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Guidelines

Community-acquired pneumonia – An EFIM guideline critical appraisal adaptation for internists

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ABSTRACT

Background: In real-life settings, guidelines frequently cannot be followed since many patients are multimorbid and/or elderly or have other complicating conditions which carry an increased risk of drug-drug interactions. This document aimed to adapt recommendations from existing clinical practice guidelines (CPGs) to assist physicians' decision-making processes concerning specific and complex scenarios related to acute CAP.

Methods: The process for the adaptation procedure started with the identification of unsolved clinical questions (PICOs) in patients with CAP and continued with critically appraising the updated existing CPGs and choosing the recommendations, which are most applicable to these specific scenarios.

Results: Seventeen CPGs were appraised to address five PICOs. Twenty-seven recommendations were endorsed based on 7 high, 9 moderate, 10 low, and 1 very low-quality evidence. The most valid recommendations applicable to the clinical practice were the following ones: Respiratory virus testing is strongly recommended during periods of increased respiratory virus activity. Assessing the severity with a validated prediction rule to discriminate where to treat the patient is strongly recommended along with reassessing the patient periodically for improvement as expected. In adults with multiple comorbidities, polypharmacy, or advanced age, it is strongly recommended to check for possible drug interactions before starting treatment. Strong graded recommendations exist on antibiotic treatment and its duration. Recommendations on the use of biomarkers such as C-reactive protein or procalcitonin to improve severity assessment are reported.

Conclusion: This document provides a simple and reliable updated guide for clinical decision-making in the management of complex patients with multimorbidity and CAP in the real-life setting.

1. Background

Community-acquired pneumonia (CAP) is defined as an acute infection of the pulmonary parenchyma acquired outside the hospital and, is one of the most important causes of morbidity and mortality worldwide. According to The Global Burden of Disease Study, lower respiratory tract infections ranked 4th in terms of disability-adjusted life-years across all ages in 2019 and as a significant subset, CAP is the most frequent cause of death from infection in Europe [1,2]. Because the diagnosis is frequently made based on clinical and radiological findings and the microbial agent is not known most of the time, management of CAP can be challenging since no single antimicrobial regimen can cover all the possible causes. Moreover, as antimicrobial susceptibility testing results of usual microbial suspects may vary across different regions, this process can be even more difficult.

Most of the published clinical practice guidelines (CPGs) are written by specialists from different specialties of medicine, for instance, infectious diseases or pulmonary medicine, and focus on an 'ideal' patient affected by a single condition, while in real-life practice internists should usually manage elderly, complex patients with comorbidities [3,4]. CAP is more common in the elderly population, in which multi-morbidity and polypharmacy are frequent [5]. Since the presence of multiple comorbidities is associated with long-term mortality and an increased risk of drug-drug interactions, and since polypharmacy is common in patients with CAP, it would be appropriate to evaluate the management of CAP as a multi-dimensional health problem from a comprehensive point-of-view of internists [6].

The aim of the analysis is to adapt recommendations from existing CPGs to assist physicians' decision-making processes concerning specific and complex scenarios related to acute CAP in immunocompetent patients. The primary goals are to identify the most important clinical problems in patients suffering from CAP, critically appraise the existing CPGs, and choose the recommendations which are most valid and applicable to the clinical practice in internal medicine departments.

2. Methods

We followed the methodology elaborated by the EFIM Practice Guidelines Appraisal Working Group (WG) [7]. The EFIM CPG-WG appointed the members of the CAP Task Force (CAP-TF) according to the previously defined structure: the chairperson of the CAP-TF (SU), two co-chairs of the CAP-TF (AGE, IML), six CAP-TF members (SB, KD, PL, HL, ARA, AS) and a methodologist (WL).

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2.1. Definition of the clinical questions

In order to figure out the potential gaps in the medical practice, we prepared a detailed questionnaire for internists. In this 7-question survey, 287 physicians (240 of them were internists) were asked questions on how they approach patients suspected of CAP, how they evaluate drug interactions, and which CPGs they follow routinely (*Supplementary File #1*). After CAP-TF members analyze and discuss the results of the questionnaire, each member suggested a list of 5 PICOs based on the results of the questionnaire and their clinical experience. Then, PICOS with the most votes were chosen accordingly (Table 1).

2.2. Searching and screening for eligible guidelines to be used for adaptation

To find relevant CPGs related to the topic, a search was performed from various sources. The Pubmed database was searched with (``community acquired pneumonia''[Title/Abstract]) AND ("guideline"[Title/Abstract]) query without time restriction and NICE database with ("community acquired pneumonia", type: Guidance) query from 1996 to 2020. Moreover, recent review articles which were published regarding CAP were also evaluated for additional resources [8–10]. After an extensive evaluation process, case series, editorials, guideline discussions, and assessments, as well as guidelines for immunocompromised patients, were excluded. After duplicate, non-English documents and guidelines for children were removed, full-text CPGs for the adult population were assessed for eligibility. The final date of the search was 15th February 2021 (Fig. 1).

