Treatment Failure in Community-Acquired Pneumonia

Rosario Menendez and Antoni Torres

Chest 2007;132;1348-1355
DOI 10.1378/chest.06-1995

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Rosario Menendez, MD; and Antoni Torres, MD

Treatment failure (TF) is defined as a clinical condition with inadequate response to antimicrobial therapy. Clinical response should be evaluated within the first 72 h of treatment, whereas infiltrate images may take up to 6 weeks to resolve. Early failure is considered when ventilatory support and/or septic shock appear within the first 72 h. The incidence of treatment failure in community-acquired pneumonia is 10 to 15%, and the mortality is increased nearly fivefold. Resistant and unusual microorganisms and noninfectious causes are responsible for TF. Risk factors are related to the initial severity of the disease, the presence of comorbidity, the microorganism involved, and the antimicrobial treatment implemented. Characteristics of patients and factors related to inflammatory response have been associated with delayed resolution and poor prognosis. The diagnostic approach to TF depends on the degree of clinical impact, host factors, and the possible cause. Initial reevaluation should include a confirmation of the diagnosis of pneumonia, noninvasive microbiological samples, and new radiographic studies. A conservative approach of clinical monitoring and serial radiographs may be recommended in elderly patients with comorbid conditions that justify a delayed response. Invasive studies with bronchoscopy to obtain protected brush specimen and BAL are indicated in the presence of clinical deterioration or failure to stabilize. BAL processing should include the study of cell patterns to rule out other noninfectious diseases and complete microbiological studies. The diagnostic yield of imaging procedures with noninvasive and invasive samples is up to 70%. After obtaining microbiological samples, an empirical change in antibiotic therapy is required to cover a wider microbial spectrum. ***(CHEST 2007; 132:1348–1355)***

Key words: mortality; nonresponding nonresolving treatment failure; pneumonia

Abbreviations: BOOP = bronchiolitis obliterans with organizing pneumonia; CAP = community-acquired pneumonia; IL = interleukin; TF = treatment failure; TLR = Toll-like receptor; TNF = tumor necrosis factor

Treatment failure (TF) in community-acquired pneumonia (CAP) is defined as a clinical condition with inadequate response to antimicrobial therapy. When response to treatment is inadequate, persistence or progression of the infection occur, resulting in the worsening of the symptoms and the slower resolution that may lead to dissemination of the infection, the appearance of complications, and even death. Whatever the circumstances, clinical stability is delayed, thereby increasing the need for hospitalization and, thus, the direct and indirect costs.

Lack of clinical stability and *treatment failure* are not synonymous terms. Although closely related, they provide different information on the evolution of CAP. While it is certain that TF leads to a delay in the achievement of clinical stability, the inverse does

*From the Servicio de Neumologia (Dr. Menendez), Hospital Universitario La Fe, Valencia; and Servei de Pneumologia i Allergia Respiratoria (Dr. Torres), Institut del Tòrax, Hospital Clínic, Universitat de Barcelona, Spain.
This work was supported by Institut de Investigacións Biomediques August Pi i Sunyer, SGR 00822, Marató TV3 04050530 and 04040210, Fondo de Investigación Sanitaria grant PI041136 and PI030113, and Centro de Investigación Biomedica en Red CB06/06/0028.
The authors have no conflicts of interest to disclose.

Manuscript received August 10, 2006; revision accepted February 15, 2007.

Correspondence to: Rosario Menendez, MD, Servicio de Neumologia, Hospital Universitario La Fe, Avda. de Campanar 21, 46009 Valencia, Spain; e-mail: rmenend@separ.es
DOI: 10.1378/chest.06-1995

not always happen because this delay may be due to other causes of varying severity and clinical consequences.

