

BRIEF CLINICAL REVIEW: NON-RESPONDING PNEUMONIA

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ABSTRACT

A slowly resolving or non-resolving pneumonia (NRP) is a common clinical dilemma, affecting 10-20% of patients hospitalised with community-acquired pneumonia. Potential causes are many and include inadequate or inappropriate antibiotic therapy, antibiotic resistant pathogens, infectious complications, or incorrect diagnosis. Objective criteria have been described to define clinical stability and represent the best current definition of adequate treatment response. The time to clinical stability varies substantially between patients, being longer in older patients, patients with comorbidities, and patients with a higher severity of pneumonia. NRP is associated with increased mortality and requirement for intensive care unit admission, and so it is essential to identify these patients. Once non-response is recognised, patients should undergo a full re-evaluation, including microbiological testing, repeat chest X-ray and consideration of further imaging, and an increased spectrum of antibiotic therapy if drug resistant pathogens are suspected. A wide range of non-infectious disorders can masquerade as bacterial pneumonia, including pulmonary embolism, malignancy, interstitial lung diseases, alveolar haemorrhage, and vasculitis. There is no uniform recommended diagnostic or treatment approach for patients with NRP. The investigations and interventions required are determined on a case-by-case basis. The present article reviews the causes, investigation, and management of NRP, and presents an algorithm for identification and management of these patients.

Keywords: Pneumonia, antibiotics, biomarkers, severity score.

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the most common acute medical conditions requiring hospitalisation.¹ The majority of hospitalised patients with CAP respond rapidly to antibiotic therapy and follow an uncomplicated course, but a proportion of patients fail to respond to initial therapy and require additional investigation and treatment.^{2,3} Despite advances in clinical care, the mortality rate remains 5-15%.^{4,5} Patients with non-responding or progressive pneumonia represent a group of patients where appropriate early intervention can improve outcome while preventing overtreatment. This article reviews the definition, causes, investigations, and management of non-responding pneumonia (NRP).

NRP is a common clinical problem that physicians will encounter regularly. The terms NRP and treatment failure are often used interchangeably by investigators, but in reality, are a quite different phenomena. Defining treatment response and non-response have important implications for clinical decision-making, since intravenous (IV) to oral switch, hospital discharge, and treatment escalation will all depend on an accurate assessment of treatment response.⁶⁻¹⁰

Treatment Response and Clinical Stability

Treatment response has traditionally been difficult to define because radiographic changes, which are used to define the presence of pneumonia, can take up to 6 weeks to resolve and often lag behind the clinical recovery of patients.¹¹ **Figure 1** illustrates

the stages of clinical recovery.¹² Microbiological resolution occurs early, with blood cultures and other microbiological samples becoming negative very quickly after commencement of antibiotic therapy. Inflammation then begins to resolve, with a reduction in inflammatory cytokines and biomarkers such as C-reactive protein (CRP).¹³ As the systemic inflammation resolves, patient symptoms start to improve until they reach a validated level of clinical symptom recovery known as 'clinical stability'.¹⁴ At this stage, pneumonia is considered to have responded to treatment, and prognosis at this point is excellent, complications are rare, and relapse is unusual.¹⁴⁻¹⁶ Patients may still have radiographic changes and will not feel fully recovered in terms of symptoms and return to usual activities. Indeed, questionnaire studies suggest that a complete return to baseline requires several weeks or even months.^{17,18}

