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COVID-19 Vaccine Hesitancy Among Parents: A Qualitative Study

Aubree Honcoop, MPS,[a] James R. Roberts, MD, MPH,[b] Boyd Davis, PhD,[c] Charlene Pope, PhD, MPH, RN, FAAN,[b] Erin Dawley,[b] Russell J. McCulloh, MD,[a] Maryam Y. Garza, PhD, MPH, MMCi,[d] Melody L. Greer, PhD,[d] Jessica Snowden, MD, MS, MHPTT,[d] Linda Y. Fu, MD,[e] Heather Young, MD,[d] Walter Dehority, MD,[f] Paul T. Enlow, PhD,[g] Delma-Jean Watts, MD,[h] Katie Queen, MD,[i] Lisa M. Costello, MD, MPH,[j] Zain Alamarat, MD,[d] Paul M. Darden, MD[d]

abstract

OBJECTIVES: Addressing parental/caregivers' coronavirus disease 2019 (COVID-19) vaccine hesitancy is critical to improving vaccine uptake in children. Common concerns have been previously reported through online surveys, but qualitative data from KII and focus groups may add much-needed context. Our objective was to examine factors impacting pediatric COVID-19 vaccine decision-making in Black, Spanish-speaking, and rural white parents/caregivers to inform the content design of a mobile application to improve pediatric COVID-19 vaccine uptake.

METHODS: Parents/caregivers of children aged 2 to 17 years from groups disproportionately affected by COVID-19–related vaccine hesitancy (rural-dwelling persons of any race/ethnicity, urban Black persons, and Spanish-speaking persons) were included on the basis of their self-reported vaccine hesitancy and stratified by race/ethnicity. Those expressing vaccine acceptance or refusal participated in KII, and those expressing hesitancy in focus groups. Deidentified transcripts underwent discourse analysis and thematic analysis, both individually and as a collection. Themes were revised until coders reached consensus.

RESULTS: Overall, 36 participants completed the study: 4 vaccine acceptors and 4 refusers via KIIs, and the remaining 28 participated in focus groups. Participants from all focus groups expressed that they would listen to their doctor for information about COVID-19 vaccines. Infertility was a common concern, along with general concerns about vaccines. Vaccine decision-making was informed by the amount of information available to parents/caregivers, including scientific research; possible positive and negative long-term effects; and potential impacts of vaccination on preexisting medical conditions.

CONCLUSIONS: Parents/caregivers report numerous addressable vaccine concerns. Our results will inform specific, targeted interventions for improving COVID-19 vaccine confidence.

NIH

WHAT'S KNOWN ON THIS SUBJECT: The coronavirus disease 2019 vaccine has shown effectiveness at limiting mortality because of the severe acute respiratory syndrome coronavirus 2 virus, but parents/caregivers have expressed hesitancy about vaccinating their children, especially among rural non-Hispanic white, both rural and urban Black, and rural and urban Spanish-speaking groups.

WHAT THIS STUDY ADDS: This study expands on reasons for decreased vaccine uptake among rural non-Hispanic white, rural and urban Black, and rural and urban Spanish-speaking groups. This study adds knowledge about parental attitudes toward the coronavirus disease 2019 vaccine by race/ethnicity and rurality.

To cite: Honcoop A, Roberts JR, Davis B, et al. COVID-19 Vaccine Hesitancy Among Parents: A Qualitative Study. *Pediatrics.* 2023;152(5):e2023062466

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Mx Honcoop participated in study design, data acquisition, data analysis and interpretation, and drafting and revising of the manuscript; Dr Roberts participated in study design, manuscript drafting, and critically revising of the manuscript; Dr Davis participated in study design, and data analysis and interpretation, and provided critical revisions to the manuscript; Dr Pope and Ms Dawley participated in study design, data acquisition, and data analysis and interpretation, and provided critical revisions to the manuscript; Drs McCulloh, Fu, and Darden participated in study design and data interpretation, and provided critical revisions to the manuscript; Dr Garza participated in study design, and data analysis and interpretation, co-led the data management, and provided critical revisions to the manuscript; Dr Greer participated in data analysis and data interpretation, and provided critical revision to the manuscript; (Continued)

Vaccine Mandates and Influenza Vaccination During the Pandemic

Claire Abraham, MD, MPH,[a,b,c] Laura F. Garabedian, PhD,[c] Robert F. LeCates, MA,[c] Alison A. Galbraith, MD, MPH[d]

abstract

OBJECTIVES: To determine whether a state influenza vaccine mandate and elevated community coronavirus disease 2019 (COVID-19) severity affected a child's probability of receiving an influenza vaccine during the 2020–2021 influenza season, given the child's previous vaccination history.

METHODS: Longitudinal cohort study using enrollment and claims data of 71 333 children aged 6 months to 18 years living in Massachusetts, New Hampshire, and Maine, from a regional insurer. Schoolchildren in Massachusetts were exposed to a new influenza vaccine mandate in the 2020–2021 season. Community COVID-19 severity was measured using county-level total cumulative confirmed case counts between March 2020 and August 2020 and linked by zip codes. The primary outcome of interest was a claim for any influenza vaccine in the 2020–2021 season.

RESULTS: Children living in a state with a vaccine mandate during the 2020–2021 influenza season had a higher predicted probability of receiving an influenza vaccine than those living in states without a mandate (47.7%, confidence interval 46.4%–49.0%, vs 21.2%, confidence interval 18.8%–23.6%, respectively, for previous nonvaccinators, and 78.2%, confidence interval 77.4%–79.0%, vs 58.2%, confidence interval 54.7%–61.7%, for previous vaccinators); the difference was 6.5 percentage points greater among previous nonvaccinators (confidence interval 1.3%–11.7%). Previously vaccinated children had a lower predicted probability of receiving an influenza vaccine if they lived in a county with the highest COVID-19 severity compared with a county with low COVID-19 severity (72.1%, confidence interval 70.5%–73.7%, vs 77.3%, confidence interval 74.7%–79.9%).

CONCLUSIONS: Strategies to improve uptake of influenza vaccination may have differential impact based on previous vaccination status and should account for community factors.

Full article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2023-061545

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Dr Abraham conceptualized and designed the study, conducted the initial analyses and interpretation of data, and drafted the initial manuscript; Dr Galbraith conceptualized and designed the study, and conducted the analysis and interpretation of data; Dr Garabedian conducted the analysis and interpretation of data; Mr LeCates coordinated and supervised data acquisition; and all authors critically reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Influenza vaccination uptake among children is suboptimal despite the clearly defined benefits of annual vaccination. The coronavirus disease 2019 pandemic may have changed vaccination behaviors because of concerns about coronavirus disease 2019 exposure and new mandates for influenza vaccination for children.

WHAT THIS STUDY ADDS: We assessed influenza vaccination uptake using insurance claims data. We found that, during the pandemic, an influenza vaccination mandate for children in school was associated with higher vaccination rates, particularly for previous nonvaccinators.

