

# A systematic review of antimicrobial therapy in children with tracheostomies

Helen Pearce<sup>1</sup>, Benjamin James Talks<sup>1</sup>, Steven Powell<sup>2</sup>, Malcolm Brodlie<sup>3</sup>, and Jason Powell<sup>2</sup>

<sup>1</sup>Newcastle University Biosciences Institute

<sup>2</sup>Royal Victoria Infirmary Great North Children's Hospital

<sup>3</sup>Great North Children's Hospital Paediatric Respiratory Unit

August 12, 2023

## Abstract

Tracheostomies are indicated in children to facilitate long-term ventilatory support, aid in the management of secretions, or to manage upper airway obstruction. Children with tracheostomies often experience ongoing airway complications, of which respiratory tract infections are common. They subsequently receive frequent courses of broad spectrum antimicrobials for the prevention or treatment of respiratory tract infections. However, there is little consensus in practice with regard to the indication for treatment/ prophylactic antimicrobial use, choice of antimicrobial, route of administration, or duration of treatment between different centres. Routine antibiotic use is associated with adverse effects and an increased risk of antimicrobial resistance. Tracheal cultures are commonly obtained from paediatric tracheostomy patients, with the aim of helping guide antimicrobial therapy choice. However, a positive culture alone is not diagnostic of infection and the role of routine surveillance cultures remains contentious. Inhaled antimicrobial use is also widespread in the management of tracheostomy associated infections; this is largely based upon theoretical benefits of higher airway antibiotic concentrations. The role of prophylactic inhaled antimicrobial use for tracheostomy associated infections remains largely unproven. This systematic review summarises the current evidence base for antimicrobial selection, duration, and administration route in paediatric tracheostomy associated infections. It also highlights significant variation in practice between centres and the urgent need for further prospective evidence to guide the management of these vulnerable patients.

## A systematic review of antimicrobial therapy in children with tracheostomies

Helen Pearce<sup>1,2</sup>, Benjamin James Talks<sup>1,2</sup>, Steven Powell<sup>2</sup>, Malcolm Brodlie<sup>3,4</sup>, Jason Powell<sup>2, 4</sup>

<sup>1</sup> Biosciences Institute, William Leech Building, Newcastle University, Newcastle Upon Tyne, NE2 4HH

<sup>2</sup> Department of Paediatric Otolaryngology, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, NE1 4LP

<sup>3</sup> Department of Paediatric Respiratory Medicine, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, NE1 4LP

<sup>4</sup> Translational and Clinical Research Institute, William Leech Building, Newcastle University, Newcastle Upon Tyne, NE2 4HH

## ABSTRACT

Tracheostomies are indicated in children to facilitate long-term ventilatory support, aid in the management of secretions, or to manage upper airway obstruction. Children with tracheostomies often experience ongoing airway complications, of which respiratory tract infections are common. They subsequently receive frequent

courses of broad spectrum antimicrobials for the prevention or treatment of respiratory tract infections. However, there is little consensus in practice with regard to the indication for treatment/ prophylactic antimicrobial use, choice of antimicrobial, route of administration, or duration of treatment between different centres. Routine antibiotic use is associated with adverse effects and an increased risk of antimicrobial resistance. Tracheal cultures are commonly obtained from paediatric tracheostomy patients, with the aim of helping guide antimicrobial therapy choice. However, a positive culture alone is not diagnostic of infection and the role of routine surveillance cultures remains contentious. Inhaled antimicrobial use is also widespread in the management of tracheostomy associated infections; this is largely based upon theoretical benefits of higher airway antibiotic concentrations. The role of prophylactic inhaled antimicrobial use for tracheostomy associated infections remains largely unproven. This systematic review summarises the current evidence base for antimicrobial selection, duration, and administration route in paediatric tracheostomy associated infections. It also highlights significant variation in practice between centres and the urgent need for further prospective evidence to guide the management of these vulnerable patients.

