REVIEW

No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media

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Abstract Corticosteroids have been used to treat infectious diseases for more than 50 years but, although it has been shown that they are highly effective in improving the clinical course of some diseases, their effects have not been clearly defined in others. Nevertheless, they are still used by a considerable number of physicians. This review analyses the role of systemic corticosteroids in the treatment of acute pharyngitis (AP), community-acquired pneumonia (CAP) and acute otitis media (AOM). A number of trials involving patients with AP have been carried out, but most are marred by methodological flaws that do not allow any firm conclusions to be drawn. The number of trials involving CAP patients is even higher, and the data suggest that corticosteroids may reduce the risk of death only in patients with severe disease. There are very few data concerning AOM, and there is currently no reason for prescribing corticosteroids to treat it. Overall, the data showed that there is, currently, no indication for the universal use of systemic corticosteroids in any of the reviewed diseases and, further, high-quality studies of all of these respiratory tract infections are needed in order to identify the patients for whom the prescription of corticosteroids is rationally acceptable.

Introduction

Attempts to use corticosteroids in infectious diseases have been made for more than 50 years. Early reports relating to typhoid fever [1], tuberculous meningitis [2], and bacterial sepsis [3]

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clearly suggested that they could significantly improve the clinical course of severe infections, and led to the widespread use of corticosteroids in a number of other infectious diseases. However, subsequent findings that they may sometimes be ineffective or harmful due to their immunosuppressive or other potential negative effects have convinced many clinicians to avoid their universal use and to limit their prescription to the clinical conditions for which there are indisputable data concerning their efficacy, safety and tolerability [4].

Corticosteroids significantly down-regulate the inflammatory response because they inhibit the migration of polymorphonuclear leukocytes from blood vessels and affect gene regulation in such a way as to reduce the transcription of a wide range of pro-inflammatory cytokines, chemokines, adhesion molecules and cellular inflammatory receptors [5]. They also reduce the expression of a number of pro-inflammatory enzymes, such as nitric oxide synthase, cyclo-oxygenase and phospholipase A2, and, consequently, reduce their inflammatory products (i.e. nitric oxide, prostaglandins, leukotrienes) [5]. In general, inflammation benefits hosts with an infectious disease because it is useful for eliminating the infecting pathogens [5, 6]. However, an excessive amplification of the inflammatory response may worsen the clinical course of infectious disease, leading to significant tissue damage and development of systemic effects. This indicates that corticosteroids can be useful in infectious diseases when the inflammation is particularly severe, but dangerous when the activation of inflammatory processes remains within the normal range [5, 6].

McGee and Hirschmann have recently reviewed most of the published studies regarding the use of corticosteroids in infectious diseases and divided their effects into five possible outcomes based on the degree of improvement in the clinical course of the disease, no effect, a lack of clear data concerning their real efficacy or the demonstration of a negative impact [4]. Their review confirmed the positive effect of corticosteroids in

some infectious diseases, especially those that are particularly severe and associated with a significant risk of death: the patients with herpes zoster who received the greatest benefit were those experiencing the most pain, and the same was true of patients with *Pneumocystis jirovecii* pneumonia and hypoxaemia [4]. Similarly, the survival advantage was greatest in the patients with diseases characterised by the highest baseline mortality rate, such as tuberculous meningitis or pericarditis and typhoid fever [4].

However, although these positive examples meant that the prescription of corticosteroids came to be considered mandatory in the treatment of these diseases, their role has not been fully defined in other infectious conditions. It cannot be said whether they really increase the impact of standard therapy or whether their possible advantages outweigh the potential harm they can cause. Acute pharyngitis (AP), community-acquired pneumonia (CAP) and acute otitis media (AOM) are, particularly in children, some of the most common infectious diseases and, at the same time, some of the diseases for which systemic corticosteroids are widely prescribed in Italy and in other countries mainly of Southern Europe, although this is not codified by official guidelines. Defining the real clinical relevance of this treatment in AP, CAP and AOM seems to be important in order to avoid clinical and economic problems in the case of inefficacy, or increase cure rates in the case of positive effects.

The aim of this review is to assess whether there are enough reasons for using systemic corticosteroids in these diseases, and whether further studies are needed. All the clinical trials concerning the use of corticosteroids in both adults and children in the last 15 years were selected from PubMed and MEDLINE using combinations of text words and thesaurus terms appropriate to the concept of AP, CAP and AOM. Related meta-analyses were used to evaluate the characteristics and the quality of the selected studies.

Acute pharyngitis (AP)

AP is very common in children and adults: in the former, it is the cause of about 5 % of medical visits [7, 8] and, in the latter, it accounts for about 2 % of all outpatient visits [8, 9]. Most cases of AP are due to viruses (mainly rhinovirus, coronavirus and adenovirus), whereas *Streptococcus pyogenes* and *Mycoplasma pneumoniae* are the most frequently encountered bacterial pathogens [10, 11]. *S. pyogenes* accounts for 15–25 % of the cases in children and 5–10 % in adults [10] but, mainly because of the difficulties in identifying the pathogen in respiratory secretions, the aetiological role of *M. pneumoniae* has not been precisely defined [8, 11]. The clinical relevance of viral pharyngitis is marginal because most cases spontaneously resolve in a few days without producing significant sequelae [8], whereas cases caused by *S. pyogenes* can be followed by severe early and late complications, such as peritonsillar abscesses, cervical

lymphadenitis, mastoiditis, glomerulonephritis and rheumatic fever [8]. This explains why all of the international guidelines produced by scientific societies recommend the use of antibiotics when streptococcal aetiology is demonstrated or strongly suspected, although there are some differences in patient selection [8, 10, 12]. *M. pneumoniae* is not considered a dangerous pathogen by all experts, and is, therefore, usually not sought and, consequently, remains untreated, although some data seem to suggest that this can cause recurrences involving both the upper and the lower respiratory tract [11].