Clinical Stability

The recommended evaluation of patients with CAP[1] after treatment is crucial within the first 72 h, when he/she is expected to reach stability. If a patient fails to reach stability, a complete reevaluation should be performed to investigate the reasons. Several definitions of clinical stability for hospitalized CAP have been proposed.[2,3] In fact, Halm et al[2] employed several threshold values for temperature, heart rate, systolic BP, respiratory rate, and oxygen saturation to define clinical stability, and found a median time to stability of 3 days.

Several factors influence clinical stability, the main factor being the initial severity of CAP. Thus, the higher the initial severity the greater the number of days required to reach stability.[2] In addition to TF, other independent factors found to be related to stability are the presence of comorbid conditions or complications and nonadherence to treatment guidelines.[4]

TF

The lack of response to antibiotic treatment, formerly described as *nonresponding pneumonia*, has been known for decades[5–7] and is based on the period of time required for the resolution of the symptoms and/or the radiographic images. The definition is empirical and depends on the criteria of the authors.

A key issue is to define when antibiotic treatment is considered to fail because it requires some time to take effect and it also depends on the causal microorganism, the initial severity of the infection, and the conditions of the host (Table 1). Furthermore, response to treatment antibiotic differs among outpatients and hospitalized patients, and also between hospitalization in the ward and in the ICU. Following the latest American Thoracic Society/Infectious Diseases Society of America guidelines, TF for outpatients should be considered when there is a need for hospital admission or a change in antibiotics. For hospitalized patients with CAP, the most frequently used period is 72 h, agreeing with the median time required to achieve clinical stability,[2] the time required to reduce bacterial concentration in the airways,[8] or the time suggested to obtain further samples and perform endoscopic studies.[9] Two patterns of TF have been described in hospitalized non-ICU patients[1]: (1) progressive pneumonia if clinical deterioration with acute respiratory failure requiring ventilatory support and/or septic shock appears within the first 72 h of hospital admission; and (2) nonresponding pneumonia if persistence of fever and clinical symptoms without achieving clinical stability. The term *early failure* used in two studies was similar to that of progressive pneumonia despite use even before 72 h of treatment. Roson et al[10] also included the need for a change in therapy or thorax drainage. In a study by Menendez et al,[11] hemodynamic instability, worsening of or the appearance of respiratory failure, or new foci of infection were also included in the definition. In brief, the concept of TF can be resumed as clinical deterioration with acute respiratory failure requiring ventilatory support and/or septic shock irrespective of the time or absence or delay in achieving clinical stability after the first 72 h.

Table 1—*Factors Related to Pneumonia Resolution*

Factors	Characteristics
Rapid resolution	
Host factors	Youth; nonsmokers; nonhospitalized CAP
Severity of CAP	Mild initial severity
Causal microorganisms	*Mycoplasma pneumoniae*; *Chlamydia pneumoniae*
Slow resolution	
Host factors	Elderly; comorbid conditions; alcohol intake; smokers
Severity of CAP	Higher severity; multilobar CAP; empyema; bacteremia
Causal microorganism	Legionella spp; polymicrobial pneumonia

The incidence of TF in CAP has not been clearly established. In a multicenter study[12] in hospitalized patients with CAP, 15% were found to have a lack of response to empirical antibiotic treatment (8% early and 7% late failure). Roson et al[10] found 6% with early failure (48 to 72 h) in CAP, and up to 39% of the patients had progressive pneumonia among those with TF pneumonia in CAP.[13]

Causes of TF in Pneumonia

Infectious Causes: Infectious and noninfectious causes are summarized in Table 2. Infections account for 40% of the causes, and have been classified as primary infections, definitive or probable persistent infections, and nosocomial infections.[13] *Streptococcus pneumoniae*, Legionella,[10] *Staphylococcus aureus*, and *Pseudomonas aeruginosa*[13] have been identified as causes of TF,[12] and methicillin-resistant *S aureus* (MRSA) [33%], enteric Gram-negative bacilli (24%), and *P aeruginosa* (14%) have been found in institutionalized elderly patients.[14]

