Intensive Care Med (2025) 51:893–903
https://doi.org/10.1007/s00134-025-07903-3

NARRATIVE REVIEW

How to approach a patient hospitalized for pneumonia who is not responding to treatment?

Pedro Povoa[1,2,3*], Luís Coelho[1,4], Jordi Carratala[5,6,7,8], Kelly Cawcutt[9], Sara E. Cosgrove[10], Ricard Ferrer[11,12], Carlos A. Gomez[13], Michael Klompas[14,15], Thiago Lisboa[16,17], Ignacio Martin-Loeches[18], Saad Nseir[19,20], Jorge I. F. Salluh[1,21], Sias Scherger[13], Daniel A. Sweeney[22] and Andre C. Kalil[13]

© 2025 The Author(s)

Abstract

Pneumonia is a frequent cause of intensive care unit (ICU) admission and is the most common infection in ICU patients across all geographic regions. It takes 48-72h for most patients to respond to appropriate antibiotic therapy. Non-response is typically defined as the persistence/worsening of clinical signs—such as fever, respiratory distress, impaired oxygenation and/or radiographic abnormalities—with rates ranging 20–30%. Several factors can contribute to non-response. Host factors, including immunosuppression, chronic lung disease, or ongoing aspiration, may impair resolution. Additionally, incorrect antibiotic dosing, atypical or resistant pathogens (such as multidrug-resistant bacteria, *Mycobacterium tuberculosis*, or fungal infections) may be responsible, requiring alternative antimicrobial strategies. A septic complication related to pneumonia (e.g., empyema) or not (e.g., acalculous cholecystitis) may need to be excluded. Finally, non-infectious conditions (e.g., pulmonary embolism, malignancy, secondary ARDS or vasculitis) that can mimic or potentiate pneumonia must be considered. Although non-responding pneumonia is frequent, its management lacks strong evidence, and its approach is based mostly on the art of medicine and clinical judgement. Clinicians should continuously reassess the medical history and physical exam, review microbiological data, and consider imaging such as chest CT. Bronchoscopy or repeat sputum sampling may aid in identifying alternative pathogens or non-infectious causes. The management of a non-responding pneumonia depends on the findings of a structured reassessment. Herein, we provide guidance on how to identify and manage non-responding pneumonia. Ultimately, addressing pneumonia that does not respond to antibiotics is crucial for preventing complications, optimizing antimicrobial stewardship, and improving patient outcomes.

Keywords: Pneumonia, Community-acquired pneumonia, Hospital-acquired pneumonia, Ventilator-associated pneumonia, Nonresponding pneumonia, Management

*Correspondence: pedro.povoa@nms.unl.pt
[3] Department of Intensive Care, Hospital de São Francisco Xavier, ULSLO, Lisbon, Portugal
Full author information is available at the end of the article

Springer

Introduction

Pneumonia constitutes one of the most frequent causes of admission to the intensive care unit (ICU) and it is the most frequent infection in ICU patients across all geographic regions [1].

After the administration of supportive care and antibiotic therapy, the clinical response of pneumonia is not immediate [2]. Clinicians recognize that the first 48–72h of treatment are crucial for determining the course of the illness. Most hospitalized patients with pneumonia recover with timely and appropriate antibiotic therapy and generally follow an uncomplicated course [3]. However, a sizable proportion of patients may experience non-response and treatment failure, leading to an increased risk of mortality, which can be greater than 40% [4–9]. There is a lack of epidemiologic data on non-responders and little to no evidence concerning the best clinical approach for this situation [10]. Currently available guidelines do not provide recommendations on how to manage these patients [11–13].

There are numerous arbitrary definitions for the critically ill patient with severe pneumonia who is not improving or who is deteriorating despite receiving presumed appropriate antibiotic therapy [4, 14]. The nuances associated with the definitions of "not resolving", "non-responding", or "progressive" pneumonia along with "treatment failure", are largely inconsequential to the clinician who is taking care of a critically ill patient with a diagnosis of pneumonia who is not improving or worsening [2].

Take-home message

This narrative review aims to provide clinicians with a structured approach to the management of non-responding pneumonia, namely the criteria to define non-response, its expected frequency, the differential diagnosis, how to investigate, and treatment strategies.

This narrative review aims to give to the clinicians a structured approach on the management of non-responding pneumonia, namely the criteria to define a non-responder and its expected frequency, the differential diagnosis, the optimal diagnostic steps and treatment strategies.

How and when to define a non-responder?

Despite the clinical importance of non-responding severe community-acquired pneumonia (sCAP), research into its definitions and causes remain limited. Nevertheless, it is accepted that a patient with sCAP should be considered a non-responder if there is no clinical improvement within the first 72h of receiving appropriate antibiotic therapy [2] (Fig. 1). Non-responding patients with sCAP may exhibit several concerning signs, including persistent or worsening fever, cough, sputum production, and shortness of breath [2, 4–6]. Moreover, clinical deterioration, characterized by hemodynamic instability, worsening respiratory status, deteriorating oxygenation, or the development of severe complications like acute respiratory distress syndrome (ARDS) are frequent findings [2,

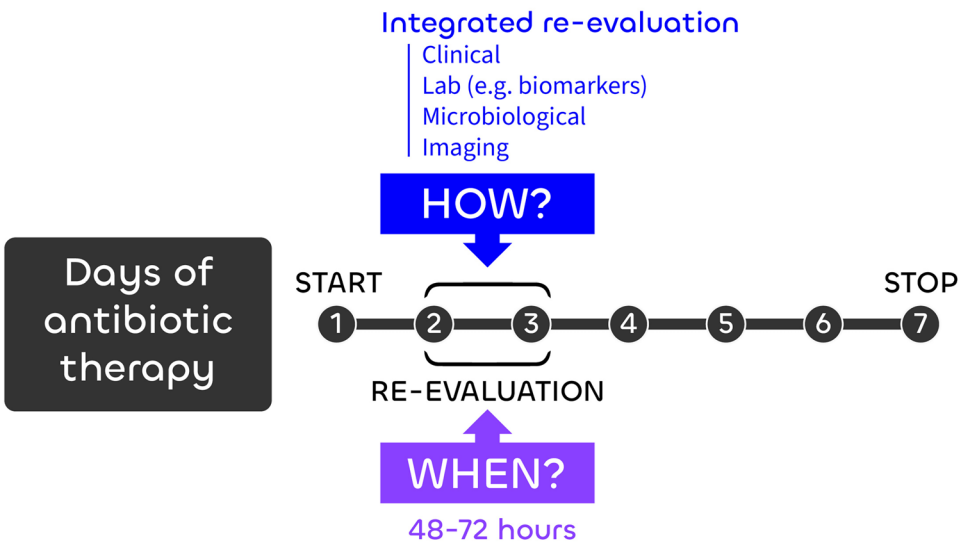

Fig. 1 How and when to define a non-responding pneumonia; a patient is considered a non-responder after at least 48-72h of appropriate antibiotic therapy; the identification of non-response results from an integrated re-evaluation of clinical signs and symptoms, lab results namely biomarkers, microbiologic results and no improvement or further progression of imaging infiltrates (see manuscript)

4–6, 15]. In addition, chest X-rays (CXR) or computed tomography (CT) scans may show no improvement or even progression of pulmonary infiltrates. Laboratory markers, such as elevated white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT), either fail to normalize or continue to increase [6, 15, 16] (Table 1).