## KEYWORDS

Antimicrobial therapy, respiratory tract infections, paediatric tracheostomy

## INTRODUCTION

Paediatric tracheostomy is mainly performed in infancy, to facilitate long-term ventilation or manage upper airway obstruction<sup>1-4</sup>. Over half of these children remain cannulated for life<sup>5,6</sup>. Paediatric tracheostomy has been identified as an area requiring care quality improvements<sup>1,7-9</sup>. Most children with tracheostomies will experience ongoing airway complications, of which respiratory tract infections are the most common, accounting for over a fifth of hospital readmissions in this group<sup>2,7,10-12</sup>. Complications increase the frequency of patients' hospital visits and healthcare costs; they can also impair the quality of life of children and their carers<sup>4,6,10,13,14</sup>. A retrospective cohort study reporting healthcare costs for 1122 children, who underwent tracheostomy insertion in England over a 5 year period, reported 1213 hospital admissions for lower respiratory tract infections (LRTI) in the first year after tracheostomy alone costing £8,446,138 (\$11,554,072).<sup>12</sup> Children with tracheostomies are frequently treated with broad spectrum antimicrobials for the prevention or treatment of respiratory tract infections. There is however little consensus in practice, with variation in the indication for treatment/ prophylaxis, choice of antimicrobial, route of administration, and duration of treatment, between different centres<sup>15-17</sup>. Of course the clinical complexity of children requiring tracheostomies undoubtedly contributes to this heterogeneity in practice; many children with tracheostomies have comorbidities affecting multiple systems. Indeed, one study of 21,541 hospital admissions of children with tracheostomies in the United States found children to have a mean of five chronic health conditions.<sup>11</sup> Further, 81% had a complex chronic condition lasting at least 1 year, as defined by Feudtner et al.<sup>18</sup>; most commonly children had underlying neuromuscular (46%), congenital/ genetic (27%), or respiratory (20%) conditions.

The long-term effect of antimicrobial exposure on microbial communities and the presence of antimicrobial resistance genes within them (their "resistome") is not fully understood and remains an active area of research<sup>19,20</sup>. Nevertheless, repeated cycles of broad spectrum antimicrobials increases the risk of drug-resistant organisms.<sup>21</sup> The increasing prevalence of antimicrobial resistance is a growing concern for the management of vulnerable patient groups, and healthcare in general; the World Health Organisation even lists antimicrobial resistance as one of their top 10 threats to humanity<sup>22</sup>. Studies of children with tracheostomies frequently demonstrate airway bacterial colonisation, often with drug resistant *Pseudomonas aeruginosa* and Methicillin-resistant *Staphylococcus aureus*.<sup>23</sup> The microbiology and antimicrobial resistance patterns of tracheostomy associated infections has been summarised in recent reviews<sup>15,24,25</sup>. This review aims to summarise the current evidence for the use of antimicrobial therapies in the management of tracheostomy dependent children and identify core areas of need for further research.

## METHODS

The aim of this systematic review was to summarise and characterise existing literature addressing the use

of antimicrobials in paediatric patients with a tracheostomy. A comprehensive search of PubMed (National Library of Medicine) and Embase (Elsevier) online databases was undertaken on 4th April 2023 using the search terms ('children' OR 'paediatric' OR 'infant' OR 'adolescent') AND 'tracheostomy' AND ('respiratory tract infection' OR 'tracheitis' OR 'anti-infective agents'). Search results were limited to English Language articles published in the last 20-years. Further articles were obtained through their bibliographies. Inclusion criteria were full-text articles of any study design reporting the use of antimicrobial agents in tracheostomy dependent children. Exclusion criteria were conference abstracts without a full-text available and literature reviews without a meta-analysis. The titles and abstracts were assessed for eligibility by one independent reviewer, and full-text copies of all of the articles deemed potentially relevant were retrieved. Two review authors then independently reviewed full text articles. PRISMA guidelines were adhered to<sup>26</sup>.

### 3. RESULTS

#### 3.1 Study Selection

Our initial search of the literature yielded a total of 454 results. Removal of duplicate articles, title and abstract screening excluded 435 articles. The full texts of the remaining 19 articles were screened and 9 articles were selected for inclusion in this review. A further three articles were sourced from bibliography searches. In total, 12 articles were selected for inclusion in this review; the search strategy is summarised in figure 1.

#### 3.2 Study Characteristics

All of the included articles were published between 2010 and 2022. The majority of studies were conducted in the United States (75%;  $n = 9$ ). The remaining three studies (25%) were conducted in Turkey, Taiwan and Canada. All were observational, retrospective cohort studies; there was no randomised controlled trial evidence published on this topic.