Table 2—*Causes of TF*

Causes	Microorganisms
Infectious	
Resistant microorganisms	
CAP	*S pneumoniae*; *S aureus*
Nosocomial pneumonia	Acinetobacter; MRSA; *P aeruginosa*
Infrequent microorganisms	*Mycobacterium tuberculosis*; Nocardia spp; fungal pneumonia; *Pneumocystis jiroveci*
Noninfectious	Neoplasia; hemorrhagic lung; eosinophilic lung; pulmonary edema; adult respiratory distress; BOOP; vasculitis

S pneumoniae resistance does not seem to be the cause of TF when the treatment is appropriate, adheres to guidelines, and the minimal inhibitory concentration of penicillin is < 4 μg/mL.[15] However, isolated cases of TF has been described with resistance to the new fluoroquinolones, specifically levofloxacin,[16] and to macrolides.[17] The presence of unusual microorganisms in CAP (Table 3) is a cause of TF[18] because these microorganisms are not adequately covered by the recommended initial empirical therapy.

Noninfectious Causes: Some diseases can mimic CAP and behave as TF; among them, pulmonary hemorrhage, diseases of inflammatory origin such as bronchiolitis obliterans with organizing pneumonia (BOOP),[7] thromboembolic diseases, pulmonary eosinophilia, hypersensitivity pneumonitis, and others have been described.[5] Pulmonary neoplasia, formerly considered to be relatively frequent, is estimated to account for 1%.[9,10,13]

In a study in an ICU, Jacobs et al[19] found 19% of noninfectious causes of TF that including drug-induced pneumonitis, aspiration of gastric contents, ARDS, pulmonary embolism, carcinomatous lymphangitis, and cardiogenic pulmonary edema. Finally, it should be taken into account that in up to 30% of cases there does not appear to be any specific cause of lack of response, despite appropriate antibiotic treatment.

Table 3—*Causal Microorganisms According to Epidemiologic Data*

Microorganisms	Source
Coxiella burnetti	Cats; goats; sheep; cattle
Tularemia	Rabbits; ticks
Leptospirosis/plague	Rats
Hantavirus	Rats
Psittacosis	Birds
Anaerobes	Nursing home; aspiration; alcoholism
Nocardia	Steroid treatment
Aspergillus	Steroid treatment
P jiroveci	Immunosuppression
Dimorphic fungi	Recent journeys
Burkholderi pseudomallei	Recent journeys
Tuberculosis	Recent journeys

Predictors of TF

Several factors (Table 4) have been associated with TF and may be classified as follows:

Factors Related to Initial Severity of Infection: It has long been known that bilateral or multilobar CAP and episodes associated with systemic shock or severe hypoxemia have a worse response to antibiotic treatment. The Fine risk scale describes that the greater the initial severity, the longer the time needed to achieve clinical stability.[2] As shown in Table 4, initial severity is an independent risk factor for early and late TF.[10,11] However, it should be taken into account that a higher Fine score may be more dependent on the comorbid condition and on patient age than the severity itself.

Host Factors: The impact of comorbidity on response to treatment has been studied by multivariate analyses. It was found that, compared to nonfailure, early TF was lower in patients > 65 years of age (odds ratio, 0.35)[10] and twofold higher in hepatic disease[11]; while, curiously, COPD improved prognosis.[11] This surprising finding has no current explanation, although it is remarkable that the mortality of CAP in patients with COPD is low, approximately 8%[20]; and, in fact, this disease is not included in the

