Dexamethasone *vs* Placebo in Children having Pneumonia with Pleural Effusion

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SUMMARY

This was a multicenter, randomized, double blind, parallel-group, placebo-controlled clinical trial of 60 children, ranging in age from 1 month to 14 years, with community-acquired pneumonia (CAP) and pleural effusion. Patients received either intravenous dexamethasone (0.25 mg/kg/dose) or placebo every 6 hours over a period of 48 hours, along with antibiotics. The primary endpoint was the time-to-recovery in hours, defined objectively. Compared with placebo recipients, the patients receiving dexamethasone had a shorter time-to-recovery, after adjustment by severity group and stratification by center (HR 1.95; 95% CI 1.10, 3.45; *P*=0.021). The median time-to-recovery for patients receiving dexamethasone was significantly shorter than patients receiving placebo (109 h *vs* 177 h; *P*=0.037). The median time-to-recovery for patients receiving dexamethasone was 76 hours (3.1 days) and 14 hours (0.5 days) shorter than in those receiving placebo, for simple and complicated effusion, respectively. The difference in the effect of dexamethasone in the two severity groups was not statistically significant. There were no significant differences in complications or adverse events attributable to the study drugs, except for hyperglycemia. The authors concluded that dexamethasone seems to be a safe and effective adjunctive therapy for parapneumonic pleural effusion.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Childhood community acquired pneumonia is sometimes complicated by parapneumonic effusion, which usually responds to appropriate antibiotic therapy and supportive care. Traditional text-book teaching suggests that parapneumonic effusions evolve over time and can have three distinct stages *viz* (*i*) initial exudative phase, progressing to (*ii*) fibrinopurulent phase, and later (*iii*) organization phase, over a period of days to weeks [1]. It is believed that the outcome in parapneumonic effusion depends on the time-gap between onset of disease and institution of therapy. Early initiation of appropriate antibiotic(s) may prevent the development of effusion, and if already developed, can restrict the progression to complicated effusion and/or empyema [2]. The only clinical clue to estimate the stage of effusion and start *appropriate* (note emphasis) therapy, is the duration of illness; but unfortunately there is no hard and fast rule for this. Some specialists use pleural ultrasonography to determine the quality and quantity of pleural fluid [3]; however, it is observer- and skill-dependent. Therefore, in general, prompt initiation of antibiotic therapy and a diagnostic pleural tap (to assess the nature of the fluid in terms of physical appearance, cytology, biochemical profile and microbiologic analysis) are the initial steps in management. Against this background, management options that obviate the need for invasive procedures would be very welcome. A recent trial by the CORTEEC Study Group [4] is a step in this direction. The investigators examined whether dexamethasone (I=Intervention) administered along with antibiotics (and standard care), in children with parapneumonic effusion, irrespective of the stage/type (P=population), could be efficacious and safe (O=Outcome), compared to placebo (C=Comparison). ***Table* I** presents a brief summary of the trial.

Critical appraisal: ***Table* II** summarizes a critical appraisal of the randomized controlled trial (RCT), using one of several tools designed for the purpose [5]. The investigators used standard definitions and standard methods in the trial. Therefore, together with the low risk of bias, the trial has high internal validity.

Could anything have been done differently? Duration of hospitalization is a relevant outcome that has been omitted in this trial; although the authors noted that they preferred time-to-recovery because hospitalization length