The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) 2007 guidelines recommend the use of Halm's¹⁴ criteria for determining the presence of clinical stability, and therefore, treatment response. These clinical criteria have been extensively validated and are a reliable measure of improvement across different healthcare systems and patient populations. These criteria consist of temperature ≤ 37.8 °C, heart rate ≤ 100

beats/minute, respiratory rate ≤ 24 breaths/minute, systolic blood pressure ≥ 90 mmHg, O₂ saturation $\geq 90\%$, or arterial O₂ tension ≥ 60 mmHg, normal mental status, and normal oral intake.¹⁴ All of these criteria have to be met for clinical stability to be reached (although allowance is made for the usual functional status of patients, for example chronic obstructive pulmonary disease [COPD] patients with low resting oxygen saturations or patients with chronic cognitive impairment).⁶ These criteria have gained widespread acceptance and the time required to achieve these stability criteria is now an FDA recommended end-point for clinical trials in community-acquired bacterial pneumonia.¹⁹ In a prospective study, Aliberti et al.²⁰ showed that once clinical stability criteria were met (n=410 patients with CAP), the prognosis was excellent, with no in-hospital deaths, no episodes of haemodynamic instability, and only five patients (1.2%) experiencing respiratory complications. Similar results were reported in studies from the UK,¹⁵ US,¹³ and Spain.¹³

Alternatives to Halm's clinical stability criteria have been proposed. The simplified ATS criteria were defined in the 2001 ATS guidelines and consist of only four criteria: improvement in cough and shortness of breath, absence of fever >37.8 °C for >8 hours, normalisation of the leukocyte count by 10% from the previous day, and adequate oral intake.²¹

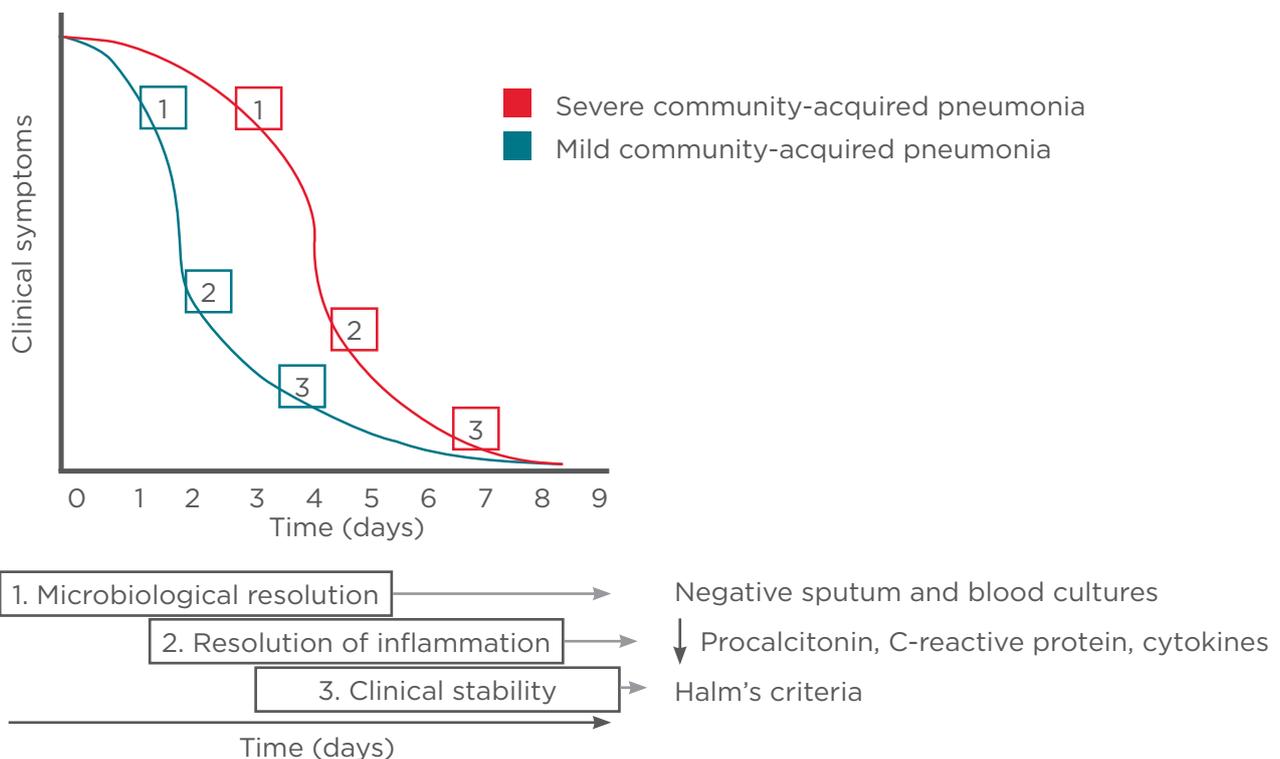


Figure 1: A schematic representation of recovery from community-acquired pneumonia.