2.3. Assessing the quality of the eligible guidelines and selecting the good quality updated evidence-based-CPG to include for adaptation

Eligible guidelines were assessed according to EFIM methodology [7]. The quality of included CPG on CAP was independently assessed by four members of the TF (SB, IML, AGE, AAR), using the AGREE-II Instrument scores for Domain 1 (Scope and Purpose) and Domain 3 (Rigor of Development) [11]. A CPG was included if: a) the mean score was at least 3 for each item (i.e., at least 9 in Domain 1 and at least 24 in Domain 3; (b) at least 50% threshold for each of the maximum possible scores for each of these two domains was reached. When the score was equal, AGREE-II Domain 3 score and recent publication date were prioritized. After this assessment, 6 CPGs were selected to address the selected PICOs [12–17].

2.4. Selecting recommendations from the existing original CPGs

Within the CAP-TF, different PICO teams (one for each PICO) of 2 panelists were formed. The choice and development of recommendations were made in a triple-round process, as previously published [18].

In the first of these rounds, each panelist independently identified the recommendations addressing the PICOs in the included CPGs and adapted these recommendations using a) the GRADE format for the quality of the evidence and the strength of the recommendation when available on the original guideline, or b) adapting the level of the evidence provided to the four levels (high, moderate, low, very low) proposed by GRADE, also integrating the information from the different CPGs that address the clinical question [19]. In the second round, the panelists of each PICO team resolved discrepancies in the conflicting recommendations. In a third face-to-face meeting, all the members of the CAP-TF resolved discrepancies and approved the final recommendations by consensus. Best practice comments were added to the recommendations if members wanted to add some clarifications and highlight some important points where they think those comments might be beneficial for internal medicine daily practice.

Table 1
List of PICOs

PICO 1	In adults with CAP, should a respiratory sample for influenza and other respiratory virus testing be taken at the time of initial diagnosis during respiratory virus season?
PICO 2	In adults with CAP, should a clinical prediction rule for prognosis be used to determine whether the patient would be admitted to the internal medicine ward or intensive care unit?
PICO 3	In adults with CAP and multiple comorbidities, should drug interactions be evaluated before starting antimicrobial treatment?
PICO 4	In adults with CAP, which factors - age, severity of pneumonia, risk factors for antimicrobial resistance, comorbidities etc. - should the internists consider while starting antimicrobial treatment?
PICO 5	In adults with CAP, should internists use biomarkers of infection to manage (to initiate, to assess the response to and to stop) antibiotic treatment?

2.5. Dissemination phase

Finally, CAP-TF elaborated and approved by consensus a draft of the document that was consequently validated by three external reviewers (MDT, AFK, NMG) who were experts in guidelines and CAP, and by the EFIM Executive Committee to be published and disseminated.

3. RESULTS

The literature search identified 342 documents from PubMed and 8 from NICE. After screening and exclusion of duplicates, 28 full-text articles remained that were independently evaluated by at least two members of the CAP-TF (Fig. 1: Flow chart). Seventeen CPGs on CAP were selected for quality assessment by the AGREE-II instrument, and 6 were finally included to address the 5 PICOs of this guideline (Table 2). Results of the assessment of all CPGs according to the AGREE-II tool were provided in Supplementary File #2.

PICO 1 - In adults with CAP, should a respiratory sample for influenza and other respiratory virus testing be taken at the time of initial diagnosis during respiratory virus season?

Four chosen CPGs address this topic with high agreement across them [12,14,15,17].

Recommendation 1.1:

- In moderate severity pneumonia (CURB-65=0-2) (Table 3): Polymerase chain reaction (PCR) test or serological investigations may be considered during periods of increased respiratory virus activity when a patient is suspected of having pneumonia caused by respiratory viruses based on clinical symptoms and/or radiographic findings [15].
- In high severity pneumonia (CURB-65 = 3-5): If available, sputum or other respiratory sample collection should be obtained for PCR (best option) or direct immunofluorescence (or other antigen detection test) for detecting a viral etiology. *Strong recommendation Quality of Evidence (QoE): low* [12,17].

Best practice comments:

- PCR for respiratory viruses and atypical pathogens is preferred over serological assays if it is readily available [14].
- For patients with a strong suspicion of a viral pathogen based on clinical, radiographic, and/or epidemiological grounds, with high severity CAP where no microbiological diagnosis has been made by other means (e.g., culture, urine antigen, PCR) and who fail to improve with beta-lactam antibiotics, paired serology tests can be considered but only for epidemiological purposes.

PICO 2 - In adults with CAP, should a clinical prediction rule for prognosis be used to determine whether the patient would be admitted to the internal medicine ward or intensive care unit?

