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REVIEW

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Diagnosis, management, and outcomes of pediatric tracheostomy-associated infections: A scoping review

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Abstract

Background: Children with tracheostomy are frequently admitted to the hospital for tracheostomy-associated respiratory infections (TRAINs). However, there remains a paucity of evidence to direct the diagnosis, treatment, and prevention of TRAINs. An important first step to addressing this knowledge gap is to synthesize existing data regarding TRAINs to inform current practice and facilitate innovation.

Data Sources: We searched PubMed, Embase, Cochrane Library, CINAHL, and Web of Science from inception to October 2020. Original research articles and published abstracts including children and young adults 0–21 years of age with tracheostomy were included. Included studies assessed the clinical definitions of and risk factors for TRAINs, microbiologic epidemiology and colonization of tracheostomies, and treatment and outcomes of TRAINs.

Data Synthesis: Out of 5755 studies identified in the search, 78 full-text studies were included in the final review. A substantial number of studies focused on the detection of specific pathogens in respiratory cultures including *Pseudomonas aeruginosa*. Several different definitions of TRAIN including clinical, microbiologic, and laboratory testing results were utilized; however, no uniform set of criteria were identified. The few studies focused on treatment and prevention of TRAIN emphasized the role of empiric antimicrobial therapy and the use of inhaled antibiotics.

Conclusions: Despite a growing number of research articles studying TRAINs, there is a paucity of prospective interventional trials to guide the diagnosis, treatment, and prevention of respiratory disease in this vulnerable population. Future research should include studies of interventions designed to improve short- and long-term respiratory-related outcomes of children with tracheostomy.

KEYWORDS

pediatrics, pneumonia, tracheitis, tracheostomy

1 | INTRODUCTION

Due to the advancement of life-sustaining medical technologies, an increasing proportion of children are living with complex chronic medical conditions and technology assistance, including children with tracheostomy.[1,2] At a cost of $1.4 billion, children with tracheostomy account for over 20,000 hospitalizations each year—most frequently due to acute TRacheostomy-Associated respiratory INfections (TRAIN) including pneumonia and tracheitis.[3] The challenges this population faces are further compounded by a frequent need for recurrent hospitalization. Indeed, children with tracheostomy frequently require ongoing inpatient care, with all-cause readmission rates of up to 60% within 6 months after initial tracheotomy[4] and up to 40% within 30 days after bacterial[5] and viral[6] TRAINs.

The advancement of care for TRAINs in children has reduced the need for hospitalization and improved other patient-related outcomes, though it has been historically limited by several factors. First, there is no universally accepted definition of TRAINs, with current practical definitions utilizing different combinations of respiratory cultures, radiographic and laboratory studies, and clinical evidence of respiratory distress or failure. This heterogeneity in definitions, and the variability in clinical presentations, limits both the accurate diagnosis of TRAINs and evidence-based guidance for treatment and management. Similarly, comparing studies investigating TRAINs is difficult given variation in protocol inclusion criteria. Second, children with tracheostomy often have significant comorbid conditions, such as neurologic impairment, that prevent effective clearance of airway secretions and predispose to recurrent infections.[7] The presence of these patient factors can introduce diagnostic and prognostic challenges. Third, children with tracheostomy are often omitted from clinical trials and guidelines. For example, guidelines put forth by the Infectious Diseases Society of America on the management of community-acquired pneumonia exclude children who are not otherwise healthy.[8] Furthermore, there is a lack of guidelines to standardize and direct effective, evidence-based care for the acute treatment and prevention of TRAINs from professional societies or clinical expert consortia.

An important first step to addressing this knowledge gap is to synthesize existing data regarding TRAINs to inform current practice and facilitate innovation. To date, there are no comprehensive, systematic reviews of pediatric TRAINs or published review protocols. The objective of this scoping review is to summarize the existing medical literature pertaining to the diagnosis, treatment, prevention, and outcomes of TRAINs in children. Additionally, we aim to identify knowledge gaps to direct future research.

