Pulmonary Hypertension in Children with Down Syndrome Increases the Risk of RSV Infections

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Background

- Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infections in children with Down syndrome (DS) younger than 5 years and significantly contributes to morbidity and mortality worldwide.
- Children with DS are frequently diagnosed with comorbid conditions that increase their risk of severe RSV infections, including congenital heart disease and chronic lung disease.
- Pulmonary hypertension (PH) is a common comorbidity in children with DS (28%) and is a known risk factor for clinically significant RSV infections in the general population.

Objectives

- Determine if a diagnosis of pulmonary hypertension will increase the risk of clinically significant respiratory syncytial virus (RSV) infection in children with Down syndrome.
- Examine if palivizumab (Synagis), a humanized monoclonal antibody against RSV, administration in the first year of life will reduce the amount of clinically significant RSV infections in children with DS who have PH.

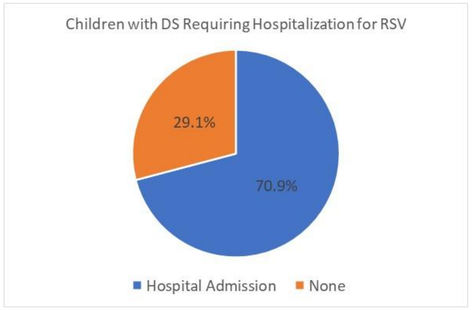
Methods

- We conducted a retrospective review of medical records for 1,252 children with DS, from birth to 21 years of age, representing 88% of children with DS in Colorado.
- Patients were identified from a clinic database and medical charts were reviewed for clinical details including medical comorbidities, PH diagnosis, and RSV testing, hospital and ICU admission, and complications.

Results

RSV Infection: Diagnosis and Severity

- Overall, 15.4% (n=199/1,291) of children with DS had a documented RSV infection.
- Average age at RSV infection was 2.38 years (SD=2.26).
- Most (70.9%) children with DS and RSV required a related hospital admission with an average length of stay of 9.24 days (SD=19.49); 13.1% required ICU admission.
  - 27.0% of children required oxygen support during their hospital stay, and 8.5% needed mechanical ventilation.



- Overall, 13.1% of children with DS had more than one episode of RSV
  - On average, the second diagnosis occurred at 4.95 years with a hospital stay of 9.40 days.

Factors that Increase Risk of Acquiring RSV in Children with DS

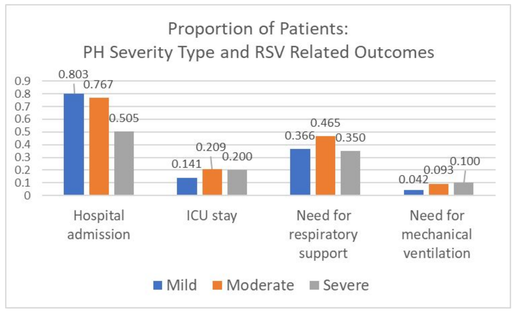
Potential risk factors for acquiring significant RSV include aspiration, obstructive sleep apnea, congenital heart disease (CHD), recurrent pneumonia, feeding problems, and PH. Risk ratios for RSV in children with DS are outlined in Table 1.

Table 1 Comorbidities/factors as risk for RSV in Children with Down syndrome (DS)

Results	No. (%) of Patients with RSV: DS With Comorbidity	DS Without Comorbidity	Risk Ratio (95% Confidence Interval)	Significance Level
Pulmonary hypertension	125 (33.9%)	48 (5.4%)	6.323 (4.638 to 8.621)	p < 0.001
Congenital heart disease	192 (18.0%)	7 (3.1%)	5.758 (2.747 to 12.072)	p < 0.001
Recurrent pneumonia	102 (33.4%)	97 (9.8%)	3.399 (2.657 to 4.350)	p < 0.001
Aspiration	46 (33.8%)	153 (13.2%)	2.553 (1.934 to 3.370)	p < 0.001
Obstructive sleep apnea	72 (24.8%)	127 (12.7%)	1.957 (1.512 to 2.533)	p < 0.001
Feeding problem	87 (23.3%)	112 (12.2%)	1.912 (1.485 to 2.462)	p < 0.001
Time spent in day care	68 (19.4%)	131 (13.9%)	1.396 (1.070 to 1.821)	0.019

PH and RSV in Children with DS

- PH is typically diagnosed before RSV by an average of 812 days.
- Children with DS who have PH are more likely to require ICU admission for RSV (15.9% vs. 4.2%, p=0.015) and require longer hospital stays (9.50 days vs. 8.21, p>0.05).
- Cochran-Armitage test of trend was run to determine whether a linear trend exists between PH severity (mild, moderate, and severe) and RSV related outcomes. The only significant relationship was the need for hospital admission, p=0.038, with milder forms of PH associated with a higher proportion of RSV related admissions.



- For children with DS and PH, 50.0% identified as WHO functional Class II had RSV, followed by 32.8% in Class I, and 0.0% in Class III.
- Children with DS and PH due to lung disease or hypoxia (WHO Group III) were significantly more likely (n=45, 40.2%) to require a hospitalization compared to other WHO Groups (n=50, 19.5%; $\chi 2(1) = 17.524$, $p < .001$)

Impact of Palivizumab on RSV in Children with DS

- Children with DS who received palivizumab in their first year had a later onset of their first episode by 0.5 years.
- There was no significant association between completion of the palivizumab series during the first winter of life and hospital stay, ICU admission, and required oxygen support or mechanical ventilation as assessed by Fisher's exact test, p>0.05.

Conclusions

- Children with DS have a significantly higher risk of RSV infection, including hospitalization, than the general pediatric population.
- Risk factors for RSV include:
  - Feeding difficulties
  - CHD
  - Recurrent pneumonia
  - Aspiration
  - Obstructive sleep apnea
  - Time spent in daycare
- Children with DS are at an increased risk of having RSV infections if they carry a comorbid prior diagnosis of PH.
  - More likely to have longer hospitalizations and require intensive care admission.
- Higher proportion of infants with PH due to lung disease or hypoxia (WHO Group III) required hospitalization compared to other PH classifications.

Implications

- PH does appear to be a significant risk factor for more severe RSV related disease and warrants specific attention in this population.
- Early treatment of PH may help reduce the severity of infections, however not all instances of PH have targeted therapies and immunoprophylaxis may be worth considering in high-risk sub-groups.
- PH due to lung disease or hypoxia appears to be a particularly risky category of PH in this population.
- The value in the administration of palivizumab beyond currently recommended age groups in all children with DS, including select sub-groups warrants further study.

Disclosures

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