The natural history of non-responder ventilator-associated pneumonia (VAP) is similar to sCAP, that is no clinical improvement within the first 72h of receiving appropriate antibiotic therapy (Fig. 1). The most reliable clinical indicator that a patient with VAP is not responding is lack of improvement in the PaO2:FiO2 within the first 3 days [17–20] (Table 1). Sustained fever is less specific but does indicate an unresolved inflammatory process, one cause of which could be inadequately treated pneumonia. Persistently elevated and/or rising CRP or PCT values after 3–4 days of treatment are also associated with treatment failure [21, 22]. However, a non-decreasing or increasing PCT during antibiotic therapy should not be used to guide antibiotic escalation or intensify diagnostics. A RCT of antimicrobial spectrum escalation in patients with persistently elevated or rising PCT values versus routine care reported that PCT-guided intensification led to more organ-related harm and prolonged ICU length of stay compared to routine care, without improvement in survival rates [39]. Sustained leukocytosis and radiographic infiltrates are features of non-responding pneumonia but are not specific for pneumonia.

Respiratory pathogen clearance rates vary by organism. Endotracheal cultures typically turn negative after the first doses of antibiotic in patients infected with *Haemophilus influenzae* or *Streptococcus pneumoniae*. Cultures can stay positive for days to weeks, however, in patients infected with *Pseudomonas aeruginosa*, despite clinical improvement [23]. This indicates that the patient is chronically colonized rather than persistently infected and makes culture clearance a poor guide to gauging clinical response [23, 24], that is potentiated with biofilm formation on endotracheal or tracheostomy tubes [25, 26].

To the best of our knowledge, no study has specifically evaluated whether sCAP and VAP differ in the speed at which clinical, biological and microbiological signs of infection resolve. However, from a pathophysiological perspective, the definition of resolution could differ between the two groups. First, the microorganisms responsible for these types of pneumonia are different. sCAP is often caused by microorganisms susceptible to first-line antibiotics; patients should respond rapidly to narrow-spectrum antimicrobials. As a result, the probability of receiving appropriate antimicrobial treatment is higher. Second the resolution of pneumonia is related to the severity of local pulmonary lesions, the presence of sepsis or septic shock, and in some cases multiorgan failure. These features may also differ in patients with sCAP vs. VAP.

In a recent multicenter study in critically ill patients with sCAP, the incidence of appropriate antimicrobial treatment was 97% [27]. On the other hand, a lower incidence of appropriate antimicrobial treatment was reported in a recent European study of VAP patients, 68% [28]. The ENIRRIs study, including different types of hospital- and ICU-acquired lower respiratory tract infections, reported higher 90-day mortality when pneumonia was caused by multi-drug-resistant (MRD) pathogens [9, 29].

It seems reasonable to suggest a common definition for non-response in sCAP and HAP/VAP including sustained fever, lack of improvement or deterioration in oxygenation, radiologic deterioration, and persistently elevated or rising biomarkers, as CRP or PCT, at day 3 compared to baseline (Fig. 2).

Table 1 Approach to non-responding pneumonia

Criteria	Expected resolution
Clinical	Fever, tachypnea, tachycardia, shortness of breath (48–72 h) Hemodynamic instability, worsening oxygenation (PaO2:FiO2), development of ARDS Fatigue and cough (up to 2-weeks)
Laboratory (Biomarkers)	Persistence of elevated PCT (PCT-ratio), CRP (CRP-ratio), WBC, lactate
Radiographic	Radiologic deterioration Time-to-resolution of lung infiltrates: 4-weeks in most cases ~ 10 weeks for severe pneumonia

ARDS acute respiratory distress syndrome; *CRP* C-reactive protein; *PCT* procalcitonin; *WBC* white blood cell count

