Cross Canada Round

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ORIGINAL ARTICLES

Dexamethasone for Parapneumonic Pleural Effusion: A Randomized, Double-Blind, Clinical Trial

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Corticoids for Pleural Effusion and Empyema (CORTEEC) Study

J Pediatr. 2017;185:117-123.e6. doi:10.1016/j.jpeds.2017.02.043.

Outline

- Background
- Hypothesis
- The study:
  - Methods
  - Results
  - Author's conclusion
- Critical appraisal
- Discussion

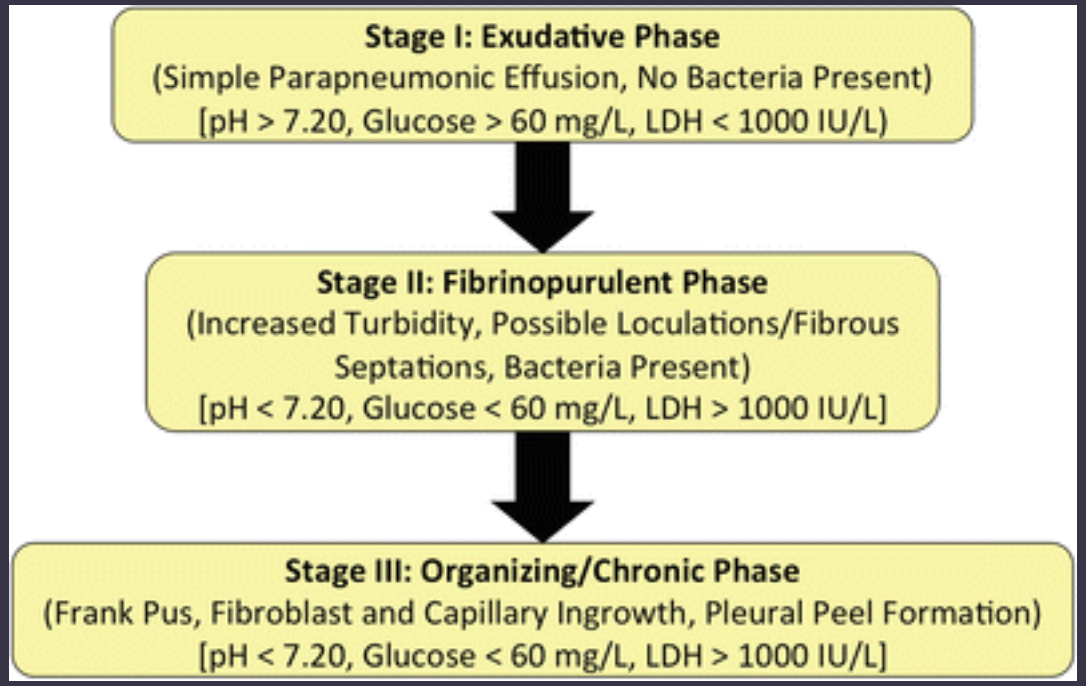
Background

- The incidence of parapneumonic effusions and empyema has been reported to be up to 10 per 100,000 children in the United States
- The most common cause of parapneumonic effusion and empyema is bacterial pneumonia
- The process of pleural fluid accumulation is mediated by increased vascular permeability secondary to mesothelial cell cytokines including IL-1, IL-6, IL-8, TNF-a, and platelet activating factor

Kendig's Disorders of the Respiratory Tract in Children, 9th Edition. Ch 69 Air and Fluid in the Plural space

- Exudative:
  - Accumulation of clear fluid with a low WBC count (simple effusion).
- Fibropurulent:
  - Deposition of fibrin leading to septation and the formation of loculations.
  - There is an increase in white cells, fluid thickening (complicated effusion)
  - Eventually becomes overt pus (empyema).
  -
- Organisational:
  - Fibroblasts infiltrate the pleural cavity, and the thin intrapleural membranes are reorganised to become thick and non-elastic.