Although simple, and therefore easier to implement in clinical practice, these criteria may be less sensitive. In the study described above by Aliberti et al.,²⁰ four patients who achieved these criteria died (compared to none using Halm's criteria) and the overall complication rate was more than double that seen with Halm's criteria. Akram et al.¹⁵ compared four strategies for determining treatment response: Halm's criteria, the simplified ATS criteria, reduction in the CURB65 score, and CRP reduction. This study found that Halm's criteria was the most effective to define treatment response (0.5% mortality, 0.3% risk of requiring mechanical ventilation or vasopressor support, and 0.7% risk of developing complicated parapneumonic effusion or empyema), although a reduction in CRP was also found to give excellent prediction.¹⁵

Biomarkers certainly appear promising as a guide to treatment response. Two studies have previously shown that a reduction in CRP by >50% from baseline indicates an excellent prognosis.^{13,22} In a prospective study of 570 patients, those achieving a reduction of CRP by \geq 50% at day 4 had a mortality rate of 0.5% compared to 18.3% in patients where the CRP failed to fall or rose despite treatment.²² A Spanish study found a reduction of CRP below 30 mg/L indicated an excellent prognosis. In the Spanish study, CRP <30 mg/L had a positive predictive value for treatment response of 97%, slightly better than procalcitonin.¹³ A combination of Halm's criteria and CRP <30 mg/L was 100% specific and had a positive predictive value of 100%, indicating no patients reaching these criteria had complications.¹³ Procalcitonin reduction certainly appears to be useful to guide treatment response, as clinical trials have indicated that antibiotic therapy can be stopped once procalcitonin falls below a threshold level (the threshold used is often different depending on the assay or disease under study), without an increase in clinical failure or mortality.^{23,24}

Treatment failure and NRP

Treatment failure is defined as persistence or progression of the infection resulting in the requirement for ventilatory support or the development of septic shock.⁶ Occurrence within the first 72 hours is referred to as early failure, and after 72 hours as late failure.²⁵ The distinction is used as it is thought that after 72 hours, late treatment failure is often due to nosocomial complications, while in the first 72 hours it is typically the result of the severity of pneumonia itself. This article will address the situation which is perhaps more difficult

to define, the one in which the patient remains unwell for longer than expected, despite apparently appropriate treatment, where they fail to improve, but without clinical deterioration.

The term 'NRP' is not clearly defined. Fein and Feinsilver²⁶ previously proposed treatment failure as delayed radiographic improvement and deterioration according to worsening of radiographic changes. As previously mentioned, radiographic changes have proven to be relatively insensitive markers of treatment response. Non-response is therefore better accepted as a lack of an adequate clinical response to treatment, and therefore, a failure of the above clinical stability criteria to improve in the expected period of time.

Improvement Rates

Patients will improve at different rates, and perhaps the most frequent cause of 'NRP' is an unrealistic expectation of how quickly patients will achieve clinical stability.⁷ The median time to clinical stability in most studies is 3 days; for this reason, the authors recommend a routine re-evaluation of all patients still hospitalised at day 3 to identify patients with NRP.¹³⁻¹⁶ The outcome of such a re-evaluation, however, may often be that the patient is progressing at the expected rate and simply requires more time. The most important predictors of delayed time to clinical stability are age, comorbidities, and disease severity. In the study by Akram et al.,²⁷ there was a direct relationship between the CURB65 score, a validated scoring system for pneumonia severity,^{28,29} and time to clinical stability, with patients with low-risk pneumonia (CURB65 0-1) responding in median 2 days, moderate pneumonia (CURB65 2) median 3 days, and patients with severe pneumonia³⁻⁵ requiring 4, 7, and 8 days, respectively.¹⁵ The same pattern is seen with other severity indices.³⁰