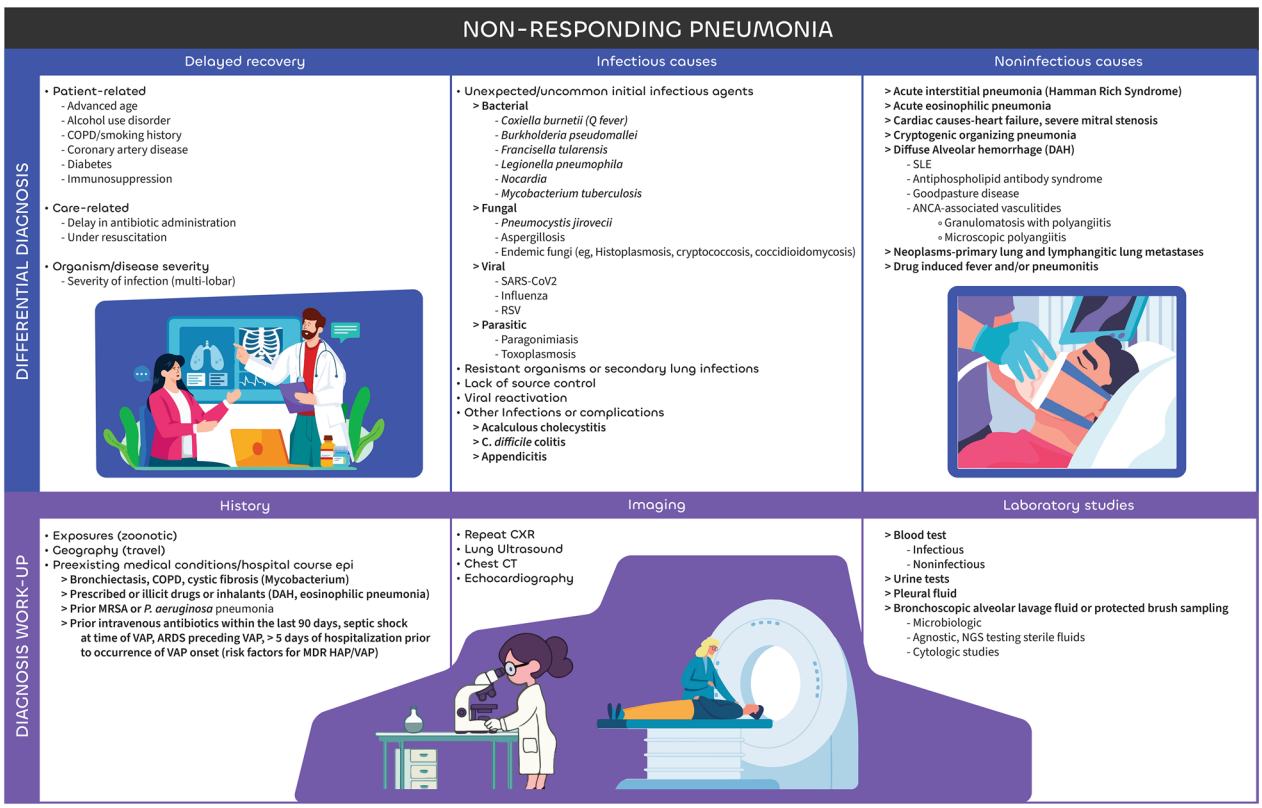

Fig. 2 Non-responding pneumonia presenting the differential diagnosis and the proposed diagnostic work-up

What is the frequency of non-responders?

In sCAP, one common reason for ICU admission is treatment failure. Even when guideline concordant antimicrobials and adequate supportive care are administered, non-response is relatively common. Studies report varying non-response rates in ICU patients with sCAP ranging from 15 to 30% [30–32]. Non-response is associated with worse clinical outcomes including longer lengths of stay and higher mortality rates. Factors such as delayed or inappropriate antibiotic therapy, infection with MDR pathogens, immunosuppression, and higher disease severity (e.g., high sequential organ failure assessment (SOFA) scores, septic shock, severe acute respiratory failure) contribute significantly to non-response rate.

HAP/VAP present even more complex therapeutic challenges, especially in critically ill patients where the risk of MDR pathogens is higher [33]. Although the impact on outcomes is unclear, treatment failure is more frequent in HAP/VAP compared to sCAP. Non-response rates in HAP/VAP range from 20 to 40%, depending on the study population and pathogen involved [11]. Factors such as the presence of *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, antibiotic resistance rate, and comorbidities like chronic obstructive pulmonary disease (COPD) and immunosuppression are associated with treatment failure. A recently published meta-analysis of treatment strategies for non-ventilator HAP, including 39 RCTs and 4807 patients, confirmed that HAP treatment failure rates are high (between 30 and 45%) [34]. Regarding VAP, case-mix and diagnostic definitions are important determinants of clinical failure rates. As with non-ventilator HAP, treatment failure rates hover around 30% [35]. Interestingly, carbapenem-based empiric regimens were associated with lower failure rates and mortality in VAP; however, this effect was not observed in trials with higher disease severity and was also not associated with the identification of *Pseudomonas* as etiologic agent [35].

Which factors are important to determine non-response?

The speed at which pneumonia signs and symptoms resolve is primarily influenced by host-intrinsic factors, particularly frailty. Conditions such as diabetes, malignancy, immunosuppression, and end-organ disease often

impair neutrophil function, as well as cell-mediated and humoral immunity, which in turn affect the rate of symptom recovery. Other factors, such as impaired cough and mucociliary clearance in COPD, malnutrition, chronic aspiration, impaired airway clearance in chronic alcoholism, certain neurological disorders, and impaired lung lymphatic drainage and pulmonary edema in heart failure, have all been associated with delayed resolution of pneumonia [36]. Typically, patients show clinical improvement within 48-72h of therapy, but cough and fatigue can persist for up to two weeks in patients who are otherwise improving/responding (Table 1) [37].

Other factors influencing the resolution time of pneumonia include the severity at presentation and the suspected pathogen. Severe cases, such as those with septic shock, multilobar or necrotizing pneumonia, or respiratory failure requiring mechanical ventilation, generally have longer recovery times. Certain pathogens are associated with slower rates of clinical improvement. Pneumonia caused by *Mycobacterium tuberculosis*, for example, responds more slowly to appropriate treatment compared to *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydia pneumoniae* [38]. Bacterial load and the presence of bacteremic pneumococcal pneumonia, and Legionella infections often have slower resolution rates compared to non-bacteremic infections [39].

Approach to the patient with unresponsive pneumonia – differential diagnosis

When faced with a non-responding patient with pneumonia, the critical care team must consider three broad possibilities (Fig. 2): 1) their prognostication regarding the expected time to improvement is unrealistic; 2) the antimicrobial treatment is inappropriate due to antimicrobial resistance, the presence of an unexpected infectious agent including a nosocomial pathogen or insufficient source control (e.g. empyema); 3) the patient is suffering from a viral or non-infectious process [2].

Expected recovery time

Determining the expected recovery time for critically ill patients with pneumonia is not a precise science; nonetheless, it is dependent upon a multitude of factors previously detailed. Delay in initiating appropriate empiric antibiotics or under resuscitation are modifiable risk factors that could result in delayed recovery time or adverse outcomes. While failure of a patient with sCAP to clinically stabilize after 72h of antibiotic therapy has been previously defined as "treatment failure," this time frame may be too long to wait before initiating a re-evaluation of the diagnosis in a critically ill patient [40]. Since appropriate recovery time cannot be accurately estimated, clinicians caring for critically ill patients diagnosed with pneumonia who fail to respond within 72h of antibiotic therapy or who are clinically worsening prior to 72h should reconsider the initial diagnosis and seek both infectious and non-infectious explanations for the patients' unanticipated clinical course (Table 1 and Fig. 2).