2 | METHODS

2.1 | Research questions

The aim of this systematic scoping review was to characterize and summarize existing literature addressing four key questions pertaining to TRAINs: (1) What diagnostic criteria are used to characterize children as having TRAINs? (2) What risk factors are associated with the development of pediatric TRAINs? (3) What is the microbiology of TRAINs? and (4) What patient-level and clinical factors are associated with short- and long-term outcomes for children with tracheostomy and TRAIN including tracheostomy colonization, acute hospitalization, and hospital readmissions? A scoping review approach was chosen to systematically map existing evidence pertaining to TRAINs while minimizing bias in study selection and characterize how TRAIN research is being conducted.[9] Specifically, we focused on characterizing study settings, designs, and funding sources to provide context to the information presented in this review. We also aimed to identify knowledge gaps in existing research identifying TRAIN diagnostic criteria, tracheostomy colonization, antibiotic stewardship, and novel factors that would aid clinicians in the prognostication of tracheostomy-related morbidity.

2.2 | Identifying relevant studies

We searched the following bibliographic databases: PubMed (National Library of Medicine), Embase (Elsevier), Cochrane Library (Wiley), CINAHL (EBSCO), and Web of Science (Clarivate Analytics). A medical librarian (LK) initially created a PubMed search strategy using a combination of Medical Subject Headings (MeSH) and keywords for the concepts of tracheostomy, infection, and pediatrics. All team members reviewed the strategy and results to modify and improve the search strategy. With approval of the team, the librarian customized the search using controlled vocabulary and keywords in the databases listed above. The search strategy for this study is included in Supplemental Information. On February 13, 2020, all resulting citations were exported into an EndNote X9 library (Clarivate Analytics), and duplicates removed.[10] No additional efforts were conducted to seek out gray literature including study registries, web search engines, websites, or conference proceedings. On October 17, 2020, we repeated the search in the same bibliographic databases to identify recently published studies.

2.3 | Study selection

All references were uploaded to Covidence systematic review software (Covidence, Melbourne, Australia; www.covidence.org), and duplicates were removed. Four reviewers (John M. Morrison, Amir Hassan, Robert A. Dudas, and Christopher J. Russell) utilized a structured screening protocol adherent to the practices outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[11] The protocol was refined after reviewing 40 pilot abstracts and five full-text articles. Articles were included if study subjects were 0–21 years of age, had an existing tracheostomy at the time of the study, and received inpatient care for a presumptive TRAIN as outlined in the systematic search strategy. Children were included regardless of the initial clinical indications for tracheotomy. Articles were excluded if they focused on: perioperative outcomes associated with the tracheotomy procedure or postsurgical infections of the stoma, skin and

TABLE 1 Characteristics of included studies

Characteristic	Number (*N* = 78)	Percentage[a]
Publication year		
2010–2020	67	85.9
Before 2010	11	14.1
Study type		
Journal article	59	75.6
Conference abstract	19	24.4
Geographic location		
United States	48	61.5
Non-US North America	6	7.7
Africa	1	1.3
Asia	1	1.3
Australia/Oceania	4	5.1
Europe	14	17.9
South America	4	5.1
Study setting		
Inpatient/Hospital	54	69.2
Outpatient/Clinic Setting	14	17.9
Skilled Nursing Facility	7	9.0
Home	4	5.1
Other	7	9.0
Number of study sites		
Single center	61	78.2
Multicenter	17	21.8
Study design		
Observational	74	94.9
Retrospective cohort	55	70.5
Retrospective Case-Control	0	0.0
Prospective cohort	19	24.4
Interventional	4	5.1
Single arm	3	3.8
Controlled	1	1.3
Study funding		
Government organization	15	19.2
Nongovernment organization	2	2.6
Institutional	6	7.7
Industry	5	6.4
No funding	50	64.1
Broad study aim(s)		
Tracheostomy-associated respiratory infections (TRAIN) diagnostic criteria	12	15.4
Colonization/Detection of specific pathogen	34	43.6
Prevention of TRAIN	9	11.5
Risk factors for TRAIN	12	15.4
Treatment of TRAIN	10	12.8
Outcomes of TRAIN	15	19.2
Rehospitalization	14	17.9
Mention of chronic mechanical ventilation status	57	73.1
Inclusive of patients that do not use English as a primary language (US-only; *N* = 48)	0	0.0
Socioeconomic factors included	10	12.8
Race/ethnicity included	13	16.7

[a]Categorical percentages may not add to 100% for categories in which studies could be counted in multiple categories (e.g., geographic location, study setting, and broad study aims).

soft tissue infections of the tracheostomy site, or children who are immunocompromised (either through medication or because of genetic/acquired immunodeficiency) to minimize the potential for undue bias of review evaluating short- and long-term morbidity. Articles not available in English or Spanish were also excluded.

