Evaluation of Non-Resolving and Progressive Pneumonia

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Introduction

The concepts of non-resolving and progressive pneumonia are difficult to define and have led to various reports that have been modified over time. In both cases, these concepts refer to a bad therapeutic response of pneumonia and, in the case of progressive pneumonia, may cause a medical emergency with vital implications for the patient requiring very rapid changes in diagnostic and therapeutic attitude.

The initial difficulty for a clinician is to decide precisely whether the patient has non-resolving or progressive pneumonia, since different authors have arbitrarily used time for definition [1]. The knowledge of the natural clinical manifestations of community-acquired pneumonia (CAP), the evolution of its symptoms, and the speed of radiographic resolution have provided the basis for defining these terms. Thus, in 1987, Fein and colleagues used clinical criteria to define non-resolving pneumonia as a clinical syndrome in which focal infiltrates clearly begin with some clinical association of acute pulmonary infection (that is fever, expectoration, malaise and/or dyspnea) and do not resolve in the expected time. In 1991, Kirtland and Winterbauer [2] added radiographic criteria and slowly resolving pneumonia was defined as a clearing of the radiographic image of less than 50% in two weeks or incomplete at 4 weeks. Another criteria includes a minimum of 10 days of antibiotic therapy and a radiographic infiltrate that has not resolved in an expected period of time based on the presumed diagnosis.

There are fewer definitions for the concept of progressive pneumonia. In the recent recommendations of the American Thoracic Society (ATS) for the management of CAP [3], the following clinical criteria were used for its identification: clinical deterioration after 24 hours of treatment with an increase of 50% in the radiographic images. In the same guidelines, therapeutic failure or non-responding pneumonia was defined as the absence of clinical stability on the third day with no known coexisting factors of slow response or response on day 7. Örtqvist et al. [4] observed progressive pneumonia in 6.5% of the patients showing intrahospital antibiotic treatment failure within the first 48–72 hours. Arancibia et al. [5] defined progressive pneumonia as clinical deterioration with respiratory insufficiency requiring mechanical ventilation or septic shock after 72 hours of treatment, and non-responding pneumonia when there is persistent fever (> 38 °C) with clinical symptoms after at least 72 hours of treatment.

The incidence of non-resolving pneumonia has not been clearly established. Approximately 10% of hospitalized patients do not adequately respond to empiric treatment and another 6% may evolve to progressive pneumonia [4, 6]. In the group of CAP patients with non-resolving pneumonia, Arancibia et al. [5] found

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that 39% evolved to progressive pneumonia. The incidence of non-resolving nosocomial pneumonia is higher. Alvarez Lerma et al. [7] found values of 36% with a lack of clinical response and Crouch et al. [8] observed up to 60% in ventilator-associated pneumonia (VAP).

The mortality of patients with CAP and non-responding pneumonia was 43% [5] in one study, a value that is three-fold higher than the global mortality reported in hospitalized patients (5–15%). Moreover, when the cause of therapeutic failure was the consequence of nosocomial infection, mortality was 88%. In fact, this cause was an independent predictive factor of death with a relative risk of 16 (RR 16.7; CI 95%: 1.4–1.94). This increased mortality did not occur if the cause of failure was due to primary or persistent infection or for other reasons. In another study of non-responding nosocomial pneumonia in patients admitted to a medical intensive care unit (ICU), Pereira et al. [9] found a similar global mortality (43.4%), although this study was not adjusted for other risk variables. In a recently finished study, the mortality was five-fold greater in a group of patients with nosocomial pneumonia (M. Ionas and A. Torres, personal communication).

Factors Associated with the Resolution of Pneumonia

Factors related to the host and the causal microorganism are implicated in the disappearance of symptoms and radiographic resolution of pneumonia.

Host Factors

The expected therapeutic response in pneumonia is the disappearance of fever within 3–5 days, improvement in leukocytosis by day 4, while the crackling on pulmonary auscultation persists for more than 7 days. With regard to the resolution of radiographic condensation, at 4 weeks up to 40% of the patients still present images [3]. In classical studies, most of which were performed in hospitalized subjects, it is known that advanced age, alcoholism and comorbidity such as diabetes mellitus, coronary artery disease and other diseases delay the resolution of CAP [1, 2, 10, 11].

