Limited Evidence on the Management of Respiratory Tract Infections in Down’s Syndrome

A Systematic Review

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Aims: To systematically review the effectiveness of preventative and therapeutic interventions for respiratory tract infections (RTIs) in people with Down’s syndrome.

Methods: Databases were searched for any published and ongoing studies of respiratory tract diseases in children and adults with Down’s syndrome. These databases were searched for controlled trials, cohort studies and controlled before–after studies. Trial registries were searched for ongoing studies. Initially, all study types were included to provide a broad overview of the existing evidence base. However, those with a critical risk of bias were excluded using the Cochrane Risk of Bias tool.

Results: A total of 13,575 records were identified from which 5 studies fulfilled the eligibility criteria and 3 fulfilled our criteria for data extraction. One randomized controlled trial of moderate risk of bias compared zinc therapy with placebo. Outcome data were only reported for 50 (78%) children who presented with extreme symptoms; no benefit of zinc therapy was found. One non-randomized controlled trial with serious risk of bias included 26 children and compared pidotimod (an immunostimulant) with no treatment; pidotimod was associated with fewer upper RTI recurrences compared with no treatment (1.43 vs. 3.82). A prospective cohort study with moderate risk of bias compared 352 palivizumab treated children with 233 untreated children and found that children treated with palivizumab had fewer respiratory syncytial virus-related hospitalization (23 untreated and 8 treated), but the same number of overall RTI-related hospitalizations (73 untreated and 74 treated) in the first 2 years of life.

Conclusions: The evidence base for the management of RTIs in people with Down’s syndrome is incomplete; current studies included children only and carry a moderate to serious risk of bias. Methodologic rigorous studies are warranted to guide clinicians in how best to prevent and treat RTIs in children with Down’s syndrome.

Key Words: Down’s syndrome, respiratory tract infection, prevention

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METHODS

Search Strategy

We developed a broad search strategy combining the terms Down’s Syndrome, Respiratory Tract Infections and relevant synonyms. To increase the yield of potential relevant articles, management
options for Down’s syndrome-related comorbidities such as sleep-disordered breathing, chronic lung disease and congenital heart disease were also included in the syntax. To obtain a broad overview of the existing evidence base, we did not limit our search strategy to specific study types, language or publication date (Appendix 1).

Information Sources
We searched the following electronic databases from their inception up to February 2015: PubMed, EMBASE, CINAHL and Cochrane Library. Trial registries such as WHO ICTRP and ClinicalTrials.gov were also searched for completed or ongoing studies. To identify any additional studies, reference lists of all included articles and relevant systematic reviews were screened.

We searched gray literature through web searches via Google Scholar, SIGLE and relevant research websites [including National Institute for Health Research (NIHR), Wellcome Trust and Medical Research Council]. Contact with research networks and charities were also made (including Trisomy 21 Research Society, Down’s Syndrome Association, Down’s Syndrome International, Down’s Heart Group and Downs Syndrome Medical Interest Group United Kingdom and Ireland).

Eligibility Criteria
We included studies of individuals with Down’s syndrome irrespective of age and covering any intervention (i.e., medical and/or surgical) for the prevention or treatment of RTIs including watchful waiting and supportive care. We anticipated that the number of randomized controlled trials (RCTs) for this topic would be limited because of the specific study population. Therefore, we included all study types except for case series and case reports.

Study Selection and Inclusion
Two review authors (L.M. and K.R.) independently screened titles and abstracts retrieved from the database searches along with the reference lists of the included studies and relevant systematic reviews. The same authors independently reviewed the full text of potentially relevant studies against the predefined eligibility criteria. A third author (R.V.) reviewed the discrepancies, and differences were resolved by consensus. Data extraction was performed by 1 reviewer (K.R.) and was independently checked by 2 reviewers (L.M. and R.V.). Two reviewers (L.M. and R.V.) independently performed the quality assessment of included studies.

Outcomes of Interest
As our systematic review aimed to identify interventions to either prevent or treat RTIs, identified papers were likely to encompass a broad range of outcome measures. As a consequence, we did not pre-specify any detailed outcome measures. We looked specifically at impact on frequency and recurrence of RTIs and any documented adverse effects.

Data Extraction
Data were extracted using a standardized form including information on study characteristics, setting, design, randomization, inclusion and exclusion criteria, data-analysis methods, interventions, outcomes and results.

Risk of Bias Assessment
We measured risk of bias in RCTs and non-randomized studies using the relevant “Risk of Bias” tools developed by Cochrane. We excluded studies with a critical risk of bias from our analyses.

![Flow diagram of search results and selecting studies for inclusion.](image-url)
Assessment of Heterogeneity

We assessed clinical heterogeneity across the included studies by reviewing differences in populations, interventions and outcomes measured. In view of the marked differences in the interventions used in the individual studies, we did not perform a meta-analysis.

