Lower respiratory tract infections treatment recommendations: An overview

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ABSTRACT

Lower respiratory tract infections represent one of the main causes of morbidity and mortality worldwide and yield a major effect on healthcare-related expenditures. The clinical and economic burden of respiratory infections was highlighted during COVID-19 pandemic. Importantly, the COVID-19 pandemic demonstrated that irrational use of antibiotics might not only be ineffective but also lead to adverse events. During the first years of the pandemic, the incidence of other respiratory infections fell dramatically; yet, the last months have seen the emergence of the well-known respiratory infections of the past, again. This article aims to highlight current evidence for the management of lower respiratory infections, including COVID-19.

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INTRODUCTION

Lower respiratory tract infections (LRTIs) represent the most frequent infectious diseases diagnosed and treated in the context of clinical practice worldwide. Several viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are main causes of LRTIs. The targeted selection of treatment regimen has a cardinal role in positive outcomes[1,2]. Importantly, several lines of evidence during COVID-19 pandemic demonstrated that irrational implementation of antibiotics might not only be ineffective but also lead to adverse events. For instance, azithromycin was not only ineffective in COVID-19 but also increased the odds ratio for arrhythmias[3]. Based on the above, identifying the causative pathogens of respiratory tract infections seems to be of paramount importance for avoiding the irrational use of broad-spectrum antibiotics. This narrative review aims to highlight recent evidence for LRTIs exerting major burden, including community-acquired pneumonia (CAP), ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), and COVID-19.

COMMUNITY-ACQUIRED PNEUMONIA (CAP)

Pneumonia represents a common cause of respiratory infection resulting at least to 0.8 million hospital admissions per year based on the American registry. CAP is a lung infectious disease acquired outside the setting of a hospital. CAP represents one of the most frequent causes of hospitalization and mortality among infectious diseases. Based on the annual recording in the US, 650 adults per 100000 population are hospitalized due to CAP every year, corresponding to 1.5 million CAP hospitalizations per year. Almost one in ten patients with CAP will experience a subsequent readmission[4]. The most frequent symptoms are fever, cough, dyspnea, exhaustion, and loss of appetite. Uncommon symptoms including headache, confusion, nausea, and abdominal pain, appear in children and the elderly. Awareness of local bacteria and their sensitivity/resistance profile is the key to effective pharmacological selection and treatment of pneumonia[1].

Etiology

The microbial etiology of CAP is quite often unspecified in clinical practice. Population-based studies for the etiology and incidence are currently lacking. Frequently identified bacteria in CAP are the following: 1) *Streptococcus pneumoniae*, 2) *Haemophilus influenzea*, and 3) *Moraxella catarrhalis*[5]. Other pathogens frequently encountered are *Staphylococcus aureus*. Gram-negative bacteria (*Pseudomonas spp, Enterobacteriaceae*), *Group A streptococci*, anaerobes (especially in adults with bad oral cavity hygiene), and micro-aerophilic bacteria may also cause CAP. *Pseudomonas spp* represent characteristic pathogens of patients with bronchiectatic lesions of the lung and end-stage Chronic Obstructive Pulmonary Disease. 'Atypical' bacteria, including *Mycoplasma pneumoniae* and *Legionella spp*, represent relatively common causes of CAP. *Influenza*

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A and *B* viruses, *Human Bocaviruses*, *Parainfluenza viruses*, *Coronaviruses, Adenoviruses, Rhinoviruses*, and *Human Metapneumovirus* represent leading causes of CAP[5,6].

Risk stratification

Pneumonia risk stratification scores, including CURB and PSI, guide management based on the 30-day mortality risk. PSI discriminates individuals with CAP into 5 groups with different 30-day mortality risk. The score is based on 20 clinical, radiographic, and laboratory parameters[7].

CURB score is a clinical prediction tool able to stratify patients with CAP based on mortality risk and is an important tool to discriminate between patients that require outpatient versus inpatient treatment. The criteria included in the CURB score are confusion, elevated BUN above 20 mg/dL, respiratory rate above 30/min, and diastolic blood pressure below 60 mmHg. These criteria did not include one of the most critical risk factors of mortality, such as age[8]. A multivariate analysis led to the modified CURB-65 score, in which age >65 years was added as a criterion. The modified CURB-65 further increased the prognostic accuracy of this widely used score. Patients presenting with ≥3 positive criteria are classified as severe CAP and need hospital admission[9].

PSI has higher prognostic accuracy with regard to mortality compared to the CURB-65 score since it considers a formal assessment of hypoxemia; yet PSI is majorly weighted by age and thus overestimates the risk of mortality in elderly male subjects with a history of active cancer (<6 months following diagnosis), irrespective of etiology. To this end, it is less valuable at extremes of age and invalid in children[9]. A main advantage of CURB-65 is the fact that it is simple and thus can provide prognostic information and guide treatment decisions in a fast manner, even in the emergency department.

While prognostic tools can provide valuable information to aid physicians in decision-making, their role is supplementary and they cannot replace clinical evaluation. For instance, although oxygen saturation is not included into the CURB 65 score, it may still be a crucial factor with regard to management decisions. Furthermore, patients with low PSI scores but no comorbidities may still require ICU care, while those with a high PSI score due to chronic illness may not. Ultimately, decisions regarding hospital admission should be also based on physician's medical expertise and clinical judgment considering the limitations of these tools in the context of individual patient care[7].