The initial severity of the presentation of pneumonia influences the posterior evolution and prognosis. Thus, the initial severity measured as PSI or Fine risk scale, graded in five classes (I–V) [13], including 20 combined prognostic variables such as age, comorbidity, and analytical and radiological alterations is associated with the resolution of signs and symptoms. Halm et al. [14] found that the number of days until disappearance of fever, respiratory insufficiency, and normalization of vital signs (heart and respiratory rate, and blood pressure) depended on the class of initial risk. Thus, the more severe, the higher the number of days necessary to achieve clinical stability, ranging from 5–7 days according to the different conservative cut offs chosen.

In the latest ATS recommendations [3], three periods of clinical response have been proposed to orient the clinician in the evaluation of therapeutic response: the first on initiation of treatment, the second begins at day 3 when the patient is expected to achieve clinical stability, and the third period is that of recovery and resolution of previous alterations.

In a cohort of immunocompetent individuals, including hospitalized and ambulatory patients, it was found that radiographic resolution is obtained in 67% of the

cases within 4 weeks and in 73% at 6 weeks [14]. The resolution was rapid in non-smokers and in those with ambulatory CAP [1, 10, 11], and an inverse correlation was observed with the number of lobes involved on radiography and age [14]. Previous studies have demonstrated the influence of some factors on clinical resolution such as bacteremic CAP with multilobar involvement.

Host inflammatory response versus infection with local and systemic production of proinflammatory cytokines has been correlated with initial severity of pneumonia and mortality. Cytokines participate in response to infection with activation of the immune cells and recruitment of monocytes and neutrophils. Although these mediators have a beneficial effect on host response, excessive production may have a deleterious effect [15–17]. Thus, high plasma levels of interleukin (IL-)6 and tumor necrosis factor (TNF)-α have been correlated with higher mortality in CAP and acute respiratory distress syndrome (ARDS) [18]. Some recent studies in patients with sepsis have suggested that the balance between proinflammatory and antiinflammatory cytokines has a role in patient outcome [17]. To date, the implication of local and systemic response of cytokines in non-responding and/or progressive pneumonia remains not very well known. Preliminary studies, in patients receiving empiric treatment for ICU-acquired pneumonia, have found that high serum levels of IL-6 on the first day represent an independent risk factor and predictor of non-responding pneumonia (A. Torres, personal communication). An adequate, balanced response to cytokines may be a key factor contributing to the lack of response despite adequate initial antibiotic treatment. In a pilot study, Monton et al. [19] found that the use of glucocorticoids in the treatment of severe pneumonia was able to reduce inflammatory response with a decrease in IL-6 and TNF-α and lower observed mortality.

Factors Related to the Causal Microorganism

The causal microorganism plays an important role in the natural evolution of CAP. The most frequent causal microorganisms of CAP are *Streptococcus pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae* and enteric Gram-negative microorganisms, and the relationship established with the host determines peculiarities in the resolution of the symptoms and radiographs. *S. pneumoniae* is the most frequent causal microorganism producing the most deaths by CAP. Its evolution largely depends on the interrelation with the host characteristics, therefore weak elderly patients with comorbidity and immunodepression have the worse prognosis and slowest resolution. Classical studies have shown that from 8–10 weeks the disappearance of radiographic images is complete in 90% of the patients. However, this resolution is also delayed in CAP with bacteremia and multilobar involvement. The risk factors associated with delay in resolution are advanced age, chronic obstructive pulmonary disease (COPD), alcoholism and multilobar pneumonia. On the contrary, in individuals under the age of 50 years, the resolution of infiltrates takes place within 12 weeks in 94% of the cases.

