

EXPERT OPINION

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Current treatment of community-acquired pneumonia

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Introduction: Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality worldwide. Management decisions regarding site of care, extent of assessment and level of treatment are based primarily on disease severity (outpatient, inpatient and ICU admission). Despite the developments in antibiotic therapy, CAP is still the most common infectious cause of death.

Areas covered: There are several challenges with the management of CAP, from the accurate diagnosis, decisions about place of therapy and the choice of appropriate antibiotics. An extensive literature review of manuscripts, in PubMed, published in the past 10 years has been performed, using combinations of words and terms appropriate to the concepts of CAP, treatment, guidelines and corticoids. Some empirical antimicrobial regimens, such as macrolides, are still being debated; some new antibiotics and adjunctive therapies (corticoids) have recently been tested. This is a review of current recommended antimicrobials regimens, novel approaches and adjunctive drugs for the treatment of CAP.

Expert opinion: Effective management of CAP requires risk stratification of patients by severity and proper place of therapy. Additional therapeutic interventions along with antibiotics may help to improve outcome in patients with CAP, especially in severe CAP.

Keywords: community-acquired pneumonia, guidelines, steroids, treatment

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1. Introduction

Community-acquired pneumonia (CAP) represents a public health problem of substantial magnitude, with an annual incidence ranging from 1.6 to 10.6 per 1,000 adult population in Europe. The incidence increases importantly with age. It has a wide spectrum of clinical severity from a self-limiting disease to septic shock and acute respiratory distress syndrome (ARDS).

Data from the German CAPNETZ Network trial showed that the mortality among patients hospitalized with CAP ranged from 5 to 20%, but was up to 50% in patients admitted to the ICU [1]. Furthermore, a study showed that mortality of CAP in the intermediate and long term is high with figures showing 8% at 90 days, 21% per year and 36% at the end of 5 years [2].

So, despite substantial progress in therapeutic options, many immunocompetent patients die from CAP, especially those with bacteremia and pneumonias due to resistant pathogens. In the area of increasing resistance of many of the usual pathogens of CAP to the most commonly antibiotics, an important consideration is the appropriate antibiotic selection and avoidance of antimicrobial overuse.

In the face of effective actual and upcoming antibiotic regimens, there continue to be major controversies concerning the treatment of this serious infection, worldwide.

The main aim of this review is to analyze what is currently the best therapeutic approach for CAP.

Article highlights.

- With the implementation of CAP guidelines, several outcomes have improved, including reduced costs and LOS and hospital mortality.
- The development of new scoring scales for identifying MDR pathogens in CAP needs validation.
- The treatment of CAP remains empirical based on the severity of the disease. Combination antibiotic therapy that includes a macrolide should be recommended for severe CAP and especially those with septic shock.
- The utility of biomarkers, as PCT, to shorten antibiotic duration and total antibiotic consumption is a new validated strategy.
- Several new antibiotics have been developed for treating CAP, including ceftaroline, tigecycline, solithromycin and cethromycin with promising results.
- Corticosteroids as an adjunctive therapy in the subgroup of patients with CAP did not demonstrate an overall benefit according to randomized trials.

This box summarizes key points contained in the article.

2. Guidelines importance

In order to achieve a more uniform approach toward empirical treatment of CAP, guidelines for the management of CAP have been developed in many countries and by different scientific committees in the past 20 years. The most widely adopted are the guidelines of the Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS), published in 2007 and those from the European Respiratory Society (ERS) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID), in 2011 [3,4]. Very recently in Spain, a new multidisciplinary guideline for the management of CAP has been released [5]. The goals of the scientific guidelines are to improve management and outcome without increasing costs or reducing patient safety.

Numerous studies have evaluated the possible clinical benefits associated with adherence to clinical practice guidelines for CAP. Dambrava *et al.* [6] showed a shortened length of stay (LOS) in patients adhered to Spanish guidelines.

The most consistent data comes from studies of severe CAP, where guideline adherence is associated with reduced mortality [7-9]. In the study by Bodí *et al.* [7] involving 529 patients with severe CAP, significantly higher mortality was documented among patients with non-adherence to guidelines treatment (33.2 vs 24.2%). In agreement, in a retrospective cohort study by Frei *et al.* [9], the guideline-discordant therapy was associated with an increase in inpatient mortality (25 vs 11%; odds ratio [OR] = 2.99 [95% CI: 1.08 - 9.54]).

One of the reasons for arguing that guidelines should be local is that the etiology could differ between different countries and regions, with regard to the resistance patterns. Therefore, the physician has to combine the knowledge of resistance patterns of the clinic or the hospital with the guideline recommendations to choose the initial empirical antibiotic therapy.

3. Therapy

Apart from host-derived factors and microbial virulence, the appropriateness of initial antimicrobial treatment and early administration of antibiotics has been shown to influence outcome in CAP patient populations [10,11].

Treatment for CAP remains largely empirical. Identifying the infecting pathogens is very difficult because it is frequently difficult to collect lung samples for microbiological evaluation and because of the lack of rapidly available diagnostic tests that allow the differentiation of viral and bacterial etiologies in most cases.