TABLE I SUMMARY OF THE TRIAL

Study design	Multi-centric, double blind, placebo-controlled, randomized controlled trial (RCT)
Study setting	Tertiary care, teaching hospitals in Spain
Study duration	55 months
Inclusion criteria	Children (1 mo-14 y) admitted for pneumonia (defined as fever >38ºC with cough and chest radiography showing parenchymal lesion) with pleural effusion.
Exclusion criteria	Known drug allergy, immune-deficiency state, contraindications to steroid therapy, and other (unspecified) conditions precluding participation in the study.
Intervention and Comparison groups	The intervention group received intravenous dexamethasone (0.25mg/kg 6 hourly) for 48 hours. The placebo group received a similar volume of normal saline in the same manner. All participants received the study medication within 12 hours of diagnosis; and concomitant with antibiotic therapy (initially cefotaxime, later co-amoxyclav) and ranitidine. Children without complicated effusion were given medical management without a diagnostic pleural tap. The procedure was done only in those with effusion size >10 mm confirmed by ultrasonography. Pleural drainage and fibrinolytic therapy, or video-assisted thoracoscopic surgery (VATS) were reserved for children with complicated effusion. However the criteria for VATS referral are unclear.
Outcomes	*Primary:* Time-to-recovery defined as duration from administration of the first dose of medication, to the fulfillment of recovery criteria (SpO_2 >92%, temperature <37ºC, absence of respiratory distress, oral intake, resolving pneumonia and end of invasive procedures). However, it is unclear how 'resolving pneumonia' was defined. *Secondary*: Disease complications (from enrolment till 30 days post-discharge); Pre-defined adverse events attributable to corticosteroids; Progression to complicated effusion (*i.e.* requirement of pleural drainage); Decline in CRP; Decrease in effusion over the first 3 days
Sample size	Sample size calculation was performed *a priori*, to detect a difference of 1 day for the primary outcome (time-to-recovery) assuming alpha error 5%, beta error 20%, and attrition of 10%. The calculated sample size was 28 in each group.
Data analysis	Intention-to-treat (ITT) analysis was performed. Missing data were handled appropriately. Appropriate statistical methods were used.
Summary of results (Dexamethasone *vs* Placebo)	*Primary outcome*: • Time to recovery (median, CI): 109 (37, 180) *vs* 177 (115, 238) h, $P<0.05$ *Secondary outcomes*: • Disease complications (from enrolment till 30 days post-discharge) * All cause mortality: 3/29 *vs* 4/29 * Pulmonary complications: 2/29 *vs* 1/29 • Adverse events * Any adverse event: 21/29 *vs* 19/29 * Hyperglycemia: 15/29 *vs* 6/29; $P<0.05$ * Anemia: 10/29 *vs* 16/29 * Allergic reaction: 0/29 *vs* 1/29 • Progression of simple effusion requiring pleural drainage: 1/18 *vs* 3/18 • Decline in CRP: Greater decline in dexamethasone group (although the statistically significant result appears to be driven by the children with simple effusion) • Change in effusion size over the first 3 days: No inter-group difference

is determined by other factors than patient well-being. But on the one hand, faster clinical recovery should translate into earlier discharge from hospital, in which case this trial should have been able to demonstrate this benefit (and perhaps consequent benefits to the healthcare system as well). On the other hand, if earlier clinical recovery did not translate to shorter hospitalization (as the authors seem to suggest), the overall benefit to the individual and the healthcare system are diminished.

TABLE II METHODOLOGICAL APPRAISAL OF THE TRIAL

Baseline characteristics of participants	Children in both groups were similar in terms of mean age, gender distribution, and day-care/school attendance. 30% in each group had received prior antibiotics, although duration is not specified.
	Clinical features such as symptom duration, median temperature, oxygen saturation, blood pressure and volume of effusion, were similar in both groups. Over 60% children in each group had received Pneumococcal conjugate vaccine (PCV) and almost all were vaccinated against *H. influenzae* type b.
	There were no significant inter-group differences in the number of children who received pleural drainage. The groups were similar in terms of etiology, type of bacteria, and other organisms identified.
	The table of baseline characteristics does not show the number of children in each group with simple and complicated effusion; although Results section reports 3:2 ratio in each group.
Randomization procedure	Adequate
	Stratified randomization was done (by center and presence of complicated/simple effusion). Complicated effusion was defined as pH<7.20, ultrasonography showing loculations/ septations, or Gram staining showing bacteria. The manufacturer of the study medication generated a 1:1 allocation sequence, using a computer programme. However, the authors certified that the commercial entity had no involvement in the study design, data collection, data analysis, and manuscript preparation.
Allocation concealment	Adequate
	The study medications (dexamethasone or normal saline) were packaged in identical appearing ampoules, and packed in serially numbered boxes designated for each study participant (as per the stratification).
Blinding	Adequate
	Participating children, their caregivers, study investigators and the data manager; were all blinded. Interim analysis (necessitated by the occurrence of two adverse events) was also conducted in a blinded fashion.
Incomplete outcome data	Of the 60 enrolled children, all were accounted for each of the outcomes.
Selective outcome reporting	The outcomes selected were appropriate and there is no apparent selectivity in reporting.
Other sources of bias	No obvious bias
Overall assessment	Low risk of bias

The study showed no significant inter-group difference in the change in effusion size over the first three days despite shorter time-to-recovery. This seems strange, considering that the mean duration to recovery was 4.5 days in the dexamethasone arm. The reason for this is unclear. Either three days are too short to expect recovery, or the time-to-recovery parameter does not correlate with the size of effusion.