Diagnosis-procalcitonin

CAP is usually diagnosed following evaluation of clinical and radiologic findings. In the context of symptoms, CAP is characterized by shortness of breath of varying severity, productive (and sometimes non-productive) cough and systemic features including fever, rigors, and/or drills coupled with general fatigue and malaise. A clinical examination might reveal crackles or bronchial breath sounds as well as tachypnea, use of accessory respiratory muscles, and cyanosis[10]. CAP can also be defined as new radiographic findings in chest imaging coupled with compatible clinical findings. These may include consolidative areas, bilateral perihilar opacities, loss of the typical cardiac, diaphragmatic, and/or mediastinal silhouette, as well as interstitial infiltrates, for which there is no other explanation[11]. Regarding bacterial infections, lab tests including complete blood count and regular biochemical tests should be done. Influenza testing is strongly recommended during the winter season, as viral superinfections can be commonly encountered. In case of availability, a molecular test for respiratory viruses using nasopharyngeal swabs methods could also be performed[4].

Procalcitonin represents one of the most important prognostic and theragnostic biomarkers in the context of pneumonia. Its use was widely spread, based on mechanistic evidence showing that pathogens induce the upregulation of the CALC-1 gene of innate immune cells such as macrophages, which subsequently results in the increased production of procalcitonin. More specifically, procalcitonin's production occurs in the pulmonary parenchyma, in the liver, as well as in the intestine. It is secreted within 120–180 min, while the maximum concentration is identified approximately at 6 hours[12]. A main advantage of procalcitonin is the fact that it exhibits higher sensitivity and specificity in bacterial infections as well as favorable kinetics compared to C-reactive protein (CRP) due to its earlier increase, thus allowing timely interventions. In addition, its high negative predictive value was established in several cohorts mainly of adults with sepsis and septic shock. To this end, procalcitonin can limit irrational antibiotic usage, as it can reduce the duration of an antibiotic course and allow clinicians to de-escalate antibiotic regimens. Negative procalcitonin values in the appropriate clinical setting can reduce the implementation of broad-spectrum antibiotics. Based on that, procalcitonin might be a tool to avoid the danger of a substantial increase in health-related budgets following advent of novel, expensive antibiotics[13].

While PCT seems to be a reliable biomarker for the reduction of antibiotic therapy duration, it cannot be utilized to determine the initiation of therapy. Serial monitoring of PCT levels can safely guide the reduction of antibiotic therapy duration for patients with severe ICU infections, including those with CAP, as observed in several large multicenter studies[11].

Empiric treatment of CAP in adults

IDSA/ATS guidelines for CAP, with regard to outpatient adults without comorbidities, recommend the use of empiric antibiotic treatment that includes amoxicillin (1 g administered/ eight hours) or doxycycline (100 mg administered/twelve hours) or a macrolide, if the resistance of *Streptococcus pneumoniae* to macrolides is less than 25% (azithromycin 500 mg as initial dose followed by half dose per day after day 1 or clarithromycin 500 mg every 12

hours)[14]. It is important to mention that monotherapy using macrolides is not an option for treating CAP in Greece due to the high incidence of *S. pneumoniae* resistance[15].

Isolation of *S. pneumoniae* resistant to second-generation cephalosporins precludes the use of cefuroxime as treatment and thus, third generation cephalosporins should be preferred, including cefditoren, a cephalosporin with the lowest MIC for *S. pneumoniae*[14]. Additionally, based on the ATS and IDSA guidelines for CAP outpatient treatment of adults with a history of alcoholism or comorbidities such as chronic heart disease, chronic lung diseases, renal dysfunction, liver abnormalities, diabetes mellitus, cancer or asplenia, the recommended treatment regimen includes a combination of amoxicillin/clavulanate (500125 mg every eight hours or 875/125 mg every twelve hours or 2000/125 mg every twelve hours), or a cephalosporin (i.e. cefuroxime 500 mg/twelve hours) with a macrolide (in the dosage previously described), or doxycycline (100 mg every twelve hours). Alternatively, monotherapy with a respiratory fluoroquinolone (mainly moxifloxacin 400 mg or levofloxacin 750 mg every twenty-four hours) is highly recommended, particularly in outpatients presenting with several comorbidities and a history of previous hospitalization within the past 6 months[4] (Table 1). Evaluation of epidemiological data of resistance against specific agents, search for prescription of specific antibiotics during the last 6 months and consideration of allergic reactions to drugs, history of cardiac arrhythmia (i.e. for avoidance of macrolides) and vascular disease (for avoidance of fluoroquinolones) are strongly recommended prior the choice of the antibiotic[4,15].

Furthermore, for inpatient adults with non-severe CAP, without risk factors for *MRSA* or *Pseudomonas Aeruginosa,* the empiric treatment includes a combination therapy with a b-lactam (ampicillin-sulbactam 1.5–3 g four times per day, ceftaroline 600 mg twice daily, cefotaxime 1–2 g thrice per day or ceftriaxone 1–2 g daily) and a macrolide (azithromycin 500 mg every twenty-four hours or clarithromycin 500 mg every twelve hours), or even monotherapy with a fluoroquinolone (same dosage as described above)[14]. Awareness that the elimination half-life of azithromycin following multiple dosing is almost 68 hours is crucial; thus, meticulous evaluation of patients receiving azithromycin is needed. If there are contraindications to quinolones and macrolides use, the indicated treatment is a combination of b-lactam and doxycycline. It is suggested that hospitalized individuals with severe CAP without risk factors for *P. aeruginosa* or *MRSA* should receive a regimen comprising a b-lactam antibiotic and a macrolide or a b-lactam antibiotic plus a fluoroquinolone[4].

Antibiotics for anaerobic coverage should not be routinely included for suspected aspiration pneumonia unless lung abscess or empyema is suspected. An aspiration represents a common event in adults, especially during sleep when gastric contents cause aspiration pneumonitis. Many of these cases resolve within 1 to 2 days simply following supportive treatment[16].