Chosen CPGs address this topic, with a high agreement among them, emphasizing that no predictive model allows unequivocal

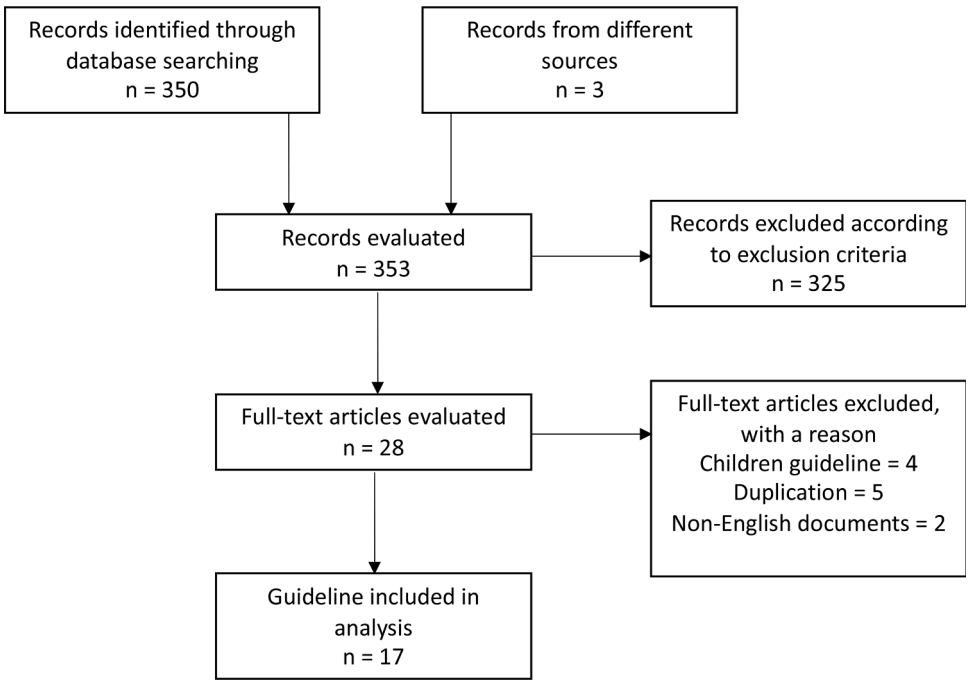

Fig. 1. Flow chart of the clinical practice guidelines (CPGs) selection process, following the PRISMA statement [Moher 2009]

Table 2
List of chosen six clinical practice guidelines (CPGs)

BTS guidelines for the management of community-acquired pneumonia in adults: update 2009. Lim et al. Thorax, 2009.
ESCMID/ERS Guidelines for the management of adult lower respiratory tract infections. Woodhead et al. Clin Microbiol Infect, 2011.
Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia. Lee et al. Infect Chemother, 2018.
IDSA/ATS Diagnosis and Treatment of Adults with Community-acquired Pneumonia. Metlay et al. Am J Respir Crit Care Med, 2019.
Management of community-acquired pneumonia in adults: 2016 guideline update from the Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). Wiersinga et al. Neth J Med, 2018.
National Institute for Health and Care Excellence (NICE). Pneumonia (community-acquired): antimicrobial prescribing [NG138]. 2019

Table 3
CURB-65 score

Confusion	
Urea > 7 mmol/L (20 mg/dl)	1 point
Respiratory rate ≥ 30 breathes/minute	1 point
Blood pressure (systolic <90 mmHg or diastolic <60 mmHg)	1 point
Age ≥65 years	1 point
CRB-65 score does not include urea level	1 point

categorization of patients into definite risk groups. Predictive models based on severity are best viewed as useful adjuncts to clinical decisions. Clinical judgment is essential in disease severity assessment. The stability of any comorbid illness and the patient's socioeconomic status should also be considered together with disease severity [12,14-17].

The guidelines propose two different scenarios to use prediction tools, i.e., to decide:

a) When to admit an ambulatory patient to an internal medicine ward?
b) When to admit a patient to an intensive care unit (ICU)?

2a: Should a clinical prediction rule for prognosis be used to determine whether the patient should be admitted to the internal medicine ward?

Recommendation 2.1: Patients with CAP may be classified according to severity: mild (treatment at home), moderate-severe (admission to an internal medicine ward), and severe CAP (admission to an ICU). *Strong recommendation. QoE: moderate.* [12, 14–17].

Recommendation 2.2: The Pneumonia Severity Index (PSI) (Table 4) and the CURB-65 Score (Table 3) are validated scoring systems, equally

Table 4
Pneumonia severity index (PSI)