Balfour-Lynn IM, Abrahamson E, Cohen G, et al. BTS guidelines for the management of pleural infection in children. *Thorax*. 2005;60(SUPPL. 1):1-22.



https://thoracickey.com/pleural-disorders/#Fig4

Hypothesis

- Corticosteroids block inflammatory cytokines that are key factors in the first, exudative stage of pleural effusion.
- Some trials have suggested that corticosteroids shorten the time to clinical stability when added to antibiotic treatment in immunocompetent adults with CAP
- Hypothesized that the concomitant treatment of antimicrobials and early administration of dexamethasone (DXM) would be beneficial in parapneumonic pleural effusion

Methods

- Multicenter, double-blind, parallel-group, placebo-controlled clinical trial

- Conducted in Spain at 9 urban university-affiliated public hospitals over a period of 55 months

PICO

- Inclusion criteria:
  - Hospitalized children, 1month to 14 years with CAP and pleural effusion.
  - CAP: fever > 38 °C, cough, and parenchymal infiltrate on chest radiography
- Exclusion criteria:
  - Proven allergies to any study drugs
  - Immunodeficiency
  - Any concomitant disease likely to worsen with corticosteroid treatment
  - Any condition that prevented participation in the study

- Randomization was stratified by center and severity of disease

Table I. Criteria for severity stratification[3]

Criteria	Complicated effusion	Simple effusion
pH of pleural fluid	<7.2	≥7.2
Echogenic features	Loculations or septations	Free-flowing fluid with no septations or loculations
Gram	Presence of bacteria	No bacteria

Fulfillment of only 1 criterion for complicated effusion was sufficient to place a patient in the complicated effusion stratum. Patients with <10 mm of free fluid on the ultrasound who did not undergo thoracentesis were classified as having simple effusion.

PICO

- Intervention group:
  - 8 IV doses of DXM, 0.25 mg/kg every 6 hours (2 mg/kg accumulated dose)
- Control group:
  - Identical volume of 0.9 NS
- Both groups:
  - DXM or placebo was administered immediately after the first dose of cefotaxime (within 12 hours of diagnosis)
  - Ranitidine (5 mg/kg/day intravenously in 2 doses over 48 hours)
  - Cefotaxime was continued until 48 hours after the patient was afebrile, then switched to amoxicillin-clavulanate to complete the 15-days

- Drainage:
  - Patients with simple effusion received only medical treatment.
  - Diagnostic thoracentesis was recommended if effusion was > 10 mm on US.
  - If biochemical data indicating complicated effusion were found, appropriate drainage was recommended.
  - The recommended management for complicated effusion was medical treatment plus pleural drainage and fibrinolytics, or VATS.
  - A conservative approach without drainage was permitted at the discretion of the clinician

PICO

- Primary outcome:
  - time to recovery, measured in hours

Table III. Recovery criteria

Recovery criteria
Temperature <37 °C*
Ambient SaO_2 >92%*
No respiratory distress (no tachypnea†, no retractions)
End of invasive procedures (pleural drainage, VATS)
Pneumonia in resolution‡
Oral feeding

*The last recovery criterion fulfilled was <37°C temperature in 52 patients (86%) and ambient SaO_2 >92% in 4 patients (6%).
†Tachypnea according to age was defined by World Health Organization standards.
‡Defined by a smaller lung infiltrate compared with the infiltrate in the first X-ray.

PICO

- Secondary outcomes:
  - Safety:
    - complications of disease from the moment of hospitalization until day 30 post d/c
    - adverse events attributable to corticosteroids during hospitalization
  - Progression to complicated effusion requiring chest drainage
  - CRP level
  - Decreased effusion during days 1-3.

Table IV. Prespecified complications of disease

Complications
All-cause mortality
Pneumothorax
Necrotizing pneumonia
Children with initial simple effusion who eventually underwent pleural drainage or surgery

Table V. Prespecified adverse events attributable to steroids

Adverse events
Hyperglycemia >126 mg/dL*
Mild (126-140 mg/dL)
Moderate (140-200 mg/dL)
Severe (>200 mg/dL)
Need of insulin
Upper gastrointestinal bleeding
Anemia (decreased hemoglobin)
Mild (⊿Hb <1 g/L from day 1 to day 3)
Moderate (⊿Hb 1-3 g/L from day 1 to day 3)
Severe (⊿Hb >3 g/L from day 1 to day 3)
Transfusion
Oropharyngeal candidiasis
Allergic reaction, rash
Other

Glycemia was checked once a day on days 1, 2, and 3 of treatment.
*One measurement >126 mg/dL was sufficient to label the event as adverse event.