However, as the van der Eerden *et al.* study confirms, the empirical antibiotic strategy with broad spectrum antibiotics for the management of hospitalized patients with CAP has comparable clinical efficacy to a pathogen-directed treatment approach [12].

Appropriate drug selection depends on the causative pathogen and its antibiotic susceptibility. The goal of appropriate antimicrobial treatment, therefore, is to maximally reduce or eradicate the bacterial load in order to achieve clinical success and minimize the potential for development of resistance. Specific risk factors (e.g., chronic obstructive pulmonary disease [COPD] and bronchiectasis) should be taken into account on an individual basis.

A universal finding, however, is that *Streptococcus pneumoniae* is the most commonly identified bacterial pathogen for CAP in all age groups.

The current IDSA/ATS guidelines for the management of CAP divide patients into three groups based on pneumonia's severity: outpatients, those admitted to the hospital and those admitted to the ICU [3,4]. The recommended treatment of ERS/ESCMID and ATS/IDSA guidelines according to the site of care are presented in Table 1.

3.1 Outpatient treatment

The greatest differences from European guidelines are the recommendation for routine atypical pathogen coverage in North America and a trend to use penicillins and to avoid quinolones in the United Kingdom [13].

- In United States, outpatient treatment with a macrolide (e.g., azithromycin, clarithromycin) or doxycycline for previously healthy adult patients with no risk factors for penicillin-resistant *S. pneumoniae* (PRSP) (Table 2).
- In patients with comorbidities or risk factors for PRSP, a respiratory fluoroquinolone (FQ) or a β -lactam antibiotic plus a macrolide or doxycycline is recommended.
- Risk factors for infection with β -lactam-resistant *S. pneumoniae* are presented in Table 2.

3.2 Inpatient treatment

- For hospitalized patients in the medical ward, monotherapy with a respiratory FQ (levofloxacin, moxifloxacin) or

Table 1. Empirical therapy for CAP according to ATS/IDSA and ERS/ESCMID [3,4].

Patient group	Initial therapy [3]	Initial therapy [4]
Previously healthy outpatients; no antibiotic use in past 3 months Outpatients with comorbidities* or antibiotic use in past 3 months [‡]	A macrolide or doxycycline A respiratory FQ (levofloxacin, gemifloxacin or moxifloxacin), or a β -lactam antibiotic (high-dose amoxicillin, amoxicillin/clavulanate, or cefpodoxime) plus a macrolide [§]	Amoxicillin or tetracycline
Inpatients, non-ICU	A respiratory FQ, or a β -lactam antibiotic plus a macrolide	Aminopenicillin \pm macrolide, [Aminopenicillin/ β -lactamase inhibitor Non-antipseudomonal cephalosporin Cefotaxime or ceftriaxone] plus macrolide Levofloxacin [#] Moxifloxacin Penicillin G \pm macrolide
Inpatients, ICU	A β -lactam antibiotic, (cefotaxime, or ampicillin/sulbactam), plus azithromycin or a respiratory FQ [¶]	Non-antipseudomonal cephalosporin III + macrolide or moxifloxacin or levofloxacin \pm non-antipseudomonal cephalosporin III
<i>Special considerations</i> Risk factors for <i>Pseudomonas</i> species	A β -lactam antibiotic (piperacillin/tazobactam, cefepime, imipenem/cilastatin, meropenem, or doripenem), PLUS either ciprofloxacin or levofloxacin OR The above β -lactam antibiotic plus an aminoglycoside and azithromycin OR The above β -lactam antibiotic plus an aminoglycoside and an antipseudomonal respiratory FQ	Antipseudomonal cephalosporin** or acyl ureidopenicillin/ β -lactamase inhibitor or carbapenem (meropenem preferred, up to 6 g possible, 3*2 in 3-h infusion) PLUS Ciprofloxacin ^{††} OR PLUS Macrolide a + aminoglycoside (gentamicin, tobramycin or amikacin)
Risk factors for MRSA	Vancomycin or linezolid	
Influenza virus	Oseltamivir or zanamivir	

*Chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancy; asplenia.

[‡]Antibiotic from a different class should be used.

[§]Also recommended in regions with a rate of high-level macrolide-resistant *S. pneumoniae* of > 25%.

[¶]For patients allergic to penicillin, a respiratory FQ plus aztreonam (Azactam) are recommended.

[#]Within the FQ s, moxifloxacin has the highest antipseudomonal activity.

**Ceftazidime has to be combined with penicillin G for coverage of *S. pneumoniae*.

^{††}Levofloxacin 750 mg/24 h or 500 mg b.i.d. is an alternative and also covers Gram-positive bacteria, if treatment is empirical.

ICU: Intensive care unit.

an intravenous β -lactam antibiotic combined with a macrolide or doxycycline should be given.

- In patients in the ICU, the therapy depends on the presence of the risk factors for *Pseudomonas aeruginosa* infection, such as chronic or prolonged use of broad-spectrum antibiotic therapy, the presence of structural lung diseases (bronchiectasis), repeated exacerbations of COPD, corticosteroid therapy, malnutrition, human immunodeficiency virus and other forms of immunosuppression [3,4].

For patients without pseudomonal risk an intravenous β -lactam plus either a macrolide or respiratory FQ is recommended.