2.4 | Data collection and synthesis

Data from each article were independently extracted by two reviewers and entered separately into a REDCap (Nashville, TN) database. Key study findings pertaining to operational definitions, microbiologic epidemiology, clinical risk factors, prevention, and treatment of TRAINs were extracted and stored in the database. Data of interest are summarized in both text and Tables 1–3 and include information relating to study characteristics, diagnostic criteria for presumptive TRAIN, and specific pathogens of interest (see Supplemental Information for full listing of data extraction elements).

3 | RESULTS

3.1 | Study selection (Figure 1)

Our initial literature search yielded a total of 5755 citations. After removing duplicates and those meeting exclusion criteria, 4452

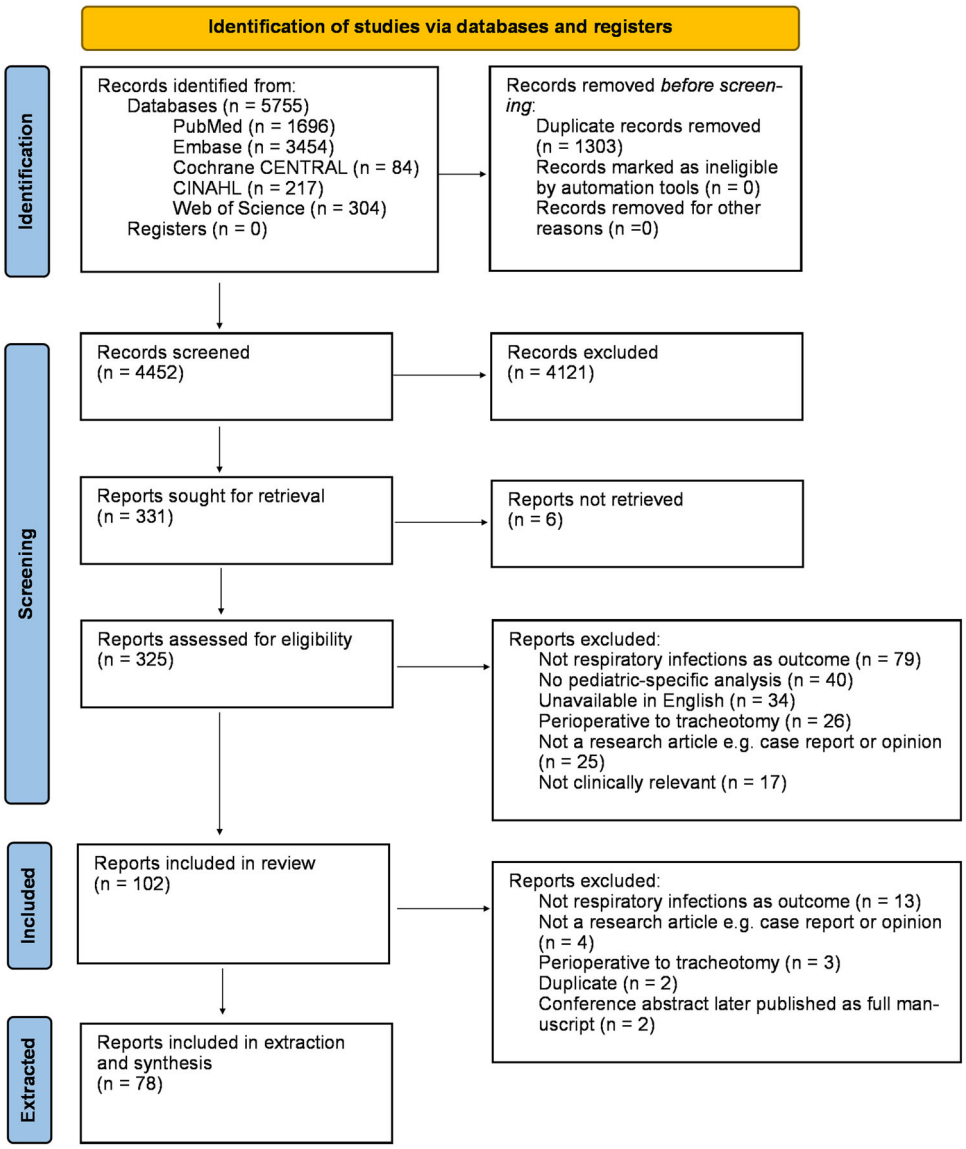

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews study flow diagram [Color figure can be viewed at wileyonlinelibrary.com]

citations were screened and 331 full-text citations were assessed for eligibility. A total of 229 articles were excluded during full-text review for reasons listed in Figure 1. From the remaining 102 full-text citations that underwent review for data extraction, 78 were ultimately included in this scoping review.