Table 4—*Independent Factors Related to TF and Early Failure**

		Early Failure	
Factors	TF[11]	Roson et al[10]	Menendez et al[11]
Age > 65 yr		0.35 (0.21–0.6)	
Influenza vaccination	0.3 (0.2–0.6)		0.2 (0.1–0.4)
COPD	0.6 (0.4–0.9)		
Legionella		2.7 (1.4–5.3)	
Gram negative		4.3 (1.04–18)	
Pleural effusion	2.7 (1.8–4.2)	2.7 (1.8–4.2)	2.6 (1.6–4.3)
Multilobar CAP	2.1 (1.4–2.9)	2.15 (1.4–3.4)	2.2 (1.4–3.2)
Cavitation	4.1 (1.3–13.5)		5.2 (1.4–18.2)
Discordant therapy		2.51 (1.61–3.94)	
Fluoroquinolone treatment	0.5 (0.3–0.9)		
Fine risk class	1.3 (1.1–1.5)	1.8 (1.11–2.9)	1.2 (1.1–1.5)
Leukopenia	3.7 (1.4–10.2)		5.9 (2.2–15.3)
Hyponatremia			1.6 (1.1–2.4)

*Data are presented as odds ratio (95% confidence interval).

pneumonia severity index score.[21] Concomitant treatment with steroids might play a protective role in the regulation of the proinflammatory cytokine response of the host.[22–24] However, Restrepo et al[25] reported significantly higher 30-day and 90-day mortality rates in patients with COPD and CAP compared to non-COPD patients.

The complex response of the host against infection requires the correct identification of the microorganism, the development of an appropriate inflammatory response, including the production of cytokines, and the ending of the inflammatory phase. Inflammatory response should be sufficient to overcome the proliferation and dissemination of the microorganism, and should also remain confined to avoid dissemination into the systemic circulation, which could induce hemodynamic disorders and/or multiorgan failure. The last decade has provided better understanding of systemic and local inflammatory response in CAP and other severe infections, especially in sepsis.[22,23,26] However, it is not as yet known what factors cause an excessive inflammatory response with deleterious effects, although it has been associated with the host and the bacterial load and the virulence of the microorganisms.[27]

A recent field of investigation is the study of genetic factors related to host response against infection. Studies on the influence of specific mutations on the different inflammation phases are grouped into four categories: antigen recognition, proinflammatory response, antiinflammatory response, and effector mechanisms.[28]

Microorganisms are recognized by members of a family of pathogen-associated molecular pattern receptors (Toll-like receptor [TLR]) that initiate innate host defense. There are at least 10 different receptors, of which TLR-4 recognizes endotoxins and lipopolysaccharide-binding proteins, and TLR-2 recognizes, especially, Gram-positive bacteria and peptidoglycans. Some mutations of the TLR-4 gene are associated with a greater propensity for severe infections. For example, carriage of the TLR-4 299Gly and Thr399Ile mutations was found more often in a cohort of patients with septic shock,[29] and mutations in a gene responsible for the lower production of the plasma opsonin mannose-binding lectin[30] have been linked to invasive pneumococcal disease in children.

Genetic variability in the production of proinflammatory cytokines has also been studied, with the polymorphisms in the tumor necrosis factor (TNF)-α gene having received considerable attention. The presence of the TNF-308A allele is associated with a higher TNF-α production and mortality,[31] while the G allele is associated with a lower production of TNF and a lower incidence of shock. There are fewer studies regarding interleukin (IL)-6. Nevertheless, the GG genotype of IL-6 (GG genotype of the IL-6–174 polymorphism) is associated with a lower production of IL-6 and a greater survival in sepsis.[32] The absence of the surfactant protein B + 1580 of the surfactant increases the susceptibility to lung injury. The CC and CT genotypes at the surfactant protein B + 1580 site are associated with an increased risk for mechanical ventilation requirement, respiratory distress, and septic shock.[33]

IL-10 has an important antiinflammatory effect and participates in the resolution phase of inflammation, but may have a harmful effect if the microorganism has not been cleared. Stimulated IL-10 release is higher in IL-10 homozygous G patients, who have the highest risk for septic shock[34]; and a higher frequency of the IL-10 G allele has been found in CAP patients who died.[35]