In patients with risk factors for pseudomonal infection, an antipseudomonal β -lactam should be combined with either levofloxacin or ciprofloxacin, or the antipseudomonal β -lactam can be combined with both an aminoglycoside and either azithromycin or a respiratory quinolone (Table 1).

In a study by Rodríguez *et al.* from CAPUCCI study group, the influence of combination treatment comparing to monotherapy on survival in ICU patients with CAP was examined. The results showed that combination antibiotic therapy improved survival only in the subset of CAP patients with shock [14].

So, FQ monotherapy are widely used in the management of CAP and provide important treatment options, in

Table 2. Risk factors for PRSP.

1. Age < 2 years or > 65 years
2. β -lactam therapy within the previous 3 months
3. Alcoholism
4. Medical comorbidities
5. Immunosuppressive illness or therapy
6. Exposure to a child in a day-care center

PRSP: Penicillin resistant *S. pneumoniae*.

outpatients with comorbidities, in patients recently treated with antibiotics other than FQs and in cases of suspected drug-resistant *S. pneumoniae* (DRSP) and as monotherapy in non-ICU-hospitalized patients.

When community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is suspected (prior influenza-like illness, necrotizing severe pneumonia), vancomycin or linezolid should be added to the other recommended agents.

Anaerobic coverage is indicated only in patients with a risk for aspiration, such as alcoholism, loss of consciousness and neurological disease and dysphagia due to mechanical or neurological upper digestive tract dysfunction.

Treatment for most of the viral pneumonias (apart from influenza) is primarily supportive. Antiviral therapy is, however, recommended in all patients with severe influenza pneumonia and at high risk of complications. Early treatment (< 48 h) with oseltamivir or zanamivir is recommended for influenza A. They reduce the duration of symptoms and the severity of the disease as well as the need for hospitalization.

3.3 Optimizing pharmacokinetic and pharmacodynamic parameters

The effort to choose the appropriate antibiotic requires the data of the pharmacokinetic/pharmacodynamic (PK/PD) parameters of the drug to ensure bacterial eradication [15,16].

Thus, the two major determinants of bacteria killing include the *concentration* and the *time* that the antibiotic remains on these binding sites: the area under the serum-concentration curve (AUC) after a dose of antibiotic measures how high (concentration) and how long (time) the antibiotic levels remain above the target minimum inhibitory concentration (MIC) during any one dosing interval. For concentration-dependent agents, as FQs, bacterial eradication ability correlates with AUC: MIC ratio. Increasing the dose of these antibiotics increases the AUC: MIC ratio, thus increasing the bactericidal activity. Today, AUC: MIC ratio values of 125 – 150 h for Gram-negative bacteria and 30 – 40 h for Gram-positive bacteria are recommended to guarantee not only the microbiological outcome but also to prevent resistance appearance [17].

Several studies are investigating the correct antibiotic dosing with the purpose of increasing bacteriological response without emerging resistance. In a study by Dunbar *et al.* patients with mild-to-severe CAP received 750 mg levofloxacin/day (intravenous or oral) for 5 days or 500 mg/day for 10 days. The results showed that, levofloxacin 750 mg/day

for 5 days was noninferior to 500 mg/day for 10 days in the treatment of mild-to-severe CAP in the overall patient population [18]. High-dose, short-course of levofloxacin (750 mg/day for 5 days) also had good efficacy in the subgroup of patients with severe CAP, demonstrating high clinical success rates of > 85% [19].

In the study by Burgess *et al.* including healthy adults, with the administration of ciprofloxacin 400 mg t.i.d. and levofloxacin 750 mg/day the probabilities of target attainment for a free AUC:MIC ratio > 90 (equivalent to a total AUC:MIC ratio > or = 125) were 47% for ciprofloxacin 400 mg b.i.d., 54% for ciprofloxacin 400 mg t.i.d. and 48% for levofloxacin 750 mg/day [20], thus, optimizing the dose of ciprofloxacin to 750 mg b.i.d. orally (instead of 500 mg/b.i.d.) and levofloxacin to 750 mg/day in 5 days regimen.

Based on PK/PD principles, the continuous infusion of time-dependent antibiotics, such as β -lactams, has certain theoretical advantages toward efficacy. Several studies have demonstrated that continuous infusion of β -lactam antibiotics is an effective dosing strategy, because it has the potential to maintain drug concentrations above the MIC over a 24-h interval resulting in enhanced clinical response rates, improvement in surrogate markers of outcome and a lower cost of therapy compared with intermittent infusion regimens [17]. Also, there are scarce reports indicating that continuous infusion antibiotic may offer better activity against resistant pathogens and may reduce the development of antibiotic resistance [21].

The most studied antibiotics in PK/PD studies are ceftazidime in CAP [22] and meropenem, piperacillin/tazobactam ceftazidime in critical ill patients [23].

On the other hand, a recently published meta-analysis of 14 prospective studies did not show a significant benefit of the continuous infusion of β -lactam antibiotics compared to higher dosed bolus administration in hospitalized patients (OR = 1.00, 95% continuous infusion: 0.48 – 2.06) [24]. The answer is on another meta-analysis, suggesting that the administration of the same total antibiotic dose by continuous infusion may be more efficient, with regard to clinical effectiveness, compared with the intermittent mode [25].