- Statistical considerations:
  - A sample size of 56 patients (28 patients per group) were needed to detect a reduction in time to recovery of ≥ 24 hours (assuming an SD of 31 hours, 80% power, a 2-sided a level of 5%, and a 10% dropout rate).
  - The SD was obtained from a small observational pilot study, where we observed an SD of 31 hours in time to recovery in children treated with steroids who had a pleural effusion

Results

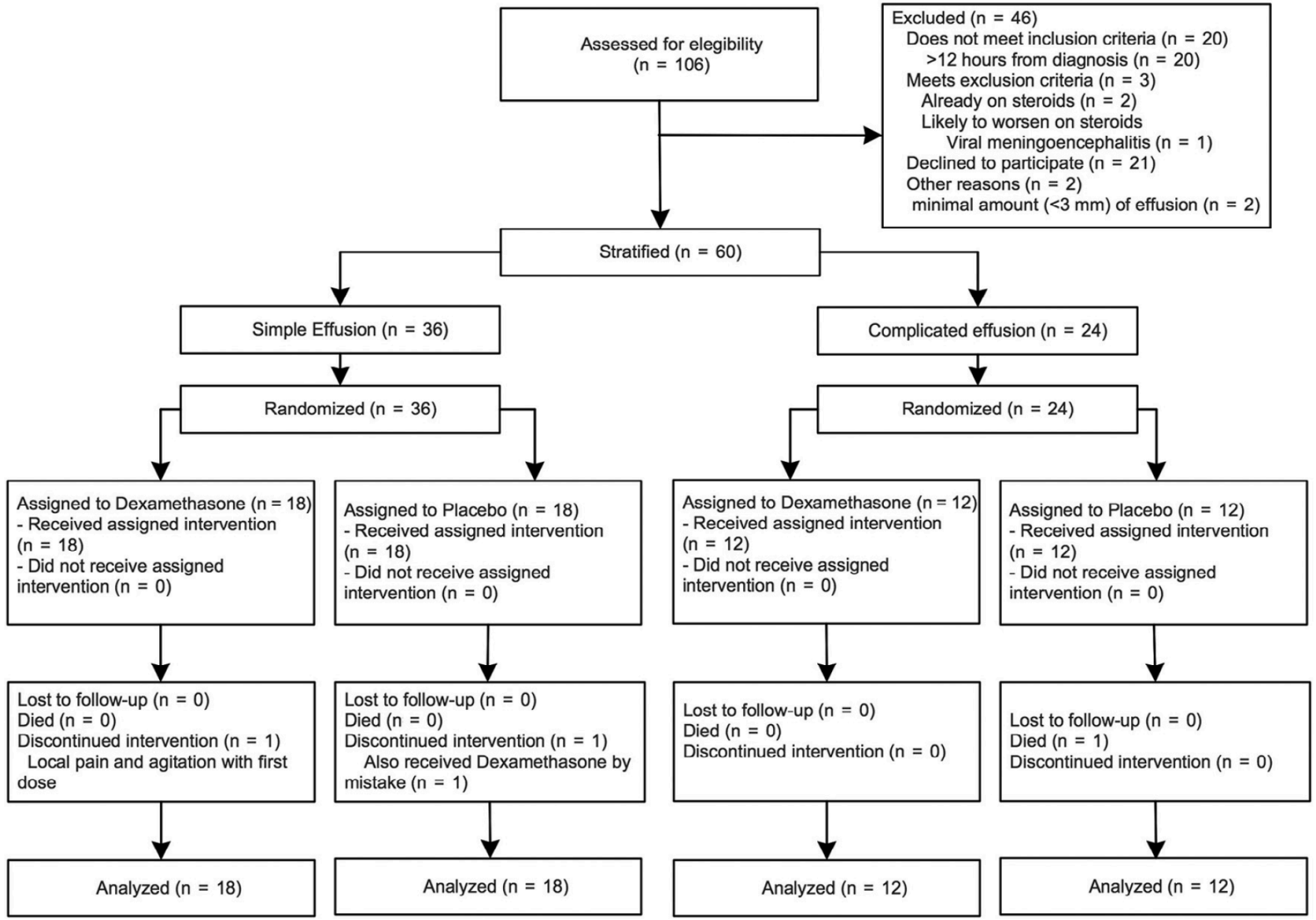


Figure 1. Enrollment, randomization, and follow-up in the trial.

Table II. Patient recruitment according to centers and years

Centers	2011	2012	2013	2014	2015	Total
University Hospital Infanta Sofía	8	0	1	4	1	14
University Hospital Ramón y Cajal	3	4	0	5	0	12
Hospital Universitario La Paz	5	1	2	1	0	9
University Hospital Gregorio Marañón	2	1	0	0	1	4
University Hospital Toledo	3	0	1	1	0	5
University Hospital Getafe	4	0	0	0	0	4
University Hospital Príncipe de Asturias	1	2	1	0	1	5
University Hospital Carlos Haya	4	0	0	0	0	4
University Hospital 12 de Octubre	0	0	0	3	0	3
Total	30	8	5	14	3	60

Table VI. Baseline patient characteristics, according to treatment group

Variables	DXM (n = 30)	Placebo (n = 30)
Age, y, mean ± SD	4.6 ± 4.2	4.8 ± 5.5
Sex, n (%)		
Males	13 (43)	12 (40)
Females	17 (56)	18 (60)
Underlying disease, n (%)	13 (43)	11 (36)
Asthma	4 (13)	5 (16)
Overweight	3 (10)	5 (16)
Neurologic disease	1 (3)	1 (3)