Sex	Class 1: For patients under the age of 51 years with no comorbidities or abnormal physical findings
Male (0 points)	
Female (-10 points)	
Demographic factors	Class 2: 0 to 70 points
Age (1 point for each year)	Class 3: 71 to 90 points
Nursing home resident (10 points)	Class 4: 91 to 130 points
Comorbid illnesses	Class 5: 131 to 405 points
Neoplastic disease (active) (30 points)	
Chronic liver disease (20 points)	
Heart failure (10 points)	
Cerebrovascular disease (10 points)	
Chronic renal disease (10 points)	
Physical examination findings	
Altered mental status (20 points)	
Respiratory rate ≥30/minute (20 points)	
Systolic blood pressure <90 mmHg (20 points)	
Temperature <35°C or ≥40°C (15 points)	
Pulse ≥125/minute (10 points)	
Laboratory and radiographic findings	
Arterial pH <7.35 (30 points)	
Blood urea nitrogen ≥30 mg/dL (11 mmol/L) (20 points)	
Sodium <130 mEq/L (20 points)	
Glucose ≥250 mg/dL (14 mmol/L) (10 points)	
Hematocrit <30% (10 points)	
Partial pressure of arterial oxygen <60 mmHg or oxygen saturation <90% (10 points)	
Pleural effusion (10 points)	

reliable in predicting 30-day mortality in patients hospitalized with CAP [20,21]. It should be noted that there can be marked differences in the categorization of severity with regard to these different scoring systems. *Strong recommendation. QoE: moderate.* [14].

Best practice comments:

- With regards to the potential discordance in severity assessment using different prediction rules, a Dutch study of 1047 patients admitted with CAP showed that using a CURB-65 score of 2 as cut-off, almost twice as many patients were classified as having severe CAP as compared with the PSI score [22]. However, with a cut-off CURB-65 score of 3, fewer patients were classified as severe CAP compared with the PSI. As there is no gold standard, the committee does not recommend any of the scoring systems over the other; however, it is recommended that each hospital consistently use only one of these scoring systems in daily practice.

Recommendation 2.3: In adults, it is recommended that healthcare professionals use clinical judgment along with CRB-65 score or CURB-65 score (Table 3) to assess the severity of CAP, to decide when to refer the patient to the hospital. *Strong recommendation. QoE: high,* [12,16,17].

Recommendation 2.4*:* The simplified CRB-65 score is recommended as the severity assessment strategy in the community or primary care settings for CAP. *Strong recommendation. QoE: low* [12,17].

Best practice comments:

- Although the American Thoracic Society and Infectious Diseases Society of America CPG recommend the PSI over CURB-65 to determine the need for hospitalization in adults diagnosed with CAP [15], in clinical practice, the major limitation of the PSI regarding its widespread and routine adoption in primary care, emergency departments or medical admission units is the complexity of the score calculation [12,13].
- As seen in this recommendation, disagreements occur across CPGs regarding the choice of clinical prediction rules. The ultimate goal should be to make an individual evaluation of the patient's clinical status complemented with a prediction rule that is consistently preferred and used in the institution.

Recommendation 2.5: It is recommended to reassess adults with CAP if symptoms or signs do not improve as expected or worsen rapidly or significantly. *Strong recommendation. QoE: high.* [12,16].

Recommendation 2.6: In the outpatient setting it is suggested to refer adults with CAP to the hospital if:

a) they have any symptoms or signs suggesting a more serious illness or condition (for example, cardiorespiratory failure or sepsis) or
b) they have symptoms that do not improve with antibiotics, i.e., if they have had a fever in the past 48 h or have more than one sign of clinical instability (systolic blood pressure less than 90 mmHg, heart rate more than 100/minute, respiratory rate more than 24/minute, arterial oxygen saturation less than 90% or arterial partial pressure of oxygen of less than 60 mmHg in room air) or
c) they cannot take oral medicines (it may be worthwhile to explore locally available options for giving intravenous antibiotics at home or in the community, rather than in hospital if this is appropriate). *Strong recommendation. QoE: high* [12,16,17] or
d) they are elderly with an elevated risk of complications, notably those with relevant co-morbidity (diabetes, heart failure, moderate and severe chronic obstructive pulmonary disease (COPD), liver disease, renal disease, or malignant disease). *Practical Consensus Statement, QoE: low.* [13].

2b: Should a clinical prediction rule for prognosis be used to determine whether the patient should be admitted to the intensive care unit?

Recommendation 2.7: Although we suggest using IDSA/ATS Severity Minor Criteria for ICU admission, in settings where CURB-65 is the standard score used, patients with CURB-65 scores of 4 and 5 should be assessed with specific consideration for the need for transfer to an ICU. *Strong recommendation. QoE: high.* [12].

Recommendation 2.8: For patients who fail to improve as expected, there should be a careful review by an experienced clinician of the clinical history, examination, prescription chart, and results of all available diagnostic tests. Referral for further diagnostic (i.e.: bronchoalveolar lavage) or to ICU should be considered. *Strong recommendation. QoE: low,* [12].

Recommendation 2.9: Direct admission to an ICU is recommended for patients with hypotension requiring vasopressors or respiratory failure requiring mechanical ventilation. *Strong recommendation. QoE: low.* [12,15,17].

Recommendation 2.10: For patients not requiring vasopressors or mechanical ventilator support, we suggest using IDSA/ATS Severity Minor Criteria (Table 5) together with clinical judgment to guide the need for higher levels of treatment intensity. The presence of three or more minor criteria may require ICU admission. *Practical Consensus Statement. QoE: low*. [15].