To cite: Abraham C, Garabedian LF, LeCates RF, et al. Vaccine Mandates and Influenza Vaccination During the Pandemic. *Pediatrics.* 2023;152(5):e2023061545

Maternal Pertussis Vaccination, Infant Immunization, and Risk of Pertussis

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abstract

OBJECTIVES: Following the introduction of jurisdictional maternal pertussis vaccination programs in Australia, we estimated maternal vaccine effectiveness (VE) and whether maternal pertussis vaccination modified the effectiveness of the first 3 primary doses of pertussis-containing vaccines.

METHODS: We conducted a population-based cohort study of 279 418 mother–infant pairs using probabilistic linkage of administrative health records in 3 Australian jurisdictions. Infants were maternally vaccinated if their mother had a documented pertussis vaccination ≥14 days before birth. Jurisdictional immunization records were used to identify receipt of the first 3 infant doses of pertussis-containing vaccines. Infant pertussis infections were identified using notifiable disease records. VE was estimated using Cox proportional hazard models.

RESULTS: Pertussis was administered during 51.7% (n = 144 429/279 418) of pregnancies, predominantly at 28–31 weeks' gestation. VE of maternal pertussis vaccination declined from 70.4% (95% confidence interval [CI], 50.5–82.3) among infants <2 months old to 43.3% (95% CI, 6.8–65.6) among infants 7–8 months old and was not significant after 8 months of age. Although we observed slightly lower VE point estimates for the third dose of infant pertussis vaccine among maternally vaccinated compared with unvaccinated infants (76.5% vs 92.9%, P = .002), we did not observe higher rates of pertussis infection (hazard ratio, 0.70; 95% CI, 0.61–3.39).

CONCLUSIONS: Pertussis vaccination near 28 weeks' gestation was associated with lower risk of infection among infants through 8 months of age. Although there was some evidence of lower effectiveness of infant vaccination among maternally vaccinated infants, this did not appear to translate to greater risk of disease.

WHAT'S KNOWN ON THIS SUBJECT: Pertussis vaccination during pregnancy protects against pertussis infection during the first 6 months of age. However, the possible "blunting" effects of maternal antibodies on infants' response to primary immunization remains an important clinical question.

WHAT THIS STUDY ADDS: Despite evidence for lower effectiveness of the third infant dose of acellular pertussis vaccine among maternally vaccinated infants, this was not associated with a higher incidence of pertussis compared with infants with no history of maternal pertussis vaccination.

To cite: Regan AK, Moore HC, Binks MJ, et al. Maternal Pertussis Vaccination, Infant Immunization, and Risk of Pertussis. *Pediatrics*. 2023;152(5):e2023062664

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Dr Regan secured research funding, contributed to the development of the original study protocol, supervised the project, led the final data analyses, and drafted the original manuscript; Drs Sarna and Dr Foo facilitated the acquisition of data, managed the study data, contributed to data analyses, and supported project administration; (Continued)

Late-Onset Sepsis in Very Low Birth Weight Infants

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abstract

BACKGROUND AND OBJECTIVES: Late–onset sepsis is associated with significant morbidity and mortality among very low birth weight (VLBW) infants. Our objective was to determine risk factors associated with late-onset sepsis and to present temporal trends in overall and pathogen-specific rates.

METHODS: Population-based study by the Israel Neonatal Network on VLBW infants (≤1500 g) born between 1995 and 2019. Late-onset sepsis required clinical symptoms and microbiologic confirmation. Bivariate and multivariable analyses were performed to identify risk factors. The study period was divided into 4 epochs. Overall and pathogen-specific late-onset sepsis rates for each epoch were compared.

RESULTS: The study population comprised 31 612 VLBW infants, of whom 7423 (23.5%) had late-onset sepsis. An increased adjusted risk of late-onset sepsis was associated with gestational age <27 w (odds ratio [OR] 8.90, 95% confidence interval [CI] 7.85–10.09) and delivery room resuscitation (OR 1.43, 95% CI 1.34–1.52) and a decreased adjusted risk among infants born between 2013 and 2019 (OR 0.32, 95% CI 0.29–0.35). Late-onset sepsis rates declined from 29.5% in 1995 to 2000 to 13.0% in 2013 to 2019. Gram-negative and fungal rates decreased in all epochs, whereas gram-positive rates decreased only in the last epoch. The adjusted hazard ratios (95% CI) decreased in the 2013 to 2019 versus 1995 to 2000 epochs and were: all late-onset sepsis, 0.40 (0.37–0.43); gram-positive, 0.47 (0.37–0.59); gram-negative, 0.54 (0.48–0.61); fungal, 0.17 (0.12–0.22).

CONCLUSIONS: The strongest risk factor for late-onset sepsis was gestational age <27 w. Over a 25-year period, the pathogen-specific rates of late-onset sepsis among VLBW infants decreased approximately twofold for gram-positive and gram-negative bacterial infections and sixfold for fungal infections.

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Drs Gil Klinger and Reichman participated in all aspects of study including, Study initiation, study design, acquisition of data, data analysis, drafting of manuscript; Drs Bromiker and Sokolover participated in study design and data interpretation and critical review of manuscript; Ms Zaslavsky-Paltiel participated in study design and performed all data analysis and critical review of manuscript; Dr Lerner-Geva participated in study design, acquisition of data and data analysis, and critical review of manuscript; Dr Sharon Klinger participated in data analysis, data interpretation, writing of manuscript and critical review of manuscript; and all authors approved the manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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WHAT'S KNOWN ON THIS SUBJECT: Late-onset sepsis among very low birth weight infants is a major health care issue and is associated with increased morbidity and mortality. The rate of late-onset sepsis varies between 12% to 30%. Coagulase negative *Staphylococci* are the most commonly isolated pathogens.

WHAT THIS STUDY ADDS: Over a period of 25 years the pathogen specific rates of late-onset sepsis among very low birth weight infants decreased by approximately 2-fold for gram-positive and gram-negative bacterial infections and 6-fold for fungal infections.