Diagnostic approach

Re-evaluation of the initial diagnosis of pneumonia

Assuming local guidelines are followed, inappropriate antibiotic therapy is seldom the cause of clinical failure in CAP but is more common in HAP/VAP, since the later is associated with a higher risk of MDR pathogens, particular in settings with high baseline MDR rates. ATS/IDSA guidelines addressing both CAP and HAP/VAP have identified risk factors for MDR organisms (Fig. 2) [11, 12]. Communication between the microbiology lab, pharmacists, and clinicians is very important to promptly identify patients with inappropriate antibiotics. In addition to the choice of empiric antibiotic therapy, it is crucial to re-evaluate its adequacy. Drug dose should be reassessed as critically ill patients experience marked pharmacokinetic changes in both the volume of distribution and drug clearance rates compared to less sick patients. In addition, antibiotic administration, namely intermittent dosing vs continuous perfusion in time dependent drugs, and antibiotic lung penetration should be checked [41]. A thorough history of the present illness can also raise the possibility of uncommon bacterial and fungal causes of severe pneumonia that may not respond to some empiric antibiotic regimens (Fig. 2). Since the COVID-19 pandemic, there is greater recognition of viral causes of severe pneumonia not responsive to empiric pneumonia therapy, including influenza (with or without bacterial co-infection), RSV, and finally HSV and CMV reactivation which have uncertain clinical impact [42].

Septic complication

Non-response could also be the result of concomitant sepsis either directly related to pneumonia or independent of a pulmonary infection. Septic complications because of pneumonia include secondary lung infection, parapneumonic pleural effusion, empyema, lung abscess, and necrotizing pneumonia [48]. Loculated or persistent effusions frequently need a chest tube for source control, often in collaboration with interventional radiology and thoracic surgery. Other septic complications not directly due to pneumonia but that could mimic a non-responding pneumonia include endocarditis, Lemierre syndrome, acalculous cholecystitis, *Clostridium difficile* colitis, or other hospital-acquired infections [2].

Wrong diagnosis

In one study conducted in the ICU, 19% of patients admitted with a diagnosis of pneumonia were ultimately diagnosed with non-infectious conditions [43]. There are several non-infectious conditions that can mimic nonresponding or worsening severe pneumonia such as heart failure, neoplasms, diffuse alveolar hemorrhage, acute interstitial pneumonitis, eosinophilic pneumonia, hypersensitivity pneumonitis, pulmonary embolism, vasculitis, and cryptogenic organizing pneumonia (Fig. 2). Another frequently overlooked diagnosis is drug induced fever. The list of antibiotics associated with drug induced fever is long and this diagnosis should be suspected particularly in the presence of eosinophilia [44]. Diagnostic uncertainty is highest when non-pulmonary conditions overlap with pulmonary inflammation.

Diagnostic work-up of non-responding patient with pneumonia

Review of patient medical history

In the setting of treatment failure, revisiting the patient's medical history can be especially useful both for identifying a possible overlooked infectious cause of pneumonia or to identify risks factors that could indicate the presence of a highly resistant organism. For example, prior animal exposures or travel history could provide clues to the presence of a rare cause of pneumonia (Fig. 2). A history, or known colonisation on surveillance swabs, of methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* infections, and receipt of intravenous antibiotics within the past 30 days should raise suspicion for a possible MDR pathogen causing pneumonia.

Imaging modalities

Radiographic findings in pneumonia generally fall into three categories: 1) focal non-segmental or lobar pneumonia, 2) multifocal bronchopneumonia, and 3) focal or diffuse interstitial pneumonia. In patients who clinically improve, ATS/IDSA guidelines do not recommend routine follow-up chest imaging [12]. However, in cases where clinical presentation is atypical despite radiographic evidence of pneumonia, repeat CXR is advised to rule out alternative diagnoses [41]. Besides, repeat CXR can show progression of disease, but more importantly may reveal fluid collections (rarely abscess, more commonly pleural effusions) which could represent lack of source control (Fig. 2), like empyema requiring drainage. Radiographic resolution can lag days to weeks beyond clinical improvement. In patients under 50 and those with mild-to-moderate pneumonia, radiographic infiltrates typically resolve within four weeks. Conversely, resolution may take up to 10 weeks in older patients, those with multiple comorbidities and COPD, or severe pneumonia [42, 43]. Slow radiographic resolution alone is not an indicator of treatment failure.

Point-of-care LUS can also be beneficial as it is more sensitive than CXR for identifying pleural effusions and can identify fluid characteristics that suggest the presence of an empyema [45]. While LUS avoids the cost and radiation of CT, it requires technical expertise and is less effective for assessing pathology deep to the lung pleura.

For non-resolving pneumonia or clinical deterioration, repeat imaging—especially chest CT scan—is strongly recommended. CT can help confirm or refute the diagnosis of pneumonia and identify alternative or concurrent conditions that may explain patients' delayed response rates, like pulmonary edema, embolism, pneumonitis, organizing pneumonia, or malignancy [46, 47]. High resolution chest CT reviewed by chest radiologists can be particularly helpful in differentiating infectious from non-infectious pathology [48]. CT also offers better delineation of radiographic patterns (e.g., lobar, interstitial, nodular) and can identify complications such as cavitation, abscess, empyema, or mediastinal lymphadenopathy, guiding further diagnostic or therapeutic interventions (Fig. 2).

Laboratory studies

For the patient with presumed severe pneumonia not responding to antibiotic therapy there are tests (both for infectious and non-infectious diseases) which can be performed on blood, urine and bronchoalveolar lavage fluid that may aid in identifying a definitive pathology (Fig. 2). Serial PCT and CRP testing can be used to assess response to antibiotics and guide antibiotic duration [16, 21, 49, 50]. The use of fibreoptic bronchoscopy and bronchoalveolar lavage-based studies may provide a more definitive diagnosis in greater than 40% ICU patients deemed to have pneumonia who are experiencing therapeutic failure [51]. In the case of clinical suspicion of a non-infectious condition, auto-immunity evaluation should be done (example – ANA, anti-DNA ss and ds, c-ANCA, and p-ANCA, anti-GBM), assess the urinary sediment, evaluate the BAL fluid namely its cellularity and perform flow cytometry.

What to do with antibiotic therapy?

There is no RCT data to guide the therapeutic approach to a non-responding patient. Clinicians must therefore rely heavily on the art of medicine and clinical judgement. If review of the relevant clinical data suggests an alternative diagnosis or pathogen or antimicrobial

resistance profile, modifications of antibiotic therapy may be needed and can be divided into verification of adequate dosing, escalation of therapy to cover MDR pathogens, or addition of agents from a different antimicrobial class to cover atypical or non-bacterial organisms.

Worsening bacterial infection due to inappropriate antibiotic coverage could occur if the offending organism was resistant to the initial antibiotic choice, if it was originally susceptible but there was emergence of resistance during therapy, or if the antibiotic chosen did not reach the lung parenchyma with adequate concentrations. Risk factors for resistant infections at baseline differ based on the type of organism, therefore assessment of individual epidemiologic and clinical risk factors is critical. For instance, ceftriaxone-resistant pneumococcus is uncommon in the United States (US) but more prevalent in Taiwan and South Korea; risk factors include extensive previous treatment with antibiotics for respiratory tract infections [52, 53]. Because high-doses of beta-lactams are used to treat CAP in the US, it is unlikely that the presence of ceftriaxone-resistance would lead to failure of treatment of pneumonia [12]. On the other hand, the use of bactericidal vs bacteriostatic antibiotics is not a risk factor for non-response. This was borne out in a recent meta-analysis of 42 studies that found no difference in clinical cure rates between patients treated with bactericidal vs bacteriostatic agents [31].

