Received: 10 August 2023 | Accepted: 10 November 2023

DOI: 10.1002/ppul.26766

REVIEW

PEDIATRIC PULMONOLOGY WILEY

A systematic review of antimicrobial therapy in children with tracheostomies

Helen Pearce BDS (Hons), MBBS (Hons)[1,2] | Benjamin James Talks BSc, MBChB[1,2] | Steven Powell MBBS, MSc, FRCS (ORL-HNS)[2] | Malcolm Brodlie BSc (Hons), MB ChB, PhD, FRCPCH[3,4] | Jason Powell MBBS, MRes, PhD, FRCS (ORL-HNS)[2,4]

[1]Biosciences Institute, William Leech Building, Newcastle University, Newcastle Upon Tyne, UK

[2]Department of Paediatric Otolaryngology, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK

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

[4]Translational and Clinical Research Institute, William Leech Building, Newcastle University, Newcastle Upon Tyne, UK

Correspondence

Jason Powell, MBBS, MRes, PhD, FRCS (ORL-HNS), Department of Paediatric Otolaryngology, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne NE1 4LP, UK.
Email: jason.powell@doctors.org.uk

Funding information

Medical Research Council, United Kingdom, Grant/Award Number: MR/X018237/1

Abstract

Tracheostomies are indicated in children to facilitate long-term ventilatory support, aid in the management of secretions, or 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 centers. Routine antibiotic use is associated with adverse effects and an increased risk of antimicrobial resistance. Tracheal cultures are commonly obtained from pediatric 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 on the theoretical benefits of higher airway antibiotic concentrations. The role of prophylactic inhaled antimicrobial use for tracheostomy-associated infections remains largely unproven. This systematic review summarizes the current evidence base for antimicrobial selection, duration, and administration route in pediatric tracheostomy-associated infections. It also highlights significant variation in practice between centers and the urgent need for further prospective evidence to guide the management of these vulnerable patients.

KEYWORDS

antibiotics, antimicrobial therapy, pediatric tracheostomy, respiratory tract infections

1 | INTRODUCTION

Pediatric tracheostomy is mainly performed in infancy to facilitate long-term ventilation or manage upper airway obstruction.[1–4] Over half of these children remain cannulated for life.[5,6] However, length of cannulation does vary by tracheostomy indication[7] and decannulation can be successful in selected patient groups.[8–10] Pediatric tracheostomy has been identified as an area requiring care quality improvements.[1,11–13] 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.[2,11,14–16] Complications increase the frequency of patients' hospital visits and healthcare costs; they can also impair the quality of life of children and their carers.[4,6,14,17,18] 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).[16] 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 centers.[19–21] 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.[15] Further, 81% had a complex chronic condition lasting at least 1 year, as defined by Feudtner et al.[22]; 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.[23,24] Nevertheless, repeated cycles of broad-spectrum antimicrobials increase the risk of drug-resistant organisms.[25] The increasing prevalence of antimicrobial resistance is a growing concern for the management of vulnerable patient groups, and healthcare in general; the World Health Organization even lists antimicrobial resistance as one of their top 10 threats to humanity.[26] Studies of children with tracheostomies frequently demonstrate airway bacterial colonization, often with drug-resistant *Pseudomonas aeruginosa* and Methicillin-resistant *Staphylococcus aureus*.[27] The microbiology and antimicrobial resistance patterns of tracheostomy-associated infections have been summarized in recent reviews.[19,21,28] This review aims to summarize 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.

