Nonantibiotic Adjunctive Therapies for Community-Acquired Pneumonia (Corticosteroids and Beyond): Where Are We with Them?

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Abstract

Community-acquired pneumonia (CAP) is a leading cause of hospitalization, morbidity, and mortality. Despite advances in antibiotic treatments, mortality among patients with CAP is still high. For this reason, interest has been focused on nonantibiotic therapeutic measures directed to the host response rather than the microorganism. The development of an efficacious adjunctive treatment has important implications for reducing mortality in CAP. Some clinical studies performed in the last decade have shown a clinically beneficial effect of corticosteroids, possibly by diminishing local and systemic inflammatory host response. Recent meta-analyses showed faster resolution of symptoms, shorter time to clinically stability, reduction of mechanical ventilation needed, and reduction of mortality in the most severe population, although some methodological limitations must be taken into account. In addition, some studies using statins also suggested improved outcomes due to its anti-inflammatory effect in CAP, although this requires further research. Other adjunctive therapies such as immunoglobulins and stem cells are being explored, but are not yet in the stage of clinical trials. In summary, the use of corticosteroids and other adjuvant treatments are promising in CAP, but more studies are needed to determine their impact on mortality.

Keywords
- community-acquired pneumonia
- corticosteroids
- statins
- immunoglobulins

Community-acquired pneumonia (CAP) is the leading cause of morbidity and mortality from infectious diseases in developed countries. It affects more than 5 million adults and accounts for more than 1 million admissions each year in the United States.[1,2] Pneumonia is the sixth leading cause of death worldwide, and age-adjusted mortality is increasing.[3]

It is well recognized that inappropriate initial antibiotic treatment is associated with worse clinical outcomes, including higher mortality, in CAP. However, it is also noted that even in the setting of initial appropriate antibiotic treatment, many patients still die.[4] CAP can induce severe lung and systemic inflammation, and high inflammatory mediator levels are associated with an impairment of alveolar gas exchange, sepsis, end-organ dysfunction,[5] and increased risk of early and late death in CAP.[6,7] For this reason, interest has been redirected toward nonantibiotic therapeutic measures trying to reduce CAP-related mortality. Different adjunctive treatments have been tested in CAP in recent years.[8] These treatments are directed to the host response rather than the microorganism and include anti-inflammatory, anticoagulant, and experimental regenerative treatments. It is well known that corticosteroid therapy attenuates the local and systemic inflammatory response in pneumonia[9] and may potentially decrease acute respiratory distress syndrome

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(ARDS), sepsis, and mortality.[10] Several studies have been performed recently to determine the role of corticosteroids as an anti-inflammatory adjunctive treatment in CAP with controversial results. In addition, other adjunctive treatments such as statins and immunoglobulins (IGs) have also been tested, trying to improve clinical outcomes in CAP.

The purpose of this review is to assess the evidence related to corticosteroids and other nonantibiotic adjunctive therapies use and clinical outcomes in patients with CAP, with special interest in studies published in the last 10 years.

Corticosteroids

Corticosteroids are the most used anti-inflammatory drugs and are involved in a wide range of physiological processes, including regulation of inflammation, immune response, carbohydrate metabolism, protein catabolism, and blood electrolyte levels.[11,12]

Mechanism of Action

Corticosteroids inhibit the expression and action of many inflammatory mediators. To exert their effects, corticosteroids need to bind to a specific cytoplasmic glucocorticoid receptor (GR) found in respiratory epithelial cells and other cell lines. The activation of the GR by the administration of the corticosteroids moves the drug–receptor complex into the nucleus of the cell and binds to the DNA.[11] The anti-inflammatory and immunosuppressive effects of corticosteroids are achieved by two distinct mechanisms. First, activated GR to specific DNA sequences located in the promoter regions of target genes to induce transcription of anti-inflammatory molecules such as interleukin (IL)-10, IL-1 receptor, or Lipocortin 1 (transactivation). Second, an indirect negative regulation of gene expression is also achieved by GR–protein interaction (transrepression). The activated GR binds to key proinflammatory transcription factors such as activator protein 1 and nuclear factor κB. The resulting complex inhibits the initiation of transcription of relevant genes that play a central role in inflammation.[11] For that reason, the synthesis of several cytokines (e.g., tumor necrosis alpha [TNFα], ILs 4, 5, 6, and 13, adhesion molecules [e.g, intercellular adhesion molecule-1 and vascular adhesion molecule-1], and chemokines [e.g., eotaxin and IL-8]) is inhibited.[13,14]