Interestingly, the inter-group time-to-recovery was not different among the children having complicated effusion, suggesting that corticosteroids are unable to work when the pleural fluid becomes infected, or thicker. This is an important observation because many children present much later (than the mean duration of 3-4 days in this study), in which case steroid therapy appears to be ineffective.

Although underpowered, the primary outcome appeared to be significantly shorter with dexamethasone, among children who had received prior antibiotics, reiterating that control of infection remains the mainstay of management in parapneumonic effusion.

The relative safety of steroid therapy in this trial [4] must be viewed in the context that the frequency of serious adverse reactions is generally much lower than what can be detected in a trial with 60 children. Only larger trials, and/or post-practice surveillance reports can identify issues with safety.

In this study, 60% children in the treatment arm and 73% in the control arm had received at least 3 doses of pneumococcal conjugate vaccine. Despite this, the etiology was attributed to Pneumococcus in16% and 36%, respectively. It is unclear how many of the vaccinated

children developed pneumococcal infection, and whether this proportion mirrors the community incidence in a highly-vaccinated cohort, but it provides food for thought for settings that are initiating pneumococcal vaccination. *Extendibility:* There are several issues that make the trial results inappropriate for extrapolation to India. The majority of children with parapneumonic effusion present much later than the children in this study, by which time, the critical 'window period' where steroids could be effective, has elapsed. Perhaps this is why, most children appear to have at least stage 2 or 3 disease. Further, majority of Indian data suggest that *Staphylococcus aureus* is the predominant organism recovered from the pleural fluid (although most studies focused on empyema rather than parapneumonic effusion).

It may be pertinent to review the efficacy of steroids in other infective clinical conditions associated with effusion. A systematic review of steroid therapy in tubercular pleural effusion [6] suggested efficacy in terms of shorter time-to-resolution and reduced complications such as pleural thickening or adhesions, but higher incidence of adverse events. Similarly, in tubercular meningitis, corticosteroids reduce mortality [7]. In contrast, in bacterial meningitis, dexamethasone does not appear to reduce mortality or significant neurological sequelae (except hearing loss, and that too in resource-rich settings) [8,9]. However, very low-quality evidence among neonates suggests that mortality may be reduced [10]. These data merely suggest that this single well-designed trial [4] may be insufficient to change clinical practice even in the same or similar settings.

Conclusion: This well-designed RCT suggests that steroid therapy administered in the very early phase of parapneumonic effusion (in addition to antibiotics) enhances recovery; there is no significant benefit in later stages of effusion.

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Contemporary Researcher's Viewpoint

Pneumonia, being one of the leading cause of morbidity and mortality in India, has culminated in the introducton of the pneumococcal vaccine in select five high-burden states in recent times as a part of the Universal immunization program [1]. Though parapneumonic effusions (PPE) and empyema are rare, studies from across the globe have shown that there is an increasing trend in PPE and empyema with higher treatment failure after chest tube drainage [2,3]. Till date most of the literature and guidelines surrounding PPE have centered around antibiotics, percutaneous or intracostal chest tube drainage (CTD), intra-pleural fibrinolytics, thoracotomy and decortication [4]. However, the morbidity associated with these modalities is high along with the time taken for recovery and overall expenses due to hospital stay, drug cost and loss of work. Our own experience has shown that in spite of the best of care, antibiotic use and CTD, a number of patients do need decortication and quite a few parents would refuse a major surgical procedure [5]. Therefore the current study is not only interesting but also eye catching as it appears to be like a beacon of hope and an important link in the existing treatment modalities offered for PPE. The scientific basis of reducing the inflammatory process by using corticosteroids has shown promising results in this study. A reduction of the inflammation – and therefore halting the progression of the simple effusion to the stage of empyema – can not only reduce the duration of stay significantly by 76 hours, and hence the cost, but also prevent the need for the more costly modes of therapy like intrapleural fibrinolytics,

CTD and decortication. Though the same effect could not be demonstrated in the complicated effusions, this could be because of small numbers, and can be validated in a larger study. Clinicians are always sceptical about the adverse effects of steroids but the study has demonstrated that short course dexamethasone can be safely used with good monitoring, and the benefits appear to outweigh the risks. Applying the findings of this study could make a significant difference to the way PPE could be managed in the future by clinicians at all levels of care, especially in high-burden countries like India, and with limited resources as far as availability of drug or clinical expertise beyond the tertiary care centers is concerned.