Role of the Funding Source

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RESULTS

Study Selection

Our searches identified 13,575 articles. After screening of titles and abstracts, 157 potentially relevant published articles were identified. After reviewing the full texts, 5 published studies were deemed suitable for inclusion (Fig. 1).18-22 An additional unpublished ongoing study was identified through our searches.23

Study Characteristics

The main characteristics of the 5 published studies are presented in Table 1. All studies evaluated preventative interventions against RTI in children with Down's syndrome: 2 studies assessed the effectiveness of passive immunotherapy, with palivizumab and pidotimod, respectively18,19; 2 studies looked at prophylactic treatment with oral zinc supplements20,22 and 1 study at the effects of a school-based infection-control program.21

All studies exclusively studied children with Down's syndrome. The studies varied in terms of design (1 RCT, 1 non-RCT, 1 cohort study and 2 controlled before-after studies), age range of included children and duration of follow-up (Table 1). Two studies were conducted in Italy,19,22 1 in Canada,20 1 in Canada and the Netherlands and 1 in the United States.21

We identified 1 postmarketing observational study ongoing in Japan, looking at the effects of palivizumab in preventing lower RTIs caused by RSV in children under the age of 2 who are either immunocompromised or who have Down's syndrome.23

Risk of Bias Across Studies

The overall risk of bias of the RCT was moderate (Table 2). The overall risk of bias of the non-randomized studies was moderate for the cohort study20 (although high quality, there was no controlled comparator arm) and serious for the non-RCT.19 For the 2 controlled before-after studies, risk of bias was noted to be critical, and they were therefore excluded from analyses (Table 3).21,22

### TABLE 1. Characteristics of Included Published Studies

| Study         | Study Design | Number of Participants | Age (yr) | Domain                          | Intervention | Control | Outcome Measures                                                                 |
|---------------|--------------|------------------------|----------|---------------------------------|--------------|---------|----------------------------------------------------------------------------------|
| Lockitch et al20 | RCT          | 64                     | 1-19     | Children with Down's syndrome   | Zinc sulfate supplements 25 mg/d for 1-9 yr and 50 mg/d for older children for 6 mo | Placebo (identical lactose pills) | Number of children with URTI (days and episodes), doctor visits, antibiotic use and school absence |
| Yi et al18     | Prospective cohort study | 765 | 2-18 months | Children with Down's syndrome | Palivizumab | No treatment | RSV-related hospitalization, respiratory infection-related hospitalization on days with fever |
| La Mantia et al19 | Non-RCT     | 26                     | 3-13     | Children with Down's syndrome at least 6 URTIs in preceding 6 mo | Pidotimod 400 mg/d for 3 mo | No treatment | Number of URTI episodes ("relapses") and days with fever |
| Krilov et al21 | CBA          | 71                     | 0-5      | Children with Down's syndrome | Infection Control Program n/a | n/a | Respiratory illness rate, doctor visits, antibiotic use and school absence |
| Licastro et al22 | CBA          | 21                     | 7-15     | Children with Down's syndrome | Zinc sulfate supplements 1 mg/kg/d for 4 mo | n/a | Infection rate (mainly upper respiratory tract infection) and days with fever |

### TABLE 2. Risk of Bias Assessment for Lockitch et al20 Using the Cochrane Risk of Bias Tool

| Domain                        | Judgment          |
|-------------------------------|-------------------|
| Random sequence generation    | Unclear risk      |
| Allocation concealment        | Unclear risk      |
| Blinding of participants      | Low risk          |
| Blinding of outcome assessment| Low risk          |
|Incomplete outcome data        | High risk         |
| Selective reporting           | Unclear risk      |
| Other bias                    | Unclear risk      |
| Overall                       | Moderate risk     |
Results of Individual Studies

Zinc Therapy

Lockitch et al randomized 64 children with Down’s syndrome to oral zinc therapy for 6 months or placebo, but reported only on the 50 children (23 treated with zinc and 27 with placebo) who had extreme numbers (ie, exceeding the 90th percentile value for siblings and age-matched unrelated children).