3.2 | Study characteristics

Table 1 summarizes the included study characteristics. Approximately 86% ($n = 67$) of studies were published between 2010 and 2020. Most of the studies were conducted in the United States (62%; $n = 48$) or Europe (18%; $n = 14$) and included predominantly acutely hospitalized children with tracheostomy (69%; $n = 54$). Only four studies (5) included in-home care of study participants. Ninety-five percent ($n = 74$) of the studies were observational, most being retrospective cohort studies (71%; $n = 55$). Among the four prospective, interventional studies, only one included a control group for comparison.[12] The most common study aim centered on the detection and colonization of specific respiratory pathogens (43%; $n = 34$); only nine studies (11%) focused on the prevention of TRAINs. Inclusion of socioeconomic factors (13%; $n = 10$) or race/ethnicity (17%; $n = 13$) as independent variables were infrequent.

3.3 | Defining TRAIN

Table 2 summarizes the various diagnostic criteria used to define TRAIN. Eighteen studies (23%) did not include a clinical outcome and thus did not mention diagnostic criteria. Of the remaining 60 studies,

TABLE 2 Diagnostic criteria for defining tracheostomy-associated respiratory infections (TRAIN)

Characteristic	Number ($N = 60$[a])	Percentage[b]
Patient factors	20	33.3
Fever	14	23.3
Cough	7	11.7
Hypoxemia/desaturations	11	18.3
Tachypnea	4	6.7
Abnormal auscultation	6	10.0
Increased work of breathing/ respiratory distress	6	10.0
Thickened/increased/abnormal tracheal secretions	14	23.3
Increased ventilatory settings	7	11.7
Microbiologic factors	19	31.7
Positive culture only	11	18.3
Semi-quantitative culture results	0	0
Quantitative culture results	9	15.0
Gram-stain findings	4	6.7
Ancillary factors	12	20.0
Viral testing	0	0.0
Inflammatory markers	4	6.7
Peripheral white blood cell count	10	16.7
Abnormal Chest X-ray	11	18.3
Provider/institutional factors	29	48.3
Billing/coding-based	21	35.0
Physician decision-to-treat	8	13.3
Other	2	3.3

[a]Only inclusive of studies that required a diagnosis of TRAIN (excluding detection of pathogen only).

[b]Percentages may not add up to 100%.

48% used billing and coding-based ($n = 21/60$) or physician decision-to-treat inclusion criteria ($n = 8/60$). A variety of databases were utilized, including institutional/regional databases,[13–17] Kids' Inpatient Database,[3,18] and the Children's Hospitals Association Pediatric Health Information System (PHIS) registry.[5,19,20] Identifying hospitalizations and other TRAIN-related outcomes can be difficult in administrative and registry-based databases without corresponding clinical or laboratory data. To address this, several studies excluded patients without documentation of positive culture and/or pathogen testing results[21] or those not receiving antibiotic therapy.[5,19,20]

Diagnostic criteria varied among the included studies that utilized a combination of clinical, radiographic, and laboratory definitions for TRAIN (Table 2). Clinical factors incorporating the Centers for Disease Control and Prevention definition of ventilator-associated pneumonia[22] were used in 33% ($n = 20/60$) of the studies, with the presence of fever (23%; $n = 14/60$) and history of hypoxemia (18%; $n = 11/60$) being the most common. Microbiologic factors from a respiratory specimen were utilized in 32% ($n = 19/60$) of the studies evaluating outcomes of TRAINs. Eleven (18%) that included microbiologic data required patients only have a positive culture to be included in the particular study.[21,23–32] The remaining eight studies (13%) reported qualitative culture results.[33–40] Although microscopic findings from a Gram-stain of a respiratory specimen can aid in identifying the presence of bacteria and host inflammatory cells, only 7% ($n = 4/60$) of studies included Gram-stain results as a diagnostic criterion.[29,35–37]

In addition to clinical and microbiologic factors, 20% ($n = 12/60$) of included studies utilized systemic inflammatory markers, peripheral white blood cell count (WBC), or the presence of an abnormal chest X-ray finding. Abnormal WBC was the most frequently utilized laboratory-based diagnostic criterion for TRAIN and was present in 10 of the included studies,[26,31–33,35–38,40,41] with elevated C-reactive protein used for TRAIN diagnosis in only four studies.[32,35–37] Abnormal chest X-ray findings were included as diagnostic criteria in 11 studies, including several different operational definitions of abnormal findings such as a pneumonia "patch,"[32] new or progressive infiltrates,[33,35,36,38,42] new consolidation/cavitation/pleural effusion,[38] or just "new changes."[12]