Factors Associated With the Causal Microorganism: In CAP due to *Legionella pneumonia* or Gram-negative microorganisms,[10] the probability of TF increases twofold and fourfold, respectively. Legionella CAP can initially behave as a progressive pneumonia, with a high mortality, and takes longer to resolve.[36] Moreover, when the etiology of CAP is mixed, the resolution is delayed.[37] Pleural effusion, and specifically empyema caused by *S pneumoniae*, are associated with early and late TF.[10,11] Recently, the presence of community-acquired MRSA (Panton-Valentine leukocidin strains) has been recognized in severe CAP, which may lead to cavitary lesions and sepsis.[38]

Treatment-Related Factors: Discordant treatments,[10] as well as to treatments nonadherent to guidelines,[39] have been associated with TF and a higher mortality.[40–43] We have reported that when the initial antibiotic treatment was selected by a pneumologist or by the clinical resident, treatment failure was lower than when selected by a nonpneumology specialist.[39]

Interestingly, TF is reportedly lower in influenza-vaccinated patients. This vaccine has a favorable impact against the appearance of pneumonia and in the reduction of hospitalization and mortality.[44] Moreover, the percentage of influenza-vaccinated patients was also found to be lower among those with early failure.[10]

Diagnostic Evaluation of TF

Approach to TF or Failure To Achieve Clinical Stability: The approach to a patient with TF requires several steps and the assessment of several aspects: the host factors that may explain delayed resolution, the clinical severity, and the evolution of infiltrates in

radiographs. Evaluation of clinical response should be performed within the first 3 days of treatment if there is no improvement in symptoms, or even before if there is early failure.

The first step includes careful revision of the clinical history and the initial microbiological results to confirm the diagnosis of CAP. Although routine initial microbiological studies have not demonstrated any impact on patient outcome, they may provide useful information if the diagnosis is confirmed.[45–47] Furthermore, the presence of some microorganisms and host factors may explain the slower resolution of infectious parameters. Therefore, CAP due to Legionella, bacteremic pneumonia, and other etiologies are responsible for a protracted clinical course and delayed resolution. Elderly patients with comorbid conditions or immunosuppression may have a slower resolution of symptoms. In these cases, if there is no clinical deterioration a conservative approach with clinical monitoring and serial radiographs would suffice. Chest radiographs may show pleural effusion, lung abscess, and/or new infiltrates. Pleural effusion is a frequent association of TF and requires thoracocentesis to rule out empyema. Noninvasive microbiological studies may rule out the persistence of infection, the appearance of resistance during treatment, or the appearance of a new nosocomial infection (Table 5).

Important epidemiologic clues may orientate differential diagnosis such as unusual microorganisms related to prior journeys, pets, hobbies, or others (Table 3). Complete reevaluation of the clinical history might suggest other alternative noninfectious diagnoses and guide the differential diagnosis.