Experimental studies confirmed these anti-inflammatory effects in pneumonia. In a model of severe pneumonia in mechanically ventilated piglets, we observed lower lung cytokine concentrations and less lung bacterial burden in piglets that were treated with corticosteroids plus antibiotic compared with those treated only with antibiotics.[15] Previous in vitro studies using human monocytic cells demonstrated that corticosteroids suppress bacterial replication and intracellular bacteria.[16] In a mouse model of pneumonia induced by *Escherichia coli*, the administration of hydrocortisone reduced inflammatory response and the risk of death.[17] And in another mouse model of *Mycoplasma pneumoniae* respiratory infection, Tagliabue et al[18] showed that the association of corticosteroids and macrolides was histologically beneficial.

From a clinical point of view, all these findings suggested that corticosteroids may modulate pneumonia-associated inflammatory response in humans, which is related to poor clinical outcomes.[11,19–21] With this aim, several clinical studies have been performed in the last 10 years.

Observational Studies

Garcia-Vidal et al[22] conducted a retrospective observational study of a cohort of 308 hospitalized patients with severe CAP, where those treated with antibiotics plus corticosteroids experienced lower mortality (odds ratio [OR]: 0.28; 95% confidence interval [CI]: 0.11–0.73). Salluh et al[23] studied the impact of corticosteroids on the clinical course and outcomes of 111 patients with CAP requiring mechanical ventilation, where 55% of the patients received corticosteroids due to bronchospasm or septic shock. In this study, the adjunctive use of corticosteroids did not influence mortality, organ failure, or withdrawal of vasopressors. However, a recent Japanese study including 2,524 patients with severe CAP showed that low-dose corticosteroid therapy reduced 28-day mortality among those patients with CAP complicated by septic shock.[24] Nevertheless, this benefit was not observed among patients with severe CAP without septic shock. All of these findings suggested that corticosteroids may reduce mortality in patients with severe CAP. However, these observations may be due to the overinclusion of patients with septic shock or with other conditions known to benefit from corticosteroids treatment, such as chronic obstructive pulmonary disease or asthma.

Randomized Controlled Trials

Several randomized controlled trials (RCTs) evaluated the effect of acute administration of corticosteroids in patients with CAP over the last past decade (►**Table 1**). Confalonieri et al[25] assessed the efficacy and safety of continuous infusion of hydrocortisone in 46 patients with CAP requiring intensive care unit (ICU) admission. These authors demonstrated a mortality reduction in the group treated with corticosteroids, a better modulation of systemic inflammatory response, and significant improvement in clinical endpoints, such as chest X-ray, multiple organ dysfunction syndrome severity scale, PaO_2:FiO_2 ratio, and ICU and hospital stay. The limitation of this study was the small sample size and differences among groups on admission, which limited the generability of these results. Snijders et al[26] studied the impact of prednisolone compared with placebo among 213 hospitalized patients with CAP. In this study, the authors found no differences regarding the rate of 30-day mortality, time to clinically stability, or length of hospital stay. Patients treated with corticosteroids had faster decline in serum C-reactive protein (CRP) levels compared with placebo. However, late clinical failure (>72 hours from admission) was more common in the corticosteroid group. Meijvis et al[27] evaluated the effect of intravenous (IV) dexamethasone versus placebo in the first 4 days after CAP admission in 304 patients. The authors found no differences in the main outcomes, including inhospital mortality, ICU admission, and severe adverse events. However, patients treated with corticosteroid had a shorter length

Table 1 Double-blind randomized controlled trials evaluating the effects of corticosteroids as adjuvant therapy in CAP in the past 10 years