2 | METHODS

The aim of this systematic review was to summarize and characterize existing literature addressing the use of antimicrobials in pediatric patients with a tracheostomy. A comprehensive search of PubMed (National Library of Medicine) and Embase (Elsevier) online databases was undertaken on April 4, 2023, using the search terms ("children" OR "pediatric" 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. We excluded studies with both adult and pediatric participants, if pediatric-specific subgroup data were not available for 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.[29]

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 summarized 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 randomized 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 summarized in Table 1. Of these studies, one covered initiation of antimicrobials in outpatient clinics,[32] four looked

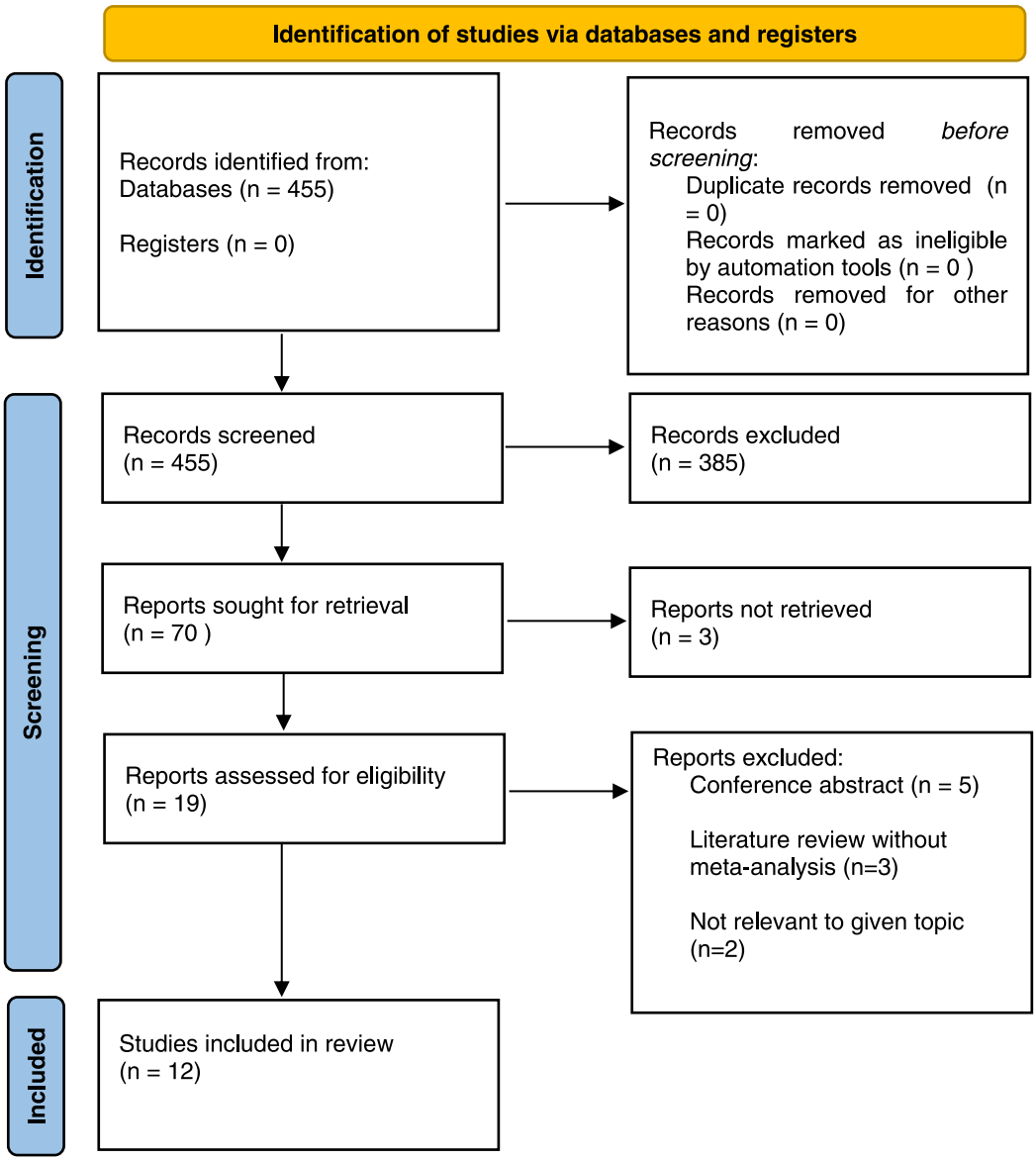

FIGURE 1 PRISMA flow diagram of identification of studies via databases.[26] [Color figure can be viewed at wileyonlinelibrary.com]

at choice of inpatient antimicrobials,[30,31,33,34] and one assessed the impact of duration of antimicrobial therapy for airway infections.[20]