To cite: Klinger G, Bromiker R, Zaslavsky-Paltiel I, et al. Late-Onset Sepsis in Very Low Birth Weight Infants. *Pediatrics.* 2023;152(5):e2023062223

Sepsis among very low birth weight (VLBW) infants is a major worldwide health care issue in NICUs associated with increased morbidity and mortality.[1–3] Neonatal sepsis is most commonly categorized into early-onset sepsis (EOS), occurring within the first 72 hours of life, and late-onset sepsis, occurring 72 hours or later after birth.[1,4] Although EOS is related to maternal and perinatal factors, late-onset sepsis is more closely related to neonatal and nosocomial factors.[1,4–7]

The rate of EOS has decreased in recent years,[1] whereas conflicting reports exist regarding whether the rate of late-onset sepsis has decreased, remained stable, or possibly increased.[5–9] When evaluating studies on late-onset sepsis, it is of note that different measurements of late-onset sepsis rates are reported and comparisons may be difficult. Some studies report the percent of infants that had at least 1 sepsis episode, others report the absolute number of sepsis episodes, and yet others report the rate of sepsis per hospital admission days. In addition, the definition of late-onset sepsis may differ between studies, and it is preferable to examine studies with culture proven late-onset sepsis and not suspected episodes of late-onset sepsis. As late-onset sepsis rates are inversely related to birth weight (BW) and gestational age (GA),[8,10] it is important to note the degree of prematurity of the reported population and to compare similar populations. In very low birth weight (VLBW) infants, the rate of late-onset sepsis varies between 11.9% to 30.0%.[7–13]

Among VLBW infants with late-onset sepsis, *coagulase negative staphylococci* (CONS) has consistently been the most commonly isolated pathogen.[9,11] Perinatal antibiotic prophylaxis and changes in neonatal antibiotic use may induce changes in rates of causative pathogens of both EOS and late-onset sepsis and should these changes occur, may require updating of current antibiotic practices.

The current study focuses on late-onset sepsis among VLBW infants in a national Israeli cohort. The aims of the study were to determine risk factors associated with late-onset sepsis and to present temporal trends in the overall rates of late-onset sepsis episodes and by specific pathogen groups over a period of 25 years.

METHODS

The Israel National VLBW Infant Database

This population-based observational study was based on analysis of data prospectively collected by the Israel National VLBW (BW ≤1500 g) Infant Database on all live infants born between January 1995 and December 2019. All 28 neonatal departments in Israel (Appendix) participated in the data collection as previously described.[13,14] The data collected included: demographic details, antenatal and perinatal history, postdelivery status, neonatal diagnoses, medical and surgical treatments including episodes of sepsis, infant's age when late-onset sepsis occurred, causative pathogen for each late-onset sepsis episode, and outcome at discharge. Data were collected on all infants until death or discharge home. A prestructured form was completed for each infant, checked for logic errors, and if necessary, returned to the participating center for clarification. Infants were usually treated from birth to discharge at a single center, regardless of unit size. Interhospital transfers were followed by the database coordinator until final discharge home. Birth hospital and patient identification remain confidential by consensus agreement of all participating centers. All departments used an operating manual and standard definitions based on those of the Vermont-Oxford Network.[15] Inclusion of all VLBW infants was confirmed by cross-checking with the Israel National Birth Registry.

Study Population

The Israel National VLBW database includes more than 99% of all VLBW infants born in Israel. From 1995 through 2019, the database included records of 38 050 VLBW infants. Figure 1 describes the study cohort after exclusion of infants with congenital anomalies, death before 72 hours of age, and births <23 weeks gestation. The final study population comprised 31 612 VLBW born ≥23 weeks, of whom 7423 (23.5%) had 1 or more episodes of late-onset sepsis.

Definitions

Late-onset sepsis required a blood culture positive for a causative pathogen obtained 72 hours or more after birth and clinical sepsis symptoms.[13,15] For CONS, the definition of late-onset sepsis before 2016, required 1 positive blood culture, 5 treatment days, and clinical features of sepsis[13,15,16] and from 2016, required 2 positive blood cultures and clinical features of sepsis. In analyzing sepsis episodes, causative pathogens were classified into 9 groups as follows: CONS, *Staphylococcus aureus,* other gram-positive cocci, *Klebsiella species, Escherichia Coli (E. coli), Pseudomonas species,* other gram-negative bacteria, all fungi, and mixed organisms. Pathogens considered contaminants included: *Micrococcci*, *Lactobacilli*, *Diphteroids*, *Bacillus* species, and *Bacteroid* species and were not included as sepsis episodes. Repeat blood cultures within 7 days that were positive for the same pathogen were considered as a single sepsis episode.

Definitions of pregnancy complications have been previously reported in detail.[13] The GA in completed weeks was defined as the best estimate of GA based on last menstrual period, obstetric history and examination, prenatal ultrasound, or early postnatal physical examination. Small for gestational age (SGA) was defined as BW below the 10th percentile for GA according to the gender specific growth charts of Kramer et al.[17] We did not use the Israeli growth charts (Dolberg et al[18]), because of the

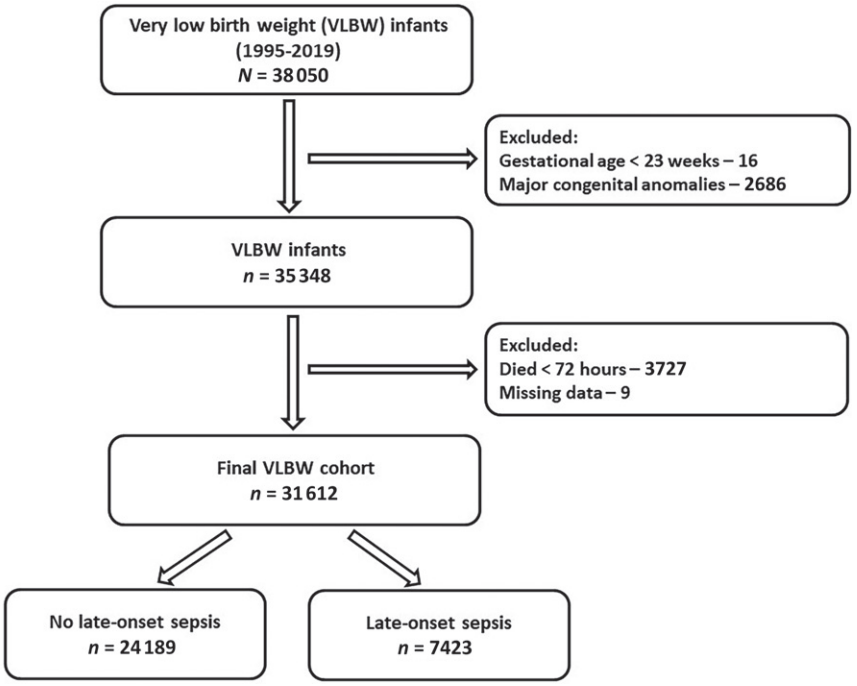

FIGURE 1
Study cohort breakdown.

very small sample at the lower GA's and inaccurate estimation of SGA in the smallest infants.[19] Delivery room resuscitation refers to intensive resuscitation measures including: intubation and/or cardiac compression and/or epinephrine administration.

Statistical Analysis

Bivariate analyses were used to compare characteristics of infants with or without late-onset sepsis. The association between late-onset sepsis and perinatal and neonatal factors was tested using the χ-square test for categorical variables and the 2-sample *t* test for continuous variables. The mutual effect of variables associated with the existence of late-onset sepsis was assessed using multivariable logistic regression analyses, applying the Generalized Estimating Equations method to control for correlations in infants from multiple births. Results of the multivariable model are presented as adjusted odds ratios (OR) with 95% confidence intervals (CI).