Patients with prolonged hospital stays, extensive antibiotic exposure, residence in a long-term acute care facility, or who live in or recently travelled to areas with a high prevalence of resistance (e.g., India or South America) may be at risk for having infection due to MDR Gram-negative organisms such extended-spectrum beta-lactamase producing Enterobacterales spp (particularly in *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*), which generally require carbapenem therapy [54]. In the case of the presence of Enterobacterales spp in which the ampC gene is constitutively expressed or is induced during therapy with 3rd generation cephalosporins to produce ampC beta-lactamases (particularly among *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella aerogenes*, and *Hafnia alvei*) generally require cefepime or carbapenem therapy [54]. Alternatively, highly resistant *Pseudomonas aeruginosa* may require treatment with a carbapenem, ceftolozane/tazobactam or ceftazidime/avibactam [54]. Patients who are clinically worsening with the aforementioned risk factors and have either not been treated for these organisms or may have acquired these organisms during hospitalization may require prompt escalation of therapy, particularly if the patient is deteriorating. If these organisms are not isolated from a respiratory sample, it is unlikely that one of these bacteria are the cause of the patient's clinical decline.

Similarly, addition of vancomycin or linezolid to treat MRSA is often considered in patients with clinical deterioration. Risk of acquisition of MRSA during hospitalization varies but is generally uncommon if good infection prevention practices are in place. The negative predictive value of MRSA nasal swabs (via polymerase chain reaction (PCR) or culture) is high; thus, if the MRSA nasal screening test is negative then it is reasonable to either discontinue or forgo the addition of anti-MRSA empiric therapy [55].

One additional caveat regarding non-responders relates to appropriate drug and adequate dose of antibiotics [56]. For example, if vancomycin is prescribed for MRSA, but therapeutic levels take 4 days to achieve, one could see a clinical decline or non-response to treatment. Similarly, if daptomycin was started for other reasons, it would not be expected to cover a secondary pneumonia with MRSA because it is inactivated by pulmonary surfactant. Underdosing of beta-lactam antibiotics directed at Gram-negative organisms occurs frequently, although patients in the ICU with sepsis have altered pharmacokinetics and pharmacodynamics that can result in increased clearance of antibiotics [56, 57]. For these reasons, many ICUs preferentially administer beta-lactam agents via continuous or extended infusion [41, 58, 59].

The need to add new antimicrobials to cover atypical bacterial pathogens or non-bacterial pathogens depends on the clinical and immune status of the patient as well as imaging finding and microbiologic work up. Overall, the need to add such agents is uncommon and generally considered only in highly immunocompromised patients. Atypical bacterial coverage, primarily for *Legionella spp*., may be considered if not given initially for patients at high risk. Clinicians should be aware of any local epidemiology regarding Legionella outbreaks and recognize that the Legionella urinary antigen only detects *L. pneumophila* serogroup 1 which accounts for 80–90% of cases but considering that other serogroups and other *Legionella* species (e.g. *L. micdadei*) can cause infections, the test sensitivity may be lower than that. A thorough assessment of a patient's clinical presentation and epidemiological history is essential in identifying uncommon pathogens responsible for non-resolving CAP, which may necessitate targeted antimicrobial therapy, often in combination (Fig. 2). Fungal pneumonia (e.g., aspergillosis, endemic fungi) that is rapidly progressive and *Pneumocystis jirovecii* pneumonia (PJP) are rare and less likely in non-immunocompromised patients without significant immunocompromising conditions; however, the addition of antifungal therapy and/or trimethoprim/sulfamethoxazole, respectively, can be considered in the immunocompromised with compatible imaging and microbiologic findings. It is also important

to recognize that viral pathogens, particularly influenza, RSV, and SARS-CoV-2, can cause pneumonia, including lobar pneumonia, and can be transmitted to hospitalized patients; if these organisms are identified through viral respiratory testing, antiviral therapy should be initiated as appropriate. In addition, CMV and HSV reactivation have been frequently identified in critically ill patients receiving mechanical ventilation (more often HSV) with varied impact on clinical outcomes. However, there are no clear recommendations regarding the utility of antiviral therapy in these situations [60, 61]. Finally, mycobacterial infections are a rare cause of an acute respiratory decompensation, but miliary tuberculosis could be considered and treated in the appropriate host.

In the absence of clinical decline or with ambiguity of diagnosis, it is reasonable to not escalate and even stop antibiotic therapy while assessing the patient [62]. If a previously identified organism has been fully treated, extending targeted therapy beyond current recommendations also has little benefit and certainly raises risk of harm [63, 64]. In general, it is uncommon to fail antibiotic coverage in the ICU with the broad coverage usually used (cefepime or piperacillin/tazobactam ± vancomycin), and the scenarios presented previously are overall uncommon. If antibiotics are broadened or other antimicrobials are added empirically, it is crucial to re-evaluate the need for these agents daily. This decision should be informed by additional diagnostic work up including obtaining respiratory cultures, ideally via bronchoalveolar lavage which also allows for collection of Legionella cultures, PJP PCR, galactomannan antigen (more sensitive than in serum), beta-D-glucan, acid fast bacilli/fungal smear and culture, and respiratory virus or pneumonia multiplex syndromic panels when indicated; broad range PCR is rarely indicated. If carbapenems or newer Gram-negative antibiotics are started empirically, they should be stopped once culture data return that do not support their continuation. If no infectious diagnosis is obtained, cessation of antibiotics with watchful waiting should be considered; it is inadvisable to assign arbitrary long courses of therapy when culture data do not support continuation of broad-spectrum antibiotic therapy.

Rational antibiotic decision making for patients not responsive to initial therapy is complex due to the heterogeneity of patient risk factors, exposure history and overlapping differential diagnoses that may be infectious or non-infectious. This requires astute clinical re-evaluation of the patient and assessment of risks and benefits of altering antimicrobial therapy or discontinuing it. Recognition that all antimicrobials carry risks is paramount in this thought process [65].