Legionella spp. is the cause of 1–8% of CAP and is somewhat higher in patients requiring admission to an ICU. The evolution of the symptoms of CAP by *Legionella* spp. is slower than that with other typical microorganisms, and may even lead to progressive pneumonia, triggering severe respiratory insufficiency and radiographic progression [20]. The radiographic evolution of this type of pneumonia may show worsening in condensation and dissemination to the contralateral lung in one third

of the patients [21], particularly in mixed infection by more than one species of *Legionella;* normalization of the images within 4 weeks is only achieved in 12%, and in up to 40% residual lesions may be present at three months [11]. In previous studies it has been shown that the percentage of patients presenting resolution in the first 4 weeks (29–52%) is lower than for *S. pneumoniae*. In immunosuppressed patients, cavitation may appear during the evolution of CAP.

Mycoplasma pneumoniae is the most frequent causal microorganism in youths, although it may affect patients of all ages. Although it may evolve, with progression in radiologic lesions in some cases, its evolution normally shows resolution of radiographic lesions in 98% of patients within 8 weeks [1, 22]. Nonetheless, if *Mycoplasma pneumoniae* causes CAP in a patient with alterated defenses, it may evolve with a more severe clinical course and worse prognosis.

Fewer studies have been performed in patients with CAP by *Chlamydia pneumoniae* but its course is more benign than that of *S. pneumoniae* and *Legionella* and radiographic lesions are cleared within 4–6 weeks. In a study comparing different parameters of CAP by *Chlamydia* alone or in association with *S. pneumoniae,* Kauppinen et al. [23] reported worse prognosis, a greater number of days of hospitalization, and slower radiographic resolution when CAP is caused by mixed organisms. Less information is available on the natural evolution and rate of radiographic resolution for other organisms, less commonly involved in CAP.

The interaction between the causal microorganism, bacterial load, and the host may trigger a determined inflammatory response with a fundamental role in clinical response and resolution. Some authors have demonstrated differences in the production of cytokines according to the causal microorganism. Lieberman et al. [24] found higher serum concentrations of IL-1β and IL-6 in CAP caused by *S. pneumoniae* than that caused by *Mycoplasma*. From another perspective, some hypotheses have indicated the possibility that persistent levels of cytokines may favor the growth of nosocomial bacteria. Thus, in *in vitro* studies with different concentrations of cytokines, Meduri et al. [25] found a higher concentration-dependent growth of *S. aureus*, *Acinetobacter* spp. and *Pseudomonas aeruginosa.*

Causes of Non-Resolving and Progressive Pneumonia

The causes of non-resolving and progressive pneumonia are classified in two groups: infectious and non-infectious origin [3].

Infectious Causes

When the clinical and/or radiographic evolution of the patient does not follow the normal previously mentioned parameters this may be due to an etiology of CAP by microorganisms resistant to antibiotics, unusual pathogens or a complicated evolution of the pneumonia itself [3, 5]. Arancibia et al. [5] found that nearly 70% of causes of treatment failure were for infectious reasons. Concerning resistance, the normal treatment schedules in CAP adequately cover resistant *S. pneumoniae.* Nevertheless, therapeutic failure has been observed due to resistance to third generation cephalosporins or the new fluoroquinolones, specifically levofloxacin [26], and, thus, surveillance is necessary since resistance may even develop during treatment.

Initial empiric treatment may fail when the etiology is due to infrequent or unusual CAP microorganisms; *S. aureus* and *P. aeruginosa* are microorganisms which are not adequately covered with the usual empiric therapeutic schedules recommended in CAP. Although these microorganisms are infrequent, their mortality, particularly with *P. aeruginosa,* is high and, thus, the risk factors for this microorganism have been reported in detail in the latest ATS recommendations with the aim of selecting the ideal initial treatment [3]. Arancibia et al. [5] found five cases of *Pseudomonas* in 49 (10.2%) cases of non-responding pneumonia due to persistent infection in three patients and the later appearance of nosocomial infection in two cases. In non-responding ventilator-associated pneumonia (VAP), multiple resistance of the microorganisms to the usual antibiotic treatments is responsible for the lack of resolution in 50% of episodes and the most frequent microorganisms were methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa* and *Acinetobacter* spp. [27].