The study period was divided into 4 epochs: 1995 to 2000, 2001 to 2006, 2007 to 2012 and 2013 to 2019. The first epoch served as a baseline to which the subsequent 3 epochs were compared. The length of hospital stay from birth until discharge home or death was determined for each infant and the pathogen specific late-onset sepsis rate for each epoch was calculated per 10 000 hospital admission days. Time trends were analyzed using the multivariable Cox regression models with consideration for repeated late-onset sepsis episodes and reported as hazard ratio's (HR) with 95% CI's. Proportionality hazard assumptions of the Cox models were met. For correction of the proportionality assumption violation, the interactions with the survival time were added and the HR with 95% CI were estimated at the median survival time. In view of the potential impact of the change in definition of CONS late-onset sepsis in 2016, we undertook a subgroup analysis excluding 3720 infants with episodes of CONS late-onset sepsis only and all 5041 episodes of CONS late-onset sepsis. In addition, a sensitivity analysis was performed for the whole study population of 31 612 infants for overall rates of late-onset sepsis, excluding all CONS sepsis episodes. All statistical analyses were 2-tailed and *P* values below .05 were considered statistically significant. Statistical analyses were performed using the SAS statistical software Version 9.4 (SAS Institute, Inc, Cary, NC). Forest plot was created using GraphPad Prism 9 (GraphPad Software, San Diego, CA).

Ethical Approval

This study was conducted in accordance with prevailing ethical principles and approved by the Human Research Committee of the Sheba Medical Center (SMC 9180-22).

RESULTS

Of 31 612 VLBW infants surviving to 72 hours, 7423 (23.5%) developed late-onset sepsis and 24 189 (76.5%) did not. Single episodes of late-onset sepsis were recorded in 5889 infants, 1151 infants had 2 late-onset

sepsis episodes and 383 infants 3 late-onset sepsis episodes. Comparison of infants with and without late-onset sepsis is provided in Table 1. VLBW infants with late-onset sepsis were of a lower mean GA (27.7±2.6 w vs 29.8±2.7 w) and required more delivery room resuscitation (36.6% vs 16.6%) than those without late-onset sepsis. The percent of infants with late-onset sepsis declined from 29.5% in 1995 to 2000 to 13.0% in 2013 to 2019 ($P < .0001$). The changes over time in late-onset sepsis rates in different GA and BW groups are presented in Table 2. Mortality rates during the initial hospitalization decreased from 9.9% to 8.8%, 8.0%, and 7.2% in the 4 epochs, respectively.

Multivariable analysis of perinatal factors associated with late-onset sepsis among VLBW infants is shown in Fig 2. In comparison with 1995 to 2000, the risk of late-onset sepsis was similar in 2001 to 2006. In contrast, the 2007 to 2012 epoch was associated with a significantly decreased risk of late-onset sepsis (OR 0.71, 95% CI, 0.66–0.77) and the 2013 to 2019 epoch with a markedly lower risk of late-onset sepsis (OR 0.32, 95% CI, 0.29–0.35) in comparison with 1995 to 2000. Lower GA (23–27 w vs 31 w or greater) was strongly associated with increased risk of late-onset sepsis (OR 8.90; 95% CI, 7.85–10.09).

A total of 9340 episodes of late-onset sepsis were recorded; CONS ($n = 5041$, 54.0%), *Staphylococcus aureus* ($n = 327$, 3.5%), other gram-positive cocci ($n = 476$, 5.1%), *Klebsiella sp.* ($n = 1116$, 11.9%), *E. coli* ($n = 383$, 4.1%), *Pseudomonas sp.* ($n = 304$, 3.3%), other gram-negative bacteria ($n = 720$, 7.7%), fungi ($n = 803$, 8.6%), and mixed organisms ($n = 170$, 1.8%). Temporal changes in the late-onset sepsis rates per 10 000 hospitalization days, by pathogen groups, are presented in Fig 3. Gram-negative and fungal late-onset sepsis rates decreased consistently in all epochs, whereas gram-positive late-onset sepsis rates decreased only in the last epoch. Temporal changes in the late-onset sepsis rates by specific pathogens are presented in Fig 4. late-onset sepsis rates declined for *Klebsiella, Pseudomonas,* and *Staph aureus* late-onset sepsis, whereas *E. coli* late-onset sepsis remained unchanged. The marked decrease in the rate of CONS sepsis in the most recent epoch may reflect the change in diagnostic criteria.

Table 3 shows the effect of epoch on rates of late-onset sepsis by pathogen groups after adjustment for significant demographic and perinatal variables. For all late-onset sepsis episodes, the HR decreased in the final epoch to 0.40 (95% CI, 0.37–0.43) as compared with 1995 through 2000. For gram-positive pathogen late-onset sepsis, the HR decreased significantly only in 2013 through 2019 to 0.47 (95% CI, 0.37–0.59). The HR for gram-negative pathogen late-onset sepsis decreased throughout all epochs to 0.54 (95% CI, 0.48–0.61) in 2013 through 2019. The most dramatic decrease in HR was achieved for fungal late-onset sepsis to 0.17 (95% CI, 0.12–0.22) in 2013 through 2019.

A subgroup analysis was performed, excluding 3720 infants with CONS late-onset sepsis only and all 5098 episodes of CONS late-onset sepsis. This analysis included 27 892 infants of whom 3703 (13.3%) had a total of 4299 episodes of late-onset sepsis. For all late-onset sepsis episodes, the adjusted HR decreased in the final epoch to 0.41 (95% CI, 0.37–0.46) as compared with 1995 through 2000. The HR in the final epoch compared with the initial epoch decreased for gram-positive late-onset sepsis excluding CONS, for gram-negative late-onset sepsis and for fungal late-onset sepsis to 0.42 (95% CI, 0.33–0.54), 0.49 (95% CI, 0.44–0.55), and 0.15 (95% CI, 0.11–0.20), respectively. In a sensitivity analysis undertaken for the whole study population of 31 612 infants, the adjusted HR for overall rates of late-onset sepsis, excluding CONS sepsis, decreased in 2001 through 2006 to 0.89 (95% CI, 0.82–0.96), in 2007 through 2012 to 0.61 (95% CI, 0.56–0.67), and in the final epoch to 0.45 (95% CI, 0.41–0.50) as compared with 1995-2000.

DISCUSSION

In a national Israeli cohort of VLBW infants, 23.5% had 1 or more episodes of late-onset sepsis. The rate of late-onset sepsis declined over the study period and decreased from 29.5% to 13.0% of the VLBW infant cohort in the final 2013 to 2019 epoch. Late-onset sepsis was most strongly associated with a lower GA. Although the pathogen specific rate of most pathogens declined with time, considerable heterogeneity exists in the magnitude of the observed change.