The disadvantages of the continuous infusion of antibiotic agents are the stability of the drug exposed for up to 24 h to environmental conditions, the possibility of developing thrombophlebitis and intravenous line infections.

Based on the above advantages, clinicians must consider the continuous infusion of antibiotics in special situations, such as the administration of β -lactams in neutropenic or cystic fibrosis patients with CAP. Large-scale prospective studies in critically ill patients confirming these advantages are still needed.

3.4 Timing of antimicrobial initiation and duration of treatment

Both guidelines recommend that therapy should be administered as soon as possible after the diagnosis of pneumonia. In a study by Menéndez *et al.* published in *ERJ*, including 4,137 patients hospitalized with CAP in 13 hospitals,

concluded that in severe sepsis only compliance to antibiotic adherence plus first antibiotic dose within 6 h was associated with lower mortality (OR = 0.60) [26].

The Spanish Respiratory Society recommend that the first dose of antibiotic should be administered in the emergency room and before the patient is transferred to a ward [27]. But for ERS, it appears that the prognostic relevance of antibiotic timing is highest in patients at a higher risk of death. So, they recommend that, only in patients with CAP and septic shock, delay in initiating therapy must not be > 1 h after diagnosis [4]. However, the American Medicare has set in 6 h as the maximum time to administer the first dose of antibiotics in emergency departments (EDs).

The duration of therapy should be a minimum of 5 days, provided the patient is afebrile for 48 to 72 h, there is no sign of extrapulmonary infection, the correct therapy was used initially and the organism identified is not *S. aureus* or *P. aeruginosa*. In CAP patients admitted in the ICU, the right duration is still not known.

Shorter course therapy has the potential not only to improve efficacy, safety and compliance but also to minimize the evolution of resistance [28].

Recently, biomarkers, such as procalcitonin (PCT), have been described as useful tools to safely reduce antibiotic treatment duration, by the application of predefined stopping rules for antibiotics [29]. Highly sensitive PCT measurements, embedded in a clearly defined setting and prospectively validated with clinical algorithms were repeatedly effective in markedly reducing the (over)-utilization of antimicrobial therapy. Based on these specific cut-off ranges, initiation or continuation of antibiotics was more or less discouraged (< 0.1 or < 0.25 µg/L) or encouraged (> 0.5 or > 0.25 µg/L, respectively) [30]. In patients with CAP, PCT-guidance reduced the initial prescription rate by about 10%, but importantly shortened the duration of antibiotic therapy by 65% with a similar outcome in patients with all degrees of severity of CAP [29].

However most of the literature concerning this issue comes from the same group.

4. Special issues

4.1 Penicillin-resistant *S. pneumoniae*

Penicillin resistance among the pathogenic organisms of CAP continues to be a growing concern. For example, rates of multidrug-resistant (MDR) *S. pneumoniae* have been reported to be 30% worldwide, with a surveillance study, from United States, in 2005 – 2006, showing penicillin resistance rates for *S. pneumoniae* varied by region from 8.7 to 22.5% [31].

Data on the prevalence of antibiotic resistance among *S. pneumoniae* have been regularly produced by the EARSS Project in 2008, with high levels of PRSP, > 25%, mainly reported from southern and eastern Europe [32].

Nowadays, if the strain of *S. pneumoniae* is not resistant to penicillin, defined as MIC < 2 µg/mL, penicillin G or

amoxicillin continue to be the drugs of choice. ERS/ESCMID guidelines report that the treatment of pneumococcal pneumonia in adults with currently used doses of ceftriaxone, cefotaxime or cefepime should be effective against all but the most highly resistant isolates with MIC > 8 µg/mL [4].

Several publications have demonstrated that low-level pneumococcal resistance to penicillin is not associated with adverse outcomes in the treatment of patients with CAP. Most studies suggest that current levels of penicillin resistance do not cause treatment failures for patients with CAP when appropriate agents (amoxicillin, ceftriaxone and cefotaxime) and doses are used [33,34].

A review of six clinical trials showed that the PK-enhanced formulation of amoxicillin/clavulanate tablets (2,000/125 mg b.i.d.) determined a high rate of both bacteriological and clinical efficacy (97.7 and 95.6%, respectively) even in CAP caused by multiple DRSP [35].

4.2 Macrolide resistance

In the EARSS database, five countries reported non-susceptibility proportions for macrolides > 25% and has continued to increase [32]. The clinical impact of macrolide resistance is well established from many studies and can be an important cause of clinical failure, especially in pneumococcal bacteremia [36]. Therefore, it should be better to avoid empirical macrolide monotherapy in CAP patients in Europe [4]. However, the current feeling is that macrolides still have a role to play and may be used as monotherapy in those with milder outpatient infections or in combination with β-lactams for those who are more seriously ill. Even in some studies [37] it has been suggested that failures with macrolides are independent of the mechanism of high or low resistance.

4.3 Combination treatment with macrolides

The controversy regarding the need to cover atypical pathogens in the empirical therapy of CAP is related to several issues, including imprecise diagnostic methods and contradictory results of published evidence.