Other predictors of delayed time to clinical stability in a prospective Spanish study of 1,424 patients included confusion, pleural effusion or multilobar consolidation, COPD, cardiac co-morbidities, and admission to an intensive care unit.³ Gram-negative pneumonia and pneumonia due to Legionella and Staphylococci are also recognised to be associated with a prolonged recovery.⁷ Therefore, it is possible to identify on admission that older patients, patients with extensive radiological findings, chronic co-morbidities, and patients with more severe disease will require more time to respond to treatment. The authors would advocate greater

use of clinical stability criteria in clinical practice, as evidence suggests that the majority rely on clinical judgement. In a European-wide audit (n=2,039 patients with CAP from 10 countries), only 28.7% of respondents used clinical stability criteria in clinical practice.³¹

IMPACT AND CAUSES OF NRP

The lack of a uniform definition of NRP makes estimating the frequency difficult. The frequency of progressive pneumonia (treatment failure) is estimated at 15% of hospitalised patients.³ If defined as a failure to achieve clinical stability by day 3, the frequency of 'non-responding' pneumonia is as high as 40%.¹³⁻¹⁶ The true frequency lies somewhere in between, as not all patients in the latter group truly have NRP, but may progress slowly due to other reasons such as age and comorbidity. Patients failing to improve as expected have a poorer prognosis with an average increased length of stay of 4 days, and an increase in mortality reported as between

15% in those failing to reach clinical stability and 49% in patients with progressive pneumonia.^{32,33}

NRP should trigger a complete re-evaluation of the patient, taking into account not only features of the acute infection but also demographic, lifestyle, and microbiological and pharmacological factors. It is essential to avoid assuming the initial diagnostic label was correct as up to 20% of cases of NRP are found to have a non-infective cause for their pulmonary infiltrate - so called 'pneumonia mimics'.³²

Causes

Despite the above, the most common reasons identified in the literature for NRP are related to infection.³² Important considerations are pneumonia due to organisms not covered by initial empirical antibiotic therapy, such as multidrug resistant pathogens, atypical pathogens or tuberculosis, or severe infections with a recognised longer response time to treatment, e.g. *Staphylococcus aureus* pneumonia.^{6,7}

Table 1: Infections and risk factors associated with non-responding pneumonia.

Risk factor	Possible organism
Comorbidities COPD/bronchiectasis ^{36,37} Alcohol abuse ³⁸ Risk factors for aspiration ³⁹	<i>P. aeruginosa</i> , Enterobacteriaceae Enterobacteriaceae including <i>K. pneumoniae</i> , tuberculosis, anaerobes Enterobacteriaceae, anaerobes
Risk factors for MDR pathogens Immunosuppression ⁴⁰ Prior hospitalisation, previous antibiotic use, tube feeding, severe functional impairment ⁴¹⁻⁴³	Opportunistic pathogens depending on severity of immunosuppression, MRSA, <i>P. aeruginosa</i> MRSA, <i>P. aeruginosa</i> , Enterobacteriaceae including MDR
Travel South Western USA South East Asia Southern Europe	Coccidioidomycosis <i>B. pseudomallei</i> Penicillin/macrolide resistant <i>S. pneumoniae</i>
Exposures Exposure to birds Exposure to rabbits	<i>C. psittaci</i> <i>F. tularensis</i>
Demographic/lifestyle Intravenous drug use	<i>S. aureus</i>
Non-pulmonary source for infection	Line sepsis, <i>C. difficile</i> , and catheter associated infection

COPD: chronic obstructive pulmonary disease; MDR: multiple drug resistance; MRSA: methicillin-resistant *Staphylococcus aureus*.