Regardless of its aetiology, AP is usually accompanied by fever and significant sore throat, and, so, antipyretics with analgesic effects such as paracetamol and ibuprofen are recommended [8, 12]; even in streptococcal cases, antibiotics only have a slight beneficial effect in reducing symptoms and fever [13].

Corticosteroids inhibit the transcription of pro-inflammatory mediators in human airway endothelial cells that cause pharyngeal inflammation and, ultimately, symptoms of pain, and may be beneficial in other upper respiratory tract infections, such as acute rhinosinusitis [14]. Consequently, it has been suggested that they could offer similar symptomatic relief from sore throat and could be used in the treatment of AP. A number of clinical trials have evaluated the effect of corticosteroid administration in combination with antibiotics in patients with AP [15–26], and Table 1 summarises the main clinical characteristics of these studies. In most cases, these studies have shown that corticosteroids are beneficial in patients with AP because, in comparison with placebo, the treatment was associated with a significantly faster reduction in pain or complete pain relief [15–26].

This has led some authors to suggest the universal use of corticosteroids in the treatment of AP, but systematic reviews or meta-analyses have shown that no definite conclusions can be drawn because some of the studies had methodological weaknesses in the way they assessed drug efficacy, and others did not adequately consider important characteristics of the enrolled patients or corticosteroid administration that may have influenced the results [8, 25–27]. Moreover, the advantage of corticosteroid use (i.e. a 4–6-h reduction in the duration of pain without any change in the number of lost school or working days) has been deemed too modest to justify their universal administration in AP [8, 25–27]. The methodological limitations in evaluating the effect of corticosteroids were highlighted by the way with which the mean times to the onset of pain relief and complete resolution of pain were reported [8, 25–27]: inadequate method of evaluation, no standard deviations or the use of graphic representations alone [16] could have led to very difficult and frequently inaccurate analyses of the collected data. Moreover, particularly in younger children, the mean time to the onset of pain relief and that of pain resolution would have been limited by recall bias because it strictly depends on the patients' memory and attention to the problem, together with the recording methods [17, 19, 20,

Table 1 Main clinical findings concerning the role of corticosteroids in the treatment of acute pharyngitis (AP)

Authors and year	Number of cases (patients/controls)	Mean age (years)	Type of AP	Intervention	Co-intervention	Main outcomes
Bulloch et al., 2003 [15]	92/92	9.7	37 % exudative (46 %S. pyogenes)	Dexamethasone 0.6 mg/kg PO (maximum 10 mg) single dose	Penicillin V if S. pyogenes; analgesia unregulated and unrecorded	Pain score after 24 h (10 cm VAS); change in pain score after 48 h; time to onset of pain relief; time to complete pain relief
Ahn et al., 2003 [16]	109/0	Not reported (age range, 16–69 years)	Not reported	Dexamethasone 5 mg PO single dose	Antibiotics in 33 % or ibuprofen in 33 %	Pain score after 24–48 h and after 1 week
Niland et al., 2006 [18]	30/30	7.7	57 % exudative (100 %S. pyogenes)	Dexamethasone 0.6 mg/kg PO (maximum 10 mg) 1 or 3 days	Antibiotics in all cases (50 % PO and 50 % i.m.); types not stated; analgesia unregulated	Time to onset of pain relief; time to complete pain relief using the Wong–Baker FACES scale; time to improvement in activity level in days
Wei et al., 2002 [19]	42/37	28.1	43 % exudative (27 %S. pyogenes)	Dexamethasone 10 mg PO single dose	Penicillin G or erythromycin; analgesic permitted and controlled	Pain score after 24 h and 48 h (10 cm VAS); change in pain scores at 24 h and 48 h; time to onset of pain relief; time to complete pain relief
Kiderman et al., 2005 [20]	40/39	33.9	87 % exudative (57 %S. pyogenes)	Prednisone 60 mg PO for 1 or 2 days	Penicillin V, amoxicillin, erythromycin stopped when culture-negative; analgesia unregulated and unrecorded	Pain reduction after 12 h, 24 h, 48 h, 72 h (10 cm VAS); proportion of patients pain-free at the different times; percentage of recurrences; complete pain relief after 24 h and 48 h; days missed from school or work
Olympia et al., 2005 [21]	57/68	11.9	Exudative not stated (56 % S. pyogenes)	Dexamethasone 0.6 mg/kg PO (maximum 10 mg) single dose	Penicillin G, erythromycin or azithromycin if S. pyogenes; analgesia recommended, unregulated and unrecorded	Change in McGrath Facial Affective Scale pain scores at 24 h and 48 h; time to onset of pain relief; time to complete pain relief
O'Brien et al., 1993 [22]	26/25	26.4	100 % exudative (S. pyogenes not tested)	Dexamethasone 10 mg i.m. single dose	Penicillin G or erythromycin; analgesic permitted but not recorded	Pain score at 24 h (15 cm VAS); time to onset of pain relief; time to complete pain relief
Marvez-Valls et al., 1998 [23]	46/46	29.2	100 % exudative (53 %S. pyogenes)	Betamethasone 8 mg i.m. single dose	Penicillin G or erythromycin; analgesia permitted not controlled	Pain score at 24 h and 48 h (10 cm VAS); change in pain scores at 24 h and 48 h; time to onset of pain relief; time to complete pain relief
Tasar et al., 2008 [24]	31/42	31.3	Not stated	Dexamethasone 8 mg i.m. single dose	Azithromycin 500 mg daily for 3 days; paracetamol for 3 days as required but not recorded	Time to onset of pain relief; time to complete pain relief

PO oral delivery; i.m. intramuscular delivery; VAS visual analogue scale

22–24]. Finally, differently efficacious visual methods were used to objectify pain, particularly in children [15, 18, 20].