Mycobacteria, *Nocardia* spp., *Pneumocystis carinii,* anaerobes, leptospires, and endemic fungi are included within the group of unusual microorganisms requiring a specific antibiotic treatment other than that recommended in the norms of initial empiric treatment for CAP. Tuberculosis may be suspected in concrete environments or in subjects from risk-related groups or countries with a high incidence of this disease. Although infrequent and with a subacute course, environmental mycobacteria may lead to middle lobe syndromes or lesions in the pulmonary apex with cavitation. *Nocardia* spp. is a microorganism which may be an etiological agent in patients treated with steroids and/or immunosuppressive therapies, such as those with COPD, systemic diseases, transplant recipients, and others [28]. Contact with animals for work, leisure, and/or housepets may lead to infection by leptospires, psittacosis, tularemia, and hantavirus.

Complications may produce a slower resolution or progression of CAP with the appearance of shock or respiratory distress or multiorgan failure (MOF). Pleural effusion is a frequent cause of lack of response requiring radiography and/or computed tomography (CT) for its exclusion since thoracocentesis and analysis of pleural fluid is necessary. Metastatic infections such as endocarditis, arthritis, and peritonitis are more frequent in bacteremic CAP.

Non-Infectious Causes

Other diseases with acute involvement of the pulmonary parenchyma may simulate CAP and therapeutic failure. This group includes: neoplasms, pulmonary hemorrhage, inflammatory diseases such as bronchiolitis obliterans and organizing pneumonia (BOOP), acute interstitial pneumonitis, eosinophilic pneumonia, hypersensitivity pneumonitis, and others. The frequency of non-infectious etiologies is not well established. Neoplasms are the most frequent, with Feinsilver et al. [29] observing 10% of lung cancers in adults with non-resolving pneumonia. Örtqvist et al. and Arancibia et al., however, found a lower percentage of neoplasms (around 1–6%) [4, 5].

Evaluation of Non-Resolving and Progressive Pneumonia

Clinical Evaluation

In a patient with non-responding or progressive pneumonia a complete reevaluation of the anamnesis and a full physical examination are required in order to rule out infectious and non-infectious causes. This evaluation includes important epidemiologic keys, which may reveal unusual microorganisms (Table 1), risk factors for resistant microorganisms, or infection by the human immunodeficiency virus (HIV).

Microbiologic investigation (Table 2) may begin with studies of non invasive samples such as sputum (with special conventional and modified Ziehl staining for *M. tuberculosis* and *Nocardia*, methenamine silver for *P. carinii)*, urinary antigens detection, blood cultures and serum antibody studies. More recent techniques include blood and urine PCR (polymerase chain reaction) which allow identification of *S. pneumoniae, Legionella* and *C. pneumoniae* and *M. pneumoniae* in pharyngeal swabs [30]. The use of these techniques, however, is not completely standardized and is still being developed.

Role of Fibrobronchoscopy

Respiratory samples may be obtained with fibrobronchoscopy (Table 2) and, at the same time, the permeability of the airway may be examined at the same site in which pneumonia is located. The diagnostic yield for some bacterial microorganisms may be reduced because of previous antibiotic administration thereby decreasing their usefulness, being around 41 [4] to 42% [5] in non-responding pneumonia, and 72% [9] in nosocomial pneumonia in the ICU.

Table 1. Possible causal microorganism according to epidemiologic data

Coxiella burnetii	Cats Goats Sheep Cattle
Tularemia	Rabbits Ticks
Leptospirosis	Rats
Plague	
Psittacosis	Birds
Anaerobes	Nursing-home Reduction in level of consciousness Alcoholism
Steroid treatment	*Nocardia* *Aspergillus*
Recent journeys	Dimorphic fungi *Burkholderia pseudomallei* Tuberculosis

Table 2. Microbiologic studies indicated in non-resolving or progressive pneumonia

Sputum	Gram stain and conventional bacterial cultures DFA *Legionella* Giemsa staining Normal and modified Ziehl staining Staining for fungi
Blood cultures	2 sets
Urine	Antigen for *Legionella* and *S. pneumoniae*
Bronchoalveolar lavage (BAL) fluid	Gram stain and intracellular bacteria Bacterial cultures (colony counts) Normal and modified Ziehl Giemsa stain Staining for fungi DFA *Legionella*
Protected specimen brush (PSB)	Gram stain and intracellular bacteria Bacterial cultures (colony counts) Normal and modified Ziehl Giemsa stain Staining for fungi DFA *Legionella* PCR
Pleura	Cultures for anaerobes Bacterial cultures Normal and modified Ziehl