The second major classification of infectious causes are infectious complications, most frequently complicated parapneumonic effusion, empyema, and lung abscess.^{34,35} These complications are difficult to predict, although risk factors include younger age, IV drug use, low albumin, low serum sodium, thrombocytosis, and the presence of pleuritic chest pain.^{34,35} Clinical features are notoriously poor at predicting the aetiology of pneumonia on admission but, in patients with NRP, they may give a clue to underlying aetiology (Table 1).

Non-infectious causes are less frequent than infectious disorders but may still affect >20% of patients with NRP. In one of the most detailed investigations, Arancibia et al.³² studied 444 patients hospitalised with CAP; 30 patients had NRP and 19 had progressive pneumonia. A cause was identified in 65% of patients, with infection being the most frequent. 23 patients had likely persistence of primary infection, 11 had developed a nosocomial infection, and non-infectious disorders were present in 9 (malignancy, interstitial lung disease, cardiac complications, foreign body).³² There is a feeling that non-infectious mimics of pneumonia are becoming more common as the population is ageing and becoming more comorbid. These mimics include: pulmonary embolism/pulmonary infarction, pulmonary oedema, lung cancer or metastatic disease, cryptogenic organising pneumonia, diffuse alveolar damage, alveolar haemorrhage, eosinophilic pneumonia, hypersensitivity pneumonitis, drug reaction/drug fever, vasculitis (e.g. Wegener's granulomatosis, Churg-Strauss syndrome), and lipoid pneumonitis. These may be suspected from their individual presenting features or from the results of investigations such as chest X-ray/computed tomography (CT) imaging. In elderly patients, however, the signs and symptoms of pneumonia may be less obvious, making diagnosis difficult based on clinical features alone. A detailed review of the presenting features of these disorders is beyond the scope of this review.

MANAGEMENT APPROACH TO NRP PATIENTS

Investigations

The authors advocate a re-evaluation of patients at day 3 if clinical stability has not been reached and clinical improvement is not satisfactory. Repeat testing of CRP can be useful alongside assessment

of the clinical criteria. Repeat physical examination may reveal evidence of a parapneumonic effusion. Consider non-pulmonary sources of infection which may include any organ system, and also consider super-added infections such as line sepsis and *Clostridium difficile* infection which is a common complication of antibiotic therapy in some healthcare systems.⁴⁴ Recent data suggest that cardiovascular complications including myocardial infarction (MI) are common in CAP patients and may be under-recognised.⁴⁵⁻⁴⁸ MI was identified in 20% of patients experiencing clinical deterioration in a retrospective US study (n=500 patients). Although lower rates are reported elsewhere, this is an important consideration.⁴⁵⁻⁴⁸ Electrocardiography (ECG) should be performed in patients with NRP, even in the absence of chest pain. Left ventricular failure is perhaps the most common pneumonia mimic and is a clinical diagnosis, though this may be supported by echocardiography and measurement of cardiac biomarkers.⁴⁹

Results of microbiological testing should be reviewed, as results from cultures performed on admission and sensitivity testing may only be available at 48-72 hours. Risk factors for unusual or resistant pathogens should be considered, and the appropriateness of the initial empirical antibiotic therapy considered in the context of the current clinical findings and clinical response. Repeat microbiological testing should be considered, particularly in patients that remain febrile or where the microbiological evaluation on admission was incomplete, as is frequently the case in clinical practice. Depending on the radiological and clinical circumstances, additional testing for Mycobacteria, fungi, or other opportunistic pathogens such as *Pneumocystis jirovecii* may be considered, the latter in populations with immunocompromise. In these cases, bronchoscopy is most likely to achieve high quality samples. Use of bronchoscopy and bronchoalveolar lavage is recommended in cases of clinical deterioration or failure to improve where non-invasive microbiological sampling has not been helpful, where opportunistic or unusual pathogens are suspected, and where certain pneumonia mimics are considered, such as endobronchial lung cancer, pulmonary haemorrhage, and acute eosinophilic pneumonia.⁶ There are rare cases where lung biopsies, e.g. video-assisted or open lung biopsies, are required.