#### 3.3 Systemic (intravenous or enteral) antibiotics

Six retrospective cohort studies looked at the use of systemic antimicrobials; these are summarised on table 1. Of these studies, one covered initiation of antimicrobials in outpatient clinics<sup>27</sup>, four looked at choice of inpatient antimicrobials<sup>28-31</sup>, and one assessed impact of duration of antimicrobial therapy for airway infections<sup>16</sup>.

Majmudar et al. compared antimicrobial prescription (enteral or inhaled) versus increased airway clearance therapies (chest physiotherapy and the use of nebulisers to assist coughing) alone for the management of LRTI in tracheostomy dependent children. In their retrospective cohort of 283 episodes of LRTI in 82 children, they found that conservative management with airway clearance alone did not result in significantly more hospitalisations within 28 days of treatment, compared to those who received an antimicrobial: adjusted OR 1.47 (95% CI: 0.75, 2.86);  $p=0.26$ <sup>27</sup>. However, clinician choice of whether to initiate antimicrobials or airway clearance was likely based upon a clinical assessment of LRTI severity with no form of randomisation, biasing the study results. In part, this may reflect the difficulties clinicians have in differentiating bacterial and non-bacterial LRTI leading to excessive antimicrobial prescribing. This challenge is highlighted by a retrospective cohort study of 90 patients who received a tracheostomy over a 14 year period<sup>32</sup>. During this time, there were 137 hospital admissions with LRTIs affecting 46.7% ( $n=42$ ) of the cohort, of which over a third were treated with antimicrobials despite only 8.5% being defined as definite bacterial pneumonia. In this study, definite bacterial pneumonia was defined as a fever plus one or more of the following signs/symptoms: i) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements; ii) new onset or worsening cough, or dyspnoea, or tachypnoea; iii) rales or bronchial breath sounds; iv) worsening gas exchange.

Anti-pseudomonal antimicrobials were the predominant choice for the treatment of tracheostomy associated airway infections in the available literature. A retrospective review of 76 episodes of ventilator-associated tracheobronchitis in 60 children reported that enteral fluoroquinolones effectively treated the majority of infections (65/76, 86%)<sup>30</sup>. Interestingly, two large retrospective cohort studies using the Paediatric Health

Information System database in the United States between 2007 and 2014 reported that use of empirical anti-pseudomonal antibiotics on an individual level, or higher use on a hospital level was associated with longer hospital admissions, but not 30-day readmission rate<sup>28,29</sup>. However, the longer length of hospital admissions observed here may have been attributable to infection severity, antimicrobial resistance limiting enteral treatment options, difficulty obtaining home intravenous antimicrobial therapy, hesitance to transition from the intravenous to enteral route, or other unmeasured confounders<sup>28</sup>.

Only one study investigated the optimal duration of antimicrobial therapy in tracheostomy dependent children. In their retrospective cohort study of 118 children diagnosed with ventilator-associated tracheobronchitis, fewer patients who received a short-courses of antimicrobials (<6 days) developed a hospital or ventilator acquired pneumonia within 10 days of completing antimicrobials. Additionally, prolonged courses of antimicrobials did significantly increase the risk of multidrug resistant organisms being identified in patients' subsequent cultures<sup>16</sup>.

### 3.4. Topical (inhaled) antibiotics

Three retrospective cohort studies evaluated the use of nebulised antimicrobials in paediatric tracheostomy patients<sup>32–36</sup>. Of these studies, one assessed the use of prophylactic nebulised antimicrobials<sup>34,36</sup>, one nebulised antimicrobials in the context of LRTIs<sup>32,33</sup> and one reported possible safety concerns regarding the ongoing use of nebulised tobramycin in paediatric tracheostomy patients<sup>35</sup>.

A small retrospective cohort study of 22 tracheostomised children looked at the use of nebulised antimicrobials to manage persistent bacterial lower airway colonisation following LRTI according to the results of the tracheal aspirate cultures<sup>33</sup>. There was no control group and no standard antimicrobial regimen: 14 received gentamicin and 8 received colistin, median antibiotic duration was 3.5 months. Nebulised antimicrobials reduced median bacterial colony count at the 12th month after the start of the nebulised antimicrobials ( $10^5$  colony-forming unit (CFU)/ml vs.  $10^4$  CFU/ml;  $p = 0.02$ ). The median number of hospitalisations following treatment with nebulised antimicrobials decreased from 2 (range 1–3.5) to 1 (range 0–1.5) ( $p = 0.04$ ). Additionally, duration of intensive care admissions reduced significantly from 89.5 days (range 43–82.5 days) to 25 days (range 7.75–62.75 days) after starting nebulised antimicrobials ( $p=0.028$ ). Gentamicin resistance was noted during treatment in almost a third of patients ( $n=6$ ).