Author (y)	*N*	Disease	Corticosteroid (dosage)	Duration of treatment (d)	Outcomes evaluated	Results	Side effects
Confalonieri et al (2005)[25]	45	CAP requiring ICU	Hydrocortisone (240 mg/d)	7	Improvement in PaO_2/FiO_2 and in multiple organ dysfunction syndrome Duration of MV, length of ICU and hospital stay, and survival to hospital discharge and to 60 d	Significant improvement in PaO_2/FiO_2 and increase incidence of delayed septic shock in the hydrocortisone group Significant reduction of duration MV, length of ICU and hospital stay, increased survival to hospital discharge and to 60 d	None
Snijders et al (2010)[26]	213	Hospitalized CAP	Prednisolone (40 mg/d)	7 d	Clinical cure at day 7 Clinical cure at day 30, length of stay, time to clinical stability, defervescence, CRP	No differences Faster defervescence and decline in serum of CRP in the prednisolone group Increase of later failure in the prednisolone group	None
Meijvis et al (2011)[27]	304	Hospitalized CAP	Dexamethasone (5 mg/d)	4	Length of hospital stay Mortality, admission to ICU, development of empyema, superinfection, readmission, time courses of CRP, IL-6, IL-10, pulmonary function at day 30, health-related quality of life	Significant reduction of length of stay Greater decline in CRP an IL6 concentrations in the dexamethasone group No other significant differences	Hyperglycemia
Fernández-Serrano et al (2011)[28]	56	Hospitalized CAP	Methylprednisolone (620 mg)	9[a]	Respiratory failure requiring MV or NPPV Improved clinical course, length of hospital stay, length of ICU, mortality, decreasing levels of systemic inflammatory response	No differences Significant improvement of the clinical course and faster reduction in blood IL-6 and CRP levels in the first 24 h of treatment in the methylprednisolone group	None
Torres et al (2015)[29]	120	Hospitalized severe CAP	Methylprednisolone (0.5 mg/kg/12 h)	5	Treatment failure Time to clinical stability, length of ICU and hospital stays, inhospital mortality	Significant decrease of treatment failure in methylprednisolone group No significant differences	None
Blum et al (2015)[30]	785	Hospitalized CAP	Prednisone (50 mg/d)	7	Time to clinical stability Time to discharge, recurrence of pneumonia, readmission, ICU admission, all-cause mortality, duration of treatment, CAP score	Significant decrease of time to clinical stability Significant reduction of median time to effective discharge and duration of IV antibiotic treatment in the prednisone group No other significant differences	Hyperglycemia

Abbreviations: CAP, community-acquired pneumonia; CRP, C-reactive protein; ICU, intensive unit care; IL, interleukin; IV, intravenous; MV, mechanical ventilation; *N*, number of patients; NPPV, noninvasive positive pressure ventilation; PaO_2/FiO_2, partial pressure of arterial oxygen/fractional inspired oxygen.
[a]Gradual withdrawal.

of hospital stay compared with the placebo group. Fernández-Serrano et al[28] described in a study of 56 hospitalized patients with CAP that combination of antibiotics with methylprednisolone improved respiratory failure rates and accelerated the timing of clinical resolution. No serious side effects related to corticosteroids were described in any of these clinical studies.

During 2015, two positive RCTs were published regarding the use of corticosteroids as adjunctive therapy in CAP. Our group demonstrated that acute administration of methylprednisolone (0.5 mg/kg/12 hours during 5 days) decrease treatment failure in a population of 120 patients with severe CAP who had high inflammatory response (defined as CRP greater than 150 mg/L on admission).[29] In this study, the primary outcome was treatment failure, a composite outcome of early treatment failure based on clinical deterioration, need for subsequent mechanical ventilation, and death within 72 hours of treatment, or a composite outcome of late treatment failure, based on radiographic progression, persistent respiratory failure, development of shock, and subsequent need for mechanical ventilation, death within 72 hours, or a composite of both early and late treatment failure. In the corticosteroid group, treatment failure was less common (13 vs. 31%), especially in late treatment failure (3 vs. 25%). When individual components of treatment failure were evaluated, differences among groups were found in the radiographic progression (2% in the corticosteroid group vs. 15% in the control group). Inhospital mortality did not differ among groups, and no side effects related to corticosteroids were found. Blum et al[30] showed that prednisone treatment for 7 days in patients admitted with CAP shortens time to clinical stability without an increase in complications. Again, no differences in mortality among groups were found and no adverse events were described.