Best practice comments:

- The decision to admit a patient to the ICU is usually not exclusively based on clinical criteria but also depends on the local settings and facilities. Therefore, it appears that criteria for ICU admission should be used as indicators for the need for intensified treatment rather than as advice for ICU admission.

PICO 3 - In adults with CAP and multiple comorbidities, should drug interactions be evaluated before starting antimicrobial treatment?

None of the available guidelines on CAP addressed checking drug-drug interactions except the 2019 NICE Guideline [16].

Recommendation 3.1: In adults with CAP and multiple comorbidity conditions or advanced age, it is recommended to check for possible drug interactions with the individual patient's concurrent treatment before starting antimicrobial therapy. Online databases can be used for this purpose. *Strong recommendation, QoE: high.* [16].

Best practice comments:

- To raise the awareness of clinicians, some potential drug interactions related to the treatment of CAP are listed in Table 6. NICE-2019 Guideline refers to summaries of product characteristics (https://www.medicines.org.uk/emc/) for drug interaction information of each individual antibiotic. However, instead of checking package insert or summary of product characteristics of each drug, using subscription programs are time-saving while checking patients' all drugs at once. Classification of drug interactions according to their significance such as contraindicated, major, moderate, minor, and mechanism/management of them are provided in these databases. (Lexicomp®/UpToDate® by Wolters Kluwer, Drug Interactions, Micromedex® Solutions Drugs Interactions by IBM Watson Health or

Table 5
IDSA/ATS severity criteria

Main criteria	Invasive mechanical ventilation
	Septic shock requiring vasopressors
Minor criteria	Respiratory rate ≥30 breaths/min
	PaO_2/FiO_2 ratio ≤250
	Multi-lobar involvement
	Confusion/disorientation Uremia (BUN ≥20 mg/dL)
	Leukopenia (leukocyte count, <4,000/mm^3)
	Thrombocytopenia (platelet count, <100,000/mm^3)
	Hypothermia (core body temperature, <36°C)
	Hypotension requiring active fluid resuscitation

Validated definition includes either one major criterion or three or more minor criteria

Table 6
Some examples of potential drug interactions with antibiotics for the treatment of community acquired pneumonia

Antibiotics	Interacting Drug/ substance	Interaction
Aminoglycosides [23]	Acyclovir, Colistin, Vancomycin,	Increased risk of toxicities such as nephrotoxicity, ototoxicity, and neurotoxicity with concurrent use of other drugs with similar toxicities.
Carbapenems [24]	Valproic acid	Carbapenems can significantly increase the risk of seizures by significant reduction in the concentration of valproic acid.
Cefoperazone, Metronidazole [23]	Alcohol	Concomitant use may cause disulfiram-like reactions.
Cephalosporins, Fluoroquinolones, Macrolides, Penicillins [25]	Oral anticoagulants	These antibiotics can cause an increase in antiaggregant effect and prolonged bleeding time when used in combination with oral anticoagulants.
Clarithromycin [26]	Atorvastatin, Colchicine, Cyclosporine, Glucocorticoids, Haloperidol, Midazolam, Tacrolimus	Due to inhibition of cytochrome P450 3A4 enzyme system, clarithromycin may increase the concentrations of these drugs with concomitant use.
Fluoroquinolones, Macrolides [27]	Insulins, Meglitinides, Sulfonylureas	Macrolides and fluoroquinolones can increase the effectiveness of these antidiabetic drugs leading to increased risk of hypoglycemia especially in elderly and patients with kidney failure.
Fluoroquinolones, Tetracyclines [28]	Drugs or nutrients containing iron, zinc, magnesium, aluminum	Decreased absorptions of fluoroquinolones and tetracyclines due to formation of insoluble complexes with concurrent use.
Fluoroquinolones [29]	Amiodarone, Escitalopram, Tramadol	Fluoroquinolones can induce cardiotoxicity in patients with cardiovascular diseases, especially with other such drugs that prolong the QT interval.
Metronidazole [23]	Cyclosporine, Lithium, Warfarin	Metronidazole is also a moderate inhibitor of the CYP3A4 enzyme which may increase blood concentrations of such drugs.
Penicillins [23]	Methotrexate	Penicillin may increase serum methotrexate concentrations by reducing its excretion from the kidneys.

open access programs such as drugs.com by the Drugsite Trust, Medscape by the WebMD Network) [30–33].

- Even though it is not practically applicable, clinicians should keep in mind that aging is not only associated with an increased risk of drug interaction with comorbidities and polypharmacy, also with an alteration of pharmacodynamics and pharmacokinetics of drugs in the elderly due to changes in renal and hepatic function and/or in body composition may result in increased volume of distribution, prolonged elimination half-life and reduced clearance [34]. In addition, elderly patients are at higher risk of drug adverse effects such as increased antiaggregant effect and prolonged bleeding time with concomitant use of penicillin G, amoxicillin, cefoperazone, and ceftriaxone with oral anticoagulants and increased risk of tendinitis and tendon rupture when with concomitant use of fluoroquinolones and corticosteroids [25,35]. Moreover, clinicians should consider the appropriateness of crushing, opening, or splitting oral dosage forms (Lexicomp®/UpToDate® by Wolters Kluwer) while prescribing antibiotics for the treatment of CAP in elderly patients with dysphagia [32].