Arnold *et al.* [38] reported the global incidence of atypical pathogens in CAP, dividing the world into four areas and found no differences in the incidence of these microorganisms in the different world areas. Mills *et al.* [39], in a meta-analysis, evaluated 18 trials including 6,749 patients with mild-to-moderate CAP, and concluded that macrolides showed no advantage for treatment failure or mortality over β-lactam therapy, except cases due to *Legionella pneumophila*. The most recent report by Maimon *et al.* [40] concluded that there was no significant difference detected regarding clinical success or mortality regardless of atypical coverage advantage in otherwise healthy outpatients.

The past decade has seen an increasing body of evidence where it has been shown that outcomes were considerably better in patients with severe CAP when a combination of antibiotics is used with a macrolide antibiotic as part of the regimen, rather than a single antibiotic. The benefit of

macrolides may also be nonbactericidal/static effects on the microorganism itself. In a number of organisms, including those with innate macrolide resistance and macrolide-resistant pneumococci expressing both the *mec* and *erm* genes, macrolides have been shown to reduce the production of key virulence factors, including quorum sensing, toxin production and biofilms [41,42].

In this setting, the potential anti-inflammatory or immunomodulatory properties of macrolides, including the reduction of TNF and pneumolysin production, may be valid, particularly in patients with severe sepsis [43].

An observational study of patients with severe CAP found that patients with CAP and shock who were treated with combination antibiotic therapy (58% with a third-generation cephalosporin plus a macrolide), compared to those treated with monotherapy (42% FQ), had a higher 28-day in-ICU survival (hazard ratio [HR] = 2.69, 95% CI: 1.09 – 2.60) [44]. Survival was not different between combination therapy and monotherapy in ICU patients without shock. In addition, Martin-Loeches *et al.* in a prospective observational study of 208 patients with severe CAP admitted to the ICU, showed that combination therapy with macrolides improves survival in intubated patients [45].

Furthermore, Metersky *et al.* found that treatment with a macrolide, but not with a FQ, was independently associated with lower mortality rates, in 2,201 patients with bacteremic pneumonia [46]. The benefit of a macrolide may also explain the finding of greater clinical relapse in patients randomized to β -lactam alone if their streptococcal urinary antigen was positive [47].

Therefore, it appears that combination treatment with macrolides in CAP should be restricted to patients with higher risk classes of Pneumonia Severity Index (PSI), but further prospective, randomized, double-blind trials are needed for this recommendation.

5. New drugs for the treatment of CAP

There is a great need for new class of antimicrobials and new molecules, in the treatment of CAP. In the case of the already used antibiotics that have been used to treat adults in clinical trials, such as daptomycin and quinupristin-dalfopristin, the data are debatable or negative, which seems to exclude their possible use in the treatment of CAP. The others are listed in Table 3.

5.1 New broad spectrum cephalosporin

Ceftaroline is a newly developed parenteral third-generation cephalosporin that exhibit broad-spectrum bactericidal activity against Gram-positive, Gram-negative and anaerobic organisms, including *S. pneumoniae* and MRSA. It lacks activity against *P. aeruginosa* [48].

Combined results of two Phase III trials were published this year [37]. In two randomized, double-blind trials (FOCUS 1 and FOCUS 2) that compared ceftaroline (600 mg i.v.

every 12 h) to ceftriaxone (1 g i.v. every 24 h) for 5–7 days in patients hospitalized with CAP (but not admitted to an ICU), ceftaroline was noninferior to ceftriaxone and had a safety profile that was similar to ceftriaxone [37]. The clinical cure rate was 83% for patients receiving ceftaroline compared with those receiving ceftriaxone (83 vs 77%; 95% CI: 1.4 – 10.7).

Ceftaroline is one of the few new antibiotics to receive Food and Drug Administration (FDA) approval on 29 October 2010 [49].

5.2 Tigecycline

Tigecycline is a first-in-class glycylglycyl antibacterial for intravenous use. A large multinational trial confirmed the high *in vitro* activity of tigecycline against clinical isolates of the most prevalent CAP pathogens, including resistant strains except *L. pneumophila* [50].

Results of two noninferiority, randomized, double-blind, multinational, Phase III studies have been published, which compared the safety and efficacy of tigecycline in comparison with levofloxacin in the treatment of CAP [51–53]. Clinical cure rates were 89.7 versus 86.3% in the clinically evaluable population and 81 versus 79.7% in the clinical modified intent-to-treat population. However, tigecycline was associated with significantly higher drug-related adverse events of nausea (20.8 vs 6.6%) and vomiting (13.2 vs 3.3%).

Recently, the drug was approved for the treatment of CAP by the FDA; however, owing to some concerns, its application in the Europe, Middle East and Africa has been withdrawn. In an a warning announcement in 2010, in FDA is reminding healthcare professionals of an increased mortality risk associated with the use of intravenous tigecycline compared to other agents in treatment of pneumonia and complicated skin and skin structure infections [54].

5.3 Cethromycin

Cethromycin is a new ketolide antimicrobial agent with *in vitro* activity against penicillin- and macrolide-resistant Gram-positive organisms, possibly due to a higher affinity for the target site on the ribosomal unit. Two global Phase III noninferiority studies (CL05-001 and CL06-001) to evaluate cethromycin safety and efficacy were designed and conducted in patients with mild-to-moderate CAP [55]. Therefore, in comparison with clarithromycin, these two noninferiority studies demonstrated the efficacy and safety of cethromycin, with encouraging findings of efficacy in subjects with *S. pneumoniae* bacteremia.