Celiac disease	1 (1)	0 (0)
Atopy	3 (10)	1 (3)
Previous antibiotics, n (%)	9 (30)	9 (30)
Oral antibiotics	4 (13)	3 (10)
Intravenous antibiotics	8 (26)	7 (23)
Daycare or school, n (%)	29 (96)	24 (80)
≥3 doses of PCV7, n (%)	14 (46)	19 (63)
≥3 doses of PCV13, n (%)	4 (13)	3 (10)
Influenza immunization, n (%)	1 (3)	3 (10)
H influenzae type B immunization, n (%)	29 (96)	29 (96)
Duration of symptoms before randomization, d, mean ±SD	3.7 ± 2.5	4.0 ± 2.5
Temperature, °C, median (IQR)	39 (1)	39 (1.4)
SaO_2 <92%, n (%)	2 (6.6)	2 (6.6)
Systolic arterial pressure, mm Hg, mean ± SD	107 ± 12	107 ± 12
Diastolic arterial pressure, mm Hg, mean ± SD	59 ± 10	66 ± 7
Effusion amount, n (%)		
<1 cm	18 (60)	16 (53)
>1 cm to 1/3 of hemithorax	9 (30)	12 (40)
>1/3 of hemithorax	3 (10)	2 (6)
Distance from chest wall, cm, median (IQR)	0.8 (0.8)	1.2 (1.5)
Thoracentesis at entry, n (%)	9 (30)	14 (46)
VATS, n (%)		
At entry (<24 h)	2 (6)	0 (0)
Delayed (>24 h)	2 (6)	1 (3)
Chest tube, n (%)	9 (30)	12 (40)
Confirmed etiology*, n (%)		
Typical bacteria identified†	8 (26)	14 (46)
S pneumoniae	5 (16)	11 (36)
S pyogenes	3 (10)	1 (3)
S aureus	0 (0)	1 (3)
Anaerobic, gram-negative bacilli	0 (0)	1 (3)
Unknown viral, other‡	22 (74)	16 (54)
M pneumoniae	4 (13)	1 (3)
C pneumoniae	1 (3)	0 (0)
Tuberculosis	0 (0)	1 (3)
Viral (influenza, adenovirus, metapneumovirus)	3 (10)	1 (3)
Not established	17 (56)	13 (43)