An aggressive approach is necessary in cases in which the microbiologic etiology has not been identified, when there are no host-related factors for delayed resolution, and/or on the appearance of clinical deterioration. Further radiologic studies, noninvasive samples, and endoscopic methods should be performed to evaluate the airways and to obtain samples for microbiological tests and other studies. Bronchoscopy allows direct observation of the airways and the obtaining of samples directly within the infected lobe. Protected brush specimen and BAL reportedly have a diagnostic yield of 41% in TF.[9,10,13] van der Eerden et al[48] found that the use of bronchoscopy in cases of TF or in whom sputum could not be obtained achieved diagnostic yields of 52% and 49%, respectively. A complete processing of BAL for microbiological and nonmicrobiological studies also provides useful diagnostic information (Table 6). The study of cell count in BAL fluid allows the orientation of differential diagnosis of noninfectious causes.[47] Thus, the presence of $> 20\%$ eosinophils makes it mandatory to rule out causes such as pulmonary eosinophilia, fungal infection, drug-induced pneumonitis, or others. Pulmonary hemorrhage is suggested by the presence of blood or $> 20\%$ of hemosiderin-loaded macrophages,[49] and hypersensitivity pneumonitis, sarcoidosis, or pulmonary fibrosis by the increase in lymphocytes. Microbiological studies of BAL and protected brush specimen should include stains and cultures for the usual bacteria, fungi, virus, and opportunistic germs, including conventional and modified Ziehl-Neilson stain for Nocardia, and direct immunofluorescence and culture for the investigation of Legionella. A Gram stain in BAL fluid after centrifugation is useful for more rapid identification of microorganisms and has predictive value for bacterial growth. To differentiate between colonization and infection, the results of bacterial cultures are expressed as colony-forming units per milliliter. However, the colony count of conventional bacteria should be interpreted together with other tests becasue previous antibiotic treatment may reduce the counts below the established cut-off point of 10^3 cfu/mL for protected brush specimen and 10^4 cfu/mL for BAL fluid. In patients with mechanical ventilation, samples of tracheal aspirates have a good diagnostic yield (93% sensitivity and 80% specificity for a cut-off of 10^5 cfu/mL).[50] Even though the diagnostic yield of invasive microbiological samples is good, its impact on prognosis is not clear.[14,51]

Table 5—*Microbiological Assessment Indicated for TF*

Sample	Variables
Sputum	Gram stain and conventional bacteria culture; Legionella direct immunofluorescence; Ziehl and Giemsa stain; stains for fungi
Blood	Two sets for culture
Urine	Legionella antigen;
Pleural fluid	Cultures for anaerobes; bacterial cultures

Table 6—*BAL Processing in TF*

Microbiological studies
Stains
Gram stain
Ziehl and modified Ziehl
Fungi
Opportunists
Colony count for bacteria
Specific cultures for mycobacteria, Legionella, fungi, virus
Histologic and cytologic studies
Giemsa stain for cell count and differential
Macrophages and hemosiderin-loaded macrophages
Leukocytes
Eosinophils
Lymphocytes
Malignancy
Lymphocyte subpopulation

The value of bronchial and transbronchial biopsy in TF has not been clearly established and depends on the pretest probability of other diagnoses. If airway abnormalities are found, a bronchial biopsy can be performed. The role and indication of transbronchial biopsy are not clear; it should be performed if airway examination rules out other findings, and if there is no evidence of infection because other diagnoses may be made. Arancibia et al[13] obtained up to 57% of diagnosis with transbronchial biopsy in patients with TF, although this procedure was performed in only 25% of the cases. The authors concluded that it was particularly useful for determining noninfectious causes, including neoplasia, BOOP, and histocytosis X.

The CT scan may suggest some specific microorganisms[52] and is useful to investigate complications such as empyema, pulmonary abscess, or other alternative diagnoses. Helicoidal CT may be indicated if thromboembolism is suspected. CT images suggest specific, albeit not pathognomonic, microorganisms. Thus, nodules surrounded by a halo of ground-grass attenuation with involvement near the pleura are suggestive of pulmonary aspergillus and/or mucor infection. Similar nodular images have been described in infections by Candida or cytomegalovirus, Wegener granulomatosis, Kaposi sarcoma, and hemorrhagic metastases. *P jiroveci* pneumonia often shows ground-glass opacity or images of interstitial pneumonia. Images of nodules or multiple masses with or without cavitation can be caused by Nocardia spp, *M tuberculosis*, or Q fever. Diffuse or mixed interstitial infiltrates may be due to virus or *M pneumoniae*.