5.4 Solithromycin

Solithromycin (CEM-101) is a novel fluoroketolide with improved antimicrobial effectiveness and has potent *in vitro* activity against a broad range of respiratory pathogens, including pneumococci, β -hemolytic streptococci, staphylococci, *Haemophilus*, *Legionella*, *Mycoplasma pneumoniae*, *Moraxella*,

Table 3. New antibiotics for CAP treatment.

Drugs	Class	Trial	Indication	Side effects
Ceftaroline	Cephalosporin	FDA approved	cSSSIs and CAP in Europe and United States	Hypersensitivity reactions, <i>C. difficile</i> -associated diarrhea
Tigecycline	Glycylcycline	Phase III	cSSSIs, complicated intra-abdominal infections, treatment of CAP	Hepatic dysfunction, nausea, vomit
Linezolid	Oxazolidinone	FDA approved	cSSTI, severe CAP, nosocomial pneumonia	Myelosuppression, serotonin syndrome, optic and peripheral neuropathy
Solithromycin (CEM-101)	Ketolide	Phase III	cSSTI, CAP	
Cethromycin	ketolide	Phase III	CAP	Diarrhea, dysgeusia, headache

cSSTI: complicated skin and skin structure infection.

Chlamydophila, CA-MRSA, *Mycobacterium avium*, malaria, enterococci and gonococci.

A pooling of Phase I and Phase II data indicated its safety. Among the subjects from a Phase I trial, 171 healthy subjects and 64 patients with pneumonia were given the drug in oral doses, with exposure up to 4,200 mg over 7 days. Across all the studies, the most common adverse events were diarrhea (13%), headache (13%) and nausea (10%), most of which were mild.

Solithromycin showed better anti-inflammatory profiles compared with macrolides currently used in the clinic [56]. The drug may provide the option of i.v.-to-oral step down monotherapy to send patients home from the hospital sooner.

The global Phase III trial of solithromycin in patients with bacterial CAP (CABP) [57] includes a double-blind, placebo-controlled, multicenter study enrolling ~ 800 patients with PORT-II to PORT-IV CABP and randomizes them to either oral solithromycin, an 800 mg loading dose followed by 400 mg/day for 5 days, or oral moxifloxacin 400 mg/day for 7 days. The results are expected with interest.

6. Increasing problem of MDR in CAP

Nowadays, resistant organisms (ROs) are increasingly implicated in pneumonia patients presenting to the hospital and are related to severe CAP [3,58,59]. Gram-negative bacteria (*P. aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp. and *Proteus* spp.) are the causal agents in up to 10 – 30% of patients with CAP, but may be more common in elderly patients having healthcare-associated pneumonia (HCAP) risk factors (dialysis, living in nursing homes, home infusion therapy and repeated hospitalization) [3]. Furthermore, the emergence of CA-MRSA is a matter of concern, occurring in patients with no prior healthcare exposure, usually after influenza, and may lead to a severe necrotizing pneumonia, with resistance to common antistaphylococcal treatment regimens [60].

Nowadays, several recent studies have questioned whether HCAP should be considered as a form of CAP or nosocomial

pneumonia with the new ERS/ESCMIC guidelines stating that this term is not relevant in Europe [4].

The concept of HCAP is based on the prediction of MDR pathogens depending on heterogeneous medical conditions and, in some studies, patients with clear immunosuppression. Most of the studies on HCAP in Europe demonstrated an increased severity of pneumonia with apparently low incidences of MDR pathogens [61,62] and an excess mortality comparing to CAP. But, this mortality is not due only to MDR pathogens but also to other factors, such as age, functional status and hidden treatment restrictions. Furthermore, the latest studies demonstrate failure of HCAP guideline concordant treatment to reduce mortality [63,64].

Following the recommended treatment for HCAP, by the ATS guidelines, such as nosocomial pneumonia, potentially leads to an overuse of broad-spectrum regimens and promotes both resistance and *Clostridium difficile* infection [3]. Ewig and Welte state that the use of HCAP means “adding fuel to the flames of worldwide increasing microbial resistance levels” [65].

From all these data, European experts do not support the HCAP concept.

In an attempt to redefine the term of HCAP, Shorr *et al.* [66] discovered a simple risk score that appeared valid for assessing the probability of an RO in patients initially hospitalized with CAP. Its parameters were as follows: recent hospitalization, living in a LTC facility, chronic hemodialysis and ICU admission within 24 h of evaluation in the ED, with an area under the receiver operating characteristic (AUROC) for the risk score 0.71, whereas the AUROC for HCAP equaled 0.62. This score performed moderately well at classifying patients regarding their risk for RO infection.

Aliberti *et al.* [67], in a study, involving 935 patients with CAP, found that hospitalization in the preceding 90 days and residency in a nursing home were independent predictors for an actual infection with a RO. The score proposed by Shorr *et al.* [66] was evaluated, in this database, in comparison with the HCAP definition with regard to both the actual infection with an RO and the in-hospital mortality. With

Table 4. Randomized controlled trials on corticosteroids in CAP.