Antibiotic coverage for *P. aeruginosa* or *MRSA* in individuals with CAP must be considered in case risk factors for these bacteria are identified[17]. Empiric treatment options for *MRSA* include linezolid (600 mg every twelve hours) and vancomycin (15–20 mg/kg every twelve hours following modification according to trough levels), and for *P. aeruginosa* regimens include piperacillin-tazobactam (4.5 g every six hours), cefepime (2 g every eight hours), ceftazidime (2 g every eight hours), aztreonam (2 g every eight hours), meropenem (1 or 2 g every eight hours), or imipenem (500 mg every six hours). With regard to vancomycin, adjusting dosage following measurement of trough levels at least before the fourth dose is strongly recommended[4].

The most important risk factors for infection with *P. aeruginosa* or *MRSA* are the following: 1) previous isolation of these microorganisms (especially from the respiratory tract), 2) recent hospitalization, and 3) exposure to parenteral antibiotics. De-escalation of antibiotic therapy is safer 48 hours after negative cultures for *MRSA* or *P. aeruginosa*[4,18].

Individuals with CAP tested positive for *Influenza* should receive oseltamivir (75 mg bid), independent of the time of onset of symptoms. The treatment is preferred to be initiated within 48 hours following symptom initiation or hospitalization, although there could be some benefits when the treatment starts 4 or 5 days after symptoms begin[19]. In the outpatient setting, the anti-influenza agents have higher efficacy if received within 2 days following the onset of symptoms. Patients (outpatient or inpatient) with clinical and radiological features of CAP and positive *Influenza* testing should receive antibacterial and anti-influenza treatment, considering the high rates of concomitant infections (almost 30%)[20]. The mortality of patients hospitalized for *Influenza*

Table 1. Initial treatment strategies for outpatients with community-acquired pneumonia

Standard regimen	Treatment[c]
No comorbidities or risk factors for *MRSA* or *Pseudomonas aeruginosa*[a]	Amoxicillin or doxycycline or macrolide (if local pneumococcal resistance is <25%)
With comorbidities[b]	Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline or monotherapy with respiratory fluoroquinolone

a Risk factors include prior respiratory isolation of *MRSA* or *P. aeruginosa* or recent hospitalization and receipt of parenteral antibiotics (in the last 90 d). **b** Comorbidities include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia. **c** Amoxicillin 1 g three times daily, doxycycline 100 mg twice daily, azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, or clarithromycin ER 1000 mg daily. Amoxicillin/clavulanate 500 mg/125 mg three times daily, amoxicillin/clavulanate 875 mg/125 mg twice daily, 2000 mg/125 mg twice daily, cefpodoxime 200 mg twice daily, or cefuroxime 500 mg twice daily and azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, clarithromycin ER 1000 mg daily, or doxycycline 100 mg twice daily. Levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily.

Table 2. Initial treatment strategies for inpatients with community-acquired pneumonia

	Standard regimen	Prior respiratory isolation of *MRSA*	Prior respiratory isolation of *Pseudomonas aeruginosa*	Recent hospitalization and parenteral antibiotics and locally validated risk factors for *MRSA*	Recent hospitalization and parenteral antibiotics and locally validated risk factors for *P. aeruginosa*
Non severe inpatient pneumonia	β-Lactam-macrolide- or respiratory fluroquinolone	Add *MRSA* coverage and obtain cultures/ nasal PCR to allow de-escalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa* and obtain cultures to allow de-escalation or confirmation of need for continued therapy	Obtain cultures but withhold *MRSA* coverage unless culture results are positive. If rapid nasal PCR is available, withhold additional empiric therapy against *MRSA* if rapid testing is negative or add coverage if PCR is positive and obtain cultures	Obtain cultures but initiate coverage for *P. aeruginosa* only if culture results are positive
Severe inpatient pneumonia	β-Lactam-macrolide or β-lactam-fluroquinolone	Add *MRSA* coverage and obtain cultures/ nasal PCR to allow de-escalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa* and obtain cultures to allow de-escalation or confirmation of need for continued therapy	Add *MRSA* coverage and obtain nasal PCR and cultures to allow de-escalation or confirmation of need for continued therapy	Add coverage for P. aeruginosa and obtain cultures to allow de-escalation or confirmation of need for continued therapy

and bacterial pneumonia is nearly 10%, mainly attributed to their complications. The most frequent bacteria related to influenza pneumonia are *S. aureus*, *S. pneumoniae,* group A *Streptococcus* and *H. influenzae* group A *Streptococcus*[21-23] (Table 2). Treatment with corticosteroids for adults with CAP is not recommended. A seminal double-blind, randomized controlled trial by Blum et al.[24] showed that administration of prednisolone for 7 days shortened clinical recovery in CAP without increasing complications; yet more data are needed to support this concept and to this end, corticosteroids do not currently belong to the standard of care in CAP.

The appropriate duration of antibiotic treatment

The duration of antibiotic therapy is related to the patient's clinical stability. It should be continued for at least 5 days until a substantial improvement in the patient is achieved. In case of other complications such as endocarditis or colonization with less-frequent pathogens (e.g. *fungi* or *Burkholderia pseudomallei*) longer courses of treatment are recommended. The duration of antibiotics can be shortened based on procalcitonin levels[13,14].

VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

VAP represents a typical complication in mechanically ventilated patients and exerts a dramatic impact on their survival rates. VAP is characterized by new pulmonary infiltrations at least 48 hours after intubation. Approximately 30% of patients who receive mechanical ventilation will develop VAP. The risk factors of VAP are many, such as aspiration of oral and gastric secretions, and colonization of nosocomial pathogens to the endotracheal tube or oropharynx[25].

Diagnosis of VAP

IDSA/ATS guidelines suggest that the diagnosis of VAP requires new pulmonary infiltrations on chest imaging, increasing oxygen requirements, leukocytosis, fever, and increasing sputum production. In patients with suspected VAP, blood or sputum cultures should be obtained. Also, PCR testing can be used, especially during the influenza period, and measuring serum procalcitonin for separate bacterial and viral infections[26].