Repeat chest radiography is recommended in non-responding patients at day 3 and is mandatory in

patients showing any evidence of deterioration. Identification of a pleural effusion should be followed by ultrasound scanning and pleural aspiration to exclude complicated parapneumonic effusion or empyema which require prompt chest drainage.^{6,7} After repeat physical examination, blood tests, microbiological evaluation, ECG, and chest radiography, the cause will be obvious in the majority of cases. Conventional or high resolution CT imaging is commonly used and is useful where history or radiological appearances suggest possible malignancy, lung abscess, or interstitial lung disease. Patients with NRP and risk factors for lung malignancy (particularly smoking) should undergo chest CT scanning. CT pulmonary angiogram is important to exclude pulmonary embolism as an alternative diagnosis and should be considered in patients with risk factors. It is important to remember that D-dimer is not helpful in pneumonia patients, as it rises in proportion with the severity of pneumonia.⁵⁰ An algorithm for recommended investigations in non-responding patients is shown in **Figure 2**. As previously mentioned, the differential

diagnosis of NRP is wide and no algorithm can satisfactorily capture all possible permutations, but this represents a useful guide. Conversely, in patients responding adequately to treatment, it is possible to recommend IV to oral switch therapy, hospital discharge, and/or short course antibiotic treatment.^{8-10,51,52}

Antibiotic Therapy and Corticosteroids

The decision to broaden antibiotic therapy is important, as excessive broad spectrum antibiotic therapy is associated with a higher risk of complications including gastrointestinal side-effects and *Clostridium difficile* infection. The impact of antibiotic related side-effects is often underestimated but the standard regime of beta lactam plus macrolide (the most commonly used worldwide) can be associated with diarrhoea in up to 20% of patients as an example.⁵²⁻⁵⁴ In the case of a patient with NRP, after careful exclusion of alternative diagnoses, escalation of antibiotic therapy should be considered.