DFA: direct fluorescent antibody

Bronchoalveolar lavage (BAL) fluid and protected specimen brush (PSB) are recommended prior to changes in therapy in order to avoid the masking of unusual microorganisms, which are persistent or resistant. False negative cultures may be found in bacteria such as *S. pneumoniae, H. influenza* or anaerobes although these microorganisms are not the most frequently found in non-responding pneumonia. If possible, respiratory samples should be obtained by both, complementary, techniques. Nonetheless, BAL fluid is the most complete sample since it analyzes an anatomical pulmonary area corresponding to around 106 alveoli, in contrast to PSB, which collects airway secretions at the level of subsegmentary bronchi. BAL fluid therefore provides valuable information for differential diagnosis and a sufficient quantity of respiratory sample for studying the cellular component and the fluid [31].

A simple differential cell count from BAL fluid provides useful diagnostic data (Table 3): the predominance of neutrophils is suggestive of infectious disease; the presence of eosinophils >20% of eosinophilic pneumonia, fungal infection, drugs or others (Table 4); the presence of blood or >20% hemosiderin macrophages (Table 5) are suggestive of pulmonary bleeding [32]; and an increase in lymphocytes due to hypersensitivity pneumonitis, sarcoidosis or pulmonary fibrosis. In patients with delayed-resolution pneumonia after 2 weeks of treatment, the persistence of an inflammatory cell pattern has been demonstrated in the BAL fluid with higher percentages of lymphocytes, neutrophils and eosinophils than in patients with complete resolution [33].

Table 3. Possible diseases depending on differential cell count in BAL fluid

↑	**Polymorphonuclear leukocytes**
	▮ Bacterial infection
	▮ BOOP (bronchiolitis obliterans and organizing pneumonia)
↑	**Lymphocytes**
	▮ Tuberculosis
	▮ Hypersensitivity pneumonitis
	▮ Sarcoidosis
	▮ Idiopathic pulmonary fibrosis
↑	**Hemosiderin-laden macrophages**
	▮ Alveolar hemorrhage
↑	**Eosinophils**
	▮ Eosinophilic pneumonia
	▮ Fungal infection
	▮ *P. carinii*
	▮ Systemic diseases
	▮ Drug-induced disease

Table 4. Studies recommended for eosinophilia in BAL fluid

▮ Parasite infection	▮ Mycobacteria
▮ Previous drugs	▮ *P. carinii*
▮ Fungi	▮ Neoplasms

Table 5. Studies recommended for macrophages with hemosiderin or blood in BAL fluid

▮ Autoantibodies: pANCA, cANCA, antibodies against basement membrane
▮ Renal function with biochemical and sediment tests
▮ Bronchial and/or transbronchial biopsy

In a group of pneumonias with bad therapeutic response in ICUs, Jacobs et al. [34] were able to orient the diagnosis towards a non-infectious etiology in 19% of cases, with the study of cytocentrifuged BAL fluid. The suspected diagnosis was achieved with May-Grünwald Giemsa staining for the identification of cells and Perls' staining for haemosiderin visualization and was confirmed by other diagnostic methods in 77% of cases.

Gram staining performed in cytocentrifuged BAL fluid is also useful in the identification of the microorganism and has a predictive value of bacterial growth. This method is rapid and may aid in decision making regarding changes in antimicrobial therapy. The process of microbiologic study should include conventional bacteria, normal and modified Ziehl staining for *Nocardia*, fungi and opportunistic bacteria [31]. The investigation of *Legionella* should be performed with direct immunofluorescence and posterior cultures. Recent PCR techniques with a greater sensitivity for the detection of microorganisms may increase the diagnostic yield,

although careful interpretation is required because of their capacity to detect molecular components or incomplete microorganisms. To identify conventional bacteria with the aim of separating contamination from infection, quantitation of cultures is necessary. Bacterial cultures should be interpreted together with clinical data and other tests since previous antibiotics may reduce the counts below the established cut offs (103 for PSB and 104 for BAL fluid).