Table 3. Risk factors for multidrug-resistant pathogens

Risk factors for MDR VAP Prior intravenous antibiotic use with 90 d Septic shock at time of VAP ARDS preceding VAP Five or more days of hospitalization prior to the occurrence of VAP Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP Prior intravenous antibiotic use within 90 d
Risk factors for MRSA VAP/HAP Prior intravenous antibiotic use within 90 d
Risk factors for MDR Pseudomonas VAP/HAP Prior intravenous antibiotic use within 90 d

ARDS: acute respiratory distress syndrome. HAP: hospital-acquired pneumonia. MDR: multidrug resistant. MRSA: methicillin-resistant *Staphylococcus aureus*. VAP: ventilator-associated pneumonia.

Empirical treatment of clinically suspected VAP

Initially, all hospitals should have a local antibiogram, according to the pathogen population of their ICU and their susceptibility profile.

If VAP is suspected, it is strongly recommended to use empirical antibiotic treatment covering bacteria such as *S. aureus* and *P. aeruginosa*. The following conditions are suggestive of empirical treatment for *MRSA*: 1) individuals having risk factors for antimicrobial resistance, 2) units where methicillin-resistant *S. aureus* is isolated >10–20% of the cases, and 3) units with an unknown prevalence of *MRSA* resistance. Typically, *MRSA* is <10–20% of *S. aureus*, which is isolated in ICUs[27].

If there are indications for *MRSA* empirical coverage, either vancomycin or linezolid should be given, while for *MSSA* (and not *MRSA*) empirical treatment, it is suggested piperacillin-tazobactam, respiratory fluoroquinolones, cefepime or carbapenems. When *MSSA* is proven as the causal pathogen of VAP, the preferred agents are oxacillin, nafcillin, or cefazolin[27].

Furthermore, antipseudomonal empirical treatment from different classes should be given in patients suspected of VAP with any of the following criteria: a risk factor for antimicrobial resistance, units with isolation >10% of gram-negative pathogens that are resistant to a compound used as single-therapy, and patients with unknown antimicrobial susceptibility in ICU[28] (Table 3). Aminoglycosides or colistin should be avoided if there are alternative agents against gram-negative pathogens in individuals with suspected VAP[26] (Table 4). The duration of treatment is suggested to be a 7-day course, and the antibiotic therapy should be de-escalated according to the antibiogram. There are some exceptions in the duration of the treatment. These include patients with VAP owing to glucose-non-fermenting gram-negative bacteria that lead to an increased risk for recurrent infections if the treatment duration is only 7–8 days. Clinical criteria and serum procalcitonin levels should guide the discontinuation of antibiotic treatment[27,28].

Table 4. Suggested empirical treatment options for clinically suspected VAP in Units where empirical MRSA coverage and double antipseudomonal/gram-negative coverage are appropriate

A. Gram-positive antibiotics with *MRSA* activity	B. Gram-negative antibiotics with antipseudomonal activity: β-lactam based agents	C. Gram-negative antibiotics with antipseudomonal activity: non-β-lactam based agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8-12h (consider a loading dose of 25–30 mg/kg ×1 for severe illness) or **Oxazolidinones** Linezolid 600 mg IV q12h	**Antipseudomonal penicillins**[b] Piperacillin-tazobactam 4.5 g IV q6h[b] or **Cephalosporins**[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h or **Carbapenemes**[b] Imipenem 500mg IV q6h[d] Meropenem 1g IV q8h or **Monobactams**[f] Aztreonam 2 g IV q8h	**Fluoroquinolones** Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h or **Aminoglycosides**[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h or **Polymyxins**[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl +30) IV q12h (maintenance dose) Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses

Choose one gram-positive option from column A, one gram-negative option from column B, and one gram-negative option from column C. Note that the initial doses suggested in this table may need to be modified for patients with hepatic or renal dysfunction. CrCl: creatinine clearance. IV: intravenous. MRSA: methicillin-resistant Staphylococcus aureus. **a** Drug levels and adjustment of doses and/or intervals required. **b** Extended infusions may be appropriate. **c** On meta-analysis, aminoglycoside regimens were associated with lower clinical response rates with no differences in mortality. **d** The dose may need to be lowered in patients weighing <70 kg to prevent seizures. **e** Polymyxins should be reserved for settings where there is a high prevalence of multidrug resistance and local expertise in using this medication. Dosing is based on colistin-base activity (CBA), for example: one million IU of colistin is equivalent to about 30 mg of CBA which corresponds to about 80 mg of the prodrug colistimethate. Polymyxin B (1 mg – 10000 units). **f** In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam-based agent because it has different targets within the bacterial cell wall.

Table 5. Recommended initial empirical antibiotic therapy for hospital-acquired pneumonia (non-ventilator associated pneumonia)

Not at high risk of mortality[a] and no factors increasing the likelihood of *MRSA*[b,c]	Not at high risk of mortality[a] but with factors increasing the likelihood of *MRSA*[b,c]	High risk of mortality or receipt of intravenous antibiotics during the prior 90 days[a,c]
One of the following: Piperacillin-tazobactam[d] 4.5 g IV q6h or Cefepime[d] 2g IV q8h or Levofloxacin 750 mg IV daily or Imipenem[d] 500 mg IV q6h Meropenem[d] 1 g IV q8h	One of the following: Piperacillin-tazobactam[d] 4.5 g IV q6h or Cefepime[d] or ceftazidime[d] 2 g IV q8h or Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h or Imipenem[d] 500 mg IV q6h Meropenem[d] 1 g IV q8h or Aztreonam 2 g IV q8h Plus: Vancomycin 15 mg/kg IV q8-12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness) or Linezolid 600 mg IV q12h	Two of the following, avoid 2 β-lactams: Piperacillin-tazobactam[d] 4.5 g IV q6h or Cefepime[d] or ceftazidime[d] 2 g IV q8h or Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h or Imipenem[d] 500 mg IV q6h Meropenem[d] 1 g IV q8h or Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h or Aztreonam[e] 2 g IV q8h Plus: Vancomycin 15 mg/kg IV q8-12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness) or Linezolid 600 mg IV q12h If MRSA coverage is not going to be used, include coverage for MSSA. Options include: Piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.