Majmudar et al. compared antimicrobial prescription (enteral or inhaled) versus increased airway clearance therapies (chest physiotherapy and the use of nebulizers 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 hospitalizations within 28 days of treatment, compared to those who received an antimicrobial: adjusted odds ratio (OR) 1.47 (95% confidence interval [CI]: 0.75–2.86); $p = .26$.[32] 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 randomization, biasing the study results. In part, this may reflect the difficulties clinicians have in differentiating bacterial and nonbacterial 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.[35] 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 dyspnea, 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

TABLE 1 Summary table of studies using systemic antimicrobials.

Study	Study type	Country	Number of participants	Indication	Antimicrobial choice	Duration of antimicrobial therapy	Outcome
Smith et al.[30]	Single-center retrospective cohort study	USA	60	Ventilator-associated pneumonia	Fluoroquinolones (ciprofloxacin or levofloxacin)	Median 8 days (range 7–10 days)	65/76 (86%) infective episodes successfully treated
Tamma et al.[20]	Single-center retrospective cohort study	USA	118	Ventilator-associated pneumonia	β-lactam (either a penicillin, cephalosporin, or carbapenem) plus an aminoglycoside	Median 5.9 days in short course cohort, 9.8 days in long course cohort	Percentage of those reinfected within 10 days of completion abx course: 19/82 (23%) prolonged-course antibiotic therapy 6/36 (20%) short-course antibiotic therapy
Russell et al.[31]	Multi-center retrospective cohort study	USA	4137	Tracheostomy-associated pneumonia	Anti-Pseudomonas antibiotics	Not specified	Increased hospital-level use of antibiotics targeting P. aeruginosa was associated with significantly longer length of stay (adjusted % difference on average LOS per 10% increase in antibiotic usage = 3.4%; 95% CI: 0%–7.0%)
Majmudar et al.[32]	Single-center retrospective cohort study	USA	82	LRTI in children with a tracheostomy	Inhaled tobramycin and amoxicillin-clavulanate	Not specified	Airway clearance alone did not have significantly higher odds of hospitalization, compared to those who received an antibiotic: adjusted OR 1.47
Russell et al.[33]	Multi-center retrospective cohort study	USA	3715	Bacterial tracheostomy–associated respiratory tract infections	Anti-*Pseudomonas aeruginosa* antibiotics	Not specified	Empirical anti-*Pseudomonas aeruginosa* antibiotics associated with increased LOS (aLOS +0.6 days; 95% CI: 0.3–0.9).
Tan et al.[31]	Single-center retrospective cohort study	Taiwan	90	Tracheostomy-associated pneumonia	Not specified	Not specified	Difficult to differentiate between bacterial and nonbacterial pneumonia episodes resulting in 35% of LRTI being treated with antibiotics within 2 weeks.

enteral fluoroquinolones effectively treated the majority of infections (65/76, 86%).[30] Interestingly, two large retrospective cohort studies using the Pediatric Health Information System database in the United States between 2007 and 2014 reported that the 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.[31,33] 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.[31]

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 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.[20]

3.4 | Topical (inhaled) antibiotics

Three retrospective cohort studies evaluated the use of nebulized antimicrobials in pediatric tracheostomy patients.[36–38] Of these studies, one assessed the use of prophylactic nebulized antimicrobials,[37] one nebulized antimicrobials in the context of LRTIs[36] and one reported possible safety concerns regarding the ongoing use of nebulized tobramycin in pediatric tracheostomy patients.[38]

