failure	Increasing oxygen requirements or the necessity of mechanical ventilation during follow-up
Gennè et al, 2006 ¹⁹	Failure to respond	Fever for more than 3 days with clinical deterioration, clinical deterioration necessitating a change in the initial empirical antibiotic therapy on the basis of the results of microbiological culture or the occurrence of a severe side effect, or death occurring after at least 48 hours of antibiotic treatment
	Development of complications	Any antibiotic-related events that required a stop in treatment
Hoogewerf et al, 2006 ²⁰	Early clinical failure	Death, need for ventilation, respiratory rate >25, SpO ₂ < 90%, PaO ₂ < 55 mm Hg, hemodynamic instability, altered mental state, fever
Kaye et al, 2008 ²⁶	Treatment failure	The persistence of symptoms after the first week following the office visit, necessitating hospitalization related to persistent or worsening pneumonia
Ye et al, 2008 ²⁷	Outpatient treatment failure	Occurrence of one of the following: a second antibiotic claim after the index prescription date, or hospital admission with a primary or secondary diagnosis of community-acquired pneumonia
Aliberti et al, 2008 ²¹	Clinical failure	Acute pulmonary deterioration with the need for either invasive or noninvasive mechanical ventilation; acute hemodynamic deterioration with the need for aggressive fluid resuscitation, vasopressors, or invasive procedures; in-hospital death <i>Early clinical failure:</i> occurring ≤3 days after hospital admission <i>Late clinical failure:</i> occurring >3 days after hospital admission
	Clinical failure related to community-acquired pneumonia	Failure with etiology directly related to the pulmonary infection and its systemic inflammatory response
	Clinical failure unrelated to community-acquired pneumonia	Failure with etiology unrelated to the pulmonary infection and its systemic inflammatory response
Menéndez et al, 2008 ²⁴	Early treatment failure	Clinical deterioration within 72 hours of treatment, as indicated by the need for mechanical ventilation or shock or death
	Late treatment failure	Persistence or reappearance of fever, radiographic progression, including pleural effusion or empyema, nosocomial infection, impairment of respiratory failure and need for mechanical ventilation or shock after 72 hours

Table 2 (Continued)

Study	Definition	Parameter
Hess G et al, 2010 ²⁵	Treatment failure	Refill for the index antibiotic after completed days of therapy, a different antibiotic dispensed > 1 day after the index prescription, or hospitalization with a pneumonia diagnosis or emergency department visit > 3 days postindex
Ott SR et al, 2012 ²²	Treatment failure	Need to switch to another antibiotic regimen \geq 72 hours after initial treatment resulting in an expansion of the antibiotic spectrum by adding another agent or replacing the initial antibiotic by another of the same class with a broader antibacterial spectrum

drug-related, and pathogen-related etiologies.²⁰ Based on this model, reasons for failure could be related to a wrong evaluation of the patient's immune system or to the presence of drug-resistant organisms or pathogens other than bacteria. Based on the fact that pathogens are currently isolated in 20% of hospitalized patients with CAP, the correct analysis of risk factors for specific microorganisms or multidrug-resistant pathogens gains importance. Finally, reasons for failure could be related to the incorrect choice of the antibiotic or its dose and route of administration, the lack of patient compliance, or the occurrence of adverse drug reactions.

The evaluation of the etiology of clinical failure both related and unrelated to CAP showed interesting results. In one paper, the most common etiologies for clinical failure related to CAP were severe sepsis and acute myocardial infarction.²¹ These findings confirmed data from Roson et al who previously recognized uncontrolled sepsis as a cause of early clinical failure in patients with CAP.²³ Over the past 10 years, evidence evaluating the impact of cardiovascular events on outcomes of CAP patients has increased.³⁰ Recent reviews suggest that CAP is associated with a significant increase in the risk of cardiovascular events and death from cardiac causes.^{31,32} The etiology of clinical failure unrelated to CAP is usually due to suboptimal care or complications related to hospitalization itself (ie, the development of hospital-acquired pneumonia).²¹ The correct understanding of causes of adverse outcomes that are related to the care of CAP patients could lead physicians to adopt important interventions at an institutional level.