Conclusion

This manuscript brings to light an understudied, underrecognized, and underappreciated clinical challenge: the hospitalized patient with severe pneumonia who is not responding to initial treatment. Clinical studies are needed to bring more robust evidence and to hopefully identify different non-response phenotypes.

We propose a common criterion that spans from sCAP to HAP/VAP, identify the most relevant risk factors, and provide a clinical pathway to investigate these patients in a timely manner to facilitate optimizing care.

The decision-making process consists of two key-components: the comprehensive search for an accurate diagnosis and treatment modification as needed to match the revised diagnosis. The former will ensure that clinicians are not missing an important diagnosis responsible for the initial treatment failure, and the later will offer a concrete approach to make the treatment successful.

In summary, there is an urgent need for better data on the epidemiology of pneumonia non-responders and how best to optimize the therapeutic approach in order to secure the best outcomes for all patients.

Author details

[1] NOVA Medical School, CHRC, NOVA University of Lisbon, Lisbon, Portugal. [2] Research Unit of Clinical Epidemiology, Department of Clinical Research, OUH Odense University Hospital, Odense, Denmark. [3] Department of Intensive Care, Hospital de São Francisco Xavier, ULSLO, Lisbon, Portugal. [4] CDP Dr. Ribeiro Sanches, Pulmonary Department, ULS Santa Maria, Lisbon, Portugal. [5] Department of Infectious Diseases, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain. [6] Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L´Hospitalet de Llobregat, Barcelona, Spain. [7] Department of Clinical Sciences, University of Barcelona, Barcelona, Spain. [8] Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain. [9] Division of Infectious Diseases & Pulmonary and Critical Care Medicine, University of Nebraska Medical Center, Omaha, USA. [10] Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, USA. [11] Servei de Medicina Intensiva, SODIR Research Group, Hospital Universitari Vall d'Hebron, Institut de Recerca Vall d'Hebron, Barcelona, Spain. [12] Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain. [13] Department of Internal Medicine, Division of Infectious Diseases, College of Public Health, University of Nebraska Medical Center, Omaha, USA. [14] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Healthcare Institute, Boston, USA. [15] Department of Medicine, Brigham and Women's Hospital, Boston, USA. [16] Hospital de Clinicas de Porto Alegre, PPG Ciencias Pneumologicas, UFRGS, Porto Alegre, Brazil. [17] Head Critical Care Department, Hospital Mae de Deus, Porto Alegre, Brazil. [18] Multidisciplinary Intensive Care, Department of Clinical Medicine, Trinity College, Wellcome Trust-HRB Clinical Research Facility, St James Hospital, St James's University Hospital, Dublin, Ireland. [19] Médecine Intensive-Réanimation, CHU de Lille, Lille, France. [20] Inserm U1285, Université de Lille, CNRS, UMR 8576-UGSF, Lille, France. [21] D'Or Institute for Research and Education (IDOR), Rio de Janeiro, Brazil. [22] Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, University of California, La Jolla, San Diego, USA.

Author contributions

Conceptualization: PP and AK; Writing—original draft: PP, LC, JC, KC, SEC, RF, CAG, MK, TL, IML, SN, JS, SS, DS and AK. Writing (review and editing): PP and AK. All authors read and approved the final manuscript.

Funding
Open access funding provided by FCT|FCCN (b-on).

Declarations

Conflicts of interest
PP received fees for lecture from Gilead and Mundipharma, consulting from MSD and Biocodex. KC received fees for lectures and advisory board from BD. RF received fees as speaker and/or advisor for Pfizer, MSD, Shionogi, Gilead, GE, AOP Health, Grifols, Thermofisher, Estor, Toray, BD, Menarini, Viatris. CAG received consultation fees from Karius Inc Diagnostics. MK has grants from CDC, AHRQ; contracts from Massachusetts Department of Public Health; royalties from UpToDate. IML received fees lectures and advisory board MSD, Menarini, Biomerieux, Mundipharma, Gilead, and Thermofisher. SN received consultation fees from Mundipharma, and lecture fees from MSD, Biomérieux, Pfizer, Fisher and Peykel, Shionogi, and Medtronic. LC, JC, SEC, TL, JIFS, SS, DS, AK declare no conflict of interest.

Open Access
This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 26 February 2025 Accepted: 8 April 2025
Published: 24 May 2025