3.4 | Clinical risk factors for TRAIN

Overall, 22% ($n = 17/78$) of studies mentioned risk factors for the development of TRAIN, with the most frequently studied category being medical comorbidities (15%; $n = 12/78$). Several clinical factors were examined among the included studies. Comorbid conditions were most often examined among the included studies, with the number of chronic complex conditions[5,20] and neurologic impairment[20,32,43] being most frequently associated with risk of TRAIN, followed by gastrointestinal disorders such as gastroesophageal reflux disease and dysphagia.[20,32,44]

Among the demographic factors studied, younger patient age was associated with risk of developing a TRAIN in only two studies.[20,43] While 13% of studies included some mention of socioeconomic factors, only a single study reported on the association between a socioeconomic factor and a clinically relevant outcome.[5] Similarly, 22% of studies included race/ethnicity data; however, only two studies reported on associations with TRAIN outcomes.[5,20] Notably, the reported association of Hispanic ethnicity with increased risk for revisit to the hospital after initial tracheotomy procedure likely reflects inequities in healthcare that may lead to differential outcomes.[20]

Colonization of the airway, or chronic infection, was the most frequently studied risk factor for the development of TRAIN, with 55% ($n = 43/78$) of all included studies reporting on the chronic presence of particular bacteria and 19% ($n = 15/78$) investigating the impact of colonization on subsequent risk of developing a

TABLE 3 Pathogens of interest mentioned in included studies (*N* = 78)

Bacterium	Primary study focus		Any mention	
	Number	Percentage[a]	Number	Percentage[a]
Pseudomonas aeruginosa	13	16.7	37	47.4
Staphylococcus aureus	5	6.4	29	37.1
Stenotrophomonas maltophilia	5	6.4	21	26.9
Moraxella catarrhalis	4	5.1	14	17.9
Serratia marcescens	2	2.6	16	20.5
Haemophilus influenzae	3	3.8	15	19.2
Streptococcus pneumoniae	6	7.7	14	17.9
Acinetobacter baumannii	2	2.6	7	9.0
Klebsiella pneumoniae	2	2.6	12	15.4
Virus				
Respiratory syncytial virus	2	2.6	8	10.3
Influenza A/B	1	1.3	3	3.8
Human metapneumovirus	1	1.3	4	5.1
Rhinovirus/enterovirus			5	6.4
Parainfluenza (1/2/3/4)			0	0.0
Adenovirus	1	1.3	3	3.8
Coronavirus (229E/HKU1/NL63/OC43)			1	1.3
Coronavirus (SARS-CoV-2)			0	0.0
Microbiome			3	3.8
Multidrug resistant organisms			4	5.1

[a]Percentages may not add up to 100%.

TRAIN.[17,25,26,28,30,35–37,39,44–49] Only 33% (*n* = 5/15) of studies investigating the relationship between colonization and TRAINs utilized clear operational definitions of colonization, including: the presence of a pathogen for 4 consecutive weeks,[26] detection of a pathogen in the lower respiratory tract in the absence of clinical symptoms suggestive of TRAIN,[35,36,42] growth of a pathogen in two separate quarters within a 12-month calendar year,[17] and ≥75% of cultures positive for a specific pathogen within a 2-year period.[50]

3.5 | Microbiology of TRAINs

Many studies focused on the contribution of specific bacteria (32%; *n* = 25/78) and viruses (6%; 5/78) to airway colonization among children with tracheostomy or outcomes related to TRAINs (Table 3). *Pseudomonas aeruginosa* was the most frequently mentioned bacterium, and was the primary study focus of 17% (*n* = 13/78) of studies and mentioned in 47% (*n* = 37/78). Less frequently, other bacterial pathogens, including *Streptococcus pneumoniae* (8%; *n* = 6/78), *Staphylococcus aureus* (6%; *n* = 5/78), and *Stenotrophomonas maltophilia* (6%; *n* = 5/78) were the primary focus. (Table 3). Twenty-eight studies (36%) discussed the microbiologic epidemiology of children with tracheostomy in several different capacities, including only children with tracheostomy (*n* = 14/28)[23,31,32,36,50–59] or combining children with tracheostomy and those with endotracheal intubation (*n* = 7/28).[21,24,60–64] Among studies focusing solely on children with tracheostomy, inhaled corticosteroid administration,[50] season/time of year,[55] mechanical ventilation dependence,[50,57] and pre-tracheotomy tracheal culture results[47,50,59] were associated with detection of specific bacteria including *P. aeruginosa*.