Predictors for Failure

Several factors seem to be associated with both clinical and treatment failure in hospitalized patients with CAP. The initial severity of the disease is an independent risk factor for failure, along with advanced age, comorbidities, and the presence of pleural effusion or empyema.^{28,33} From a pathogen perspective, patients with a pneumonia caused by *Legionella*, gram-negative microorganisms, or a mixed infection had a higher risk for failure.²³ Finally, some experiences reported that the use of an antibiotic therapy not in compliance with guidelines could lead to a failure in hospitalized patients with CAP.³⁴

Recently, it has been observed that patients undergoing treatment failure show an increase in systemic proinflammatory response on the first day and after 72 hours of treatment compared with those with a good response.²⁴ Thus serum

levels of C-reactive protein or procalcitonin could be useful as predictors of treatment failure in CAP patients.

Nonresolving Pneumonia

Although nonresolving pneumonia (NRP) is one of the most relevant outcomes in patients with CAP, there is a deficiency of studies evaluating its definition and etiology.³⁵ NRP (also mentioned as slow-resolving pneumonia) is usually considered as a clinical syndrome characterized by the presence of signs and symptoms compatible with respiratory infection and infiltrates on chest radiography that persist after initiation of antibiotic therapy, with the patient's clinical status neither improving nor deteriorating. Some authors have arbitrarily chosen a cutoff of a minimum of 10 days of antibiotic treatment to define the clinical picture as NRP.³⁶ Although the precise incidence of NRP is not well established, early studies reported that as many as 25% of patients had slowly resolving or nonresolving disease. A recent experience found an incidence of NRP in hospitalized patients with CAP of 15% and identified different causes of NRP, including the severity of CAP on admission, an empirical antibiotic therapy not compliant with guidelines, and the development of a comorbidity during the first week of hospitalization.³⁷ A practical approach in identifying possible causes of NRP along with diagnostic considerations is reported in **Table 3**.

Conclusions

Identification of clinical outcomes in patients with CAP should be based on definitions that could be used in the everyday clinical practice. Strict criteria for the patient's improvement or deterioration are useful for research purposes only, to compare findings from different studies. From a clinical point of view, more simple definitions of clinical outcomes are needed, primarily based on both subjective and objective criteria.

To improve our knowledge of clinical outcomes of CAP patients, several issues should also be addressed in the coming years. Clinical evaluations of the most useful and practical criteria for defining clinical stability are needed, especially in selected populations such as immunocompromised patients other than HIV-infected and neutropenic subjects. Due to the fact that severe sepsis is one of the main causes of clinical failures of CAP patients, its definition and early identification should be improved, particularly in

Table 3 Causes of Non-Resolving Pneumonia and Diagnostic Approaches

Causes		Diagnostic Considerations
1. Incorrect diagnosis	Collagen vascular disease, congestive heart failure, embolism, carcinoma, pulmonary infarction, drug reaction, acute respiratory distress syndrome	Review of history (travel, exposure) Review of laboratory data (eosinophilia) Consider bronchoscopy
2. Host-related issues	Overwhelming infections (i.e., empyema) Immunosuppression or immunocompromise Mechanical reasons (obstructed bronchus due to carcinoma; sequestration of a segment of lung)	Review/repeat chest radiograph or consider chest computed tomography (CT) Evaluate for other infection (echocardiography, sinus CT, empyema) Consider superinfection Reevaluation of risk factors for specific or multidrug-resistant pathogens Consider bronchoscopy
3. Drug-related issues	Incorrect active principle Incorrect dose Patient not compliant	Review antibiotic regimen Confirm patient's compliance
4. Pathogen-related issues	Unsuspected pathogen (viruses, mycobacterium, fungi) Resistant pathogen	Consider unusual pathogen Review microbiological data Review antibiotic sensitivity
5. Other	Drug fever	Review medications

the outpatient setting. Among clinical outcomes, studies focused on patients with NRP need to be performed to better define this condition and identify potential risk factors. Based on recent experiences, the follow-up of biomarkers seems to play a role in evaluating clinical outcomes in pneumonia. Although different biomarkers were described in the literature during the past decade, the exact evaluation of their role and feasibility in clinical practice as well as their application in the immunocompromised host is still unknown. Finally, substantial evidence has suggested an important effect of cardiovascular events on adverse outcomes of CAP patients both during hospitalization and up to 1 year after discharge. Randomized, controlled trials evaluating the use of alternative drugs to prevent death for cardiovascular events in CAP patients are, thus, needed.

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