References

1. Vincent JL, Sakr Y, Singer M et al (2020) Prevalence and outcomes of infection among patients in intensive care units in 2017. JAMA 323:1478–1487. https://doi.org/10.1001/jama.2020.2717
2. Goncalves-Pereira J, Conceicao C, Povoa P (2013) Community-acquired pneumonia: identification and evaluation of nonresponders. Ther Adv Infect Dis 1:5–17. https://doi.org/10.1177/2049936112469017
3. Halm EA, Fine MJ, Marrie TJ et al (1998) Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA 279:1452–1457. https://doi.org/10.1001/jama.279.18.1452
4. Arancibia F, Ewig S, Martinez JA et al (2000) Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. Am J Respir Crit Care Med 162:154–160. https://doi.org/10.1164/ajrccm.162.1.9907023
5. Roson B, Carratala J, Fernandez-Sabe N et al (2004) Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. Arch Intern Med 164:502–508. https://doi.org/10.1001/archinte.164.5.502
6. Mendez R, Gonzalez-Jimenez P, Mengot N et al (2024) Treatment failure and clinical stability in severe community-acquired pneumonia. Semin Respir Crit Care Med 45:225–236. https://doi.org/10.1055/s-0043-1778139
7. Menendez R, Torres A, Zalacain R et al (2004) Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. Thorax 59:960–965. https://doi.org/10.1136/thx.2003.017756
8. Blasi F, Ostermann H, Racketa J et al (2014) Early versus later response to treatment in patients with community-acquired pneumonia: analysis of the REACH study. Respir Res 15:6. https://doi.org/10.1186/1465-9921-15-6
9. Martin-Loeches I, Reyes LF, Nseir S et al (2023) European Network for ICU-Related Respiratory Infections (ENIRRIs): a multinational, prospective, cohort study of nosocomial LRTI. Intensive Care Med 49:1212–1222. https://doi.org/10.1007/s00134-023-07210-9
10. Bassetti M, Montero JG, Paiva JA (2018) When antibiotic treatment fails. Intensive Care Med 44:73–75. https://doi.org/10.1007/s00134-017-4962-2
11. Kalil AC, Metersky ML, Klompas M et al (2016) Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by The infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 63:e61–e111. https://doi.org/10.1093/cid/ciw353
12. Metlay JP, Waterer GW, Long AC et al (2019) Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 200:e45–e67. https://doi.org/10.1164/rccm.201908-1581ST
13. Martin-Loeches I, Torres A, Nagavci B et al (2023) ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. Intensive Care Med 49:615–632. https://doi.org/10.1007/s00134-023-07033-8
14. Ortqvist A, Kalin M, Lejdeborn L et al (1990) Diagnostic fiberoptic bronchoscopy and protected brush culture in patients with community-acquired pneumonia. Chest 97:576–582. https://doi.org/10.1378/chest.97.3.576
15. Menendez R, Cavalcanti M, Reyes S et al (2008) Markers of treatment failure in hospitalised community acquired pneumonia. Thorax 63:447–452. https://doi.org/10.1136/thx.2007.086785
16. Povoa P, Coelho L, Cidade JP et al (2024) Biomarkers in pulmonary infections: a clinical approach. Ann Intensive Care 14:113. https://doi.org/10.1186/s13613-024-01323-0
17. Luna CM, Blanzaco D, Niederman MS et al (2003) Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med 31:676–682. https://doi.org/10.1097/01.CCM.0000055380.86458.1E
18. Combes A, Luyt CE, Fagon JY et al (2007) Early predictors for infection recurrence and death in patients with ventilator-associated pneumonia. Crit Care Med 35:146–154. https://doi.org/10.1097/01.CCM.0000249826.81273.E4
19. Povoa P, Coelho L, Almeida E et al (2005) C-reactive protein as a marker of ventilator-associated pneumonia resolution: a pilot study. Eur Respir J 25:804–812. https://doi.org/10.1183/09031936.05.00071704
20. Rabello L, Povoa P, Lapa ESJR et al (2017) Patterns of C-reactive protein ratio predicts outcomes in healthcare-associated pneumonia in critically ill patients with cancer. J Crit Care 42:231–237. https://doi.org/10.1016/j.jcrc.2017.07.021
21. Povoa P, Coelho L, Dal-Pizzol F et al (2023) How to use biomarkers of infection or sepsis at the bedside: guide to clinicians. Intensive Care Med 49:142–153. https://doi.org/10.1007/s00134-022-06956-y
22. Povoa P, Martin-Loeches I, Ramirez P et al (2017) Biomarkers kinetics in the assessment of ventilator-associated pneumonia response to antibiotics - results from the BioVAP study. J Crit Care 41:91–97. https://doi.org/10.1016/j.jcrc.2017.05.007
23. Dennesen PJ, van der Ven AJ, Kessels AG et al (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 163:1371–1375. https://doi.org/10.1164/ajrccm.163.6.2007020
24. Montravers P, Fagon JY, Chastre J et al (1993) Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. Am Rev Respir Dis 147:38–44. https://doi.org/10.1164/ajrccm/147.1.38
25. Coelho L, Moniz P, Guerreiro G et al (2023) Airway and respiratory devices in the prevention of ventilator-associated pneumonia. Medicina (Kaunas). https://doi.org/10.3390/medicina59020199
26. Fernandez-Barat L, Torres A (2016) Biofilms in ventilator-associated pneumonia. Future Microbiol 11:1599–1610. https://doi.org/10.2217/fmb-2016-0040