Prophylactic inhaled antimicrobials have also shown some promise in a small retrospective case series of six tracheostomised children, which trialled the use of either inhaled colomycin or tobramycin for a median of 74 days (range 22–173 days)<sup>34</sup>. Although they reported a reduction in median days of systemic antimicrobial use (18 vs 2 days) and episodes of LRTI (2 vs 1 episode) in the 3-months pre-treatment versus 3-months post-treatment, neither finding was statistically significant.

Inhaled antimicrobials appear to have a good safety profile; however, Hughes et al. did highlight the need for caution in using inhaled tobramycin in paediatric patients with concomitant renal disease<sup>35</sup>. In their retrospective cohort of 12 tracheostomy-dependent paediatric patients, 11 had undetectable trough concentrations (defined as  $<0.6$  mcg/mL), whilst one patient with known polycystic kidney disease had a steady-state trough concentration of 2.1 mcg/mL after only 5 doses of inhaled tobramycin.

### 3.4 Culture-guided antibiotics

Three retrospective cohort studies investigated the use of antibiotics in the context of tracheal aspirate cultures.

Two studies aimed to establish the usefulness of endotracheal aspirate cultures in guiding choice of antimicrobial therapy. Prinzi et al. looked at the association between over-reporting of such cultures in tracheostomised paediatric patients and its subsequent effect on antimicrobial prescribing.<sup>37</sup> Over-reporting was defined according to the American Society of Microbiology guidelines as reporting organisms not known to be respiratory pathogens. During the one-year study period, 826 endotracheal aspirate cultures were collected from 448 children. From these cultures, 310 isolates were identified in tracheostomised children. Of which, 25 (8%) organisms were over-reported, resulting in 48 days of excess antimicrobial therapy. Cline

et al. aimed to assess the utility of surveillance cultures (routine tracheal aspirate cultures) in children with tracheostomies in guiding antimicrobial selection for subsequent LRTIs.<sup>38</sup> The study concluded that due to the dynamic nature of the tracheal microbiome on serial cultures, historical cultures are of little value to dictate antimicrobial choice in subsequent infections. Indeed, they report that in over half of cases (n = 36), limiting empirical antimicrobials to a previous culture result would not cover organisms isolated on subsequent cultures.

Yalamanchi et al. explored whether microscopic purulence, which is the quantitative assessment of neutrophils, in positive tracheal aspirate cultures could be used to predict subsequent antimicrobial use in a single centre retrospective review<sup>39</sup>. In their study cohort of 231 children admitted to intensive care units (81 tracheostomised), there were 361 positive tracheal aspirate cultures, of which a fifth (22%, n=81) were treated with antibiotics. Using multivariate logistic regression, they showed microscopic purulence to be an independent predictor of antimicrobial use, alongside pyrexia and respiratory failure. However, microscopic purulence was not associated with clinical symptoms of infection (hypotension, fever, or increased respiratory support). It should also be noted that this regression model aimed to predict current antibiotic prescribing practice rather than a “gold-standard” benchmark of confirmed bacterial infections. As such it may represent a useful metric in aiding the decision to initiate antimicrobial therapy, but only in the clinical context of suspected infection.

#### 4. DISCUSSION

This systematic review summarises the current evidence base for the use of antimicrobials in tracheostomy dependent paediatric patients. All 12 studies identified were retrospective cohort studies. These highlight three core themes that should be the topic of future research: i) route of antimicrobial administration (systemic versus topical); ii) the role of cultures in guiding antimicrobial use; and iii) timing of antimicrobial use (reactive versus prophylactic). All of which would help clinicians optimise management for these children, reducing the need for escalation of care and improving antimicrobial stewardship. There is an urgent need for prospective, randomised controlled trial evidence to address these issues and guide the management of this vulnerable patient group.

Systemic antimicrobials are in routine use for tracheostomy associated infections, with empirical treatment often aiming to cover *Pseudomonas* and *Staphylococcus* as common causative organisms. Although anti-pseudomonal antimicrobial usage has been associated with increased hospital admission duration both on an individual level<sup>29</sup> and hospital level<sup>28</sup>, this likely reflects other clinical confounders such as their use in severe infections. The relationship between longer hospital admissions and hospital level prescribing rates may also represent poorer antimicrobial stewardship leading to increased antimicrobial resistance.