PICO 4 - In adults with CAP, which factors - age, severity of pneumonia, risk factors for antimicrobial resistance, comorbidities, etc. - should the internists consider while starting antimicrobial treatment?

Chosen CPGs address this topic, with a high agreement among them [12–17].

Recommendation 4.1: In the outpatient settings, for patients without comorbidities, amoxicillin or macrolides (clarithromycin, azithromycin) or doxycycline are recommended as first-line agents. *Strong recommendation. QoE: Moderate* [15,36] The use of macrolides or doxycycline may only be suitable in the presence of low-resistance rates, however, monotherapy with these agents is not advised in areas where increased resistance has been reported. [13,14]. For patients with comorbidities, such as chronic heart, lung, liver, or renal diseases, diabetes, alcoholism, malignancy, or asplenia, combination therapy (beta-lactam and macrolide) or monotherapy with respiratory fluoroquinolones is recommended. However, in countries with low resistance rates, recommendations of local guidelines (treatment with amoxicillin or doxycycline, or macrolide) should be followed. *Strong recommendation. QoE: low.* [15].

Best practice comments:

- Surveillance of local antimicrobial resistance data is necessary. Oral antibiotic regimens are preferred if the patient is capable of oral intake. If the patient cannot take oral medications, possibilities of parenteral treatment at home or in the community should be explored, rather than treatment in the hospital [16].
- Antibiotic choice should be based on a risk-benefit analysis in patients with a documented history of beta-lactam and macrolide allergy, cardiac arrhythmia (for macrolides), cardiovascular diseases, such as QT interval prolongation and aortic aneurysm and dissection (for fluoroquinolones) and *Clostridium difficile* infection [15]. The ecological impact should also be considered while deciding antibiotic regimen, quinolones have a bad reputation in this regard and the risk of inducing extended-spectrum beta-lactamases is significant as well [37]. Patients with immediate hypersensitivity to penicillin may also react to cephalosporins and other beta-lactams [16]. Intolerance and cost should also be considered [13].

Recommendation 4.2: For inpatients with or without ICU need, risk factors for Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas* should be evaluated and locally validated for empirical treatment for MRSA and *P. aeruginosa*. When a broad-spectrum therapy is initiated due to the presence of risk factors, culture results should be closely followed, and the treatment should be quickly de-escalated. *Strong recommendation. QoE: moderate.* [15,17].

Best practice comments:

- Risk factors for Pseudomonas and MRSA infection have been reported to be prior isolation of the organism, history of a recent hospitalization or previous exposure to parenteral antibiotics, alcohol consumption, structural lung disease, and frequent use of steroids [15,17]. The infrequency of these pathogens should also be considered while starting the treatment [38].

Recommendation 4.3: For inpatients without ICU need, beta-lactam-macrolide combination therapy or monotherapy with respiratory fluoroquinolones are recommended. [15]. Doxycycline can be used as an alternative to macrolide in the presence of documented allergies or contraindications to the use of macrolide and fluoroquinolones. *Strong recommendation. QoE: moderate.* [15].

Recommendation 4.4: For patients with ICU need and without risk factors for MRSA and *Pseudomonas*, a beta-lactam plus a macrolide or a beta-lactam plus a respiratory fluoroquinolone is recommended. *Strong recommendation. QoE: Moderate.* [15,17].

Recommendation 4.5: For all patients with severe CAP, pneumococcal urinary antigen test may be performed. *Practical consensus statement. QoE: low* [14,15,17]. For patients with high severity CAP, with specific risk factors, and during outbreaks, *Legionella* urinary antigen test should be performed. *Strong recommendation. QoE: moderate.* [12]. In hospitals where multiplex PCR tests for respiratory pathogens are in use, they may be preferred over urinary antigen tests depending on the cost and reimbursement policies.

Recommendation 4.6: Coverage for anaerobes is not routinely recommended for aspiration pneumonia. However, if lung abscess or empyema is suspected, anaerobic coverage with a beta-lactam/beta-lactamase inhibitor or a combination of cephalosporin and clindamycin should be considered. The choice depends on the risk of resistance (e.g., recent antibiotic use or hospitalization), local resistance rates to these antimicrobials, and risk of *C. difficile* infection. *Practical consensus statement. QoE: very low.* [15].

Recommendation 4.7: If there is a delayed response to antimicrobial treatment or the presence of comorbidities such as diabetes, chronic renal disease, COPD, or long-term steroid use, tuberculosis should be considered. If tuberculosis is considered, respiratory fluoroquinolones should be avoided. *Weak recommendation. QoE: low.* [17].