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Pediatric Pulmonologist's Viewpoint

In order to understand the impact of current paper, we shall try to find answers through a logical framework. The need for corticosteroids as adjunctive therapy for managing pneumonia with parapneumonic effusions can be justified if it leads to faster recovery of serious symptoms like breathlessness (due to mechanical effect of excessive fluid), prevents progression to acute lung injury, decreases occurrence of septic shock and consequent mortality, and decreases the hospital stay without increasing any complications. The inherent risk and hurdle in the use of steroids is the likely progression of illness due to ongoing infection, which may not be adequately covered by the antibiotics being used as primary treatment. In countries like India, which have variable and often significant level of resistance to commonly used antibiotics, adjunctive steroid therapy may be deleterious. Most of the existing and limited literature on adjunctive use of steroids in pneumonia has been aimed at adult patients with community-acquired pneumonia [1,2]. A study among adults with pneumonia and high inflammatory response showed a lower failure rate with adjunctive steroid therapy, and the authors concluded that their results needs to be confirmed further due to lack of power in their study [2]. There are not many studies done among children.

Another set of studies have reported benefits of concurrent use of steroids with macrolides among patients with non-responding *Mycoplasma pneumoniae* pneumonia [3,4]. In a small study from China, concomitant use of steroids and macrolides in refractory cases of PCR-confirmed mycoplasma pneumonia among children, defined as persistent fever or deterioration after 7 days therapy with macrolides, resulted in faster clinical and radiological resolution of symptoms [3,4]. The results have not been replicated elsewhere.

There are not many studies on the role of concomitant use of steroids and antibiotics in pneumonia with parapneumonic effusion. The present study has shown that adjunctive steroid usage helps in faster symptom resolution though it does not report any difference in duration of treatment. The resolution was faster by about 3 days in those with simple effusion and by about 14 hours in those with complicated effusions. The complications like pneumothorax and necrotizing pneumonia were similar in both treatment groups. The authors also do not report any significant side effects other than mild and transient hyperglycemia, but one child, who was later found to be a unrecognized pre-diabetic, required insulin therapy. While the baseline characteristics were similar in the two groups, there were more patients with bacteriological etiology in the control arm as compared to the intervention arm, which might have impacted the outcome given the small sample size.

Should this study prompt us to change our practice for all our complicated pneumonia cases? The study being from a different milieu – with many viral pneumonia cases with parapneumonic effusion – cannot be considered to be reflective of our situations. It has not shown a clinically significant benefit in complicated effusions. Further, steroids are hypothesized to help by culminating the increased injury due to the cytokine storm associated with infections. It still needs to be established, whether this benefit shall be seen as well in communities with high prevalence of malnutrition as children with severe

malnutrition are usually not able to raise fierce inflammatory reaction.

In summary, while the study brings up an area for further exploration for the use of steroids in a subset of complicated pneumonia in children, it does not generate enough confidence for changing our practices for the present. It undoubtedly raises a possibility that there may be subsets of patients, as yet not well understood, who may benefit from adjunctive steroid therapy, and challenges us to explore further to identify and establish these potential beneficiaries.

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Pediatrician's Viewpoint

This study by Tagarro, *et al.* concluded that in patients with parapneumonic pleural effusion (PPE), addition of dexamethasone (DXM) as adjunct resulted in earlier recovery by 3.1 days in simple effusion and 14 hours in complicated effusion when compared with placebo. As the simple effusion accounted for 60% of the patients and significant recovery occurred only in this group, these results cannot be extrapolated to the entire PPE.

The present study had chosen the median time-to-recovery, after defining the recovery criteria as the primary endpoint in contradiction to 'length of hospital stay', as adopted by many studies [1]. Though the recovery was earlier by 3 days in the DXM group of simple effusion, the patients in this group were subjected for monitoring of their glycemic status to prevent hyperglycemia. These investigations are unnecessary burden to the resources. The study identified variety of microorganisms. The inflammatory cytokines produced by the host in response to these organisms might be specific and protective in nature. Suppressing the host response may not be appropriate except in situations like bacterial meningitis [2].

The authors used an accumulated dose of 2 mg/kg in all the 56 children ranging from 1 month to 14 years of age, and this dosage uniformity could lead to more adverse effects in the infants. Though the study findings appear to reduce the duration of stay in hospital, until larger trials are conducted on this subject, let the existing management protocol of PPE be continued.

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