All these findings suggested a corticosteroid benefit in patients with pneumonia and concomitant corticosteroid treatment, especially in the most severe population. However, the main limitations of these studies that could explain differences in results included the selection of nonsevere CAP in most of the studies, the inclusion of patients independently of their inflammatory response (e.g., CRP level), and the use of inadequate dosage of corticosteroids (low or excessive high).

Meta-Analyses

Given the variability of the results and the severity of CAP, different meta-analyses evaluating the effect of corticosteroids in different clinical outcomes have been performed in the recent years (►**Table 2**). A Cochrane meta-analysis[31] selected six RCTs of corticosteroids in pneumonia including 437 participants. The use of corticosteroids accelerated the resolution of symptoms and time to clinical stability. However, corticosteroids did not provide a benefit in mortality, and the authors concluded that it was not possible to make any definitive recommendations because the studies taken account in the meta-analysis were not strong enough. Nie et al[32] performed another meta-analysis including nine RCTs with 1,001 patients and showed that the use of corticosteroids was not associated with significant lower mortality considering all the patients (OR: 0.62; 95% CI: 0.37–1.04). However, a survival benefit was detected in the subgroup of patients with severe CAP (OR: 0.26; 95% CI: 0.11–0.64) and among patients with prolonged corticosteroids treatment (OR: 0.51; 95% CI: 0.26–0.97). Prolonged corticosteroid treatment was defined as more than 5 days of corticosteroids treatment with a maximum of 9 days. Considering the adverse effects, corticosteroids increased the risk of hyperglycemia (OR: 2.64; 95% CI: 1.68–4.15), but without increasing the risk of superinfection (OR: 1.36; 95% CI: 0.65–2.84) and gastroduodenal bleeding (OR: 1.67; 95% CI: 0.41–6.80). These results were very similar with another more recent systematic review and meta-analysis that included 2,077 patients from 14 trials.[33] Again, adjunctive corticosteroid therapy was associated with decreased 30-day mortality among patients with severe CAP (relative risk [RR]: 0.47; 95% CI: 0.23–0.96) but not in the whole CAP population. In addition, corticosteroid treatment was associated with a reduction of severe complications (RR: 0.36; 95% CI: 0.23–0.56), a shorter length of stay (9.0 vs. 10.6 days), and a shorter time to clinical stability (3.3 vs. 4.3 days). The main limitation of these meta-analyses was the inclusion of trials with heterogeneous severity (from mild to severe) and different dosage of corticosteroids.

Two more meta-analyses have been published recently. Wan et al[34] included nine RCTs (1,667 patients) and six cohort studies (4,095 patients). In this study, the authors showed that the use of corticosteroids was not associated with a significant reduction in mortality in patients with CAP (RR: 0.72; 95% CI: 0.43–1.21) and neither in the subgroup of patients with severe CAP (RCTs: RR, 0.72; 95% CI, 0.43–1.21; evidence rank, low; cohort studies: RR, 1.00; 95% CI, 0.86–1.17). However, corticosteroids produced a benefit in terms of reduction of ARDS, length of hospital and ICU stay, duration of IV antibiotics, and time to clinical stability without increasing side effects. In contrast, another meta-analysis[35] including 13 RCT (2,005 patients) demonstrated a reduction in all causes of mortality in patients receiving corticosteroids (risk ratio: 0.67 [95% CI: 0.45–1.01]; risk difference: 2.8%). Moreover, it confirmed the reduced risk of ARDS, need for mechanical ventilation, decreased time to clinical stability, and length of hospital stay, with increased episodes of hyperglycemia requiring treatment but no increase in the frequency of gastrointestinal hemorrhage.

In conclusion, all the aforementioned meta-analyses confirmed that the use of corticosteroids in CAP is associated with shortening the time to clinical stability, length of hospital stay, and prevention of ARDS. There is still no definitive answer regarding the effect of corticosteroids on the decrease in mortality. Some meta-analysis suggested that corticosteroids can decrease mortality in the subgroup of patients with severe CAP.[32,33,35] However, main limitations of these studies are related to the inclusion of different classification of severity of illness and the use of different corticosteroid types and dosage, which make it difficult to compare the final results.

