

Should Children with Parapneumonic Effusions Receive Steroids?

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The short answer is no, but it takes some careful consideration of this randomized, placebo controlled, double-blind study to come to that conclusion.

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This was a pretty carefully designed study that serves all the more to point out how difficult it is to find definitive answers for treatment decisions. A group of investigators at 9 hospitals in Spain enrolled 60 hospitalized children with pneumonia and effusion, randomized to receive either dexamethasone or placebo for 48 hours, with the main outcome of interest as time to recovery. They found a pretty remarkable difference: children in the dexamethasone group achieved recovery almost 3 days sooner than the placebo group, and that difference was statistically significant. They also found no concerns regarding complications or adverse events when comparing the groups, although 1 child in the steroid group required insulin therapy for hyperglycemia. Let's look a little closer at a few features of the report.

1. What does recovery mean? For this study, 6 criteria needed to be met: a) continuous oxygen saturation of at least 92% while on room air; b) "continuous" temperature less than 37 C; c) no respiratory distress (no tachypnea by World Health Organization criteria and no retractions); d) no further invasive procedures, such as chest tube; e) resolving pneumonia on radiograph; and f) oral feeding. I was a little puzzled by the part about temperature, I'm not sure if these children had temperatures recorded continuously, and I also wonder why they chose a cutoff less than 37 C, since it would seem to me that many children might have normal temperatures slightly above this point. Overall, it's not surprising to me that children receiving steroids would meet the above recovery criteria sooner than placebo, but it could just be "cosmetic" (afebrile children are

less tachypneic and feel more like eating), rather than a true effect on the disease process. Still, the endpoint measurements are mostly straightforward, except for the radiograph readings, so they would be less prone to bias even if the study were not double-blinded.

2. Which brings me to my second point: is this study really double-blinded? The investigators explain their blinding procedure very well in the supplemental material supplied online. **My past experience** with a placebo-controlled, double-blinded steroid study of bacterial meningitis helps me here. Dexamethasone is a powerful antipyretic, especially at the doses used here. It would be difficult for an experienced clinician not to suspect a child was randomized to the steroid group when (s)he has a very short duration of fever. Also, fever might rebound when the steroid is stopped, but it isn't clear to me how long the patients in the study were monitored after recovery was declared. In the meningitis study mentioned above (which I helped design, so bear part of the blame), I was able to correctly guess which of my patients were receiving dexamethasone, based on fever patterns. I verified this when the randomization code was revealed at the end of the study. I now use this study as an example of pitfalls and nuances of study blinding.

3. How generalizable is this pneumonia study? The investigators needed 5 years and 9 centers to enroll 60 patients. That's a long time to continue a complex multicenter study, it invites errors in enrollment and protocol violations since no single study is enrolling patients very often. For example, the most enrolled in 1 year by 1 hospital was 8, in the first year of the study, and that hospital enrolled only 6 more in the ensuing 4 years. I would have liked to have seen more information from the authors about how many patients had missing data, such as pleural fluid pH and the like.

Also in the generalizability arena, a large number of these patients likely had mild viral pneumonia with simple pleural effusion. In fact, a subgroup analysis suggested that most of the benefit of dexamethasone was in this group. Only 22 of the 60 children had typical bacterial etiologies confirmed. Which leads me to

4. Is this a mixed bag of patients? Clearly the answer is yes, though it does reflect all comers with pneumonia and effusion, most of whom are likely viral. I'm most interested, however, in the bacterial pneumonia patients, and here we are limited mainly to pneumococcal pneumonia, with the addition of 4 children with *S. pyogenes* and 1 with *S. aureus* infection.

I need to see larger numbers of patients with proven pneumonia etiologies to understand whether dexamethasone can make a difference in the more severe cases. Unfortunately, these researchers needed a long time to enroll just 22 bacterial pneumonia patients, which doesn't bode well for others attempting to validate their results.

At this point, I'm not planning to use dexamethasone routinely for children with parapneumonic effusions.

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