Most of the trials were conducted in an emergency department setting, which suggests that, in some studies, particularly in those carried out in geographic areas where it is difficult to reach the hospital, at least a part of the enrolled patients could have very severe throat pain, and the results may not apply to primary care. In a study that enrolled fewer than 50 % of patients with exudative sore throat (i.e. with milder baseline symptoms) and showed no significant change in the time to the onset of pain relief, Hayward et al. found that the effects of corticosteroids on the mean time to the onset of pain relief were only homogeneous in severe, exudative or bacteria-positive sore throat [25].

Furthermore, most of the studies included both children and adults, and analysed the pooled data. This could lead to wrong conclusions because meta-regression analysis of the data regarding children showed no significant effect in the mean time to the onset of pain relief [25], which suggests a possible age-related difference in the clinical effect of steroids or that younger patients find it more difficult to estimate when pain relief begins. However, the wide confidence interval could be due to the small sample size of the paediatric population.

Other points that need to be taken in account when evaluating the available data are concomitant therapy and the role of aetiology. In most cases, corticosteroids were given together with antibiotics and (at least in the first days of treatment) paracetamol or ibuprofen. As antibiotics can have an, albeit slight, effect on pain by eliminating bacteria and, consequently, reducing inflammation, it may be difficult to identify the independent effect of corticosteroids on sore throat symptoms. Furthermore, in a trial in which a small group of children with a negative latex agglutination test for *S. pyogenes* were treated with dexamethasone or placebo, Bulloch et al. did not find a statistically significant difference between the two groups in the mean time to clinically significant pain relief (respectively, 15 and 9 h; $p=0.32$; effect size of 4 h with a 95 % confidence interval [CI] of −2 and 10 h) or in the time to complete pain relief (50 vs. 48 h; $p=0.61$; effect size of 2 h with a 95 % CI of −11.8 and 15.8 h) [15]. In terms of aetiology, some studies differentiated the *S. pyogenes* positive and negative cases and found that corticosteroids were more effective in the former, although the differences were limited to a few hours and were, consequently, of marginal clinical importance [15, 19]. There are still no data concerning *M. pneumoniae* and, given the possible positive role of corticosteroids in lower respiratory tract infections due to this pathogen [28], this may be an important gap to fill.

The small sample sizes of the available studies have prevented the identification of the best type of corticosteroid, dose regimen or route of administration. As most of the studies found that a single corticosteroid dose given at the time of diagnosis reduced the pain, and there was no advantage in prolonging the treatment, some authors have concluded that a single dose may be the best way of using corticosteroids in AP [15–24]. However, these studies used different drugs (dexamethasone, prednisone and betamethasone) at different doses, and they were administered by different routes (orally or intramuscularly).

The risk of adverse events has never been investigated in long-term studies. This seems to be particularly important in paediatrics because children can suffer from repeated episodes of AP over a short period, and the administration of corticosteroids can lead to negative effects. The impact on bone density, the risk of avascular necrosis, psychosis, blood sugar concentration and many other potential negatives have to be taken in account. Furthermore, the absence of a detailed long-term follow-up means that it is not known whether corticosteroids increase the risk of a few extra cases of streptococcal sore throat as a consequence of their immunosuppressive activity, as has been suggested in the case of streptococcal pneumonia [29]. Finally, there is no published study of the effects of corticosteroid administration on the development of acute rheumatic fever.

On the basis of the above, it can be concluded that the available data do not support the use of corticosteroids in patients with AP. In everyday clinical practice, some episodes of AP are treated with antibiotics despite their unknown aetiology and cause very severe pain. For this reason, some authors [25] have suggested using a single dose of systemic corticosteroids in the hope that a more rapid reduction in throat pain will avoid the need for antibiotics. However, according to what is reported in official guidelines [30, 31], we feel that there is no place for the use of corticosteroids in AP independently from the age of the patients and the aetiology of disease. If present, positive effects are too modest to justify the use of drugs for which, particularly in case of repeated administration, the potential adverse events have not been clearly evaluated. If the main reason to administer corticosteroids is to reduce antibiotic administration, we think that the systematic use of the Centor and McIsaac scores to predict group A streptococcal pharyngitis [32] or of the rapid test for the identification *S. pyogenes* antigens can be significantly more effective without any risk for the patient [33].

Community-acquired pneumonia (CAP)

Although antibiotics and vaccines have greatly reduced the morbidity and mortality associated with CAP, particularly in industrialised countries [34, 35], it remains a significant clinical problem for children and adults worldwide, and has a considerable impact on healthcare costs [36, 37]. Additional therapeutic interventions are, therefore, urgently needed.