A small retrospective cohort study of 22 tracheostomised children looked at the use of nebulized antimicrobials to manage persistent bacterial lower airway colonization following LRTI, according to the results of the tracheal aspirate cultures.[36] There was no control group or standard antimicrobial regimen: 14 received gentamicin and 8 received colistin, median antibiotic duration was 3.5 months. Nebulized antimicrobials reduced median bacterial colony count at the 12th month after the start of the nebulized antimicrobials (10^5 colony-forming unit [CFU]/mL vs. 10^4 CFU/mL; $p = .02$). The median number of hospitalizations following treatment with nebulized antimicrobials decreased from 2 (range 1–3.5) to 1 (range 0–1.5) ($p = .04$). Additionally, the 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 nebulized antimicrobials ($p = .028$). 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 trialed the use of either inhaled colomycin or tobramycin for a median of 74 days (range 22–173 days).[37] 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-month pretreatment versus 3-month posttreatment, 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 pediatric patients with concomitant renal disease.[38] In their retrospective cohort of 12 tracheostomy-dependent pediatric 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.

3.5 | 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 the choice of antimicrobial therapy. Prinzi et al. looked at the association between over-reporting of such cultures in tracheostomised pediatric patients and its subsequent effect on antimicrobial prescribing.[39] Over-reporting was defined according to the American Society of Microbiology guidelines as reporting organisms not known to be respiratory pathogens. During the 1-year study period, 826 endotracheal aspirate cultures were collected from 448 children. From these cultures, 310 isolates were identified in tracheostomised children. Of these, 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.[40] 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 the 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-center retrospective review.[41] 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 as 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 practices 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 summarizes the current evidence base for the use of antimicrobials in tracheostomy-dependent pediatric patients. All 12 studies identified were retrospective cohort studies. These highlight four core themes that should be the topic of future research: (i) route of antimicrobial administration (systemic vs. topical); (ii) the role of cultures in guiding antimicrobial use; (iii) timing of antimicrobial use (reactive vs. prophylactic); and (iv) clinical decision aids to help determine which patients would benefit from antimicrobial therapy. All of these would help clinicians optimize management for these children, reducing the need for escalation of care and improving antimicrobial stewardship. There is an urgent need for prospective, randomized 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[33] and hospital level,[31] 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 on theoretical benefits, such as higher tracheal antibiotic concentrations and reduced side effects. As well as the extrapolation of evidence from the management of adult ventilator-associated pneumonia,[42] cystic fibrosis,[43] and non-cystic fibrosis bronchiectasis.[44] 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 nebulized antimicrobials have been used in the treatment of respiratory illness for over 70 years,[45] further studies are needed to evaluate and compare alternate antimicrobial use in children with tracheostomies.[29]

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.[46] Prophylactic antimicrobials have also been investigated in the context of recurrent LRTI[37,47] and persistent bacterial colonization after LRTI.[36] 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.[48] Although early evidence on prophylactic inhaled antibiotic use is promising, it is very weak, limited to two small retrospective cohort studies.[37,47] One of these studies was a retrospective case series of six tracheostomised children, which reported a reduction in antimicrobial use and episodes of LRTI; however, neither finding was statistically significant. The second study was excluded from our analysis as it included a mixed cohort of (11 tracheostomised and 9 non-tracheostomised) children and adults (age range 0–37 years). Subgroup analysis of the mixed adult and pediatric tracheostomised patients indicated that inhaled antibiotics resulted in a significant reduction in respiratory tract infection, systemic antibiotic use and importantly hospitalizations. Given the already troubling prevalence of multidrug-resistant organisms in this population,[27] randomized 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 pediatric 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 colonization 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.[41] Whilst Prinzi et al. demonstrated the potential harms of over-reporting aspirate cultures, which can lead to unnecessary antimicrobial exposure.[39] Further, Cline et al. demonstrate the danger of utilizing historical culture results to guide current treatment, which they estimate would only be effective in half of cases.[40] 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.[49,50] 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.[28]

The data summarized here have four main overriding limitations. First, the populations studied were heterogeneous in terms of design, intervention, and outcome measures, limiting their generalizability. Second, there was no standardized definition of tracheostomy-associated respiratory infections across different studies, which often just reported clinical diagnoses, 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 the interpretability of their results and subsequent meta-analysis. Third, 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. It is worth noting that only 12 studies met our inclusion criteria, highlighting the paucity of research on this topic. Prospective, randomized, 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 randomized controlled trial evidence to date. The studies included in our review highlight the significant variation in antimicrobial usage between centers, including antimicrobial selection, duration, and administration route. There is an urgent need for future research to help rationalize antibiotic usage for this vulnerable patient cohort.