Best practice comments:

- Elderly patients with CAP more frequently present with non-specific symptoms and confusion is common. Aspiration more frequently occurs in the elderly [12]. Fluoroquinolones should be used with special caution in patients over 60 years. There are restrictions and precautions regarding the use of fluoroquinolones because of rare reports of disabling and potentially long-lasting or irreversible side effects affecting musculoskeletal (tendon damage/rupture) and nervous systems. Their use may also be associated with a small increased risk of aortic aneurysm and dissection, particularly in older people. Simultaneous use of corticosteroids should be avoided [16].

PICO 5 - In adults with CAP, should internists use biomarkers of infection to manage (to initiate, assess the response to, and stop) antibiotic treatment?

Four of the chosen CPGs address topics related to this PICO [12, 15-17]. And some topics are only addressed by an outdated, although well-developed CPG [13].

Recommendation 5.1: Biomarkers to assess the presence of a bacterial pathogen are not recommended in primary care. *Strong recommendation. QoE: high* [13].

Recommendation 5.2: In patients with suspected pneumonia, a test for serum level of C-reactive protein (CRP) can be done. A CRP level of <20 mg/L at presentation, with symptoms for >24 h, makes the presence of pneumonia highly unlikely, a level of >100 mg/L makes pneumonia likely. *Strong recommendation. QoE: high* [13]. In primary care settings, for people presenting with findings of lower respiratory tract infection, a point-of-care CRP level measurement can be considered if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed, this can help to identify patients with lower respiratory tract infections who will, and will not, benefit from antibiotics:

a) Do not routinely offer antibiotic therapy if the CRP concentration is less than 20 mg/L
b) Consider a delayed antibiotic prescription (a prescription for use later if symptoms worsen) if the CRP concentration is between 20 mg/L and 100 mg/L
c) Offer antibiotic therapy if the CRP concentration is greater than 100 mg/L *Strong recommendation. QoE: high.* [39].

Recommendation 5.3: In suspected patients with COVID-19, high CRP levels do not necessarily indicate whether pneumonia is due to bacteria or *SARS-COV-2*, low CRP level indicates that secondary bacterial infection is less likely. *Strong recommendation. QoE: low. [40].*

Best practice comments:

- Procalcitonin (PCT) seems to be more helpful than CRP in COVID-19 patients to recognize bacterial co- or superinfection [41]. Low PCT levels in combination with clinical judgment appear to reliably identify COVID-19 patients not requiring antibiotic therapy, and PCT-based algorithms may allow to safely reduce unnecessary antibiotic use in COVID-19 patients with pneumonia [42–46].
- Point-of-care procalcitonin level measurement is available as well [47].

Recommendation 5.4: CRP should be measured on days 1 and 3/4, especially in those with unfavorable clinical parameters. Failure of CRP to drop by 50% by day 4 was associated with a fivefold increase in mortality, ventilation, and complications. CRP levels may be repeatedly measured to assess the risk of treatment failure and complications in patients who do not clinically show clear symptom improvements (a chest radiograph repeated in patients who are not improving satisfactorily after 3 days of treatment). PCT may also be useful in such a case. *Strong recommendation. QoE: moderate* [12,17,48].

Best practice comments:

- Failure of biomarkers to drop by 50% in a well-responding patient should not be used as a criterion for prolongation of the duration of antibiotics.

Recommendation 5.5: It is recommended that the duration of antibiotic therapy should be guided by a validated measure of clinical stability. Antibiotic therapy should be stopped after a total of 5 days if the patient fulfills the criteria of clinical stability. *Strong recommendation. QoE: moderate.* [15].

Best practice comments:

- Clinical evaluation (by validated measures including heart rate, respiratory rate, blood pressure, oxygen saturation, temperature, ability to eat, and normal mentation) of the patient under antibiotic treatment is key in the decision on how long to proceed with this treatment.

Recommendation 5.6: It is recommended that empiric antibiotic therapy should be initiated in adults with clinically suspected and radiographically confirmed CAP regardless of initial serum PCT level. *Strong recommendation. QoE: moderate* [15].

Recommendation 5.7: PCT may guide shorter treatment duration, it may be used in the process of deciding to safely reduce antibiotic duration in patients who show clinical improvement. It has been shown that the application of predefined stopping rules for antibiotics works even in most severe cases, including pneumonia with septic shock, and even if clinicians are allowed to overrule the predefined stopping rule. *Strong recommenda*tion. *QoE: high* [17].

Best practice comments:

- PCT could be useful in identifying whether there is a bacterial infection. Several RCTs used a PCT algorithm with several thresholds to guide decisions about antibiotics. This algorithm and its thresholds have been proved to be safe and efficacious in reducing antibiotic exposure. But in clinical practice using PCT for the decision to start antibiotics or for severe conditions such as pneumonia with septic shock should be considered based on the clinical findings. In various centers, PCT tests are encouraged for research and data collection purposes [40].

Recommendation 5.8: Serial PCT measurement is suggested to be useful primarily in settings where the average duration of antibiotic therapy for CAP exceeds normal practice (e.g., 5-7 days). *Weak recommendation, QoE: low.* [15].