The inflammatory response triggered by the entry of pathogens into the alveolar space is useful for controlling and eliminating primary CAP, provided that it remains localised. However, when the cytokine response is unbalanced and excessively amplified, the clinical course can worsen and lead to systemic effects [38–40]. It has, consequently, been suggested that systemic corticosteroids could be used as adjunctive therapy in order to accelerate the resolution of systemic and pulmonary inflammation in the early phase of the disease.

Since 1956 [41], a number of studies have been published [42–54]. However, only a few were prospective and methodologically appropriate because, in most of the cases, these studies were not randomised, double-blind and placebo-controlled [42]. Moreover, even the few high-quality studies were characterised by considerable heterogeneity in their populations, the aetiology of CAP, the severity of disease, the choice of drug and dosing regimens, the route of administration and outcome measures (see Table 2 for characteristics of the most relevant studies). This makes it difficult to compare the results and draw firm conclusions [43–54], and also explains why, in some cases, studies reported conflicting results that have lead, in a recently performed meta-analysis, to conclude that corticosteroids do not improve the clinical outcome of CAP [55].

However, the analysis of the single studies seems to suggests that the severity of the disease and the aetiology of CAP can play a role in conditioning response to corticosteroids. The importance of CAP severity was suggested by the data collected by Confalonieri et al. [46] and Mikami et al. [47]. These authors respectively studied the effects of hydrocortisone and prednisolone on several vital signs as well as radiological and laboratory tests of adults with CAP. The former included only severe CAP cases and reported that, after 8 days of corticosteroid administration, treated patients had, compared with control subjects, a significant improvement in $PaO_2:FiO_2$ ($p=0.002$) and chest radiograph score ($p<0.0001$), and a significant reduction in C-reactive protein levels ($p=0.01$), MODS score ($p=0.003$) and delayed septic shock ($p=0.001$) [46]. On the contrary, Mikami et al. enrolled patients with CAP of different degrees of severity and found that the positive effect of corticosteroids was marginal in mild cases and significantly more prominent in the moderate severe subgroups [47]. Regarding aetiology, Confalonieri et al. [46] and Marik et al. [45] found that the use of hydrocortisone reduced the need for mechanical ventilation in adults with CAP, as well as the length of stay in an intensive care unit (ICU), whereas van Woensel et al. [44] found that corticosteroid treatment was negative in children. These last groups enrolled children (aged <2 years) mechanically ventilated for respiratory syncytial virus lower respiratory tract infection. Children were pre-stratified for severity of oxygen abnormalities on admission. A superiority approach was used in the subgroup of patients with mild oxygen abnormalities (arterial partial pressure of oxygen/fractional inspired oxygen concentration [PaO(2)/FIO(2)] >200 mmHg and/or mean arterial pressure ≤10 cmH(2)O)

and a non-inferiority approach in those with severe oxygen abnormalities [PaO(2)/FIO(2) ≤200 mmHg and mean arterial pressure >10 cmH(2)O]. The primary outcome was the duration of mechanical ventilation. In the subgroup with mild oxygenation abnormalities, 45 of the 89 included patients received dexamethasone (0.6 mg/kg/day, 48 h) and 44 placebo; in the subgroup with severe oxygenation abnormalities, 28 of the 56 included patients received dexamethasone and 28 placebo. The results showed no evidence of a beneficial effect of dexamethasone [44], as it has been repeatedly demonstrated that corticosteroids have no effect in children with respiratory syncytial virus infection [55, 56]. On the other hand, Snijders et al. found that prednisolone had a marginal or negative effect in adults [48]: they enrolled 213 patients (93 with severe CAP) and found that the rate of clinical cure after 7 and 30 days was 84/104 (80.8 %) and 69/104 (66.3 %) in the prednisolone group, and 93/109 (85.3 %) and 84/109 (77.1 %) in the placebo group ($p=0.38$ and $p=0.08$, respectively). The patients on prednisolone experienced more rapid defervescence and a faster decrease in serum C-reactive protein levels than those receiving placebo. A sub-analysis of the patients with severe CAP did not reveal any differences in clinical outcomes, but late failures (>72 h after admission) were more frequent in the prednisolone group (20 vs. 10 patients, 19.2 % vs. 6.4 %; $p=0.04$).

Despite these conflicting results, some experts think that the administration of corticosteroids may favour a more rapid resolution of disease symptoms, reducing the rate of relapses in mild cases, but that the most relevant effect of these drugs occur in severe cases where they reduce hypo-oxygenation, the need for mechanical ventilation and the length of ICU stay, particularly in patients lacking a high adrenal response [50, 51, 56]. Patients with severe CAP usually have high serum cytokine and cortisol levels, which are, respectively, the expression of severe inflammation and the consequence of the adrenal response trying to reduce the damage caused by inflammation. When the adrenal response is lacking, CAP tends to become more severe and have a negative evolution. Remmelts et al. measured IL-6, IL-8, MCP-1 and cortisol levels in the serum of CAP patients and found that adjuvant corticosteroid administration was associated with a significant decrease in the risk of death and ICU admission only in the patients with high cytokine levels and cortisol levels of <10 μg/dL [51]. This suggests that measuring cortisol levels can help to identify the patients with severe CAP who will benefit the most from corticosteroid treatment.