AUTHOR CONTRIBUTIONS

Helen Pearce: Investigation; writing—original draft. **Benjamin James Talks**: Investigation; conceptualization; writing—original draft. **Steven Powell** and **Malcolm Brodlie**: Writing—review and editing. **Jason Powell**: Conceptualization, supervision; writing—review and editing.

ACKNOWLEDGMENTS

This work was supported by the Medical Research Council, United Kingdom (grant MR/X018237/1 MRC Clinician Scientist Fellowship to Jason Powell).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Helen Pearce http://orcid.org/0009-0005-5768-1518
Benjamin James Talks http://orcid.org/0000-0003-4896-2324
Steven Powell http://orcid.org/0000-0001-7181-4608
Malcolm Brodlie http://orcid.org/0000-0003-4591-8299
Jason Powell http://orcid.org/0000-0002-1199-8406

REFERENCES

1. Watters KF. Tracheostomy in infants and children. *Respir Care*. 2017;62(6):799-825.
2. Pérez-Ruiz E, Caro P, Pérez-Frías J, 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, et al. Pediatric tracheostomy: a large single-center experience. *Laryngoscope*. 2020;130(5):E375-E380.
4. Hall N, Rousseau N, Hamilton DW, et al. Impact of COVID-19 on carers of children with tracheostomies. *Arch Dis Child*. 2022;107(3):e23.
5. Özmen S, Özmen ÖA, Ünal ÖF. 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. Funamura JL, Durbin-Johnson B, Tollefson TT, Harrison J, Senders CW. Pediatric tracheotomy: indications and decannulation outcomes. *Laryngoscope*. 2014;124(8):1952-1958.
8. Canning J, Mills N, Mahadevan M. Pediatric tracheostomy decannulation: when can decannulation be performed safely outside of the intensive care setting? A 10 year review from a single tertiary otolaryngology service. *Int J Pediatr Otorhinolaryngol*. 2020;133:109986.
9. Chauhan N, Mohindra S, Patro SK, Mathew PJ, Mathew J. Investigation of the paediatric tracheostomy decannulation: factors affecting outcome. *Iran J Otorhinolaryngol*. 2020;32(110):139-145.
10. Bandyopadhyay A, Cristea AI, Davis SD, et al. Retrospective analysis of factors leading to pediatric tracheostomy decannulation failure. A single-institution experience. *Ann Am Thorac Soc*. 2017;14(1):70-75.
11. Mahida JB, Asti L, Boss EF, et al. 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.
12. 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.
13. 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.
14. Berry JG, Graham DA, Graham RJ, et al. Predictors of clinical outcomes and hospital resource use of children after tracheotomy. *Pediatrics*. 2009;124(2):563-572.
15. Zhu H, Das P, Roberson DW, et al. Hospitalizations in children with preexisting tracheostomy: a national perspective. *Laryngoscope*. 2015;125(2):462-468.
16. 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.
17. Meier JD, Valentine KJ, Hagedorn C, et al. Emergency department use among children with tracheostomies: avoidable visits. *J Pediatr Rehabil Med*. 2015;8(2):105-111.
18. Hall N, Rousseau N, Hamilton DW, et al. Providing care for children with tracheostomies: a qualitative interview study with parents and health professionals. *BMJ Open*. 2023;13(1):e065698.
19. Gipsman A, Prero M, Toltzis P, Craven D. Tracheobronchitis in children with tracheostomy tubes: overview of a challenging problem. *Pediatric*. 2022;57(4):814-821.
20. 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.
21. 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.
22. Feudtner C, Christakis DA, Connell FA. Pediatric deaths attributable to complex chronic conditions: a population-based study of