Study	Country	Type of study	n, (steroid treated/control)	Intervention	Setting	Severity of CAP	Results
Confalonieri 2005 [70]	Italy	RCT	23/23	HC 200 mg bolus, 10 mg/h, 7 days	ICU	severe	Earlier PaO ₂ : FiO ₂ improvement with HC, improved survival in hospital and at 2 months
Mikami 2007 [75]	Japan	RCT	15/16	P 40 mg, 3 days	Ward*	Moderate-to-severe	Shortened antibiotic duration
Snijders 2010 [73]	Netherlands	RCT	104/109	P 40 mg, 7 days	Hospital	Mild-to-severe (10% ICU)	NR
Meijvis 2011 [74]	Netherlands	DB placebo-controlled RCT	151/153	DEX 5 mg, 4 days	Ward*	Mild-to-severe	LOS reduction with DEX
Fernandez-Serrano 2011 [72]	Spain	DB placebo-controlled RCT	28/28	MP 200 mg bolus	Hospital (16% ICU)	Severe	Improved PO ₂ : FiO ₂ earlier than placebo
Sabry 2011 [71]	Egypt	RCT	40/40	300 mg/day, HC, 7 days	ICU	Severe	HC significantly improved PaO ₂ :FiO ₂ and SOFA score at day 7

*Patients admitted to the ICU on day 1 were excluded.

CI: Confidence interval; DB: Double-blind; DEX: Dexamethasone; HC: Hydrocortisone; ICU: Intensive care unit; LOS: Length of hospital stay; MP: Methylprednisolone; NR: Not reported; P: Prednisone; PSI: Pneumonia Severity Index; RCT: Randomized controlled trial.

regard to the actual infection with an RO, the area under the ROC curve was 0.704 and 0.709 for the score and HCAP classification, respectively. The authors concluded that this score is better performed in populations of severe CAP, as the cohort of Shorr's study.

These studies are two attempts for predicting the RO in patients with CAP in order to manage them properly.

7. Adjunctive therapies

Attempts to improve outcomes of CAP by setting measurable process of care standards are to be applauded. Simple measures, such as quick assessment of oxygenation in the ED, had a great potential to influence outcomes. Other kind of therapy are:

i) Corticosteroids are the most powerful inhibitors of inflammation, reducing the production of the main inflammatory cytokines (TNF α , IL-1 β , IL-8 and IL-6) and subsequently recruiting inflammatory cells into the alveolar space leading to a more equilibrated response. Additionally, in patients with severe CAP and septic shock, a relatively insufficient adrenal response has been observed during infection, associated with a higher risk of death [68]. Therefore, corticosteroid replacement therapy might be effective in patients with severe CAP.

Because of the weak evidence of survival benefit of corticosteroids in CAP therapy, their use in pneumonia remains highly controversial.

The best evidence for the use of corticoids in CAP comes from studies of *Pneumocystis jirovecii* pneumonia in AIDS patients [69].

A limited number of trials have investigated corticosteroids treatment in patients with non-severe and severe pneumonia (Table 4).

Prospective, randomized trials referring to corticosteroids in severe CAP are the Confalonieri *et al.* [70] in 2005, Sabry and Omar [71] and Fernandez-Serrano *et al.* [72] in 2011. These trials that investigated steroid treatment for severe CAP for at least 7 days showed improvement in oxygenation (PO₂/FiO₂); however, the trial by Confalonieri *et al.* found a mortality benefit [70].

Three randomized trials [73-75] that were published in the past 2 years examined whether the addition of corticosteroids will help hospitalized patients with non-severe CAP and found only decreased hospital LOS in the largest of them [74]. No study has showed survival benefit.

In agreement, the recent study by Polverino *et al.* showed that in patients who were receiving steroids as medical prescription for CAP had no difference in mortality comparing to the other patients. Moreover, patients on corticosteroids had longer hospital stay in the multivariate analysis [76].

Two meta-analysis on this subject, Nie *et al.* [77] from China and the Confalonieri *et al.* [78], confirmed the above finding and suggested that only in severe CAP, a prolonged corticosteroids therapy resulted in a beneficial effect on mortality.

Recent guideline for sepsis recommended that corticosteroids are not to be used for treating sepsis in the absence of shock, unless the patients' endocrine function is not intact or that patients have corticosteroid history [79].

The effects of corticosteroids as an adjunct to antibiotic therapy is currently being evaluated in two placebo-controlled trials, one in Switzerland aiming to include 800 patients hospitalized with CAP and one in Spain targeting about 120 CAP patients with PSI class V [80].

ii) Low molecular heparin should be given to patients with acute respiratory failure [4]. Activation of the coagulation system appears to be a major pathophysiological event in severe pneumonia, possibly even more so than for sepsis in general [81].

Patients who received heparin in the control group of several clinical trials of sepsis appeared to have better outcomes than those who were not anticoagulated. However, a randomized, controlled trial did not demonstrate any survival or organ failure benefit [82]. Prophylaxis for thromboembolism, due to acute medical illness, is recommended for severe CAP in the evidence-based clinical practice guidelines [83].

iii) The use of noninvasive ventilation (NIV) is not yet the standard care but can be considered, particularly in patients with COPD and ARDS. Several studies indicate that NIV may also work in patients with pneumonia, particularly in patients with COPD [4].