Moreover, data collected in children support the hypothesis that corticosteroids may be effective in cases of severe CAP associated with *M. pneumoniae* infection and those accompanied by wheezing. Lee et al. [53] and Tamura et al. [52] retrospectively evaluated the effect of prednisolone and methylprednisolone in children with CAP or documented *M. pneumoniae* infection whose clinical and radiographic findings progressively worsened, despite theoretically adequate macrolide therapy, and found that corticosteroids were associated

Table 2 Main clinical findings concerning the role of corticosteroids in the treatment of community-acquired pneumonia (CAP)

Authors and year	Number of cases (patients/controls)	Mean age (years)	Type of CAP	Intervention	Co-intervention	Main outcomes
McHardy and Schonell, 1972 [43]	40/86	56.7–64.3	Clinical or radiographically confirmed CAP	Prednisolone PO 20 mg/day for 7 days	Ampicillin various dosages	Death; duration of treatment; change of treatment; resolution of temperature; clearance of pathogens from sputum or laryngeal swabs
Marik et al., 1993 [45]	14/16	Over 30	CAP requiring admission to ICU	Hydrocortisone 10 mg/kg for 1 day	Antibiotics i.v.	TNF-α levels; length of stay in ICU, APACHE score; mortality
Confalonieri et al., 2005 [46]	24/24	Over 60	CAP requiring admission to ICU	Hydrocortisone 200 mg as bolus followed by hydrocortisone 240 mg in 500 saline at a rate of 10 mg/h for 7 days	Protocol-guided antibiotic treatment	Improvement in PaO_2:FiO_2; multiple organ dysfunction syndrome score by study day 8; development of delayed septic shock; duration of mechanical ventilation; length of ICU and hospital stay; survival until hospital discharge and for 60 days after discharge
Mikami et al., 2007 [47]	15/16	Over 70	CAP not requiring mechanical ventilation; sputum culture positive for bacteria in 39 % of the patients	Prednisolone 40 mg i.v. daily for 3 days	Antibiotics i.v., mainly macrolides	Length of hospital stay; duration of i.v. antibiotic treatment; time required to stabilise vital signs
Snijders et al., 2010 [48]	104/109	Over 60	Radiographically confirmed CAP of various degrees of severity	Prednisolone 40 mg daily for 7 days, initially i.v., then PO when antibiotics were switched from i.v. to PO	Antibiotics i.v. followed by PO	Clinical cures after 7 and 30 days; length of hospitalisation; time to clinical stability, defervescence and C-reactive protein normalisation
Fernández-Serrano et al., 2011 [49]	28/28	Over 60	Severe CAP	200 mg of methylprednisolone, 30 min before starting antibiotic treatment. Thereafter, a maintenance intravenous dose (20 mg/6 h) for 3 days, then 20 mg/12 h for 3 days and, finally, 20 mg/day for a further 3 days	1 g/day of ceftriaxone and 500 mg/day of levofloxacin i.v.	Respiratory failure requiring conventional MV or non-invasive positive pressure ventilation; benefit in terms of an improved clinical course as measured by the PaO_2/FiO_2 ratio, radiological improvement; TRM score; length of hospital stay; length of ICU stay; mortality; decreasing levels of systemic inflammatory response (IL-6, TNF-α, IL-8, IL-10 and CRP)
Meijvis et al., 2011 [50]	151/153	Over 60	Radiographically confirmed CAP not requiring admission to ICU	Dexamethasone 5 mg i.v. once a day for 4 days	Various antibiotics	Length of hospital stay; mortality; admission to ICU; development of empyema; superinfection; re-admission; time courses of CRP, IL-6 and IL-10 concentrations; pulmonary function after 30 days
Remmelts et al., 2012 [51]	131/144	Over 60	Radiographically confirmed CAP not requiring admission to ICU	Dexamethasone 5 mg/day i.v. for 4 days	Various antibiotics	Need for ICU admission; mortality; duration of hospital stay

Table 2 (continued)

Authors and year	Number of cases (patients/controls)	Mean age (years)	Type of CAP	Intervention	Co-intervention	Main outcomes
Tamura et al., 2008 [52]	6/no controls (retrospective study)	5.8	Refractory M. pneumoniae CAP	Methylprednisolone 30 mg/kg i.v. once daily for 3 days	A macrolide not stated	Improvement in clinical and radiological findings
Lee et al., 2006 [53]	15/no controls (retrospective study)	6.1	Refractory M. pneumoniae CAP	Prednisone 1 mg/kg PO for 3–7 days	A macrolide not stated	Improvement in clinical and radiological findings
Weiss et al., 2011 [54]	7,234/13,472 (retrospective study)	4	All types of CAP	Type and dose of corticosteroids not stated	Antibiotics in most cases; chronic asthma medication in 31.8 % of those receiving systemic steroids	Length of hospital stay

CRP C-reactive protein; ICU intensive care unit; i.v. intravenous delivery; MV mechanical ventilation; PO oral delivery

with a marked improvement in all of the signs and symptoms of disease in most cases. A more recent multi-centre retrospective cohort study of 20,703 children aged 1–18 years found that the 7,234 treated with corticosteroids enjoyed a shorter period of hospitalisation only if they also received β-agonists (adjusted odds ratio 1.36; 95 % CI 1.28–1.45) [50]. Among the patients who did not receive β-agonists, those who received corticosteroids were hospitalised for longer than those who did not (adjusted odds ratio 0.85; 95 % CI 0.75–0.96) [50]. Moreover, corticosteroids were associated with the re-admission of the patients not receiving concomitant β-agonist therapy (adjusted odds ratio 1.97; 95 % CI 1.09–3.57).