Study of nonbacterial causes of TRAINs were rare. Five studies evaluated virologic causes of TRAINs, including rhinovirus/enterovirus,[65] adenovirus,[66] respiratory syncytial virus,[16,67] and viral co-infection with bacterial TRAINs.[68] Only a single study investigated invasive candida infections.[69] Three studies investigated the respiratory microbiome, including changes in bacterial diversity between clinical states with and without respiratory illness.[39,48,70]

3.6 | Prevention of TRAIN

Thirteen (16%) of the included studies investigated the prevention of TRAINs. Three studies (4%) mentioned inhaled antibiotic use;[44,62,71] however, only one was a peer-reviewed manuscript.[62] Ten studies described tracheostomy-related care and respiratory secretion clearance strategies on TRAIN outcomes. Several interventions were

studied, including: in-home suctioning frequency and techniques,[72] patient positioning and oral care,[33] topical application of antibiotics to the tracheal stoma,[35] use of heated humidified air,[12] and respiratory clearance strategies.[73,74] Parental report of tracheostomy tube reuse at home was associated with an increased risk of TRAIN.[72] Fewer children with tracheostomy experienced a TRAIN with the use of nocturnal heated humidification compared to continuous heat-moisture exchange use[12] and those receiving intrapulmonary percussive ventilation compared to those with high-frequency chest wall oscillation.73Patients also experienced a clinically (but not statistically) significant reduction in hospitalization for TRAIN when receiving an aggressive respiratory airway clearance consisting of cough-assist mechanical insufflator-exsufflator and high-frequency chest wall oscillation.[74] A care bundle consisting of standardized elevation of the head of the bed, oral care, tracheostomy tube cuff pressure, and ventilator circuit changes was 9-times more effective at reducing the incidence of ventilator-associated respiratory infections in children with tracheostomy.[33] Finally, two studies describing multidisciplinary and interprofessional approaches to coordinating care of the child within the post-acute care[41] and in-home settings[75] were also identified.

3.7 | Treatment of TRAIN

Nearly 17% (n = 13/78) of the included studies specifically focused on the acute treatment of TRAINs.[5,6,19,23–25,31,41,43,60,73,76,77] Four studies focused on the effect of empiric treatment options on clinically relevant outcomes. Brook et al. reported that more children with tracheostomy and pneumonia receiving antimicrobials with activity against anerobic bacteria had a positive response to therapy (defined as improvement in clinical signs and/or radiographic findings during therapy) compared to those receiving other antibiotics (92% vs. 40%).[76] More recently, Russell et al. reported that empiric treatment with anti-pseudomonal antibiotics among hospitalized children with tracheostomy is common (median rate of 67.3%)[19] and associated with longer durations of hospitalization (adjusted length of stay = +0.6 days).[5] Although several studies mention the relationship of duration of antimicrobial therapy to TRAIN outcomes,[23,24,41,43,60] no study addressed an optimal duration of treatment for TRAINs.

3.8 | Outcomes of TRAIN

Twenty-eight percent (n = 22/78) of the included studies focused on TRAIN clinical outcomes. Fourteen studies (18%) investigated factors associated with readmission or re-presentation to an emergency department setting, and eight studies (10%) evaluated factors associated with longer hospital LOS. Reported readmission rates among included studies ranged from 20%–40%,[5,14,15,78–80] although not all studies reported readmission rates specifically due to TRAINs. Broad categories associated with readmissions included dependence on mechanical ventilation/supplemental oxygen,[5,14,78] younger age,[5,14] number of medical comorbidities,[5] administration of corticosteroids,[14] and changes in medical management preceding discharge from the hospital.[15] Studies identifying factors associated with longer LOS were less frequent and did not always provide sufficient detail to establish a relationship between clinical factors and hospital LOS. A single multicenter study by Russell et al. identified mechanical ventilation, younger age, public insurance status, and number of chronic conditions to be associated with longer LOS.[5]

4 | DISCUSSION

We conducted a scoping review of 78 articles to describe the current literature pertaining to criteria used for defining TRAINs, risk factors associated with the development of pediatric TRAINs and the patient-level and clinical factors associated with short and long-term outcomes for children with tracheostomy and TRAINs. While research involving children with tracheostomy has expanded in the last decade, there continues to be a significant gap in the literature regarding diagnosing, preventing, and treating TRAINs. Several key knowledge gaps important to the clinical care of children with tracheostomy and future research opportunities were identified.