If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam based antibiotic, include coverage for MSSA. HAP: hospital acquired pneumonia. IV: intravenous. MRSA: methicillin resistant Staphylococcus aureus. MSSA methicillin sensitive Staphylococcus aureus. **a** Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock. **b** Indications for MRSA coverage include intravenous antibiotic treatment during the prior 90 days, and treatment in a Unit where the prevalence of MRSA among S. aureus isolates is not known or is >20%. Prior detection of MRSA by culture or non-culture screening may also increase the risk of MRSA. The 20% threshold was chosen to balance the need for effective initial antibiotic therapy against the risks of excessive antibiotic use, hence individual units can elect to adjust the threshold in accordance with local values and preferences. If MRSA coverage is omitted, the antibiotic regimen should include coverage for MSSA. **c** If patient has factors increasing the likelihood of gram-negative infection, 2 antipseudomonal agents are recommended. If patient has structural lung disease increasing the risk of gram-negative infection (i.e. bronchiectasis or cystic fibrosis), 2 antipseudomonal agents are recommended. A high-quality gram stain from a respiratory specimen with numerous and predominant gram-negative bacilli provides further support for the diagnosis of a gram-negative pneumonia, including fermenting and non-glucose fermenting microorganisms. **d** Extended infusions may be appropriate. Meropenem dosage usually is 2 g tid, even if meropenem is still used at a regimen of 1 g tid in some countries, including the US. **e** In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam based agent because it has different targets within the bacterial cell wall.

Taken together, despite the devastating impact of VAP, a considerable proportion of patients receiving the appropriate regimen can be extubated after the onset of VAP.

HOSPITAL-ACQUIRED PNEUMONIA (HAP)

HAP represents a lower respiratory tract infection which did not exist at the time of hospitalization and is shown at least 48 hours after that time point.

In case HAP is suspected (non-VAP), patients are treated according to the microbiological profile. Respiratory samples for culture can be obtained via multiple ways, including spontaneous expectoration or sputum induction. Hospitals in their entirety should regularly produce a local antibiogram, ideally based on their HAP population. Therefore, the empirical antibiotic regimens are tailored to the local pathogens' distribution and susceptibility profile[29].

The empirical management of clinically suspected HAP (Non-VAP)

With regard to individuals who are treated empirically for HAP, it is suggested to use an antibiotic against *S. aureus*, *P. aeruginosa* and other gram-negative bacilli. On the contrary, in case that patients with HAP are receiving empirical treatment and present with risk factors for MRSA infection (such as: 1. previous intravenous antibiotic use within 90 days; 2. hospitalization in a unit where methicillin-resistant *S. aureus* accounts for over 20% of isolates; 3. in case the prevalence of MRSA is unknown; and 4. when there is a high risk of mortality), healthcare providers are advised to administer an antibiotic with MRSA activity (vancomycin or linezolid)[30].

For patients with HAP who are not at high risk of *MRSA* infection or high risk of mortality, the treatment should include an established anti-*MSSA* antibiotic such as piperacillin-tazobactam, levofloxacin, cefepime, meropenem or imipenem. In the context of *MSSA* specifically, the preferred treatment includes oxacillin, nafcillin, or cefazolin. However, one of the above medications does not need to be used. Patients with HAP under empirical treatment that have factors increasing the possibility of *P. aeruginosa* or other gram (-) bacilli infection (such as prior iv antibiotic treatment in the past 90 days) or high risk of mortality must be treated with 2 compounds of different categories with established activity against *P. aeruginosa*. An aminoglycoside should not be used as the only antipseudomonal agent[27,29] (Table 5). The duration of antibiotic therapy for HAP should be approximately 7 days. The exact regimen and duration are typically decided on a case-by-case basis[27].

COVID-19

Therapeutic algorithm for non-hospitalized patients

All outpatient individuals with mild to moderate COVID-19 require symptoms management. Palliative treatment including adequate hydration, use of antipyretics, antitussives, or analgesics on a case-by-case basis and depending on the symptoms is encouraged. Monitoring of temperature and oxygen saturation is highly recommended[31].

With regard to patients at high risk of progression to severe COVID-19, antiviral compounds such as ritonavir-nirmatrelvir (Paxlovid) and remdesivir can reduce the risk of death or hospitalization[32]. Particular attention should be paid to the use of nirmatrelvir/ritonavir, given that its combination is contraindicated with drugs that are potent CYP3A inducers. Alternative therapies include bebtelovimab and molnupiravir[33]. Antiviral compounds have shown far higher efficacy if implemented as early as possible. Treatment should be initiated immediately or at least seven days after symptom onset[34]. Especially for nirmatrelvir/ritonavir, treatment initiation within the first 3 days of symptoms is crucial, given that administration during this window reduces the risk for COVID-19 related hospitalization or death by 89%[32]. Evaluation of the risk of disease progression is important to decide whether to prescribe an antiviral drug to patients that have been vaccinated. The risk is linearly associated with the underlying comorbidome. Patients of older age, immunocompromised individuals, as well as patients with substantial latency time since the most recent COVID-19 vaccine dose (i.e. >4–6 months) are among the groups that are more likely to benefit from antiviral compounds[35].