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Delayed (>24 h)	2 (6)	1 (3)
Chest tube, n (%)	9 (30)	12 (40)

Table VII. Time to recovery (primary endpoint)

Characteristics	Placebo	DXM	*P* value
Total			
No. of patients	30	30	
Duration, h, median (95% CI)	177 (115-238)	109 (37-180)	.037*
HR (95% CI)	1	1.95 (1.10-3.45)	.021†
Simple effusion			
No. of patients	18	18	
Duration, h, median (95% CI)	124 (49-198)	48 (35-60)	.017
Complicated effusion			
No. of patients	12	12	
Duration, h, median (95% CI)	240 (129-350)	226 (187-265)	.66

*Log-rank test.
†Cox HR.

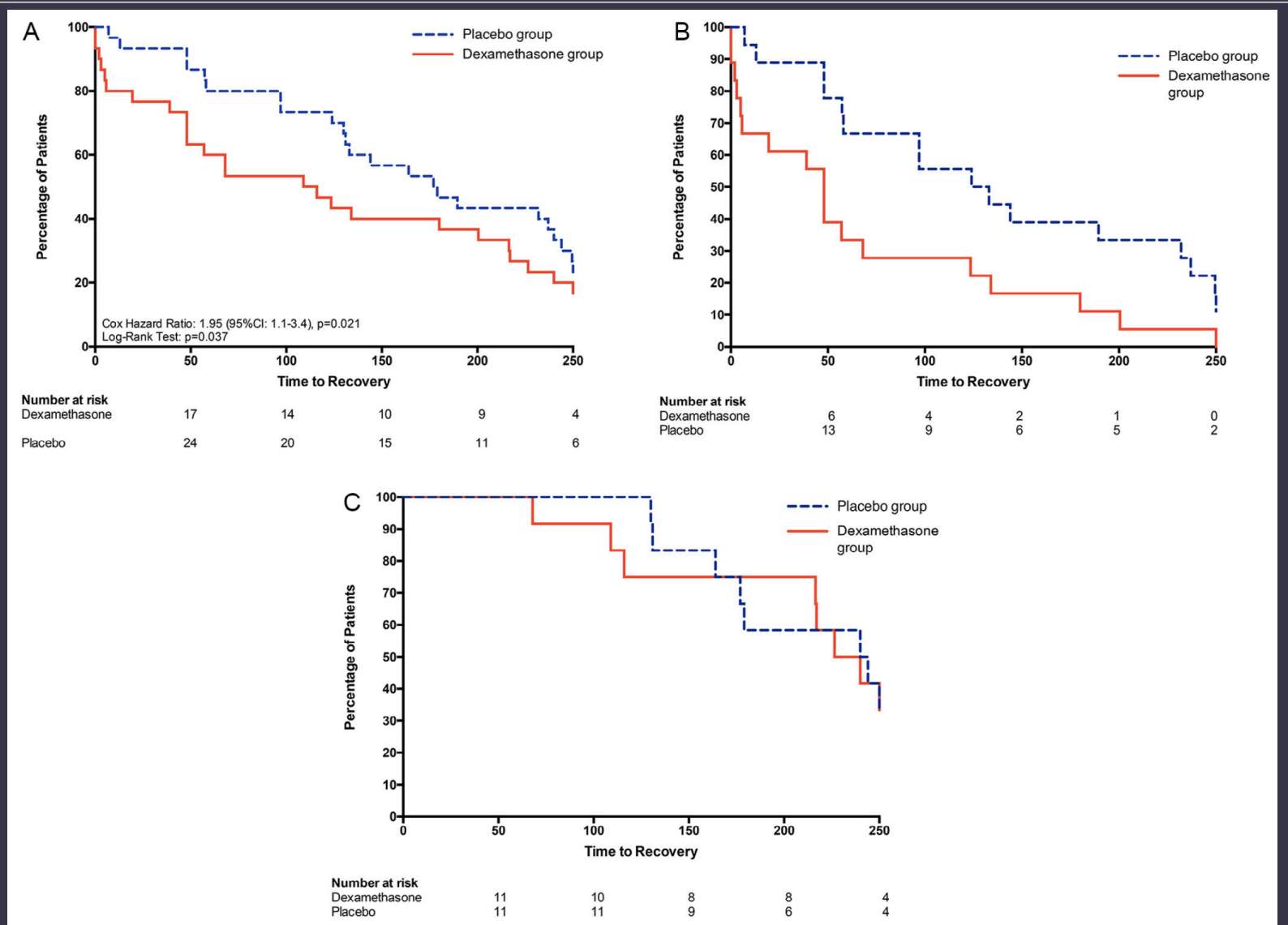

Figure 2. Kaplan-Meier analysis of the effect of DXM on time to recovery. **A,** All enrolled patients. The patient who died was censored on the day of death (608 hours). **B,** Patients with simple pleural effusion. **C,** Patients with complicated pleural effusion.

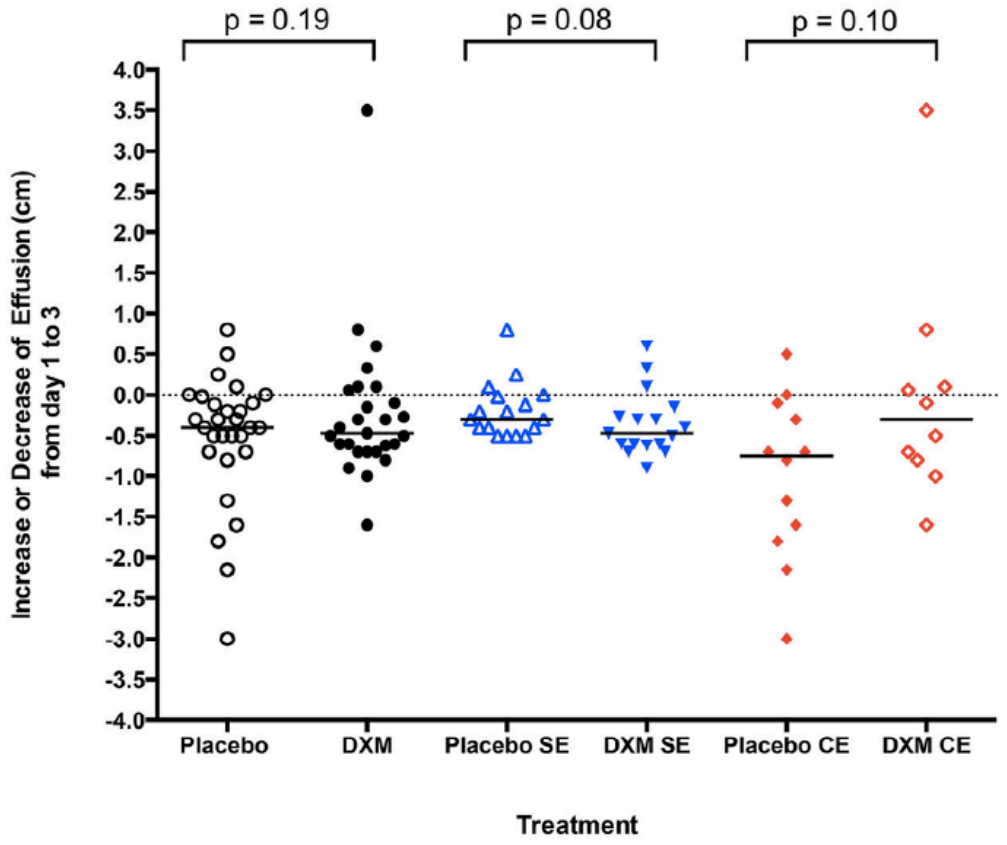

Figure 4. Difference of pleural effusion from day 1 to day 3 according to treatment group—placebo and dexamethasone (DXM)—and stratified according to severity group—simple effusion (SE) and complicated effusion (CE).