As in the case of AP, no long-term data are available concerning the safety and tolerability of the addition of corticosteroids to standard CAP treatment. However, the data collected during and immediately after the end of therapy suggest that it is not associated with any significant adverse events [42].

In conclusion, even for CAP, the available data do not permit to draw firm conclusions on the use of corticosteroids in the treatment of this disease. The administration of corticosteroids in mild to moderate CAP cases cannot be recommended. The open point is the use of these drugs in very severe cases, particularly those requiring admission to the ICU. However, further studies are needed in order to better define the characteristics of the patients and pathogens for whom this addition is really needed, the type of drug and dosage to prescribe, as well as to precisely discover the real safety and tolerability of the treatment.

Acute otitis media (AOM)

Although the incidence of AOM has been significantly reduced by the widespread use of vaccines against its possible causative pathogens [57], the disease remains one of the most common infectious diseases of childhood, as almost all children experience at least one episode in the first 3 years of life. In most cases, AOM is preceded by an upper respiratory tract viral infection, but it is considered to be a bacterial disease because a bacterial pathogen (mainly S. pneumoniae and untypeable Haemophilus influenzae) is found in the middle ear fluid during about 70 % of acute episodes [58].

Given its aetiology, the only effective primary treatment for AOM is antibiotic administration. However, one consequence of antibiotic therapy is bacterial death and the release of inflammatory bacterial products (i.e. lipopolysaccharides, peptidoglycans and DNA), which can exacerbate and prolong inflammation in the middle ear and lead to otitis media with effusion (OME) and further episodes of AOM [59]. It has been shown that higher levels of inflammatory mediators are correlated with a negative outcome, and that antibiotics do not reduce cytokine levels in middle ear effusion [60, 61]. However, because of their anti-inflammatory properties, systemic

corticosteroids may reduce cytokine production and limit the risk of a negative evolution. In experimental animals with purulent AOM, they have been found to have positive effects by reducing early vascular leakage and leukocyte infiltration, and lowering the concentration of leukotriene B4 in the middle ear fluid [62].

However, only one study has evaluated the impact of systemic corticosteroids on the course of AOM, and that was carried out about 10 years ago [60]. Chonmaitree et al. enrolled 179 children with AOM (aged between 3 months and 6 years) in a randomised, double-blind and placebo-controlled trial [62], all of whom were given one intramuscular dose of ceftriaxone and then assigned to receive prednisolone (2 mg/kg/day) or placebo for 5 days. The main outcome measures were the rate of treatment failures during the first two weeks, the duration of middle ear effusion and the 6-month rate of AOM recurrences, none of which was significantly changed by treatment. The only (clinically marginal) advantage of systemic corticosteroid treatment was a higher frequency of temporarily normalised tympanometric findings on day 5 ($p=0.04$) [62]. However, the authors themselves admitted that the results were debatable because the rate of failures in the receiving the antibiotic alone group was very low, thus, leaving less room to show the efficacy of the adjunctive drug, and because the higher proportion of temporary improvement in tympanometric findings may have reflected the positive effect of corticosteroids on Eustachian tube function, which might have led to a reduced risk of OME with longer administration. Unfortunately, as no further high-quality studies have been carried out, the effect of corticosteroids on AOM is still undefined.

Conclusions

Acute pharyngitis (AP), community-acquired pneumonia (CAP) and acute otitis media (AOM) are some of the most common infectious diseases often treated with systemic corticosteroids, at least in some countries, although this is not codified by official guidelines. This review showed that there is no evidence for the effectiveness of systemic corticosteroids in these diseases. In AP, positive effects demonstrated in some studies (i.e. a more rapid reduction in throat pain with the possibility to avoid the need for antibiotics) are too modest to justify the use of drugs for which, particularly in case of repeated administration, the potential adverse events have not been clearly evaluated. In CAP, the administration of corticosteroids in mild to moderate cases cannot be recommended and the open point remains only the use of these drugs in exceptional situations like very severe cases requiring admission to the intensive care unit (ICU). In AOM, no further high-quality studies have been carried out. This means that there is currently no indication for the universal use of systemic corticosteroids in any of the

reviewed diseases, although the available data does suggest that their use may be discussed in very severe cases of CAP. The use of corticosteroids to treat AOM does not seem to be justified because many cases spontaneously resolve without sequelae and, in most cases, otitis media with effusion (OME) is not a serious clinical problem.