Approach To Persistence of Infiltrates in Radiographs: Another clinical situation involves the persistence of residual radiographic images. The period during which a more active diagnostic process should be decided has not been completely elucidated. The approach should be more conservative on reduction of the infiltrates in the radiographs, an improvement in symptoms and when the time lapse is < 6 weeks.[5] However, if the infiltrate does not diminish after this period or if symptoms persist, a bronchoscopic evaluation and CT scan may be indicated. Feinsilver et al[7] reported that bronchoscopy was most likely to yield a specific diagnosis in nonsmoking patients with multilobar infiltrates of long duration and could be avoided in older, smoking, or otherwise compromised patients with lobar or segmental infiltrates. Although infrequent, lung carcinoma may explain unresolved images.[53] CT scan and high-resolution CT allow the identification of abnormalities in the airways, interstitium, mediastinun, or pleura, and are useful in improving the yield of transbronchial biopsy. Furthermore, in a study on the usefulness of high-resolution CT scan in acute pulmonary parenchymatous disease, Tomiyama et al[54] were able to correctly classify the etiology as infectious or noninfectious in 90% of the patients. Open-lung biopsy is indicated when other diagnostic methods are unsuccessful. Dunn et al[55] highlighted that this procedure seldom provides relevant information to improve prognosis. However, Feinsilver et al[7] achieved diagnosis by open-lung biopsy in 2 of 35 patients with nonresponding pneumonia and negative prior bronchoscopy results.

Therapeutic Management

Since infections are the most frequent causes of TF, an empirical adjustment must be made in the antibiotic therapy. An interval of 72 h is usually recommended before this change, except in cases with severe clinical deterioration and/or a worsening of the radiologic infiltrates. In early TF, broad antibiotic therapy may be administered even before 72 h. Nonetheless, prior to making the adjustment, new invasive samples should be obtained for microbiological studies whenever possible, although results may not be available until up to 48 h.

In TF, the new antibiotic regime should broaden the spectrum to cover not only the usual bacteria, but also resistant *S pneumoniae*, *P aeruginosa*, *S aureus*, and anaerobic bacteria. Treatment should include antipseudomonal β-lactams (cefepime, imipenem, meropenem, piperacillin/tazobactam) and IV fluoroquinolones. Recently, the presence of community-acquired MRSA (Panton-Valentine leukocidin strains) has been recognized in severe CAP evolving with cavitary lesions and sepsis. Depending on susceptibility tests, antimicrobial treatments may include linezolid, clindamicin, vancomycin, or combinations of these with or without rifampicin.[38] In patients with severe COPD, prolonged treatment with steroids, or those undergoing immunosuppressive treatment, the coverage of Aspergillus spp should be taken into account. In early failure and/or severe physiologic compromise, the use of activated drotecogin alfa and other sepsis strategies should be considered.

Prognosis and Outcome

TF is an independent risk factor for mortality after adjustment for the pneumonia severity index. Mortality in patients with CAP and TF is up to 43%,[11,13] depending on the cause: 88% in cases of nosocomial infection, 38% in those with primary infection, 40% in persistent infection, and 27% in the absence of diagnosis.[13] The period in which TF appears is

important because the earlier the failure the higher the mortality (27 to 30% vs 17%).[12]

Future Research

Several issues should be addressed in the next years. First, the new techniques for microbiological diagnosis such as real-time polymerase chain reaction[56,57] or microchips may yield a rapid etiologic diagnosis or identification of resistance. This faster etiologic diagnosis would increase the probability of appropriate antimicrobial therapy and reduce discordant therapy. Second, additional studies aimed at identifying the population susceptible to TF are needed. Several previous studies[58–60] using C-reactive protein, procalcitonin, and cytokines have achieved promising results. However, the predictive value for TF and the best timing for its study remain unclear. That is, we need to recognize which or when patients will have TF and, even more importantly, whether it is possible to restrain excessive cytokine release and improve the final outcome. Finally, more studies aimed at evaluating the impact of other therapies such as drotrecogin or immunomodulatory treatments on mortality are required. Some pilot reports[61,62] have demonstrated a favorable impact of glucocorticosteroid treatment on the prognosis of severe CAP. Further research with randomized studies and larger groups of patients is necessary, and the role of other anticytokines should be investigated.

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