Many NICU practices may potentially influence late-onset sepsis rates among VLBW infants. Quality improvement measures are often implemented in the NICU, however the evidence that these measures actually achieve improvement is not always present. This is especially true when prevention of late-onset sepsis is the goal because of the multifactorial etiology of late-onset sepsis. The current study examined late-onset sepsis trends over a 25-year period in a national VLBW cohort. We have shown that in the final study epoch (2013–2019), late-onset sepsis rates declined to 25.6 of 10 000 hospital days, representing a greater than 50% decrease in late-onset sepsis rates over time. This decrease is even more impressive when considering the fact that during the study period mortality rates of the most immature infants, who are at the highest risk for late-onset sepsis, decreased. It is evident that during the first 2 epochs, no effective intervention was achieved as late-onset sepsis rates slightly increased. During the third epoch, late-onset sepsis rates decreased, and during the final epoch a more dramatic decrease in late-onset sepsis rates was achieved. In 2016, in Israel, a national prevention program was initiated aimed at reducing late-

TABLE 1 Bivariate Analysis of the Rates of Late-onset Sepsis by Temporal and Perinatal Characteristics of Very Low Birth Weight Infants ($n = 31\,612$)

Characteristics	Sepsis	No Sepsis	*P*
	$n = 7423$ (23.5%)	$n = 24\,189$ (76.5%)	
Study period, *n* (%)			<.0001
1995–2000	2089 (29.5)	4998 (70.5)	
2001–2006	2285 (29.8)	5387 (70.2)	
2007–2012	1894 (23.9)	6041 (76.1)	
2013–2019	1155 (13.0)	7763 (87.0)	
Gestational age group, *n* (%)			<.0001
23–25 wk	1561 (51.0)	1497 (49.0)	
26–27 wk	2108 (39.0)	3296 (61.0)	
28–29 wk	1993 (25.1)	5959 (74.9)	
30–31 wk	1147 (14.5)	6748 (85.5)	
≥32 wk	614 (8.4)	6689 (91.6)	
Mean gestational age, (weeks), m (SD)	27.7 (2.6)	29.8 (2.7)	<.0001
Birth wt group, *n* (%)			<.0001
<750 g	1626 (48.5)	1726 (51.5)	
750–999 g	2355 (37.4)	3946 (62.6)	
1000–1249 g	1918 (21.9)	6859 (78.1)	
1250–1500 g	1524 (11.6)	11 658 (88.4)	
Premature labor, *n* (%)			<.0001
Yes	4234 (25.8)	12 153 (74.2)	
No	3181 (20.9)	12 019 (79.1)	
Prolonged rupture of membranes and amnionitis, *n* (%)			<.001
Rupture of membranes <24 h, no amnionitis	20 268 (76.9)	6092 (23.1)	
Rupture of membranes ≥24 h, no amnionitis	2391 (75.5)	775 (24.5)	
Amnionitis	1530 (73.3)	556 (26.7)	
Antenatal steroids, *n* (%)			<.0001
None	2060 (24.8)	6238 (75.2)	
Partial	1354 (26.7)	3718 (73.3)	
Complete	3990 (21.9)	14 193 (78.1)	
Antepartum hemorrhage, *n* (%)			<.0001
Yes	1359 (28.4)	3432 (71.6)	
No	6048 (22.6)	20 723 (77.4)	
Multiple birth, *n* (%)			<.0001
Yes	3049 (22.4)	10 569 (77.6)	
No	4374 (24.3)	13 619 (75.7)	
Delivery mode, *n* (%)			<.0001
Cesarean	5262 (22.4)	18 216 (77.6)	
Vaginal	2160 (26.6)	5969 (73.4)	
Sex, *n* (%)			<.0001
Male	3952 (25.2)	11 740 (74.8)	
Female	3471 (21.8)	12 449 (78.2)	
Small for gestational age, *n* (%)			<.0001
Yes	1544 (16.2)	7976 (83.8)	
No	5879 (26.6)	16 213 (73.4)	
Intensive delivery room resuscitation[a], *n* (%)			<.0001
Yes	3987 (36.6)	6918 (63.4)	
No	3436 (16.6)	17 271 (83.4)	

[a] Intubation and/or cardiac compression and/or epinephrine administration.

onset sepsis.[20] Multiple measures were implemented, including staff education, improvement of infection control, aseptic technique, and care of central lines and many other measures, however, which specific measures may have resulted in the dramatic decrease in late-onset sepsis rate in the final study epoch is unknown. The Israel national infection prevention program used the Central for Disease Control definitions for late-onset sepsis, which

TABLE 2 Changes Over Time in Late-onset Sepsis Rates in Different Gestational Age and Birth Weight Groups				
	1995–2000, %	2001–2006, %	2007–2012, %	2013–2019, %
23 w–27 w gestation (n = 8462)	51.4	54.1	44.5	27.7
28 w–31 w gestation (n = 15 847)	26.9	25.6	19.7	9.1
≥32 w gestation (n = 7303)	12.3	10.5	8.3	3.3
≤750 g (n = 3352)	53.7	58.1	49.2	35.4
751–1000 g (n = 6301)	44.9	46.1	38.0	22.0
1001–1250 g (n = 8777)	29.9	27.9	21.6	10.3
1251–1500 g (n = 13 182)	16.0	14.8	12.2	5.1

differ somewhat from previously applied definitions. The main change was a stricter definition for CONS late-onset sepsis. This change may have resulted in an overestimation in the magnitude of the decrease of CONS late-onset sepsis, however, it did not influence the rates of late-onset sepsis caused by other pathogens.

Although previous studies have shown conflicting results regarding changes in late-onset sepsis rates, many recent reports support a trend toward a decrease in late-onset sepsis rates. Greenberg et al[21] have shown in a study on extremely premature infants from the National Institute of Child Health and Human Development Neonatal Research Network, that the incidence of late-onset sepsis decreased over time from 41% to 34% of infants. Boel et al[22] in a study from the UK and Kim et al[23] in a Korean study have both similarly shown trends toward decreased late-onset sepsis in extremely preterm infants. In VLBW infants, in a South American study, D' Apremont et al[24] reported a significant decrease in late-onset sepsis rates from 21.1% to 19.5%. The current study is comparable to the previous study regarding the incidence of late-onset sepsis, however it has a higher incidence of late-onset sepsis compared with a report from the German Neonatal Network.[9] When evaluating the magnitude of the decrease in late-onset sepsis rate achieved, it is important to appreciate that when the baseline late-onset sepsis rate is higher, it is easier to achieve a larger decrease in the rate of late-onset sepsis compared with countries that have an initial low rate. This may be the reason that the German study failed to show a decrease in culture-confirmed late-onset sepsis.