References

1. Wisseman CL Jr, Paterson PY, Smadel JE, Diercks FH, Ley HL Jr (1954) Studies on cortisone and antibiotics for prompt therapeutic control of typhoid fever and scrub typhus. J Clin Invest 33:264–275
2. Ashby M, Grant H (1955) Tuberculous meningitis treated with cortisone. Lancet 268:65–66
3. Breen GE, Talukdar PK (1965) Corticosteroids in the acute infections. Lancet 1:158–160
4. McGee S, Hirschmann J (2008) Use of corticosteroids in treating infectious diseases. Arch Intern Med 168:1034–1046
5. Barnes PJ (2006) How corticosteroids control inflammation: Quintiles Prize Lecture 2005. Br J Pharmacol 148:245–254
6. Esposito S, Picciolli I, Semino M, Principi N (2012) Steroids and childhood encephalitis. Pediatr Infect Dis J 31:759–760
7. Shaikh N, Leonard E, Martin JM (2010) Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. Pediatrics 126:e557–e564
8. ESCMID Sore Throat Guideline Group, Pelucchi C, Grigoryan L, Galeone C, Esposito S, Huovinen P et al (2012) Guideline for the management of acute sore throat. Clin Microbiol Infect 18(Suppl 1):1–28
9. Schappert SM (1998) Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1996. Vital Health Stat 13 134:1–37
10. Ebell MH, Smith MA, Barry HC, Ives K, Carey M (2000) The rational clinical examination. Does this patient have strep throat? JAMA 284:2912–2918
11. Esposito S, Bosis S, Begliatti E, Droghetti R, Tremolati E, Tagliabue C et al (2006) Acute tonsillopharyngitis associated with atypical bacterial infection in children: natural history and impact of macrolide therapy. Clin Infect Dis 43:206–209
12. Chiappini E, Regoli M, Bonsignori F, Sollai S, Parretti A, Galli L et al (2011) Analysis of different recommendations from international guidelines for the management of acute pharyngitis in adults and children. Clin Ther 33:48–58
13. Bisno AL (2001) Acute pharyngitis. N Engl J Med 344:205–211
14. Mygind N, Nielsen LP, Hoffmann HJ, Shukla A, Blumberga G, Dahl R et al (2001) Mode of action of intranasal corticosteroids. J Allergy Clin Immunol 108(1 Suppl):S16–S25
15. Bulloch B, Kabani A, Tenenbein M (2003) Oral dexamethasone for the treatment of pain in children with acute pharyngitis: a randomized, double-blind, placebo-controlled trial. Ann Emerg Med 41:601–608
16. Ahn JH, Woo WK, Kim YS, Song YJ, Jeon IK, Jung JR et al (2003) Efficacy of adjuvant short term oral steroid therapy for acute pharyngitis. Korean J Otolaryngol Head Neck Surg 46:971–974
17. Hahn EO, Houser HB, Rammelkamp CH Jr, Denny FW, Wannamaker LW (1951) Effect of cortisone on acute streptococcal

infections and poststreptococcal complications. J Clin Invest 30:274–281

18. Niland ML, Bonsu BK, Nuss KE, Goodman DG (2006) A pilot study of 1 versus 3 days of dexamethasone as add-on therapy in children with streptococcal pharyngitis. Pediatr Infect Dis J 25:477–481

19. Wei JL, Kasperbauer JL, Weaver AL, Boggust AJ (2002) Efficacy of single-dose dexamethasone as adjuvant therapy for acute pharyngitis. Laryngoscope 112:87–93

20. Kiderman A, Yaphe J, Bregman J, Zemel T, Furst AL (2005) Adjuvant prednisone therapy in pharyngitis: a randomised controlled trial from general practice. Br J Gen Pract 55:218–221

21. Olympia RP, Khine H, Avner JR (2005) Effectiveness of oral dexamethasone in the treatment of moderate to severe pharyngitis in children. Arch Pediatr Adolesc Med 159:278–282

22. O'Brien JF, Meade JL, Falk JL (1993) Dexamethasone as adjuvant therapy for severe acute pharyngitis. Ann Emerg Med 22:212–215

23. Marvez-Valls EG, Ernst AA, Gray J, Johnson WD (1998) The role of betamethasone in the treatment of acute exudative pharyngitis. Acad Emerg Med 5:567–572

24. Tasar A, Yanturali S, Topacoglu H, Ersoy G, Unverir P, Sarikaya S (2008) Clinical efficacy of dexamethasone for acute exudative pharyngitis. J Emerg Med 35:363–367

25. Hayward G, Thompson M, Heneghan C, Perera R, Del Mar C, Glasziou P (2009) Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. BMJ 339:b2976. doi:10.1136/bmj.b2976

26. Wing A, Villa-Roel C, Yeh B, Eskin B, Buckingham J, Rowe BH (2010) Effectiveness of corticosteroid treatment in acute pharyngitis: a systematic review of the literature. Acad Emerg Med 17:476–483

27. Korb K, Scherer M, Chenot JF (2010) Steroids as adjuvant therapy for acute pharyngitis in ambulatory patients: a systematic review. Ann Fam Med 8:58–63

28. Tagliabue C, Techasaensiri C, Torres JP, Katz K, Meek C, Kannan TR et al (2011) Efficacy of increasing dosages of clarithromycin for treatment of experimental *Mycoplasma pneumoniae* pneumonia. J Antimicrob Chemother 66:2323–2329

29. Garcia-Vidal C, Carratalà J, Fernández-Sabé N, Dorca J, Verdaguer R, Manresa F et al (2009) Aetiology of, and risk factors for, recurrent community-acquired pneumonia. Clin Microbiol Infect 15:1033–1038

30. Chiappini E, Principi N, Mansi N, Serra A, De Masi S, Camaioni A et al (2012) Management of acute pharyngitis in children: summary of the Italian National Institute of Health guidelines. Clin Ther 34:1442–1458.e2

31. Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH; Infectious Diseases Society of America (2002) Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Diseases Society of America. Clin Infect Dis 35:113–125

32. Fine AM, Nizet V, Mandl KD (2012) Large-scale validation of the Centor and McIsaac scores to predict group A streptococcal pharyngitis. Arch Intern Med 172:847–852

33. Giraldez-Garcia C, Rubio B, Gallegos-Braun JF, Imaz I, Gonzalez-Enriquez J, Sarria-Santamera A (2011) Diagnosis and management of acute pharyngitis in a paediatric population: a cost-effectiveness analysis. Eur J Pediatr 170:1059–1067

34. Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR (2007) Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. Lancet 369:1179–1186

35. Ruhnke GW, Coca-Perraillon M, Kitch BT, Cutler DM (2010) Trends in mortality and medical spending in patients hospitalized for community-acquired pneumonia: 1993–2005. Med Care 48:1111–1116

36. Peck AJ, Holman RC, Curns AT, Lingappa JR, Cheek JE, Singleton RJ et al (2005) Lower respiratory tract infections among American Indian and Alaska Native children and the general population of U.S. children. Pediatr Infect Dis J 24:342–351

37. Thomas CP, Ryan M, Chapman JD, Stason WB, Tompkins CP, Suaya JA et al. (2012) Incidence and cost of pneumonia in medicare beneficiaries. Chest. Epub Mar 8

38. Sibille Y, Reynolds HY (1990) Macrophages and polymorphonuclear neutrophils in lung defense and injury. Am Rev Respir Dis 141:471–501

39. Mizgerd JP (2008) Acute lower respiratory tract infection. N Engl J Med 358:716–727

40. Cazzola M, Matera MG, Pezzuto G (2005) Inflammation—a new therapeutic target in pneumonia. Respiration 72:117–126

41. Wagner HN Jr, Bennett IL Jr, Lasagna L, Cluff LE, Rosenthal MB, Mirick GS (1956) The effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin. Bull Johns Hopkins Hosp 98:e197–e215

42. Chen Y, Li K, Pu H, Wu T (2011) Corticosteroids for pneumonia. Cochrane Database Syst Rev 3:CD007720

43. McHardy VU, Schonell ME (1972) Ampicillin dosage and use of prednisolone in treatment of pneumonia: co-operative controlled trial. Br Med J 4(5840):569–573

44. van Woensel JB, Vyas H; STAR Trial Group (2011) Dexamethasone in children mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus: a randomized controlled trial. Crit Care Med 39:1779–1783

45. Marik P, Kraus P, Sribante J, Havlik I, Lipman J, Johnson DW (1993) Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia. A randomized controlled study. Chest 104:389–392

46. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G et al (2005) Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 171:242–248

47. Mikami K, Suzuki M, Kitagawa H, Kawakami M, Hirota N, Yamaguchi H et al (2007) Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. Lung 185:249–255

48. Snijders D, Daniels JM, de Graaff CS, van der Werf TS, Boersma WG (2010) Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med 181:975–982

49. Fernández-Serrano S, Dorca J, Garcia-Vidal C, Fernández-Sabé N, Carratalà J, Fernández-Agüera A et al (2011) Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. Crit Care 15:R96

50. Meijvis SC, Hardeman H, Remmelts HH, Heijligenberg R, Rijkers GT, van Velzen-Blad H et al (2011) Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet 377:2023–2030

51. Remmelts HH, Meijvis SC, Heijligenberg R, Rijkers GT, Oosterheert JJ, Bos WJ et al. (2012) Biomarkers define the clinical response to dexamethasone in community-acquired pneumonia. J Infect 65:25–31

52. Tamura A, Matsubara K, Tanaka T, Nigami H, Yura K, Fukaya T (2008) Methylprednisolone pulse therapy for refractory *Mycoplasma pneumoniae* pneumonia in children. J Infect 57:223–228

53. Lee KY, Lee HS, Hong JH, Lee MH, Lee JS, Burgner D et al (2006) Role of prednisolone treatment in severe *Mycoplasma pneumoniae* pneumonia in children. Pediatr Pulmonol 41:263–268

54. Weiss AK, Hall M, Lee GE, Kronman MP, Sheffler-Collins S, Shah SS (2011) Adjunct corticosteroids in children hospitalized with community-acquired pneumonia. Pediatrics 127: e255–e263

55. Pugh RJ, Roy N. Systemic corticosteroids in community acquired pneumonia in adults: a systematic review and meta-analysis. Available online at: http://cdn.f1000.com/posters/docs/211027821. Accessed on 30 Jun 2012

56. Zorc JJ, Hall CB (2010) Bronchiolitis: recent evidence on diagnosis and management. Pediatrics 125:342–349

57. Principi N, Baggi E, Esposito S (2012) Prevention of acute otitis media using currently available vaccines. Future Microbiol 7:457–465

58. Coker TR, Chan LS, Newberry SJ, Limbos MA, Suttorp MJ, Shekelle PG et al (2010) Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. JAMA 304:2161–2169

59. Chonmaitree T, Patel JA, Lett-Brown MA, Uchida T, Garofalo R, Owen MJ et al (1994) Virus and bacteria enhance histamine production in middle ear fluids of children with acute otitis media. J Infect Dis 169:1265–1270

60. Chonmaitree T, Patel JA, Sim T, Garofalo R, Uchida T, Sim T, et al (1996) Role of leukotriene B4 and interleukin-8 in acute bacterial and viral otitis media. Ann Otol Rhinol Laryngol 105:968–974

61. Hamaguchi Y, Juhn SK, Sakakura Y (1988) Antiinflammatory effects of a corticosteroid and protease inhibitor agents on antigen-induced otitis media in chinchillas. Am J Otolaryngol 9:142–148

62. Chonmaitree T, Saeed K, Uchida T, Heikkinen T, Baldwin CD, Freeman DH Jr et al (2003) A randomized, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. J Pediatr 143:377–385