Ortqvist et al. [4] found that BAL fluid and PSB provided diagnostic information in 79% of patients, with 50% showing positive findings and 29% negative findings including another diagnosis or adequate treatment due to the lack of demonstration of the microorganism. Arancibia et al. [5] isolated microorganisms in 40% of the BAL carried out in patients with prior therapeutic failure and in 42% of the PSB samples. In the same study, the most frequent causes of therapeutic failure were determined corresponding to primary, persistent or nosocomial infections and 18.3% were due to non-infectious illness.

Pereira et al. [9] studied the impact of BAL fluid on nosocomial pneumonia with previous therapeutic failure in a medical ICU with a diagnostic yield of 75% (>103 cfu/ml if receiving treatment or >104 cfu/ml) and found resistant nosocomial microorganisms despite previous antibiotic treatment. These findings allowed modification of antibiotic treatment in more than half of the patients (54.8%), which, however, was not accompanied by a reduction in mortality.

In non-resolving pneumonia, BAL fluid allows identification of resistant microorganisms (generally *P. aeruginosa*). Confirmation of the high concentrations of these microorganisms with levels of >104 cfu/ml is useful for predicting bad prognosis. However, the therapeutic changes carried out with the information obtained do not reduce the probability of mortality. Likewise, Luna et al. [35] found that the results of BAL fluid analysis confirmed the adequacy or inadequacy of initial treatment and determined the difference in mortality in these two groups, 35 versus 91%. In a review of the role of serial bronchoscopy in non-resolving nosocomial pneumonia, Niederman [36] concluded that, although this technique provides useful information in regard to etiology, its possible impact on reducing mortality has not been demonstrated.

The diagnostic yield of bronchial and transbronchial biopsy in non-resolving or progressive pneumonia has not been established and depends on the probability of other suspected etiologies. Arancibia et al. [5] made a diagnosis in up to 57% of cases when transbronchial biopsy was performed in non-resolving pneumonia, despite this sample only being obtained in 25% of cases. In this study, in which 18% of the causes of therapeutic failure were of non-infectious origin, the authors concluded that this technique is particularly useful in the diagnosis of this group which includes neoplasms, BOOP, and histiocytosis X.

Role of Radiologic Studies

The follow-up by chest radiograph in pneumonia, when clinical evolution is adequate, is not required to indicate sequential treatment or hospital discharge and one control after 4 weeks of discharge is sufficient [3]. In progressive pneumonia, the clinical deterioration and the extension of the chest radiograph lesions may even appear prior to the 72 hours after initiation of treatment. In non-resolving pneumonia, conventional chest radiographs, posteroanterior and lateral, may show pleural effusion, the appearance of cavitation and/or new infiltrates. These findings

are more evident on CT scan that also allows detailed study of the parenchyma, the interstitium, the pleura, and the mediastinum.

Pulmonary CT findings may be characteristic of some microorganisms although not being pathognomonic [37]. The appearance of nodular images with a halo sign (nodules surrounded by a halo of ground-glass attenuation) or pleura-based wedge-shaped areas of consolidation is suggestive of pulmonary aspergillosis and/or mucor. Nodular images of a similar appearance have also been described in *Candida*, cytomegalovirus (CMV) infection, Wegener's granulomatosis, Kaposi's sarcoma, and hemorrhagic metastases. The finding of ground-glass opacity or images of interstitial pneumonia are characteristic features of pneumonia by *P. carinii*. Bacterial infection with nodules or multiple masses with or without cavitation may be caused by *Nocardia* spp., *M. tuberculosis* or Q fever. Diffuse or mixed interstitial infiltrates may be due to virus or *M. pneumoniae*.

High-resolution CT (HRCT) is useful for differential diagnosis between an infectious and non-infectious etiology, although it does not specifically identify the disease. In a recent study on the usefulness of HRCT in acute parenchymatous lung disease, Tomiyama et al. [38] found that this technique correctly classified the infectious or non-infectious etiology in 90% of the subjects. This study, which was carried out in non-immunosuppressed patients without the aid of clinical data, also showed that the identification of the diagnosis was correct in 90% of the acute interstitial pneumonias, in 72% of the hypersensitivity pneumonias, and, to a lesser extent, pulmonary hemorrhages and eosinophilic pneumonia. Although the study was not undertaken in similar conditions to those of real practice, the key finding of identifying an image as infectious or not is interesting and hopeful.