Inhaled antimicrobial use is also widespread in the management of tracheostomy associated infections; this is largely based upon theoretical benefits, such as higher tracheal antibiotic concentrations and reduced side effects. As well as extrapolation of evidence from the management of adult ventilator associated pneumonia<sup>40</sup>, cystic fibrosis<sup>41</sup>, and non-cystic fibrosis bronchiectasis<sup>42</sup>. Clearly, none of these populations represent children with tracheostomy associated infections well due to differences in both pathology and between children and adults, including physiology, anatomy, and risk factor exposure profiles (such as smoking). Although nebulised antimicrobials have been used in the treatment of respiratory illness for over 70 years<sup>43</sup>, further studies are needed to evaluate and compare alternate antimicrobial use in children with tracheostomies<sup>30</sup>.

Prophylactic inhaled antimicrobials are often used in clinical practice; however, there is little international consensus on their use in children with tracheostomies. To the best of our knowledge the only guidelines endorsing their use in this patient cohort are by the Brazilian Society of Paediatrics, specifically in the post-tracheostomy period<sup>44</sup>. Prophylactic antimicrobials have also been investigated in the context of recurrent LRTI<sup>34,36</sup> and persistent bacterial colonisation after LRTI<sup>33</sup>. Indeed, the most recent British Thoracic Society guidelines support the use of both enteral and inhaled antibiotics to reduce infection frequency in individuals with learning disabilities suffering from recurrent community acquired pneumonia<sup>45</sup>. Although early evidence on prophylactic inhaled antibiotic use in children with tracheostomies is promising, suggesting reduced

frequency of LRTIs and systemic antimicrobial use, it is very weak, limited to two small retrospective cohort studies<sup>30,31</sup>. Given the already troubling prevalence of multidrug resistant organisms in this population<sup>23</sup>, randomised controlled trial evidence is needed to ensure this common practice is actually beneficial and not detrimental to patients' health.

Tracheal cultures are commonly obtained from paediatric tracheostomy patients, with the aim of guiding subsequent antimicrobial therapy. However, a positive culture alone is not diagnostic of infection. Positive cultures may represent normal respiratory organisms or colonisation of the respiratory tract, which is common after tracheostomy. Yalamanchi et al. highlight this challenge of knowing which culture results to act upon, reinforcing the need to interpret culture results as part of a wider clinical assessment<sup>39</sup>. Whilst Prinzi et al. demonstrated the potential harms of over-reporting aspirate cultures, which can lead to unnecessary antimicrobial exposure.<sup>37</sup> Further, Cline et al. demonstrate the danger of utilising historical culture results to guide current treatment, which they estimate would only be effective in half of cases.<sup>38</sup> The increasing uptake of next generation sequencing techniques, which are currently mainly limited to the research environment, may offer hope for the future. Comprehensive profiling of microbial communities will help us better understand the dynamic interplay between the tracheal microbiome and host-immune system.<sup>46,47</sup> In turn, improved understanding of what factors predispose individuals to microbial dysfunction and subsequent infection could provide alternatives to antimicrobial therapy to break the cycle of recurrent infections<sup>25</sup>.

The data summarised here have four main overriding limitations. Firstly, the populations studied were heterogeneous in terms of design, intervention, and outcome measures, limiting their generalisability. Secondly, there was no standardised definition of tracheostomy-associated respiratory infections across different studies, which often just reported clinical diagnosis, limiting their comparability. Features of interest when comparing datasets include the presence of positive tracheal aspirate cultures, radiographic changes, changes in gas exchange, and other clinical features (such as cough, sputum production, and pyrexia). Attention should be paid to infection definition when designing future studies to support interpretability of their results and subsequent meta-analysis. Thirdly, the small sample size of these studies precludes subgroup analysis, compounding the first two issues. Finally, all studies in our systematic review are retrospective cohort studies, which by design provide low level evidence for the efficacy of antimicrobial interventions. Prospective, randomised, controlled studies are needed to guide clinical decision making for this vulnerable patient cohort.

## 5. CONCLUSIONS

Children with tracheostomies are at high risk of respiratory tract infections and are routinely treated with broad spectrum antimicrobials. Most evidence for antimicrobial use for these patients comes from retrospective cohort studies; there is no randomised controlled trial evidence to date. The studies included in our review highlight the significant variation in antimicrobial usage between centres, including antimicrobial selection, duration, and administration route. There is an urgent need for future research to help rationalise antibiotic usage for this vulnerable patient cohort.