Our scoping review identified an urgent need for prospective studies involving children with tracheostomy. Over 70% of studies were retrospective in nature and accompanied by the limitations of data granularity and uncertain causal relationships of interest. Furthermore, the inclusion of large cohorts of patients from retrospective periods of time prohibits the consideration of institutional secular trends that may affect key outcomes related to TRAIN, such as efforts to reduce the number of respiratory cultures and other laboratory testing that may influence diagnostic and treatment decisions.[81] Of the prospective studies including only children with tracheostomy, the detection of bacterial or other pathogens was the primary outcome of interest. Studies focused on the outcomes of children acutely hospitalized were most often set in the PICU and included children mechanically ventilated via endotracheal intubation as well as tracheostomy tube. The heterogeneity between these populations, especially children with existing tracheostomy and the chronic presence of bacteria in the airway, prove difficult in assessing individual conclusions given how respiratory culture results influence a clinician's decision to administer antibiotic therapy.[36,50] Furthermore, the extrapolation of findings to children with tracheostomy not requiring chronic mechanical ventilation may not be valid. Prospectively collected data combined with clinically relevant case definitions and adjudication of data discrepancies would provide an invaluable database of knowledge to investigators and clinicians interested in outcomes for children with tracheostomy. Future studies focused on interventional trials would be particularly beneficial to advancing the care for TRAINs. Currently, clinicians are limited by a lack of high-quality evidence to identify which children with tracheostomy would benefit from antibiotic therapy.

4.1 | Definition of TRAIN

There remains no standardized definition for TRAIN among published studies. Most studies utilized billing and coding and physician decision-to-treat criteria for identifying patients diagnosed with TRAIN. While administrative databases and registries can increase the sample size and statistical power, reliance solely on administrative data lacking granular detail could potentially result in the misclassification of patients due to an inherent inability to examine results of respiratory cultures, viral testing, and other adjunctive diagnostic testing. Although a uniformly accepted definition may not be possible, an endorsed agreement among professional societies and research consortia on specific criteria would assist with standardizing research and clinical diagnostic definitions for children with tracheostomy.

4.2 | Treatment of TRAIN

While only 10/78 (13%) of studies included treatment-related outcomes, several key themes emerged. First, identifying the optimal empiric and treatment antibiotics remains challenging, including the benefit of coverage with anti-pseudomonal antibiotics given the frequent airway colonization of children with tracheostomy with *P. aeruginosa*. Limiting therapy based on previously obtained cultures is also largely ineffective, as empiric antibiotics based on prior respiratory cultures provide adequate antimicrobial coverage in only 56% of patients and assist with narrowing the spectrum of antimicrobial activity in only ~20% of patients.[25] No other studies explicitly examined duration of treatment and clinically relevant outcomes. While recent data investigating community-acquired pneumonia suggest shorter duration of antimicrobial therapy may be effective, these studies do not include children with existing pulmonary disease.[82,83] In the absence of high-quality, reliable evidence, clinicians extrapolate data from related but clinically distinct populations (i.e., endotracheally intubated patients) to guide therapy.

4.3 | Host-pathogen interactions

While children with tracheostomy often are colonized, or chronically infected, with bacteria,[50] it remains unclear why certain bacteria, including *P. aeruginosa* and *S. aureus*, persist in the host despite frequent exposure to seemingly appropriate antibiotics. In our scoping review, few studies investigated the persistence of bacteria within the airway, the result of this persistence in mediating host inflammation and immune response, and the resultant effect on clinically relevant outcomes. While existing studies suggest that the acquisition of *P. aeruginosa* in the airway is associated with worsening pulmonary disease, the etiologies behind this observation are unclear.[4,19,20] Our scoping review did not identify any full articles or abstracts focused on describing the mechanisms behind the frequent and recurrent TRAINs experienced by children with tracheostomy. The absence of such studies further dampens efforts to identify novel therapeutic and preventative strategies to mitigate the risk of recurrent infection in children with tracheostomy.