Washington State, 1980–1997. *Pediatrics*. 2000;106(Suppl_1): S205-S209.
23. Sommer MOA, Dantas G, Church GM. Functional characterization of the antibiotic resistance reservoir in the human microflora. *Science*. 2009;325(5944):1128-1131.
24. Apjok G, Számel M, Christodoulou C, et al. Characterization of antibiotic resistomes by reprogrammed bacteriophage-enabled functional metagenomics in clinical strains. *Nat Microbiol*. 2023;8(3): 410-423.
25. Wang C, Chen Y-H, Fang C, 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.
26. Antimicrobial Resistance. Accessed June 8, 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
27. Pozzi M, Pellegrino P, Galbiati 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.
28. Powell J, Powell S, Mather MW, et al. Tracheostomy in children is associated with neutrophilic airway inflammation. *Thorax*. 2023;78: 1019-1027.
29. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160.
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. Russell CJ, Mack WJ, Schrager SM, Wu S. Care variations and outcomes for children hospitalized with bacterial tracheostomy-associated respiratory infections. *Hospital Pediatr*. 2017;7(1): 16-23.
32. Majmudar P, Sanders DB, Slaven J, Cristea AI. Outpatient treatment of lower respiratory tract infections in children with tracheostomy—a single institution experience B51. PEDIATRIC SLEEP II. American Thoracic Society. In: American Thoracic Society International Conference Abstracts; 2020:A3685.
33. 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. *Hospital Pediatrics*. 2018;8(2):72-80.
34. Brook I. Treatment of aspiration or tracheostomy-associated pneumonia in neurologically impaired children: effect of anti-microbials effective against anaerobic bacteria. *Int J Pediatr Otorhinolaryngol*. 1996;35(2):171-177.
35. Tan C-Y, Chiu N-C, Lee K-S, et al. Respiratory tract infections in children with tracheostomy. *J Microbiol Immunol Infect*. 2020;53(2): 315-320.
36. Atag E, Unal F, Arslan H, et al. The effect of nebulized antibiotics in children with tracheostomy. *Int J Pediatr Otorhinolaryngol*. 2021;143:110665.
37. Jutras C, Autmizguine J, Chomton M, et al. Inhaled antibiotics for the prevention of respiratory tract infections in children with a tracheostomy. *Front Pediatr*. 2021;9:633039.
38. 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.
39. Prinzi AM, Wattier RL, Curtis DJ, et al. Impact of organism reporting from endotracheal aspirate cultures on antimicrobial prescribing practices in mechanically ventilated pediatric patients. *J Clin Microbiol*. 2022;60(11):e0093022.
40. 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.
41. 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.
42. Zampieri FG, Nassar Jr, AP, 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.
43. Smith S, Rowbotham NJ. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database Syst Rev*. 2022;11(11):001021.
44. 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.
45. Kuhn RJ. Formulation of aerosolized therapeutics. *Chest*. 2001;120 (3 Suppl):94S-98S.
46. Avelino MAG, Maunsell R, Valera FCP, et al. First clinical consensus and national recommendations on tracheostomized children of the Brazilian Academy of Pediatric Oto-rhinolaryngology (ABOPe) and Brazilian Society of Pediatrics (SBP). *Braz J Otorhinolaryngol*. 2017;83:498-506.
47. 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):00149-2018.
48. Legg J, Allen J-L, Andrew M, et al. BTS Clinical Statement on the prevention and management of community-acquired pneumonia in people with learning disability. *Thorax*. 2023;78(Suppl 1):s1-s31.
49. Pérez-Losada M, Graham RJ, Coquillette M, et al. Tracheal microbiota in patients with a tracheostomy before, during and after an acute respiratory infection. *Pediatr Infect Dis J*. 2018;37(11): e269-e271.
50. Pérez-Losada M, Graham RJ, Coquillette M, et al. The temporal dynamics of the tracheal microbiome in tracheostomised patients with and without lower respiratory infections. *PLoS One*. 2017; 12(8):e0182520.

How to cite this article: Pearce H, Talks BJ, Powell S, Brodlie M, Powell J. A systematic review of antimicrobial therapy in children with tracheostomies. *Pediatr Pulmonol*. 2023;1-8. doi:10.1002/ppul.26766