Our study focused on perinatal factors associated with late-onset sepsis. As in previous studies,[8,12,13] GA was the factor most strongly associated with late-onset sepsis. Birth epoch was also associated with risk of late-onset sepsis, similar to the report by Greenberg et al.[21] Infants requiring delivery room resuscitation are at an increased risk for late-onset sepsis that may be related to increased severity of the infants' initial condition or to an undiagnosed infection. Of note, Cesarean section delivery and antenatal corticosteroids had no significant effect on the risk of late-onset sepsis.

Few studies have examined temporal changes in pathogen specific late-onset sepsis rates in a population-based cohort of infants. Possibly the most important data from this study are changes in pathogen specific late-onset sepsis rates, which provides insight both to the effectiveness of prevention measures employed and to the

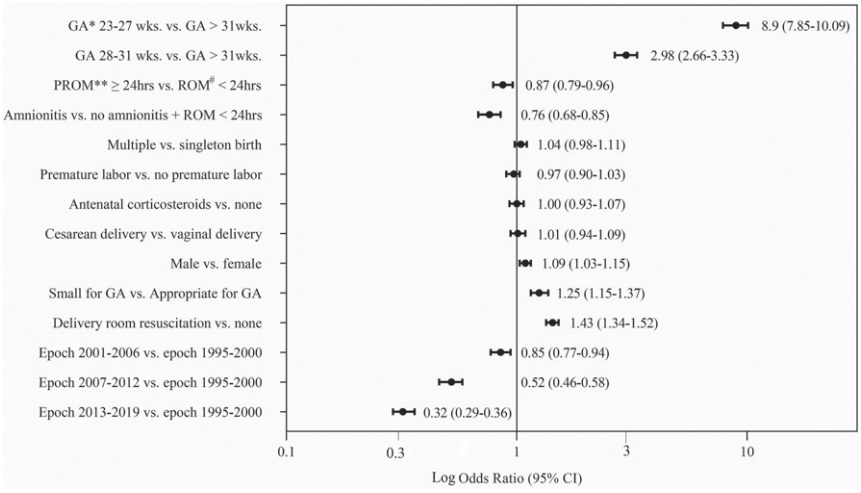

FIGURE 2

Forest plot of multivariable analysis of factors associated with late-onset sepsis among very low birth weight infants. Delivery room resuscitation refers to intensive resuscitation measures including: intubation and/or cardiac compression and/or epinephrine administration; *GA, gestational age; **PROM, prolonged rupture of membranes; #ROM, rupture of membranes.

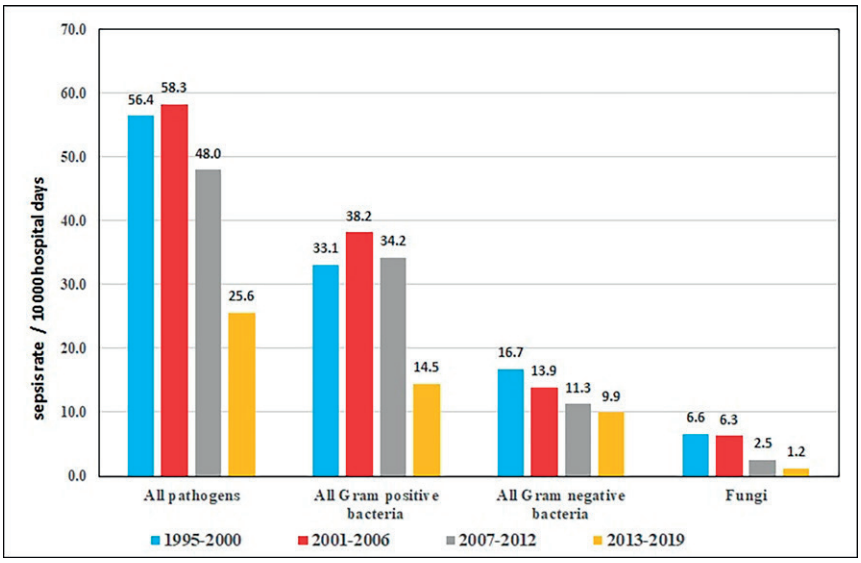

FIGURE 3
Temporal changes in late-onset sepsis rates by pathogen groups among very low birth weight infants.

empirical treatment required when sepsis is considered. During the study period we have shown a consistent decrease in the rate of gram-negative infections. There is no single identifiable measure that is responsible for this decrease, and it is likely related to an overall improvement in the care of VLBW infants and possibly to the increased use of breast milk. Despite the decrease in gram-negative infections, they have become relatively more important because other infections have decreased to a greater extent. Ran et al,[25] in a study from the Netherlands, have noted an increase in gram-negative infections among extremely low birth weight infants with late-onset sepsis and show that their rate increased from 0% to 27%, with an overrepresentation among infants with the lowest GA and BW. The increasing importance of gram-negative late-onset sepsis should prompt adequate coverage of these pathogens when

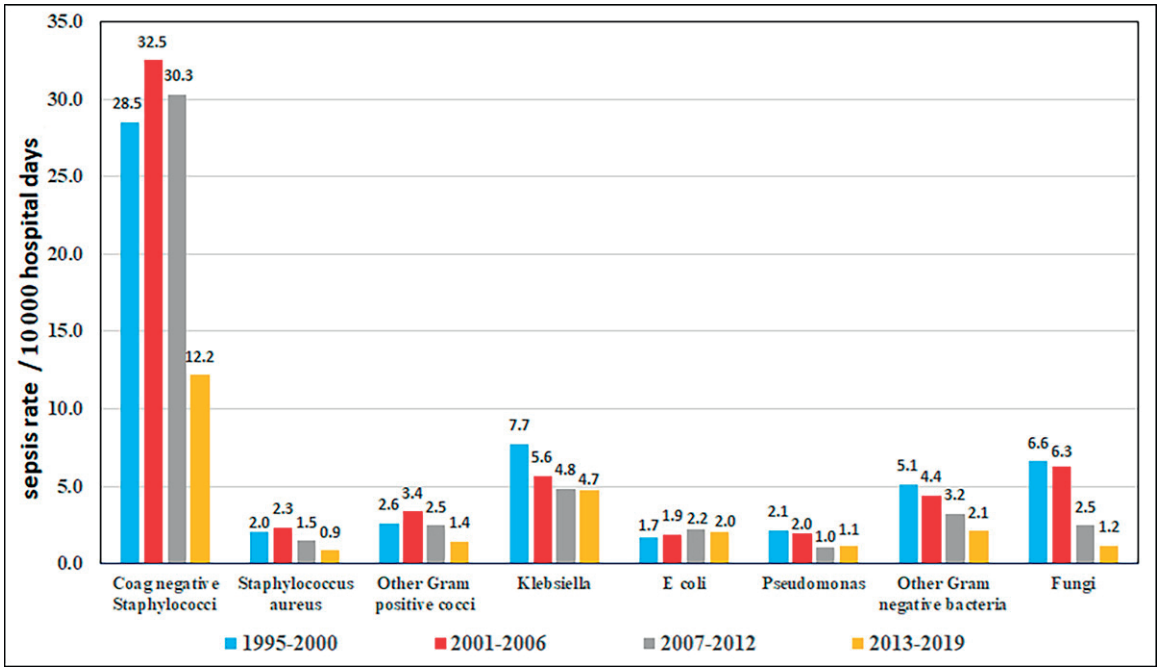

FIGURE 4
Temporal changes in pathogen-specific late-onset sepsis rates among very low birth weight infants.