Except the treatment of COVID-19 per se, meticulous evaluation for co-infection is needed even if the coexistence is not that common. Concomitant viral infections in the setting of COVID-19 are generally rare (1–2%)[36]. Community-acquired bacterial pneumonia can also exist, but it is uncommon, as it can be identified in 4–6% of the subjects with SARS-CoV-2 infection[2]. Antibiotics are not generally recommended unless additional evidence for bacterial pneumonia is observed[36].

Therapeutic algorithm for hospitalized patients

Hospitalized patients for a different reason than COVID-19 not requiring supplementary oxygen

Patients with mild to moderate illness from COVID-19 at high risk of progression may benefit from the administration of remdesivir. Those who are at greater risk of getting seriously ill from COVID-19, are patients with cancer, cerebrovascular disease, chronic lung diseases such as COPD, liver diseases, renal failure, cystic fibrosis, disabilities, diabetes mellitus, HIV (human immunodeficiency virus), chronic heart conditions, mental health disorders, neurological conditions limited to dementia, tuberculosis, solid organ or hematopoietic cell transplantation, primary immunodeficiencies, obesity (BMI: >30 kg/m^2), pregnancy, smokers, patients with limited physical inactivity, and patients using corticosteroids or other immunosuppressive medications. An age >65 years remains the strongest risk factor for severe disease[37].

Hospitalized patients for COVID-19 not in need of supplementary oxygen

Implementation of remdesivir is recommended for patients not in need of supplementary oxygen that have increased risk of progression to severe COVID-19[35]. It is not recommended to use dexamethasone for the management of COVID-19 in patients not requiring supplementary oxygen. In case there is no indication for therapeutic anticoagulation, a prophylactic dose of heparin is typically recommended[38].

Hospitalized patients for COVID-19 who require conventional oxygen

The use of remdesivir without corticosteroids is recommended if the needs for oxygen supplementation are minimal. For individuals who require conventional oxygen, administration of dexamethasone plus remdesivir is suggested. If dexamethasone is unavailable in medical care, an equivalent dose of another corticosteroid category

may be used. If remdesivir is not available, the use of dexamethasone alone is suggested[38-40]. For non-pregnant patients requiring conventional oxygen with D-dimer levels exceeding the upper limit of normal and without an increased risk of bleeding, administration of a therapeutic dose of heparin is suggested. Patients not meeting the criteria for therapeutic heparin, including pregnant individuals, should be given a prophylactic dose of heparin, unless this is not recommended due to contraindications in pregnancy[41]. Patients have increased bleeding risk with any of the following: 1) bleeding within the past 30 days, 2) need of dual antiplatelet therapy, 3) Hgb <8 g/dL, 4) platelet count $<50\times10^9$ per L, 5) history of a bleeding disorder, or 6) acquired bleeding disorder[42]. In patients with rapidly progressive disease, a second immunomodulatory compound (e.g. the IL-6R antagonist denominated tocilizumab or the Janus Kinase 1/2 inhibitor denominated baricitinib) should be added to dexamethasone[43,44]. Several studies have shown clinical improvement and improved survival in hospitalized patients treated for COVID-19 with tocilizumab and other monoclonal antibodies[43].

Hospitalized patients for COVID-19 requiring support with non-invasive ventilation or high-flow nasal cannula oxygen

For this group of patients, the guidelines suggest the administration of dexamethasone plus either per os baricitinib or tocilizumab iv. Our group conducted an open-label, randomized-controlled trial in patients with severe COVID-19, which showed non-inferiority of baricitinib to tocilizumab for mechanical ventilation or death and the time to discharge[45]. If baricitinib and tocilizumab are not available, tofacitinib and sarilumab can be implemented instead, respectively. If none is available, the use of dexamethasone alone is recommended. Remdesivir should also be included in the treatment regimen for this group of patients. The treatment should typically include a prophylactic dose of heparin as well. A therapeutic or intermediate dose of anticoagulation for VTE prophylaxis should not be administered[42].

Patients who are hospitalized for COVID-19 requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)

With regard to patients who need mechanical ventilation or ECMO, the administration of dexamethasone plus tocilizumab or baricitinib is suggested. If baricitinib, tocilizumab, sarilumab and tofacitinib are not available, it is recommended to use dexamethasone alone. For patients progressing to invasive mechanical ventilation or ECMO, despite having started remdesivir, it is suggested to continue remdesivir until the treatment course is completed. A prophylactic dose of heparin should be typically administered as well. Patients who were given a therapeutic dose of heparin in a hospital ward without evidence of thromboembolism and then transferred to the ICU, should continue a prophylactic dose[42,46,47].

Finally, the Greek guidelines for COVID-19 in hospitalized patients are worth mentioning. According to these guidelines, patients with mild disease who do not require supplementary oxygen should not receive any specific medication. In patients with risk factors for disease progression, oxygen therapy is administered within hospital early treatment to avoid progression to severe disease. Risk factors include an age >65 years, obesity BMI >35 kg/m^2, immunosuppression, hemodialysis, chronic heart disease, chronic obstructive pulmonary disease, chronic respiratory deficiency under oxygen therapy, idiopathic pulmonary fibrosis, diabetes mellitus, hemoglobinopathies, 3rd trimester pregnancy. Non-vaccination, or an interval >6 months since vaccination, increases additionally the risk posed by the individual risk factors. For hospitalized patients who require conventional oxygen and do not exhibit symptoms or signs of severe disease such as oxygen saturation <90% on room air (or <94% but rapidly worsening), signs of severe respiratory distress (>30 breaths/min, inability to complete sentences, use of accessory respiratory muscles), extensive infiltrates (>50%) on chest imaging, or laboratory combination (lymphocytes <1000/μL, ferritin >1000 mg/mL, CRP >75 mg/L with normal value <5 mg/L), remdesivir plus a prophylactic dose of heparin should be administered. With regard to patients with increasing oxygen needs, dexamethasone should be implemented[38,39]. Anakinra can be administered to patients with pneumonia who have a high risk of respiratory failure, as determined by serum levels of soluble urokinase plasminogen activator receptor (suPAR) ≥6 ng/mL[48]. Antibiotics are administered for documented or suspected bacterial pneumonia based on clinical, imaging, or laboratory findings, following the guidelines of the Hellenic Society of Infectious Diseases for community-acquired pneumonia. Remdesivir, dexamethasone plus a prophylactic dose of heparin should be administered to patients on high-flow oxygen supply on non-invasive ventilation, or those exhibiting symptoms and signs of severe disease. Baricitinib or tocilizumab should be added in non-improving patients with increased markers of inflammation[43-45]. Anakinra may be used for patients with pneumonia receiving high levels of oxygen supply and who are at serious risk of respiratory failure, as determined by serum levels of soluble urokinase plasminogen activator receptor (suPAR) ≥6 ng/mL[48]. Additionally, the patient should be positioned in a prone position. The administration of antibiotics for bacterial pneumonia, either documented or suspected, is based on clinical, imaging, or laboratory findings, and follows the guidelines established by the Hellenic Society of Infectious Diseases for community-acquired pneumonia[36]. If patients are on mechanical ventilation or ECMO and have not received or completed a 10-day course of dexamethasone, or if tocilizumab has not already been administered and there are no contraindications, the patient should be given the appropriate medication. To ensure optimal treatment,