Table 2 Meta-analysis evaluating the effect of corticosteroids in pneumonia

Author (y)	*N*	Disease	Corticosteroid (dosage)	Duration of treatment (d)	Outcomes evaluated	Results	Side effects
Chen et al (2011)[31]	6 RCTs ($n = 437$)	CAP	Confalonieri et al[25]: hydrocortisone (240 mg/d)	7	Mortality Time to resolution, relapse of pneumonia, need of MV or inotropic support, admission to ICU, time to discharge from ICU	No significant differences Faster resolution of symptoms and time to clinical stability in the corticoid group	Hyperglycemia
			Marik et al[61]: hydrocortisone (10 mg/kg/d)	1			
			McHardy and Schonell[62]: prednisolone (20 mg/d)	7			
			Mikami et al[63]: prednisolone (40 mg/d)	3			
			Van Woensel et al[64]: dexamethasone (0.15 mg/kg/6 h)	1			
			Cao et al[65]: budesonide (250–500 g/d)	7			
Nie et al (2012)[32]	9 RCTs ($n = 1,001$)	CAP of any severity	Wagner et al[66]: hydrocortisone (560 mg)	5	Mortality Adverse events	No significant differences Significant survival benefit in the subgroup of severe CAP More hyperglycemia events in the corticosteroids group	Hyperglycemia
			McHardy and Schonell[62]: prednisolone (20 mg/d)	7			
			Marik et al[61]: hydrocortisone (10 mg/kg)	1			
			Confalonieri et al[25]: hydrocortisone (240 mg/d)	7			
			Mikami et al[63]: prednisolone (40 mg/d)	3			
			Snijders[26]: prednisolone (40 mg/d)	7			
			Meijvis et al[27]: dexamethasone (5 mg/d)	4			
			Sabry and Omar [67]: hydrocortisone (300 mg/d)	7			
			Fernández-Serrano et al[28]: methylprednisolone (620 mg/d)	9[a]			
Marti et al (2015)[33]	13 RCTs ($n = 2,077$)	CAP of any severity	Included 9 RCTs of Nie et al[32] and:		30-d mortality Length of stay, time to clinical stability, need of MV or vasopressors, severe complications	No significant differences Significant survival benefit in the subgroup of severe CAP Reduction of severe complications, shorter length of stay and shorter time to stability in the corticosteroid group	Hyperglycemia
			Bennett et al[68]: hydrocortisone (300 mg/d)	6			
			Blum et al[30]: prednisone (50 mg/d)	7			
			Klastersky et al[69]: betamethasone (1 mg/kg/d)	3			
			Nafae et al[70]: hydrocortisone (200 mg + 10 mg/h)	7			
			Torres et al[29]: methylprednisolone (1 mg/kg)	5			
Siemieniuk et al (2015)[35]	13 RCTs ($n = 2,005$)	CAP of any severity	Included the 9 RCTs: Nie et al[32] + Blum et al,[30] Nafae et al,[70] and Torres et al[29]	7	All-cause mortality Need of MV, ICU admission, risk for ARDS, length of stay, time to clinical stability, adverse effects	No significant differences Significant survival benefit in the subgroup of severe CAP Significant reduction of MV, decreased time to clinical stability and length of stay in the corticosteroid group	Hyperglycemia requiring treatment
			In addition to: El-Ghamrawy et al[71]: hydrocortisone (200 mg bolus followed by 10 mg/h)				
Wan et al (2016)[34]	9 RCTs ($n = 1,667$) 6 cohort studies ($n = 4,095$)	RCT: CAP of any severity Cohort studies: Severe CAP	RCT Marik et al[61]: hydrocortisone (10 mg/kg/d)	1	Mortality	No significant differences	No significant differences
			Confalonieri et al[25]: hydrocortisone (200 mg bolus followed by 10 mg/h)	7			
			Mikami et al[63]: prednisolone (40 mg/d) Snijders et al[26]: prednisolone (40 mg/d) Fernández-Serrano et al[28]:	3 7			

(*Continued*)

Table 2 (*Continued*)