27. Meduri GU, Shih MC, Bridges L et al (2022) Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. Intensive Care Med 48:1009–1023. https://doi.org/10.1007/s00134-022-06684-3
28. Rouze A, Martin-Loeches I, Povoa P et al (2021) Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. Intensive Care Med 47:188–198. https://doi.org/10.1007/s00134-020-06323-9
29. Reyes LF, Torres A, Olivella-Gomez J, Ibáñez-Prada ED, Nseir S, Ranzani OT, Povoa P, Diaz E, Schultz MJ, Rodríguez AH, Serrano-Mayorga CC, De Pascale G, Navalesi P, Skoczynski S, Esperatti M, Coelho LM, Cortegiani A, Aliberti S, Caricato A, Martin-Loeches I, on behalf of the European Network for ICU-Related Respiratory Infections (ENIRRIs) European Respiratory Society-Clinical Research Collaboration Investigators (2025) Factors Associated with Mortality in Nosocomial Lower Respiratory Tract Infections: An ENIRRI Analysis. Antibiotics (Basel). https://doi.org/10.3390/antibiotics14020127
30. Shindo Y, Ito R, Kobayashi D et al (2015) Risk factors for 30-day mortality in patients with pneumonia who receive appropriate initial antibiotics: an observational cohort study. Lancet Infect Dis 15:1055–1065. https://doi.org/10.1016/S1473-3099(15)00151-6
31. Saleem N, Ryckaert F, Snow TAC et al (2022) Mortality and clinical cure rates for pneumonia: a systematic review, meta-analysis, and trial sequential analysis of randomized control trials comparing bactericidal and bacteriostatic antibiotic treatments. Clin Microbiol Infect 28:936–945. https://doi.org/10.1016/j.cmi.2021.12.021
32. Dinh A, Duran C, Ropers J et al (2021) Factors associated with treatment failure in moderately severe community-acquired pneumonia: a secondary analysis of a randomized clinical trial. JAMA Netw Open 4:e2129566. https://doi.org/10.1001/jamanetworkopen.2021.29566
33. Papazian L, Klompas M, Luyt CE (2020) Ventilator-associated pneumonia in adults: a narrative review. Intensive Care Med 46:888–906. https://doi.org/10.1007/s00134-020-05980-0
34. Ghadimi M, Siemieniuk RAC, Guyatt G et al (2024) Empiric antibiotic regimens in adults with non-ventilator-associated hospital-acquired pneumonia: a systematic review and network meta-analysis of randomized controlled trials. Clin Microbiol Infect 30:1351–1363. https://doi.org/10.1016/j.cmi.2024.05.017
35. Howatt M, Klompas M, Kalil AC et al (2021) Carbapenem antibiotics for the empiric treatment of nosocomial pneumonia: a systematic review and meta-analysis. Chest 159:1041–1054. https://doi.org/10.1016/j.chest.2020.10.039
36. Kuru T, Lynch JP 3rd (1999) Nonresolving or slowly resolving pneumonia. Clin Chest Med 20:623–651. https://doi.org/10.1016/s0272-5231(05)70241-0
37. Fine MJ, Stone RA, Singer DE et al (1999) Processes and outcomes of care for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team (PORT) cohort study. Arch Intern Med 159:970–980. https://doi.org/10.1001/archinte.159.9.970
38. Fein AM, Feinsilver SH, Niederman MS et al (1987) When the pneumonia doesn't get better. Clin Chest Med 8:529–541
39. Rello J, Lisboa T, Lujan M et al (2009) Severity of pneumococcal pneumonia associated with genomic bacterial load. Chest 136:832–840. https://doi.org/10.1378/chest.09-0258
40. Morgan AJ, Glossop AJ (2016) Severe community-acquired pneumonia. BJA Educ 16:167–172. https://doi.org/10.1093/bjaed/mkv052
41. Abdul-Aziz MH, Hammond NE, Brett SJ et al (2024) Prolonged vs intermittent infusions of beta-lactam antibiotics in adults with sepsis or septic shock: a systematic review and meta-analysis. JAMA 332:638–648. https://doi.org/10.1001/jama.2024.9803
42. Kalil AC, Florescu DF (2009) Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit. Crit Care Med 37:2350–2358. https://doi.org/10.1097/CCM.0b013e3181a3aa43
43. Jacobs JA, De Brauwer EI, Ramsay G et al (1999) Detection of non-infectious conditions mimicking pneumonia in the intensive care setting: usefulness of bronchoalveolar fluid cytology. Respir Med 93:571–578. https://doi.org/10.1016/s0954-6111(99)90157-9
44. Patel RA, Gallagher JC (2010) Drug fever. Pharmacotherapy 30:57–69. https://doi.org/10.1592/phco.30.1.57
45. Tu CY, Hsu WH, Hsia TC et al (2004) Pleural effusions in febrile medical ICU patients: chest ultrasound study. Chest 126:1274–1280. https://doi.org/10.1378/chest.126.4.1274
46. Garin N, Marti C, Scheffler M et al (2019) Computed tomography scan contribution to the diagnosis of community-acquired pneumonia. Curr Opin Pulm Med 25:242–248. https://doi.org/10.1097/MCP.0000000000000567
47. Claessens YE, Debray MP, Tubach F et al (2015) Early Chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia. Am J Respir Crit Care Med 192:974–982. https://doi.org/10.1164/rccm.201501-0017OC
48. Tomiyama N, Muller NL, Johkoh T et al (2000) Acute parenchymal lung disease in immunocompetent patients: diagnostic accuracy of high-resolution CT. AJR Am J Roentgenol 174:1745–1750. https://doi.org/10.2214/ajr.174.6.1741745
49. Dias RF, de Paula A, Hasparyk UG et al (2023) Use of C-reactive protein to guide the antibiotic therapy in hospitalized patients: a systematic review and meta-analysis. BMC Infect Dis 23:276. https://doi.org/10.1186/s12879-023-08255-3
50. Schuetz P, Wirz Y, Sager R et al (2017) Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev 10:CD007498. https://doi.org/10.1002/14651858.CD007498.pub3
51. Sialer S, Liapikou A, Torres A (2013) What is the best approach to the nonresponding patient with community-acquired pneumonia? Infect Dis Clin North Am 27:189–203. https://doi.org/10.1016/j.idc.2012.11.009
52. Choi MJ, Noh JY, Cheong HJ et al (2019) Spread of ceftriaxone non-susceptible pneumococci in South Korea: Long-term care facilities as a potential reservoir. PLoS ONE 14:e0210520. https://doi.org/10.1371/journal.pone.0210520
53. Lee HY, Wu TL, Su LH et al (2018) Invasive pneumococcal disease caused by ceftriaxone-resistant Streptococcus pneumoniae in Taiwan. J Microbiol Immunol Infect 51:500–509. https://doi.org/10.1016/j.jmii.2016.12.004
54. Tamma PD, Heil EL, Justo JA et al (2024) Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. Clin Infect Dis. https://doi.org/10.1093/cid/ciae403
55. Chotiprasitsakul D, Tamma PD, Gadala A et al (2018) The role of negative methicillin-resistant staphylococcus aureus nasal surveillance swabs in predicting the need for empiric vancomycin therapy in intensive care unit patients. Infect Control Hosp Epidemiol 39:290–296. https://doi.org/10.1017/ice.2017.308
56. Dyer CJ, De Waele JJ, Roberts JA (2024) Antibiotic dose optimisation in the critically ill: targets, evidence and future strategies. Curr Opin Crit Care 30:439–447. https://doi.org/10.1097/MCC.0000000000001187
57. Hagel S, Bach F, Brenner T et al (2022) Effect of therapeutic drug monitoring-based dose optimization of piperacillin/tazobactam on sepsis-related organ dysfunction in patients with sepsis: a randomized controlled trial. Intensive Care Med 48:311–321. https://doi.org/10.1007/s00134-021-06609-6
58. Dulhunty JM, Brett SJ, De Waele JJ et al (2024) Continuous vs Intermittent beta-lactam antibiotic infusions in critically Ill patients with sepsis: the BLING III randomized clinical trial. JAMA 332:629–637. https://doi.org/10.1001/jama.2024.9779
59. Karaba SM, Cosgrove SE, Lee JH et al (2024) Extended-infusion beta-lactam therapy, mortality, and subsequent antibiotic resistance among hospitalized adults with gram-negative bloodstream infections. JAMA Netw Open 7:e2418234. https://doi.org/10.1001/jamanetworkopen.2024.18234
60. Boers LS, van Someren GF, van Hattem JM et al (2024) Pulmonary herpes simplex virus and cytomegalovirus in patients with acute respiratory distress syndrome related to COVID-19. Intensive Care Med 50:1251–1264. https://doi.org/10.1007/s00134-024-07529-x
61. Luyt CE, Girardis M, Paixao P (2024) Herpes simplex virus and cytomegalovirus lung reactivations in severe COVID-19 patients: to treat or not to treat? That is (still) the question. Intensive Care Med 50:1317–1319. https://doi.org/10.1007/s00134-024-07562-w

62. Singh N, Rogers P, Atwood CW et al (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. a proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 162:505–511. https://doi.org/10.1164/ajrccm.162.2.9909095
63. Klompas M, Li L, Menchaca JT et al (2017) Ultra-short-course antibiotics for patients with suspected ventilator-associated pneumonia but minimal and stable ventilator settings. Clin Infect Dis 64:870–876. https://doi.org/10.1093/cid/ciw870
64. Moniz P, Fustiga J, Herculano MM et al (2024) Optimization of antibiotic use in the intensive care unit: how we do it. Crit Care Sci 36:e20240017en. https://doi.org/10.62675/2965-2774.20240017-en
65. Curran J, Lo J, Leung V et al (2022) Estimating daily antibiotic harms: an umbrella review with individual study meta-analysis. Clin Microbiol Infect 28:479–490. https://doi.org/10.1016/j.cmi.2021.10.022