**Chest hyperinflation and response to corticosteroids and inhaled adrenaline in children with bronchiolitis admitted to intensive care**

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**Introduction**

The DAB study was a pragmatic, randomised study of corticosteroids and nebulised adrenaline in children with bronchiolitis admitted to intensive care. [1] It showed that, compared to standard care alone, the combination of steroids and nebulised adrenaline reduced the duration of positive pressure respiratory support (PPS). The evidence was particularly strong in the sickest children requiring, continuous positive airway pressure (CPAP) and mechanical ventilation (MV), and those who had Respiratory Syncytial Virus (RSV) infection.

Chest hyperinflation is a common clinical sign in children with severe bronchiolitis. It occurs because of lower airway obstruction during expiration and subsequent gas trapping in the lung. Chest hyperinflation can be identified clinically but it is also a chest x-ray finding with varying severity. Chest x-ray findings include, flattened hemidiaphragms, an increased number of rib markings and widened intercostal spaces. Children with bronchiolitis and hyperinflation may be more responsive to the bronchodilator effects of combination corticosteroid and adrenaline therapy compared to those without hyperinflation. Moreover, hyperinflation may be associated with RSV infection, and the presence of hyperinflation in this group may explain the strong effect of steroids and adrenaline. We hypothesise that the degree of hyperinflation predicts the response to steroids and adrenaline on duration of PPS in children with bronchiolitis. We also hypothesise that hyperinflation is associated with the presence of RSV infection.

The primary aim of this study is to investigate whether chest hyperinflation, based on x-ray findings, predicts the response to corticosteroids and inhaled adrenaline on the duration of PPS in children enrolled in the DAB study. The secondary aims are to investigate whether chest hyperinflation predicts the presence of RSV and human metapneumovirus or other viruses, and to assess the concordance between radiologists of their assessment of the degree of hyperinflation.

**Methodology**

A study will be performed using prospectively collected data from children enrolled in the DAB trial. The trial was conducted between 2014 and 2019 in 211 children admitted to four intensive care units in Australia and New Zealand. For this current study, children who were enrolled in the DAB trial and had a chest x-ray performed within 24 hours prior to enrolment will be eligible; if no chest x-ray is available before enrolment, the first x-ray after enrolment will be used but marked as post-enrolment. The time from the chest x-ray to enrolment will be recorded. Chest x-rays that were performed during routine clinical care, immediately prior to enrolment will be analysed for hyperinflation. Children who did not have a chest x-ray performed will be excluded.

*Radiographic grading of hyperinflation*

A single chest x-ray performed within 24 hours of study enrolment will be assessed for hyperinflation. If multiple images are available, the chest x-ray performed closest to enrolment will be selected for analysis; if no x-ray was taken before enrolment, the first x-ray after enrolment will be used if performed within 2 hours from commencement of the trial.

Three radiologists (one from RCH, Perth Children’s Hospital and Starship Hospital) will grade and score the degree of hyperinflation of all images included in the analysis. All three radiologists will be blinded to each other’s scores and the child’s treatment group and RSV status.

*Definition of hyperinflation*

There are no recognised grading systems for hyperinflation in children with bronchiolitis. Therefore, prior to the main analysis, a scoring tool was developed. (Appendix 1) The scoring tool has eight domains, each scored as none, mild, moderate or severe. The scoring tool will be calibrated between the three radiologists using ten chest x-rays of children with bronchiolitis not included in the main analysis.

The date and time of the image will be recorded and time from enrolment calculated.

*Primary outcome*

1. The relationship between the degree of lung hyperinflation and the effect of corticosteroid-adrenaline treatment on the duration (geometric mean hours) of positive pressure support (PPS) from enrolment until discharge from the intensive care unit, where PPS is defined as high-flow nasal oxygen, nasopharyngeal continuous positive airway pressure (NCPAP) and mechanical ventilation.

*Secondary outcomes*

1. The relationship between the degree of lung hyperinflation and the effect of corticosteroid-adrenaline treatment on the duration of NCPAP plus the duration of mechanical ventilation.
2. The association between lung hyperinflation and RSV infection.
3. The association between lung hyperinflation and infection with any virus.

*Statistical analysis*

The demographic and clinical characteristics will be described using frequencies, proportions and median (interquartile range).

For outcome 1, log-linear regression analysis will be performed to investigate the interaction between lung hyperinflation and the effect of treatment with corticosteroid-adrenaline on the duration of PPS. The analysis will be adjusted for the stratification factors at randomisation (the level of respiratory support, and the presence of chronic lung disease or cyanotic congenital heart disease) with an interaction term for corticosteroid-adrenaline treatment and the degree of lung hyperinflation, and the Stata margins and contrast commands used to determine whether any interaction is uniform across degrees of lung hyperinflation or maximal at mild, moderate or severe lung hyperinflation.

For outcome 2, negative binomial regression adjusted for the stratification variables with robust estimates of variance will be used to investigate the effect of lung hyperinflation and corticosteroids-adrenaline on the duration of CPAP and MV.

For outcomes 1 and 2, for each level of lung hyperinflation, the geometric mean (95% confidence interval) adjusted for the stratification variables will be reported, as well as the median (and interquartile range) duration of PPS, and NCPAP plus mechanical ventilation.

For outcomes 3 and 4, the associations will be assessed using the Mann-Whitney U test and illustrated with bar graphs.

Analyses will be performed to investigate domains within the hyperinflation score that contribute to overall impression of hyperinflation, the linear outcome of duration of PPS and those who received CPAP or mechanical ventilation.

We will investigate the inter-observer agreement of a radiological score of hyperinflation. The inter-observer agreement of the chest x-ray hyperinflation score will be presented in a contingency table of the ordinal rating scale in columns and participants in rows with the number of scores by the raters in each cell. Fleiss’ Kappa will be calculated, and the agreement reported as Coefficient between -1 (absolute disagreement) and 1 (absolute agreement).

*Ethical considerations*

Participant data collected during the DAB study will be used for this analysis. The data will remain de-identified and participant confidentiality will be strictly held in trust by the Principal Investigator, participating investigators, research staff, and the sponsoring institution and their agents.

Chest x-rays from each study site will be identified by local investigators from the hospital radiology imaging system using hospital identifiers; the hospital identifiers will be removed and replaced with the DAB study participant identifier. Images will be stored on password-protected computers at each study site. The radiologists tasked with analysis of the chest x-rays will not have access to identifiable data outside their hospital. All chest x-rays will be graded by all radiologists. Video conferencing between the 3 study sites will occur to enable all reviewers to analyse all images. The data collected will be limited to that required to address the primary and secondary objectives. The radiologists will be blind to the treatment group and the viruses detected.

*Consent*

This study is retrospective in design and will analyse routinely performed clinical data (chest x-rays) and previously collected trial data. No additional data will be sought. There is no additional participant risk. Consent will not be sought in addition to that already obtained for participation in the DAB trial. We will seek a waiver of consent to conduct the study.

*Data management*

Hyperinflation score data will be entered into an Excel spreadsheet and stored with the DAB trial data on a password protected RCH computer. DAB trial data are currently stored on an RCH password-protected computer. Data will be stored for a minimum of 5 years from completion of the study.

**References**

1. Gelbart, B., et al., *Pragmatic Randomized Trial of Corticosteroids and Inhaled Epinephrine for Bronchiolitis in Children in Intensive Care.* J Pediatr, 2022. **244**: p. 17-23 e1.