TABLE 3 Effect of Epoch on Late-onset Sepsis by Pathogen Group				
EPOCH	All Pathogens	Gram-negative Bacteria	Gram-positive Bacteria	Fungi
	Hazard ratio[a]	Hazard ratio[a]	Hazard ratio[a]	Hazard ratio[a]
	(95% CI)	(95% CI)	(95% CI)	(95% CI)
2001–2006 vs 1995–2000	1.07 (0.99–1.14)	0.81 (0.73–0.89)	1.19 (0.99–1.43)	0.93 (0.79–1.09)
2007–2012 vs 1995–2000	0.78 (0.74–0.83)	0.65 (0.58–0.72)	0.82 (0.67–1.01)	0.37 (0.30–0.46)
2013–2019 vs 1995–2000	0.40 (0.37–0.43)	0.54 (0.48–0.61)	0.47 (0.37–0.59)	0.17 (0.12–0.22)

CI, confidence interval.
[a] Hazard ratios adjusted for: gestational age, prolonged rupture of membranes, amnionitis, antepartum hemorrhage, antenatal steroid therapy, mode of delivery, sex, small for gestational age and intensive delivery room resuscitation.

choosing initial empirical treatment. Possibly the most striking change among pathogens causing late-onset sepsis is the near elimination of fungal infections. Most NICU's in Israel started antifungal prophylaxis during the third epoch and the remainder in the most recent epoch. It is highly likely that the dramatic decrease in fungal infections was caused by prophylactic antifungal therapy practiced by nearly all NICU's, and to a lesser extent, to empirical antibiotic regimens, avoiding broad-spectrum antibiotics that are associated with increased fungal infections.[26] The very low fungal infection rate among VLBW infant in Israel may lead to discontinuation of antifungal prophylaxis in the future.

The current study is one of the largest to date to evaluate pathogen specific late-onset sepsis rates among VLBW infants. Our study population was a national cohort, exclusion criteria were minimal, and infants were followed when transferred between hospitals, avoiding selection bias. All NICUs in Israel participated and used standard definitions that have undergone minimal changes throughout the study period. A strict definition of late-onset sepsis was used, excluding infants without microbiologic confirmation.

Some study limitations should be acknowledged. We preferred a strict definition of late-onset sepsis, and this may have led to misclassification of a small number of infants in whom the blood culture was considered a contamination. The definition of late-onset sepsis caused by CONS was changed during the study period, preventing us from accurately estimating the magnitude of the decrease in late-onset sepsis caused by CONS in the final study epoch. In view of the potential impact of the change in definition of CONS late-onset sepsis in 2016, we undertook both a subgroup analysis excluding 3720 infants with episodes of CONS late-onset sepsis only and a sensitivity analysis for the whole study population excluding all CONS late-onset sepsis. These analyses however, revealed only minor changes in the study results, and the marked decrease in the HR for late-onset sepsis, especially in the last epoch occurred irrespective of the change in diagnostic criteria for CONS late-onset sepsis. Because of the study duration, some NICU practices have changed and, in particular, during the final epoch when a national program was implemented to reduce the rate of late-onset sepsis. The effect of antibiotic practices on late-onset sepsis could not be estimated because this data are not included in the database.

CONCLUSIONS

The strongest risk factor for late-onset sepsis was GA <27 w. Over a period of 25 years, the pathogen specific rates of late-onset sepsis among VLBW infants decreased approximately twofold for gram-positive and gram-negative bacterial infections and sixfold for fungal infections. Although late-onset sepsis rates and gram-negative sepsis rates have decreased, gram-negative bacteria still account for a significant proportion of late-onset sepsis.

APPENDIX

The Israel Neonatal Network, participating centers in the Israel National Very Low Birth Weight Infant Database:

Coordinating center: The Women and Children's Health Research Unit, Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer.

Neonatal departments: Assaf Harofeh Medical Center, Rishon Le Zion; Assuta Hospital, Ashdod; Barzilay Medical Center, Ashkelon; Bikur Holim Hospital, Jerusalem; Bnei Zion Medical Centre, Haifa; Carmel Medical Center, Haifa; English (Scottish) Hospital, Nazareth; French Hospital, Nazareth; Hadassah University Hospital Ein-Karem, Jerusalem; Hadassah University Hospital Har Hazofim, Jerusalem; Haemek Medical Center, Afula; Hillel Yafe Medical Center, Hadera; Italian Hospital, Nazareth; Kaplan Hospital, Rehovot; Laniado Hospital, Netanya; Maayanei Hayeshua Hospital, Bnei-Brak; Meir Medical Center, Kefar Saba; Misgav Ladach Hospital, Jerusalem; Naharia Hospital, Naharia; Poria Hospital, Tiberias; Rambam Medical Center, Haifa; Rivka Ziv Hospital, Zefat; Schneider Children's Medical Center of Israel and Rabin Medical Center, Petach-Tikva; Shaare-Zedek Hospital, Jerusalem; Sheba Medical Center, Tel-Hashomer; Soroka Medical Center, Beer-Sheva; Sourasky Medical Center, Tel-Aviv; Wolfson Medical Center, Holon; Yoseftal Hospital, Eilat.

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ABBREVIATIONS

BW: birth weight
CI: confidence interval
CONS: coagulase negative *Staphylococci*
E. Coli: *Escherichia Coli*
EOS: early-onset sepsis
GA: gestational age
HR: hazard ratio
OR: odds ratios
VLBW: very low birth weight

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CONFLICT OF INTEREST DISCLOSURES: The authors have no potential conflicts of interest to disclose.

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Early Postnatal Infection of Neonates Born to Mothers Infected by SARS-CoV-2 Omicron Variant

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abstract

OBJECTIVES: To evaluate the rate of postnatal infection during the first month of life in neonates born to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive mothers during the predominant circulation of the omicron (B.1.1.529) variant.

METHODS: This prospective, 10-center study enrolled mothers infected by SARS-CoV-2 at delivery and their infants, if both were eligible for rooming-in, between December 2021 and March 2022. Neonates were screened for SARS-CoV-2 RNA at 1 day of life (DOL), 2 to 3 DOL, before discharge, and twice after hospital discharge. Mother-infant dyads were managed under a standardized protocol to minimize the risk of viral transmission. Sequencing data in the study area were obtained from the Italian Coronavirus Disease 2019 Genomic platform. Neonates were included in the final analysis if they were born when the omicron variant represented >90% of isolates.