remdesivir should be administered only as part of a treatment regimen and for the complete 5-day duration. Additionally, all patients should receive a prophylactic dose of low molecular weight heparin[41].

CONCLUSION

Respiratory tract infections represent a major cause of morbidity and mortality, and the emergence of SARS-CoV-2 has led to unprecedented global health and economic consequences. In the context of personalized medicine, targeted therapeutic strategies are needed to optimize patient outcomes. Thus, there is a growing consensus in favor of treatment regimens based on guidelines rather than the indiscriminate use of broad-spectrum antibiotics. Local guidelines are crucial for the evidence-based management of infections, given the variable resistance profiles observed worldwide. Such guidelines are essential complements to international guidelines in the effort to promote rational antimicrobial use and combat antimicrobial resistance.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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REFERENCES

1. Grief SN, Loza JK. Guidelines for the Evaluation and Treatment of Pneumonia. Prim Care. 2018;45(3):485-503. doi:10.1016/j.pop.2018.04.001
2. Hedberg P, Johansson N, Ternhag A, Abdel-Halim L, Hedlund J, Nauclér P. Bacterial co-infections in community-acquired pneumonia caused by SARS-CoV-2, influenza virus and respiratory syncytial virus. BMC Infect Dis. 2022;22(1):108. doi:10.1186/s12879-022-07089-9
3. Zequn Z, Yujia W, Dingding Q, Jiangfang L. Off-label use of chloroquine, hydroxychloroquine, azithromycin and lopinavir/ritonavir in COVID-19 risks prolonging the QT interval by targeting the hERG channel. Eur J Pharmacol. 2021;893:173813. doi:10.1016/j.ejphar.2020.173813
4. Metlay JP, Waterer GW, Long AC, et al. 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. 2019;200(7):e45-e67. doi:10.1164/rccm.201908-1581ST
5. Bjarnason A, Westin J, Lindh M, et al. Incidence, Etiology, and Outcomes of Community-Acquired Pneumonia: A Population-Based Study. Open Forum Infect Dis. 2018;5(2):ofy010. doi:10.1093/ofid/ofy010
6. Cilloniz C, Martin-Loeches I, Garcia-Vidal C, San Jose A, Torres A. Microbial Etiology of Pneumonia: Epidemiology, Diagnosis and Resistance Patterns. Int J Mol Sci. 2016;17(12):2120. doi:10.3390/ijms17122120
7. Steel HC, Cockeran R, Anderson R, Feldman C. Overview of Community-Acquired Pneumonia and the Role of Inflammatory Mechanisms in the Immunopathogenesis of Severe Pneumococcal Disease. Mediators Inflamm. 2013;2013:490346. doi:10.1155/2013/490346
8. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58(5):377-382. doi:10.1136/thorax.58.5.377
9. Welte T. Risk factors and severity scores in hospitalized patients with community-acquired pneumonia: prediction of severity and mortality. Eur J Clin Microbiol Infect Dis. 2012;31(1):33-47. doi:10.1007/s10096-011-1272-4
10. Eshwara VK, Mukhopadhyay C, Rello J. Community-acquired bacterial pneumonia in adults: An update. Indian J Med Res. 2020;151(4):287-302. doi:10.4103/ijmr.IJMR_1678_19
11. Aliberti S, Dela Cruz CS, Amati F, Sotgiu G, Restrepo MI. Community-acquired pneumonia. Lancet. 2021;398(10303):906-919. doi:10.1016/S0140-6736(21)00630-9
12. Karakioulaki M, Stolz D. Biomarkers in Pneumonia—Beyond Procalcitonin. Int J Mol Sci. 2019;20(8):2004. doi:10.3390/ijms20082004
13. Christ-Crain M, Müller B. Procalcitonin and pneumonia: is it a useful marker? Curr Infect Dis Rep. 2007;9(3):233-240. doi:10.1007/s11908-007-0037-9
14. Cao B, Huang Y, She DY, et al. Diagnosis and treatment of community-acquired pneumonia in adults: 2016 clinical practice guidelines by the Chinese Thoracic Society, Chinese Medical Association. Clin Respir J. 2018;12(4):1320-1360. doi:10.1111/crj.12674
15. Maraki S, Papadakis IS. Antimicrobial Resistance Trends among Community-Acquired Respiratory Tract Pathogens in Greece, 2009–2012. ScientificWorldJournal. 2014;2014:941564. doi:10.1155/2014/941564