In one of the first studies, Confalonieri *et al.* conclude that in selected patients with ARF caused by severe CAP, noninvasive positive pressure ventilation was associated with a significant reduction in the rate of endotracheal intubation and duration of ICU stay [84].

In a study by Ferrer *et al.* in three hospitals in Spain, compared with oxygen therapy, NIV decreased the need for intubation (13, 25 vs 28, 52%, $p = 0.010$), the incidence of septic shock (6, 12 vs 17, 31%, $p = 0.028$) and the ICU mortality (9, 18 vs 21, 39%, $p = 0.028$) and increased the cumulative 90-day survival ($p = 0.025$), in patients with severe respiratory failure [85].

iv) New anti-inflammatory agents have been studied for the treatment of CAP, such as statins. Statins have pleiotropic effects – immunomodulatory [86], anti-inflammatory, anti-thrombotic [87] and a direct microbicidal action; all of which may have potential beneficial role in the prevention and treatment of CAP.

Multiple observational studies have suggested that patients who were taking statins at the time of development of pneumonia or other infection were less likely to develop sepsis or death from sepsis [88,89].

Another possible explanation of the beneficial effect of statins use was its role in acute coronary syndrome and myocardial infarction, as 20% of patients had an acute cardiovascular event, while hospitalized with CAP [90]. Studies reported that the statins reduced the risk of developing sepsis or complications of CAP [91]. Further research is needed on this drug in patients with CAP.

One late meta-analysis reveals a beneficial role of statins for the risk of development and mortality associated with CAP [92].

8. Conclusion

We have reviewed some, but certainly not all, aspects and controversies in the management of CAP. When managing patients with CAP, it is important to choose the most appropriate site of care and the appropriate empirical antimicrobials.

Implementation of guidelines for CAP treatment should be emphasized in order to increase survival. Rapid initiation of appropriate antimicrobial therapy and optimizing dosage of antibiotics are critical for achieving successful clinical outcomes. Shorter antimicrobial regimens (< 7 days) are generally favorable for mild-to-moderate CAP. New antibiotics, such as ceftaroline and cethromycin are expected to widen our treatment options.

9. Expert opinion

Guideline adherence, especially ATS/IDSA, in the management of CAP is associated with improved outcomes, according to large prospective studies.

After classification of severity of CAP and choosing an appropriate initial antimicrobial agent, it is important to use a regimen that optimizes a drug's PK/PD parameters to ensure bacterial eradication. Optimizing PK/PD parameters is the rationale for the development of the 750 mg, 5-day levofloxacin regimen in contrast to the traditional 500 mg, 10-day course and 750 mg ciprofloxacin regimen in hospitalized CAP. New studies, using Monte Carlo stimulation, are needed to determine the best antibiotic dosing for bacterial eradication and avoidance of resistance.

Several studies supported the use of CI of β -lactams (ceftazidime) instead of intermittent administration in CAP patients regardless of severity.

According to recent studies, the benefit of providing empirical therapy directed at atypical pathogens was variable, being more important in some countries and years than in others. As already described, their role is thought to be less important in European guidelines and in recommendations from the British Thoracic Society. Because of the high resistance of macrolide to *S. pneumoniae*, monotherapy with macrolide is not recommended in outpatients with mild CAP, in Europe.

Despite the large number of publications, obligatory use of a macrolide in severe CAP as combination therapy, based on its anti-inflammatory properties, has so far not been included in guidelines because of the observational, and usually retrospective, nature of all the studies that showed a clear benefit.

The benefits of corticosteroids treatment in CAP are still uncertain. Some reports have demonstrated a favorable impact of glucocorticosteroid treatment on the prognosis of severe CAP, but not a survival benefit. Newer studies are

investigating prolonged low-dose glucocorticoid treatment in septic shock and/or early ARDS.

Several new antibiotics, including ceftaroline, tigecycline, cethromycin and solithromycin have been developed and studied in populations with mild-to-moderate CAP, with good results. During the last couple of years, two of them have been approved by FDA for use in CAP. A new cephalosporin, ceftaroline fosamil was approved in 2010, and in two Phase III double-blinded, randomized, prospective trials, it was shown to be noninferior to ceftriaxone for the treatment of CAP in hospitalized patients. And a glycylicycline, tigecycline in 2009 has been shown to be as effective as levofloxacin in clinical trials involving hospitalized patients with CAP. They could offer an alternative option to decrease the use of quinolones as therapy in moderate CAP. Data from the other new antibiotics regarding their efficacy and safety in patients with severe CAP are lacking.

As the understanding of the pathophysiological mechanisms of severe pneumonia improves, the development of immunomodulatory drugs (immunoglobulin or interferon g) will bring specific therapies for particular patient groups in CAP. Statins, except their protective role in cardiologic events in CAP evolution, have potent anti-inflammatory effects in laboratory studies of pulmonary inflammation. Studies suggest that statin use is associated with reduced markers of systemic inflammation and is the mechanism that explains the improved outcomes in patients admitted with CAP. More randomized trials are needed on the continuation of statins during the course of the disease and their impact on short- and long-term mortality.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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