4.4 | Future directions

Taking the results of our scoping review and the primary knowledge gaps identified, several study areas warrant particular emphasis in future research. First, there is an urgent need to identify which patients benefit from antibiotic treatment. Unnecessary exposure to broad-spectrum antibiotics carries a risk of driving antibiotic resistance, although this has not yet been shown specifically in children with tracheostomy. Further considerations to the cost of hospitalization of expensive intravenous antibiotics and antibiotic-associated adverse events are becoming increasingly recognized. Thus, future research focused on understanding the most appropriate empiric antibiotic choice and what clinical factors (e.g., viral testing and respiratory Gram-stain results) influence the need for empiric antibiotic therapy is needed.

A second area for future research is the role of inhaled antibiotic delivery. Inhaled antimicrobial therapy targeting *P. aeruginosa* has been effective in children and adults with cystic fibrosis in reducing frequency of pulmonary exacerbations and preserving pulmonary function.[84–88] Only four studies included in our scoping review at least mentioned the use of inhaled antibiotics for the prevention of TRAIN.[43,44,62,71] While early evidence of small cohorts of children suggests a potential benefit, there lacks prospective, high-quality evidence to support the use of inhaled antibiotics in this population.

Third, research on the evolution of the respiratory microbiome in children with tracheostomy is needed. While the respiratory microbiota vary between patients with and without lower respiratory tract infections [70] and during the course of an acute respiratory illness,[39] how the microbiome affects clinically relevant outcomes and whether interventions can be effective in reducing infection and hospitalization is unclear. In other childhood respiratory illness, such as asthma, changes in microbiota during the neonatal period have been linked with atopy and the development of childhood asthma.[89–92] Similarly, alterations in gut microbiota have been linked to differences in pulmonary outcomes among children with cystic fibrosis.[93] The role of microbiota diversity in children, particularly the evolution after tracheotomy, and its relationship with TRAIN outcomes may help to identify children at risk for recurrent infections and hospitalizations.

Finally, a mechanistic understanding of the factors that contribute to the chronic presence of otherwise pathogenic bacteria within the airway, the interactions with the host immune and respiratory system, and resultant effects on clinical outcomes is needed. While a growing amount of evidence suggests that the mere presence of a bacterium in a respiratory culture is not synonymous with acute infection, it is unclear what effects the chronic presence of a bacterium does exhibit on its host. More importantly, there is a lack of understanding about when a chronic infection, which may not confer appreciable clinical symptoms, transitions to acute infection associated with clinical symptoms and the need for hospitalization. Several potential avenues of research could provide insight into this important knowledge gap, including the investigation of acute and convalescent host immune responses,[94–100] importance of pathogen-specific signaling

molecules in mediating host-pathogen interactions,[101–106] and molecular determinants of antibiotic susceptibility.[107] Exploration of these topics, and others, could provide important mechanistically plausible and potentially modifiable targets for the development of precision-based therapeutics aimed at improving the short- and long-term outcomes of children with tracheostomy.

While we utilized a structured article selection process with broad search terms, relevant studies may have been missed. Studies from the gray literature and studies published in non-English or -Spanish languages were excluded from this review. The heterogeneity of study designs and data reporting precluded synthesis of information pertaining to chronic mechanical ventilation and the review aims. Additionally, although disagreements in article inclusion and data extraction were adjudicated by group consensus, conduction of this review by other reviewers may have yielded different results. Finally, we did not formally assess the methodologic rigor of each article.

5 | CONCLUSION

While a significant amount of research has focused on describing the prevalence of TRAIN and the resultant impact on the health care system, there is a critical need for research investigating the diagnosis, treatment, and prevention of TRAINs. In this scoping review, we outlined several knowledge gaps that, if addressed, could result in the improvement of care provided to children with tracheostomy. We have also identified several areas of research that extend beyond the description of TRAINs as a clinical entity and could aim to address the "why" and "how" of acute and recurrent TRAINs.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

John Morrison: Conceptualized and designed the scoping review, participated in article review and data extraction, contributed to the interpretation of results, drafted the initial manuscript, and reviewed and revised the manuscript. Amir Hassan and Robert Dudas: Designed the scoping review, participated in article review, contributed to the interpretation of results, and reviewed and revised the manuscript. Lynn Kysh: Designed and executed the scoping review article extraction protocol, created and ran the database search strategies, contributed to the interpretation of results, and reviewed and revised the manuscript. Christopher Russell: Conceptualized and designed the study, participated in article review and data extraction, supervised initial drafting of the manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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