Other Studies

Other imaging studies are performed according to the initial suspicion such as perfusion ventilation scintigraphy to exclude pulmonary embolism, which should be suspected in the absence of microorganisms and in patients with risk factors, such as recent surgery, prolonged immobilization or signs of deep vein thrombosis or right ventricular failure. Spiral CT and pulmonary angiography complement this diagnosis.

An echocardiogram should be performed if endocarditis, pericarditis or congestive cardiac failure are suspected.

Open biopsy is indicated when other diagnostic methods have been given no results. However, in immunocompetent patients, Dunn et al. [39] reported that relevant information for improving prognosis is seldom provided with this technique.

Empiric Therapeutic Changes in Non-Responding Pneumonia

Infectious causes are the most frequently observed in non-responding pneumonia and the results of microbiologic studies may be delayed up to 48 hours. Thus, after obtaining the samples, an empiric therapeutic change is indicated. To carry out this change, all the initial microbiologic results should be reviewed and treatment should be adjusted with the determination of positive results. However, the initial results will probably provide little information. In these circumstances, the empiric therapeutic change should be aimed at extending the bacteriologic spectrum

including the possibility of resistant or unusual microorganisms. In the study by Arancibia et al. [5], the most frequent microorganisms found in non-responding pneumonia were *S. pneumoniae* and *P. aeruginosa.*

The treatment of non-responding CAP patients should include combined therapy and coverage should be extended to cover anerobes, *P. aeruginosa* and *S. aureus* and maintain therapy towards usual microorganisms such as *S. pneumoniae* and *Legionella*, with antipseudomonal betalactamic drugs (piperacillin/tazobactam, imipenem, meropenem, cefepime) and intravenous antipneumococcal fluoroquinolones (trovafloxacin or levofloxacin) or an intravenous macrolide (azithromycin or clarithromycin). If suspicion of *Pseudomonas aeruginosa* is very high (the risk factors are defined in the latest ATS guidelines [3]), the antimicrobial therapy should include at least two antipseudomonal agents: antipseudomonal betalactam (piperacillin/tazobactam, imipenem, meropenem, cefepime) plus intravenous ciprofloxacin or aminoglucosides and intravenous macrolide (azithromycin or clarithromycin).

In non-responding nosocomial pneumonia, combinations occasionally including up to three antibiotics may be required to cover *P. aeruginosa,* MRSA, and, according to the local flora of each hospital, *Acinetobacter* spp. or others. The most frequent causes of treatment failure are inappropriate initial treatment with resistant microorganisms and superinfections by the flora of the hospital (Ionas M., Torres A., personal communication). The evaluation of the empiric therapeutic changes must, therefore, take into account the patterns of resistance themselves. The associations in these cases should include antipseudomonal betalactamic drugs (piperacillin-tazobactam, imipenem, meropenem) or antipseudomonal quinolones, aminoglucosides and vancomycin until MRSA is safely eliminated.

Conclusion

The concepts of non-resolving and progressive pneumonia are difficult to define: both refer to a failure in the therapeutic response, which in the case of progressive pneumonia may cause a medical emergency even in the first 72 hours after empiric treatment. The incidence of non-resolving pneumonia in CAP is approximately 10%, and >30% in nosocomial pneumonia. Mortality in non-responding pneumonia increases three-fold in CAP and five-fold in nosocomial pneumonia compared to global mortality in hospitalized patients. Factors associated with the resolution of pneumonia are related to host, microorganisms and the relationship between them, which may modulate the cytokine response that plays a key role in resolution. Causes of non-resolving or progressive pneumonia may be infectious or non-infectious. Management of non-responding patients requires a reevaluation of epidemiological data, a complete microbiologic investigation, with conventional and invasive respiratory samples, and performance of a new radiographic study. Empiric therapeutic changes are aimed at broadening the bacteriologic spectrum in order to cover resistant or unusual microorganisms.

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