## AUTHOR CONTRIBUTIONS

H.Pearce and B.Talks were involved in conceptualisation, the literature search and overall synthesis of the manuscript, J.Powell, S.Powell and M.Brodlie critically reviewed the manuscript for intellectual content and approved its final version.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## CORRESPONDING AUTHOR

Mr Jason Powell

Translational and Clinical Research Institute

William Leech Building

Newcastle University  
Newcastle upon Tyne NE2 4HH  
United Kingdom  
Email: Jason.powell@ncl.ac.uk

## REFERENCES

1. Watters KF. Tracheostomy in Infants and Children. *Respir Care* 2017;62(6):799–825.
2. Perez-Ruiz E, Caro P, Perez-Frias J, Cols M, Barrio I, Torrent A, Garcia MA, Asensio O, Pastor MD, Luna C, et al. Paediatric patients with a tracheostomy: a multicentre epidemiological study. *Eur Respir J* 2012;40(6):1502–1507.
3. Roberts J, Powell J, Begbie J, Siou G, McLarnon C, Welch A, McKean M, Thomas M, Ebdon A-M, Moss S, et al. Pediatric tracheostomy: A large single-center experience. *Laryngoscope* 2020;130(5):E375–E380.
4. Hall N, Rousseau N, Hamilton DW, Simpson AJ, Powell S, Brodlie M, Powell J. Impact of COVID-19 on carers of children with tracheostomies. *Arch Dis Child* 2022;107(3):e23.
5. Ozmen S, Ozmen OA, Unal OF. Pediatric tracheotomies: A 37-year experience in 282 children. *Int J Pediatr Otorhinolaryngol* 2009;73(7):959–961.
6. Watters K, O’Neill M, Zhu H, Graham RJ, Hall M, Berry J. Two-year mortality, complications, and healthcare use in children with medicaid following tracheostomy. *Laryngoscope* 2016;126(11):2611–2617.
7. Mahida JB, Asti L, Boss EF, Shah RK, Deans KJ, Minneci PC, Jatana KR. Tracheostomy Placement in Children Younger Than 2 Years: 30-Day Outcomes Using the National Surgical Quality Improvement Program Pediatric. *JAMA Otolaryngol Head Neck Surg* 2016;142(3):241–246.
8. Shah RK, Stey AM, Jatana KR, Rangel SJ, Boss EF. Identification of opportunities for quality improvement and outcome measurement in pediatric otolaryngology. *JAMA Otolaryngol Head Neck Surg* 2014;140(11):1019–1026.
9. Thomas AN, McGrath BA. Patient safety incidents associated with airway devices in critical care: a review of reports to the UK National Patient Safety Agency. *Anaesthesia* 2009;64(4):358–365.
10. Berry JG, Graham DA, Graham RJ, Zhou J, Putney HL, O’Brien JE, Roberson DW, Goldmann DA. Predictors of clinical outcomes and hospital resource use of children after tracheotomy. *Pediatrics* 2009;124(2):563–572.
11. Zhu H, Das P, Roberson DW, Jang J, Skinner ML, Paine M, Yuan J, Berry J. Hospitalizations in children with preexisting tracheostomy: a national perspective. *Laryngoscope* 2015;125(2):462–468.
12. Powell J, Keltie K, Sims A, Richardson H, Brodlie M, Powell S. National Cohort Study of Health Care Resource Use After Pediatric Tracheostomy. *JAMA Pediatr* 2022;176(8):817–819.
13. Meier JD, Valentine KJ, Hagedorn C, Hartling C, Gershan W, Muntz HR, Murphy NA. Emergency department use among children with tracheostomies: Avoidable visits. *J Pediatr Rehabil Med* 2015;8(2):105–111.
14. Hall N, Rousseau N, Hamilton DW, Simpson AJ, Powell S, Brodlie M, Powell J. Providing care for children with tracheostomies: a qualitative interview study with parents and health professionals. *BMJ Open* 2023;13(1):e065698.
15. Gipsman A, Prero M, Toltzis P. Tracheobronchitis in children with tracheostomy tubes: Overview of a challenging problem. *Pediatric* 2022.