In this subset of children with Down’s syndrome, during 6 months of treatment, no significant differences in terms of upper RTI episodes, doctor consultations and antibiotic use were found between children receiving zinc and children receiving placebo.20

Piidotimod

In a non-RCT, La Mantia et al followed 26 children with Down’s syndrome who had experienced at least 6 upper RTIs in the preceding 6 months and who received either the immunostimulant piidotimod for 3 months (14 children) or no treatment (12 children). While on piidotimod treatment, children with Down’s syndrome had fewer parent-reported upper RTI recurrences [mean 4.5, SD 3.5 vs. mean 16.9, SD 6.7] compared with those not receiving this treatment.19

Palivizumab

In a prospective cohort study, Yi et al followed 532 Canadian children with Down’s syndrome treated with the palivizumab for 2 RSV seasons and 233 Dutch children with Down’s syndrome who did not receive this immunostimulant. In the first 2 years of life, treatment with palivizumab resulted in a 3.6-fold reduction in the incidence rate ratio (adjusted incidence rate ratio 3.63, 95% confidence interval: 1.11, 95% confidence interval: 0.80–1.55).18

DISCUSSION

By a broad systematic search and review of the literature, we identified only 5 published studies on the management of RTIs in children with Down’s syndrome. This is remarkable in the light of the large body of literature in this field: Most high-quality studies have excluded this vulnerable group that are at high risk of these infections.

We found that piidotimod, an immunostimulant, and palivizumab, a human monoclonal antibody, may have a role in preventing RTIs in children with Down’s syndrome with the latter particularly effective in young children (until 2 years of age) against RSV-RTI hospitalizations. Currently, the American Academy of Pediatrics recommends the use of palivizumab in children with Down’s syndrome who are at risk of severe RSV-related infections (eg, congenital heart disease, airway clearance issues, prematurity).24 Once published, the ongoing postmarketing observational study is likely to add to this evidence base. Oral zinc was not noted to be effective in preventing RTIs.

The evidence base for RTI management in people with Down’s syndrome is incomplete, with only a limited number of moderate to serious risk of bias studies available on the prevention of RTIs in children. As such, clinical management of RTIs in this vulnerable group is currently guided by studies including either no or only limited number of children with Down’s syndrome. Methodologically rigorous studies are warranted to guide clinicians on how best to prevent and treat RTIs in children with Down’s syndrome.

APPENDIX 1. DOWN’S SYNDROME TERMS

MeSH: “Down Syndrome” OR TiAB: Down* syndrome* OR mongolism OR trisomy 21 OR aneuploidy OR down* disease* OR mongoloid idiocy OR Trisomy G AND

INFECTION TERMS

MeSH: Respiratory tract diseases OR Otitis media OR Respiratory syncytial virus, human OR Empyema OR TiAB: respiratory tract infection* OR upper respiratory infection* OR lower respiratory infection* OR RTI OR URTI OR LRTI OR rhinitis OR common cold* OR head cold* OR sinusitis OR rhinosinusitis OR pharyngitis OR laryngitis OR tracheitis OR tonsillitis OR sore throat* OR group A OR epiglottitis OR otitis media OR AOM OR OME OR glue ear OR ear discharge OR ototrauma OR otitis media OR bronchitis OR bronchopneumonia OR pneumonia OR cough* OR bronchiolitis OR respiratory syncytial virus OR RSV OR emphyema OR influenza* OR lung abscess* OR pulmonary tract infection* OR respiration tract infection* OR human flu OR pulmonary abscess* OR Nasal Catarrh* OR middle ear inflammation* OR bronchial pneumonia* OR lung inflammation* OR

ASSOCIATED CONDITION TERMS

MeSH: cardiovascular diseases OR TiAB: respiratory tract disease* OR lung disease* OR cardiovascular disease* OR obstructive sleep apnea* or pleural cyst* or congenital heart disease* or atrioventricular canal defect* or atrial septal defect* or ventricular septal defect* or patent ductus arteriosus or tetralogy of fallot OR double outlet right ventricle or mitral valve prolapse or aortic regurgitation or acquired valve disease* or OSAHS or fallot* tetralogy or AVC defect* or heart atriun septum defect or heart ventricle septum defect or floppy mitral valve* or aortic incompetence or aortic valve insufficiency or heart valve disease*

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TABLE 3. Risk of Bias Assessment for Nonrandomized Studies Using the ACROBAT-NSRI14

| Domain                                  | Yi et al18 | La Mantia et al19 | Licastro et al20 | Krilov et al21 |
|-----------------------------------------|------------|-------------------|------------------|----------------|
| Bias because of confounding             | Moderate   | Serious            | Serious          | Moderate       |
| Bias in selection of participants into  | Moderate   | Moderate           | Critical         | Serious        |
| the study                               | Moderate   | Moderate           | Moderate         | Moderate       |
| Bias in measurement of interventions    | Moderate   | Moderate           | No information   | Moderate       |
| Bias because of departures from         | Moderate   | Low                | Moderate         | Critical       |
| intended interventions                  | Moderate   | Serious            | Moderate         | Serious        |
| Bias because of missing data            | Low        | Low                | Moderate         | Low            |
| Bias in measurement of outcomes         | Low        | Serious            | Moderate         | Serious        |
| Bias in selection of the reported result| Moderate   | Serious            | Critical         | Critical       |
| Overall                                  |            | Moderate           | Critical         | Critical       |

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