Author (y)	*N*	Disease	Corticosteroid (dosage)	Duration of treatment (d)	Outcomes evaluated	Results	Side effects
			methylprednisolone (620 mg/d) Meijvis et al[27]: dexamethasone (5 mg/d)	9[a] 4 7			
			Nafae et al[70]: hydrocortisone (200 mg + 10 mg/h)	7			
			Blum et al[30]: prednisone (50 mg/d)	5			
			Torres et al[29]: methylprednisolone (1 mg/kg)	11			
			Cohort studies				
			Garcia-Vidal et al[22]: methylprednisolone (24 mg/d)/prednisone (30 mg/d)	7			
			Salluh et al[23]: equivalent methylprednisolone (60 mg/d)	4–7			
			Chon et al[72]: NA	7			
			Ugajin et al[73]: methylprednisolone, prednisolone, or dexamethasone (20–60 mg/d)	7			
			Polverino et al[74]: methylprednisolone P (0.5–2.5 mg/kg/d or equivalent dose) Tagami et al[24]: methylprednisolone P (0.5–2.5 mg/kg/d or equivalent dose)				

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; MV, mechanical ventilation; *N*, number of patients; NA, not available; RCT, randomized controlled trials.
[a]Gradual withdrawal.

Other Nonantibiotic Adjunctive Therapies

Statins

Statins are lipid-lowering drugs widely used in the prevention of adverse cardiovascular events.[36–38] In addition to their cardiovascular effect, different studies have also demonstrated that they have anti-inflammatory and direct antimicrobial activity effects,[39–41] which are related to improved outcomes in severe bacterial infections.[42–44]

Several studies compared retrospectively outcomes in patients with CAP who were taking chronic statins at the time of the diagnosis. Van de Garde et al[45] showed that the use of statins was associated with a considerable reduction in the risk of pneumonia in diabetic patients (adjusted OR: 0.49; 95% CI: 0.35–0.69). In a large study of patients admitted with CAP in Taiwan, Chung et al[46] concluded that patients with regular previous statin use had better clinical outcomes such as less admission to ICU (OR: 0.81; 95% CI: 0.74–0.89), less acute respiratory failure (OR: 0.80; 95% CI: 0.71–0.89), less need of mechanical ventilation (OR: 0.84; 95% CI: 0.75–0.94), and less likely death in hospital (OR: 0.69; 95% CI: 0.57–0.85). Polgreen et al[47] analyzed a cohort of patients admitted with a diagnosis of myocardial infarction and performed an instrumental variables analysis using geographic treatment rates as an instrument. They concluded that the protective effect of statins against pneumonia was most likely the result of nonrandom treatment assignment.

However, different RCT have been performed in the last 10 years with conflicting results (►**Table 3**). Novack et al[41] evaluated the effect of statin therapy on inflammatory cytokines in patients with bacterial infections. In this study, the authors concluded that statin therapy was associated with a reduction in levels of inflammatory cytokines (TNFα and IL-6 levels). Two other RCTs evaluated the effect of statin therapy on mortality in patients with ventilator-associated pneumonia (VAP). Makris et al[48] found a trend of increased survival in the pravastatin group but this did not reach statistical significance ($p = 0.7$). In this study, the authors stratified data according to median APACHE (Acute Physiology and Chronic Health Evaluation) scores and found a significantly increased probability of being free from VAP during the whole ICU period ($p = 0.04$) in the pravastatin group. However, in another RCT including 284 patients having suspected VAP, Papazian et al[49] showed that adjunctive statins therapy in VAP did not improve 28-day survival. In 2015, Viasus et al[50] evaluated the clinical outcomes and concentration of inflammatory cytokines in a randomized trial in patients with CAP treated with simvastatin and concluded that the use of simvastatin did not reduce the time to clinical stability or the levels of inflammatory cytokines in hospitalized patients with CAP.

In summary, there is controversial evidence for the protective effect of statins for CAP, probably due to the limitations of retrospective studies and the pleiotropic effect of statins. Furthermore, none of RCTs suggested clinical benefits that justify the use of statins in patients with CAP.

Immunoglobulin

Low levels of IGs in serum are frequently detected in patients with severe sepsis and septic shock.[51,52] In addition, de la

Table 3 Randomized clinical trials evaluating the effect of statins in bacterial infections and pneumonia