16. Tamma PD, Turnbull AE, Milstone AM, Lehmann CU, Sydnor ERM, Cosgrove SE. Ventilator-associated tracheitis in children: does antibiotic duration matter? *Clin Infect Dis* 2011;52(11):1324–1331.
17. Morrison JM, Hassan A, Kysh L, Dudas RA, Russell CJ. Diagnosis, management, and outcomes of pediatric tracheostomy-associated infections: A scoping review. *Pediatr Pulmonol* 2022;57(5):1145–1156.
18. Feudtner C, Christakis DA, Connell FA. Pediatric Deaths Attributable to Complex Chronic Conditions: A Population-Based Study of Washington State, 1980–1997. *Pediatrics* 2000 [accessed 2023 Aug 1];106(Supplement\_1):205–209.
19. Sommer MOA, Dantas G, Church GM. Functional characterization of the antibiotic resistance reservoir in the human microflora. *Science* 2009;325(5944):1128–1131.
20. Apjok G, Szamel M, Christodoulou C, Seregi V, Vasarhelyi BM, Stirling T, Eszenyi B, Sari T, Vidovics F, Nagrand E, et al. Characterization of antibiotic resistomes by reprogrammed bacteriophage-enabled functional metagenomics in clinical strains. *Nat Microbiol* 2023;8(3):410–423.
21. Wang C-Y, Chen Y-H, Fang C, Zhou M-M, Xu H-M, Jing C-M, Deng H-L, Cai H-J, Jia K, Han S-Z, et al. Antibiotic resistance profiles and multidrug resistance patterns of *Streptococcus pneumoniae* in pediatrics: A multicenter retrospective study in mainland China. *Medicine* 2019;98(24):e15942.
22. Antimicrobial resistance. [accessed 2023 Jun 8]. <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>
23. Pozzi M, Pellegrino P, Galbiati S, Granziera M, Locatelli F, Carnovale C, Perrone V, Antoniazzi S, Perrotta C, Strazzer S, et al. Prevalence of respiratory colonisations and related antibiotic resistances among paediatric tracheostomised patients of a long-term rehabilitation centre in Italy. *Eur J Clin Microbiol Infect Dis* 2015;34(1):169–175.
24. Morrison JM, Hassan A, Kysh L, Dudas RA, Russell CJ. Diagnosis, management, and outcomes of pediatric tracheostomy-associated infections: A scoping review. *Pediatr Pulmonol* 2022;57(5):1145–1156.
25. Powell J, Powell S, Mather MW, Beck L, Nelson A, Palmowski P, Porter A, Coxhead J, Hedley A, Scott J, et al. Tracheostomy in children is associated with neutrophilic airway inflammation. *Thorax* 2023 Feb 20.
26. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;372:n160.
27. Majmudar P, Sanders DB, Slaven J, Cristea AI. Outpatient Treatment of Lower Respiratory Tract Infections in Children with Tracheostomy - A Single Institution Experience. In: B51. PEDIATRIC SLEEP II. American Thoracic Society; 2020. p. A3685–A3685. (American Thoracic Society International Conference Abstracts).
28. Russell CJ, Mack WJ, Schrager SM, Wu S. Care Variations and Outcomes for Children Hospitalized With Bacterial Tracheostomy-Associated Respiratory Infections. *Hosp Pediatr* 2017;7(1):16–23.
29. Russell CJ, Mamey MR, Koh JY, Schrager SM, Neely MN, Wu S. Length of Stay and Hospital Revisit After Bacterial Tracheostomy-Associated Respiratory Tract Infection Hospitalizations. *Hosp Pediatr* 2018;8(2):72–80.
30. Smith CJ, Sierra CM, Robbins J, Cobbina E. Enteral antipseudomonal fluoroquinolones for ventilator-associated tracheobronchitis in children with pre-existing tracheostomy. *Pediatr Pulmonol* 2022;57(4):1064–1071.
31. Brook I. Treatment of aspiration or tracheostomy-associated pneumonia in neurologically impaired children: effect of antimicrobials effective against anaerobic bacteria. *Int J Pediatr Otorhinolaryngol* 1996;35(2):171–177.