Best practice comments:

- The duration of antibiotic therapy should in the first place be guided by clinical parameters (see Recommendation 5.5). Serial PCT measurement may help to safely reduce unnecessary antibiotic use in CAP patients [15].

4. Discussion

In this EFIM document on the management of patients with acute CAP, we have selected 27 recommendations focusing on five clinical scenarios dealing with real-life problems, including frail elderly patients and patients with multiple comorbidities. The recommendations were selected from 6 good-quality evidence-based CPG. With this adaptation process, we aim to facilitate the decision-making process in the real-life setting and to disseminate updated secondary evidence where it is available. Overall, 27 recommendations are based on 7 high, 9 moderate, 10 low, and 1 very low-quality evidence supported by 23 strong, 2 weak, and 2 practical consensus statements. Besides, there are 13 best practice comments, as we want to add some clarifications to recommendations. The adaptation process was reproducible, following previously published explicit methods that strengthen its external validity, as was the selection of well-founded primary guidelines and recommendations [7]. When evidence appeared to be lacking, remarks have been made to stimulate new research, as in elderly patients or patients with multimorbidity and polypharmacy.

Patients with CAP are a heterogeneous population, implying that, from severity assessment to the prescription of appropriate medications, patients should always be evaluated with a comprehensive approach. For instance, in a Swiss cohort study of approximately 42,000 adult patients discharged from the general internal medicine department of three Swiss tertiary teaching hospitals, seventy-nine percent of them had multimorbidity, with a median of four chronic diseases. Chronic heart disease, chronic kidney disease, solid malignancy, and substance consumer-related disorders were the most prevalent comorbidities [49]. Therefore, since CAP is frequently observed in such populations, patients should be managed with an internal medicine background by harmonizing knowledge from different subspecialties.

It should be considered that the writing process of this document was started before the emergence of COVID-19, which is drastically modifying the challenges in patient care. Therefore, there are only few data regarding COVID-19 in this document. However, the demonstration of even other viral agents, such as influenza, can affect the management of CAP patients as well. In the VIRCAP study, it was seen that in patients hospitalized with CAP, the frequency rate of viral respiratory tract infections was 31.8% among all patients and associated with higher PSI [50]. Although the overall outcomes of the patients with and without viral respiratory tract infections were found similar in this study, patient-specific approaches should have been developed in diagnosis and treatment for appropriate selection of antivirals and surveillance, as stated in PICO 1.

This guideline's prioritization of clinical judgment can be considered a remarkable element. While choosing the right approach in the management of patients with CAP, as highlighted in relevant PICOs, not only clinical scoring systems or biomarkers but also different parameters such as clinical stability, presence of different comorbidities, age, and even socioeconomic status of patients, should always be considered in the evaluation. As stated in the International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP) Position Statement, one physician should coordinate the management of the patient ideally with a pharmacist partner while facing these complicated situations [51].

A special focus has been put on the drug treatment of CAP and the concurrent risk in comorbid patients. Noor et al. detected potential drug-drug interactions in 73.1% of pneumonia patients; approximately 4% of drugs were contraindicated and 43% of them have major interactions [52]. It has been reported that any patient using eight or more medications is at risk of at least one potential drug-drug interaction [53]. In the study of Bayles et al., at least one potentially interacting drug with clarithromycin (such as statins, digoxin, warfarin) has been identified in 68% of the hospitalized patients with CAP or COPD exacerbation [23]. As it was shown in Table 6 when prescribing antibiotics, drug interactions should be considered, and recommended drug interaction database programs should be used as well. Even in this paper, in which CPGs with high AGREE-II scores are evaluated, the fact that only one selected CPG mentions drug interactions shows that there is a need for increased awareness for a comprehensive and patient-tailored approach.

Our guideline has some limitations. Firstly, this is a secondary summary of existing CPGs, and our aims were not to review the original evidence supporting those guidelines or new ones not yet included in CPGs, but rather to gather the current and practical recommendations. Secondly, although the narrow scope of our guideline to very specific clinical situations in CAP patient management is a limitation, this has also the advantage to provide a summary of recommendations for a frequently encountered group of patients that are underrepresented in most general CPGs. Thirdly, to harmonize the different methodologies to rate recommendations from the selected guidelines, we prioritized the quality of evidence recorded in the GPCs to formulate the strength of the recommendation adapted to the GRADE procedure. Moreover, as cancer or HIV positivity are prevalent morbidities in CAP patients, the exclusion of CPG on immunosuppressed patients can be stated as a limitation as well.

These limitations do not downgrade the clinical relevance of this EFIM CPG that highlights practical recommendations for the management of CAP patients, which can easily be reached and facilitate everyday patient care in the Internal Medicine wards. As internal medicine is the backbone discipline of various subspecialties (such as infectious diseases or respiratory medicine), the internist or the subspecialist who remembers the ancestral roots of his/her medical training seems to be the best candidate for the management of elderly patients and patients with multi-morbidity [7,54].

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.10.009.

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