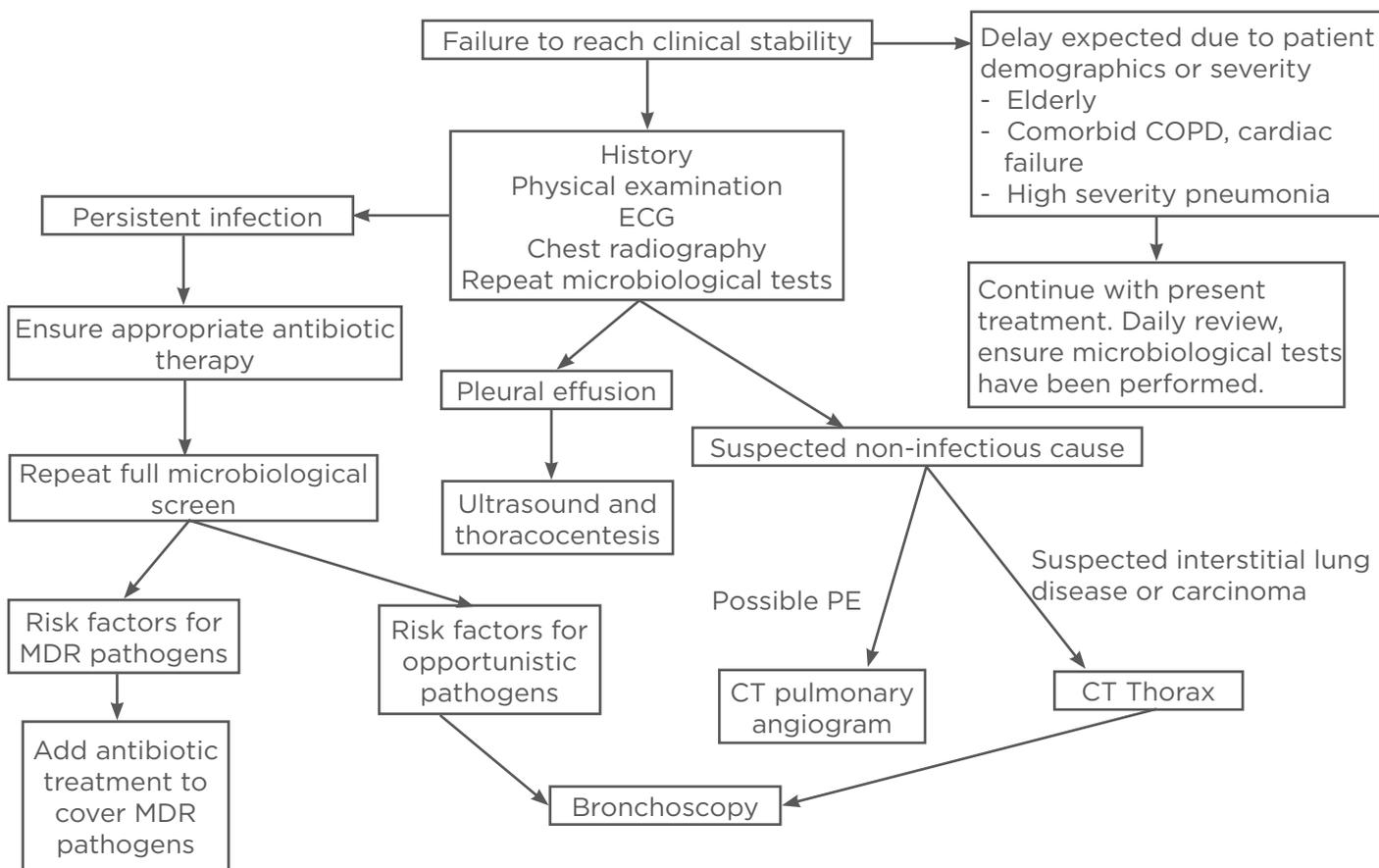


Figure 2: An algorithm for the investigation and management of non-responding pneumonia.

ECG: electrocardiography; MDR: multidrug resistance; COPD: chronic obstructive pulmonary disease; CT: computerised tomography; PE: pleural effusion.

Standard antibiotic therapy varies greatly between different healthcare systems and so no general guidance is possible here. Initial therapy should include coverage of typical organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *S. aureus*) and atypical pathogens (*Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae*).^{6,7} This is usually achieved with the combination of a beta-lactam and macrolide or a fluoroquinolone.⁶ Therefore, in a patient with NRP - if initial therapy did not include atypical coverage - this should be amended. The most frequent organisms not covered by initial antibiotic therapy include *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus* (MRSA), and resistant Enterobacteriaceae.⁴⁰⁻⁴³ The frequency of these organisms vary substantially, being more common in North America and Asia and less frequent in Northern Europe.⁴¹ In general, therefore, if an infectious cause for non-response is suspected, antibiotic therapy should be escalated to include broader coverage of *P. aeruginosa* and Enterobacteriaceae, plus MRSA in the presence of risk factors or in high prevalence regions.

Although commonly used in clinical practice for patients with NRP, there is no evidence that corticosteroids are beneficial in this context. Several randomised controlled trials of corticosteroid administration on admission have failed to demonstrate benefit, with the exception of one trial in which a 0.5 day shortening of length of stay was reported.⁵⁵⁻⁵⁸ One small pilot trial of IV dexamethasone in severe patients showed a dramatic reduction in mortality in the steroid arm, but was affected by imbalances between groups at baseline and was prematurely terminated. Therefore, corticosteroids are reserved for cases where a steroid responsive alternative diagnosis is considered, such as cryptogenic organising pneumonia or eosinophilic pneumonia.

CONCLUSION

NRP is common, and represents a difficult clinical problem as the cause may vary from a benign delay in recovery to life-threatening progressive pneumonia. A systematic approach to investigation and management is recommended with consideration of both infectious and non-infectious causes.

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