16. Jaoude P, Badlam J, Anandam A, El-Solh AA. A comparison between time to clinical stability in community-acquired aspiration pneumonia and community-acquired pneumonia. Intern Emerg Med. 2014;9(2):143-150. doi:10.1007/s11739-012-0764-2
17. Fujitani S, Sun HY, Yu VL, Weingarten JA. Pneumonia due to Pseudomonas aeruginosa: part I: epidemiology, clinical diagnosis, and source. Chest. 2011;139(4):909-919. doi:10.1378/chest.10-0166
18. Restrepo MI, Babu BL, Reyes LF, et al. Burden and risk factors for Pseudomonas aeruginosa community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. Eur Respir J. 2018;52(2):1701190. doi:10.1183/13993003.01190-2017
19. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet. 2015;385(9979):1729-1737. doi:10.1016/S0140-6736(14)62449-1
20. Segreti J, House HR, Siegel RE. Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting. Am J Med. 2005;118(7A):21-28. doi:10.1016/j.amjmed.2005.05.010
21. Metersky ML, Masterton RG, Lode H, File TM Jr, Babinchak T. Epidemiology, microbiology, and treatment considerations for bacterial pneumonia complicating influenza. Int J Infect Dis. 2012;16(5):e321-e331. doi:10.1016/j.ijid.2012.01.003
22. Lee N, Choi KW, Chan PK, et al. Outcomes of adults hospitalised with severe influenza. Thorax. 2010;65(6):510-515. doi:10.1136/thx.2009.130799
23. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303(15):1517-1525. doi:10.1001/jama.2010.479
24. Blum CA, Nigro N, Briel M, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2015;385(9977):1511-1518. doi:10.1016/S0140-6736(14)62447-8
25. Modi AR, Kovacs CS. Hospital-acquired and ventilator-associated pneumonia: Diagnosis, management, and prevention. Cleve Clin J Med. 2020;87(10):633-639. doi:10.3949/ccjm.87a.19117
26. Rea-Neto A, Youssef NC, Tuche F, et al. Diagnosis of ventilator-associated pneumonia: a systematic review of the literature. Crit Care. 2008;12(2):R56. doi:10.1186/cc6877
27. Kalil AC, Metersky ML, Klompas M, et al. 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. 2016;63(5):e61-e111. doi:10.1093/cid/ciw353
28. Li HY, Wang HS, Wang YL, Wang J, Huo XC, Zhao Q. Management of Ventilator-Associated Pneumonia: Quality Assessment of Clinical Practice Guidelines and Variations in Recommendations on Drug Therapy for Prevention and Treatment. Front Pharmacol. 2022;13:903378. doi:10.3389/fphar.2022.903378
29. Erb CT, Patel B, Orr JE, et al. Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia. Ann Am Thorac Soc. 2016;13(12):2258-2260. doi:10.1513/AnnalsATS.201608-641CME
30. Pickens CI, Wunderink RG. Methicillin-Resistant Staphylococcus aureus Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia. Semin Respir Crit Care Med. 2022;43(2):304-309. doi:10.1055/s-0041-1740583
31. Kikuchi A, Arita R, Ono R, et al. Response to Glucocorticoid Therapy in Patients with Mild to Moderate Coronavirus Disease 2019 at a Japanese Care Facility. Tohoku J Exp Med. 2022;257(2):97-106. doi:10.1620/tjem.2022.J022
32. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022;386(15):1397-1408. doi:10.1056/NEJMoa2118542
33. Westendorf K, Žentelis S, Wang L, et al. LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. bioRxiv. Preprint posted online March 24, 2022. doi:10.1101/2021.04.30.442182
34. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med. 2022;386(4):305-315. doi:10.1056/NEJMoa2116846
35. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2020;324(11):1048-1057. doi:10.1001/jama.2020.16349
36. Wu CP, Adhi F, Highland K. Recognition and management of respiratory co-infection and secondary bacterial pneumonia in patients with COVID-19. Cleve Clin J Med. 2020;87(11):659-663. doi:10.3949/ccjm.87a.ccc015
37. Gao YD, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2021;76(2):428-455. doi:10.1111/all.14657
38. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(8):693-704. doi:10.1056/NEJMoa2021436
39. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764
40. Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. CMAJ. 2022;194(7):E242-E251. doi:10.1503/cmaj.211698
41. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. JAMA Intern Med. 2021;181(12):1612-1620. doi:10.1001/jamainternmed.2021.6203

42. REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med. 2021;385(9):777-789. doi:10.1056/NEJMoa2103417
43. Karampitsakos T, Malakounidou E, Papaioannou O, et al. Tocilizumab improves 28-day survival in hospitalized patients with severe COVID-19: an open label, prospective study. Respir Res. 2021;22(1):317. doi:10.1186/s12931-021-01914-6
44. Karampitsakos T, Vraka A, Bouros D, Liossis SN, Tzouvelekis A. Biologic Treatments in Interstitial Lung Diseases. Front Med (Lausanne). 2019;6:41. doi:10.3389/fmed.2019.00041
45. Karampitsakos T, Papaioannou O, Tsiri P, et al. Tocilizumab versus baricitinib in hospitalized patients with severe COVID-19: an open label, randomized controlled trial. Clin Microbiol Infect. 2023;29(3):372-378. doi:10.1016/j.cmi.2022.10.015
46. INSPIRATION Investigators, Sadeghipour P, Talasaz AH, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA. 2021;325(16):1620-1630. doi:10.1001/jama.2021.4152
47. Zhang X, Shang L, Fan G, et al. The Efficacy and Safety of Janus Kinase Inhibitors for Patients With COVID-19: A Living Systematic Review and Meta-Analysis. Front Med (Lausanne). 2022;8:800492. doi:10.3389/fmed.2021.800492
48. Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med. 2021;27(10):1752-1760. doi:10.1038/s41591-021-01499-z