Table X. Complications and adverse events attributable to study treatment, according to severity and type (per-protocol analysis)

Complications and adverse events	DXM (n = 30), n (%)	Placebo (n = 30), n (%)	Risk ratio (95% CI)	*P* value
All participants				
Any complication	3 (10)	4 (13)	0.7 (0.1-3.0)	.68
All-cause mortality	0 (0)	1 (3)	N/A	N/A
Pulmonary complications	3 (10)	4 (13)	0.7 (0.1-3.0)	.68
Pneumothorax	2 (6)	1 (3)	2 (0.1-24)	.56
Necrotizing pneumonia	2 (6)	3 (10)	0.6 (0.1-4.5)	.64
Any adverse event attributable to the study drug	22 (73)	19 (63)	1.5 (0.5-4.7)	.40
Hyperglycemia	15 (50)	6 (20)	2.5 (1.2-5.5)	.02
Mild (126-140 mg/dL)	6 (20)	4 (13)	1.6 (0.4-6.4)	.49
Moderate (140-200 mg/dL)	7 (23)	3 (10)	2.7 (0.6-11.8)	.17
Severe (>200 mg/dL)	2 (6)	0 (0)	N/A	N/A
Need for insulin	1 (3)	0 (0)	N/A	N/A
Upper gastrointestinal bleeding	0 (0)	0 (0)	N/A	N/A
Anemia	10 (34)	16 (55)	0.4 (0.1-1.2)	.12
Mild (⊿Hb <1 g/L from day 1 to day 3)	6 (20)	7 (24)	0.8 (0.3-2.8)	.75
Moderate (⊿Hb 1-3 g/L from day 1 to day 3)	3 (10)	3 (10)	1 (0.1-5.4)	1
Severe (⊿Hb >3 g/L from day 1 to day 3)	1 (3)	6 (20)	0.1 (0.02-1.3)	.08
Transfusion	1 (3)	3 (10)	0.3 (0.03-3.1)	.32
Oropharyngeal candidiasis	0 (0)	0 (0)	N/A	N/A
Allergic reaction, rash	0 (0)	1 (3)	N/A	N/A
Other				
Local pain, agitation	1 (3)	0 (0)	N/A	N/A
Simple effusion				
Children with simple effusion who eventually underwent pleural drainage	1/18 (5)	3/18 (16)	0.2 (0.02-3.1)	.31

Author's conclusion

- This trial, DXM appeared to be a safe and effective adjunctive therapy for decreasing the time to recovery in children with parapneumonic pleural infection.
- This trial provides a basis for a larger and definitive trial that should be powered to confirm the findings and determine whether DXM performs equally or differently across the severity groups.
- Future trials should demonstrate the effect of DXM on the long-term complications of parapneumonic pleural effusion.

Critical appraisal

- Study Question
- Population identification
- Selection bias
- Were the groups similar at the start of the trial?

- Aside from the allocated treatment, were groups treated equally?
- Were all patients who entered the trial accounted for?
- Were the patients and clinicians kept “blind” to which treatment was being received?

- Results:
  - How precise was the estimate of the treatment effect?
    - Primary outcome definition
  - How large was the treatment effect?
    - A mean of 3 days seem to be a significant duration clinically but the CI is up to 7.7 days (mean for placebo is 7 days)

- Will the results help me in caring for my patient?
  - First RCT, small number
  - The effect is mostly seen in simple rather than complicated effusion
  - Only 1/3 of patients had a chest tube inserted at presentation
  - Time to hospital discharge not reported
  - Is n of 60 enough to study acute side effects ?
  - Long term side effects not studied

- The short answer is no
- What does recovery mean? Steroid is a strong antipyratic -> afebrile children are less tachypneic, better appetite.
- Is this study really double-blinded ? It would be difficult for an experienced clinician not to suspect a child was randomized to the steroid group
- In the meningitis study "I was able to correctly guess which of my patients were receiving dexamethasone, based on fever patterns"
- 5 years and 9 centers to enroll 60 patients is 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
- Is this a mixed bag of patients? A large number of these patients likely had mild viral pneumonia with simple pleural effusion

Questions ?

Comments ?