32. Tan C-Y, Chiu N-C, Lee K-S, Chi H, Huang F-Y, Huang DT-N, Chang L, Kung Y-H, Huang C-Y. Respiratory tract infections in children with tracheostomy. *J Microbiol Immunol Infect* 2020;53(2):315–320.
33. Atag E, Unal F, Arslan H, Teber BG, Telhan L, Ersu R, Karakoc F, Oktem S. The effect of nebulized antibiotics in children with tracheostomy. *Int J Pediatr Otorhinolaryngol* 2021;143:110665.
34. Jutras C, Autmizguine J, Chomton M, Marquis C, Nguyen TT-D, Roumeliotis N, Emeriaud G. Inhaled Antibiotics for the Prevention of Respiratory Tract Infections in Children With a Tracheostomy. *Front Pediatr* 2021;9:633039.
35. Hughes KM, Cristea AI, Tillman EM. Tobramycin Serum Concentrations in Tracheostomy-Dependent Children Receiving Inhaled Tobramycin. *Pediatr Allergy Immunol Pulmonol* 2020;33(2):92–95.
36. Eckerland M, Bock C, Olivier M, Pichlmaier L, Steindor M, Stehling F. Reducing the frequency of respiratory tract infections in severe neurological disorders by inhaled antibiotics: a retrospective data analysis. *ERJ Open Res* 2019;5(3).
37. Prinzi AM, Wattier RL, Curtis DJ, Ziniel SI, Fitzgerald A, Pearce K, Parker SK. Impact of Organism Reporting from Endotracheal Aspirate Cultures on Antimicrobial Prescribing Practices in Mechanically Ventilated Pediatric Patients. *J Clin Microbiol* 2022;60(11):e0093022.
38. Cline JM, Woods CR, Ervin SE, Rubin BK, Kirse DJ. Surveillance tracheal aspirate cultures do not reliably predict bacteria cultured at the time of an acute respiratory infection in children with tracheostomy tubes. *Chest* 2012;141(3):625–631.
39. Yalamanchi S, Saiman L, Zachariah P. Decision-Making Around Positive Tracheal Aspirate Cultures: The Role of Neutrophil Semiquantification in Antibiotic Prescribing. *Pediatr Crit Care Med* 2019;20(8):e380–e385.
40. Zampieri FG, Nassar AP Jr, Gusmao-Flores D, Taniguchi LU, Torres A, Ranzani OT. Nebulized antibiotics for ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care* 2015;19(1):150.
41. Smith S, Rowbotham NJ. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database Syst Rev* 2022;11(11):CD001021.
42. Laska IF, Crichton ML, Shoemark A, Chalmers JD. The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis. *Lancet Respir Med* 2019;7(10):855–869.
43. Kuhn RJ. Formulation of aerosolized therapeutics. *Chest* 2001;120(3 Suppl):94S–98S.
44. Avelino MAG, Maunsell R, Valera FCP, Lubianca JF, Schweiger C, Miura CS, Chen VG, Manrique D, Oliveira R, Gavazzoni F, et al. First Clinical Consensus and National Recommendations on Tracheostomized Children of the Brazilian Academy of Pediatric Otorhinolaryngology (ABOPe) and Brazilian Society of Pediatrics (SBP). *Braz J Otorhinolaryngol* 2017;83:498–506.
45. Legg J, Allen J-L, Andrew M, Annesley C, Chatwin M, Crawford H, Elverson J, Forton J, Oulton K, Renton K, et al. BTS Clinical Statement on the prevention and management of community-acquired pneumonia in people with learning disability. *Thorax* 2023;78(Suppl 1):s22–s52.
46. Perez-Losada M, Graham RJ, Coquillet M, Jafarey A, Castro-Nallar E, Aira M, Hoptay C, Freishtat RJ, Mansbach JM. Tracheal Microbiota in Patients With a Tracheostomy Before, During and After an Acute Respiratory Infection. *Pediatr Infect Dis J* 2018;37(11):e269–e271.
47. Perez-Losada M, Graham RJ, Coquillet M, Jafarey A, Castro-Nallar E, Aira M, Freishtat RJ, Mansbach JM. The temporal dynamics of the tracheal microbiome in tracheostomised patients with and without lower respiratory infections. *PLoS One* 2017;12(8):e0182520.

## Hosted file

Figure 1 SR .docx available at <https://authorea.com/users/622855/articles/659648-a-systematic-review-of-antimicrobial-therapy-in-children-with-tracheostomies>

### Hosted file

Table 1 SR.docx available at <https://authorea.com/users/622855/articles/659648-a-systematic-review-of-antimicrobial-therapy-in-children-with-tracheostomies>