Author (y)	*N*	Disease	Statin (dosage)	Duration of treatment	Evaluated outcomes	Results
Novack et al (2009)[41]	83	Bacterial infection	Simvastatin (40 mg/d first dose followed by 20 mg/d)	Until hospital discharge or development of severe sepsis	Development of severe sepsis Changes in the levels of cytokines	No significant differences Significant reduction of IL-6 and TNFα levels after 72 h of treatment
Makris et al (2011)[48]	152	VAP	Pravastatin (40 mg/d)	30 d	Frequency of VAP Mortality	Significantly reduction of VAP in statin group with APACHE score > 15 p during the whole ICU period ($p = 0.4$) Significantly increased probability of survival during the 30-d treatment period in statin group with APACHE > 15 p
Papazian et al (2013)[49]	300	VAP	Simvastatin (60 mg/d)	Until ICU discharge	28-d mortality 14-d mortality, ICU, hospital mortality rates, MV, number of ventilator-free days by day 28, coronary events, ARDS	No significant differences
Viasus et al (2015)[50]	34	Hospitalized CAP	Simvastatin (20 mg/d)	Until hospital discharge	Time from hospital admission to clinical stability Serum concentrations of cytokines and PaO_2/FiO_2 at 48 h after treatment	No significant differences

Abbreviations: ARDS, acute respiratory distress syndrome; CAP, community acquired pneumonia; ICU, intensive care unit; IL, interleukin; MV, mechanical ventilation; *N*, number of patients; PaO_2/FiO_2, partial pressure of arterial oxygen/fractional inspired oxygen; TNFα, tumor necrosis alpha; VAP, ventilator-associated pneumonia.

Torre et al[53] showed low levels of IGs, particularly total IgG and IgG2, in patients with CAP compared with healthy controls.

Some studies have evaluated the effects of exogenous administration of IGs in patients with sepsis (most of them due to CAP), with controversial results.[54] In a prospective RCT including 653 patients with severe sepsis, the administration of IgG did not show differences in 28-day mortality among groups.[55] However, two meta-analyses have reported improved outcomes in patients with sepsis. Kreymann et al[51] reported a reduction of mortality (around 20%) in adult patients with sepsis and septic shock who received administration of polyclonal IGs and a more evident effect on mortality in the subgroup receiving IgM-enriched IG. A more recent meta-analysis by Cochrane[56] showed a reduction in mortality in the group treated with IG, although this effect disappeared analyzing only the methodological strongest trials. In summary, there is not enough evidence supporting the benefit of IGs for treatment of sepsis. Further studies for individualized treatment with IG are needed.

For this purpose, the ongoing CIGMA study[57] seeks to determine the safety and efficacy of the novel IgM-enriched IG preparation as an adjunctive therapy in mechanically ventilated patients with CAP. The increase of ventilator-free days is the primary outcome evaluated in this multicenter, randomized, placebo-controlled, parallel-group, adaptive group-sequential phase II study.

Stem Cells

Experimental studies in the previous years have shown that human bone marrow-derived mesenchymal stem cells (MSCs) may improve survival in animal models of pneumonia. Using a murine model of *E. coli* pneumonia, Gupta et al[58] demonstrated that treatment with syngeneic MSCs enhanced survival and bacterial clearance. In a sheep model of bacterial pneumonia due to *Pseudomonas aeruginosa*, the administration of human MSCs was well tolerated and improved oxygenation and decreased pulmonary edema in those animals that developed severe ARDS.[59] Finally, Hackstein et al[60] demonstrated for the first time the feasibility and in vivo immunomodulatory capacity of prospectively defined stem cells in pneumonia. In this study, the authors isolated MSCs from murine bone marrow that were applied intratracheally 4 hours after acute respiratory *Klebsiella pneumoniae* induced infection. Those treated animals exhibited reduced airway inflammation and improved pneumonia survival. Further studies are needed to determine the clinical importance of this promising experimental data.

Conclusions

CAP remains a significant health problem despite advances in antibiotic therapies. Research into the development of modifiers of the host immune response has been developed in the previous years. Corticosteroids have been shown to decrease associated inflammatory response in pneumonia, which is related to poor outcomes when excessive. Several RCT and meta-analyses has been performed, suggesting a clinical benefit of corticosteroids use, especially in the most severe population, although its impact on mortality remains controversial. Other adjunctive therapies such as statins and IGs have been tested, although the role of these options in the

treatment of CAP is still not clear. Promising new therapies with stem cells demonstrated dramatic results in experimental studies, but they have not been tested in humans yet. In summary, the use of corticosteroids and other nonantibiotic adjuvant treatments are promising in CAP, but more studies are needed to determine their impact on mortality.

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