RESULTS: Eighty-two percent (302/366) of mothers had an asymptomatic SARS-CoV-2 infection. Among 368 neonates, 1 was considered infected in utero (0.3%), whereas the postnatal infection rate during virtually exclusive circulation of the omicron variant was 12.1%. Among neonates infected after birth, 48.6% became positive during the follow-up period. Most positive cases at follow-up were detected concurrently with the peak of coronavirus disease 2019 cases in Italy. Ninety-seven percent of the infected neonates were asymptomatic.

CONCLUSIONS: The risk of early postnatal infection by the SARS-CoV-2 omicron variant is higher than that reported for previously circulating variants. However, protected rooming-in practice should still be encouraged given the paucity of symptoms in infected neonates.

WHAT'S KNOWN ON THIS SUBJECT: Postnatal mother-to-neonate transmission of SARS-CoV-2 in cases of maternal infection is more common than intrauterine infection. We previously reported a rate of postnatal transmission with non-omicron variants of ∼1.6%.

WHAT THIS STUDY ADDS: In a multicenter study, the rate of postnatal SARS-CoV-2 omicron-variant infection was 12.1%, a much higher rate compared with previously circulating variants. Postnatal infections at home were detected only when the omicron-variant was predominant in the region.

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The Beginning of a New Era in RSV Control

H. Cody Meissner, MD

Since the initial isolation in 1956 of what is now identified as respiratory syncytial virus (RSV), seasonal outbreaks of illness attributable to this enigmatic respiratory virus have troubled generations of pediatricians and parents because of the absence of therapeutic options other than supportive care.[1] Recognition that RSV infection is the most common cause of hospitalization among children in the first 12 months of life resulted in numerous attempts to prevent or treat this disease. Three distinct avenues have been explored: antiviral therapy, passive immunity with hyperimmune globulins and monoclonal antibodies, and active immunity with vaccines. After >65 years of investigation, 2 types of effective and practical disease prevention finally are available (Table 1).

The report in this issue of *Pediatrics* reveals important recommendations from the Advisory Committee on Immunization Practices regarding an improved option for RSV prophylaxis for infants and young children.[2]

ANTIVIRAL THERAPY

Ribavirin, a synthetic nucleoside with antiviral activity, was licensed in 1986 for aerosolized treatment of hospitalized infants and young children with severe lower respiratory tract infection (LRTI) due to RSV. Because of limited efficacy, difficult administration, concerns about teratogenicity, and high cost, the drug is seldom used. Despite many efforts to develop direct-acting antiviral small molecules for the treatment of RSV, including fusion inhibitors and postentry viral replication inhibitors, clinical studies have not revealed acceptable efficacy and safety from these drugs.

PASSIVE IMMUNOPROPHYLAXIS

Passive immunoprophylaxis for the prevention of RSV first became available in 1996 with RespiGam, a polyclonal, hyperimmune globulin licensed for prophylaxis of high-risk infants.[3] RespiGam received limited use because of the requirement for monthly intravenous administration, concern for contaminating adventitious agents, adverse events among infants with cyanotic heart disease who underwent surgery, an unstable supply, and potential interference with the immune response to measles immunization.

In 1998, palivizumab was licensed by the Food and Drug Administration (FDA) as a humanized murine monoclonal antibody directed against the RSV surface fusion glycoprotein. Recommendations for the optimal use of palivizumab first were issued by the American Academy of Pediatrics in 1998, followed by several iterations as the understanding of RSV epidemiology and the limited efficacy of palivizumab evolved.[4] At present, ~2% of the annual birth cohort is eligible to receive palivizumab prophylaxis based on American Academy of Pediatrics guidance, indicating the need for an improved approach to immunoprophylaxis.

Advancements in understanding the pathogenesis of RSV disease led to the recognition of the importance of viral surface glycoprotein F in stimulating a protective immune response. In a critical breakthrough, collaborators in Graham's National

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TABLE 1 Milestones in the Development of RSV Vaccines and Immunoprophylaxis	
Date	Event
1956	Initial isolation of virus from a colony of chimpanzees with upper respiratory tract symptoms at Walter Reed Army Institute
1966	Randomized, placebo-controlled trials with a formalin inactivated vaccine revealed vaccine-enhanced disease among infants <6 mo of age the following RSV season
1984	Surface glycoproteins F and G isolated
1986	Ribavirin licensed as aerosol therapy for hospitalized children
1993	First placebo-controlled vaccine trial with fusion protein conducted in adults
1996	RespiGam (a polyclonal, hyperimmune antibody preparation requiring monthly IV administration) licensed for monthly prophylaxis for infants at increased risk of severe disease
1998	Palivizumab (a neutralizing humanized monoclonal antibody to F) licensed for monthly intramuscular dosing for prophylaxis of infants at increased risk of severe disease
2006	Structure of paramyxovirus prefusion F protein published
2010	Motavizumab (a humanized monoclonal antibody to F derived from palivizumab using affinity maturation techniques) not licensed by FDA because of limited increase in efficacy over palivizumab as well as concern for an increased risk of side effects
2013	PreF confirmation of fusion protein demonstrated to display previously unrecognized, potent neutralizing epitopes
2017	Suptavumab (a fully human monoclonal antibody to F with extended half-life) failed to reach efficacy endpoint in global phase 3 trial
2023	FDA licenses and CDC issues guidance for 2 stabilized, recombinant RSV preF vaccines for adults ≥60 y
	FDA licenses and CDC issues guidance for nirsevimab (a fully human, long half-life human monoclonal antibody to F) for prophylaxis of newborns with a single seasonal intramuscular dose
	FDA licenses a recombinant preF vaccine for administration during pregnancy at 32–36 wks' gestation (CDC guidance pending)
F protein, RSV surface fusion glycoprotein	

Institutes of Health laboratory recognized that the surface F glycoprotein exists in >1 configuration.[5] The unstable prefusion configuration of F possesses potent neutralizing epitopes not detected on the postfusion conformation, identifying previously unknown targets for neutralizing antibodies. Nirsevimab binds to one of the epitopes on the prefusion molecule (antigenic site θ) that is not accessible on the postfusion molecule because of the 9 dynamic restructuring of the prefusion protein once the virus interacts with a cell receptor. When nirsevimab binds to prefusion fusion protein (preF), the glycoprotein is unable to change configuration and fuse the viral membrane with the cell membrane, thus stopping infection.

In July 2023, the FDA licensed nirsevimab, and the Centers for Disease Control and Prevention (CDC) subsequently recommended a single dose of nirsevimab (Beyfortus, Sanofi-Pasteur, AstraZeneca) shortly before or soon after discharge for all newborns who are <8 months of age and are born during or entering their first RSV season.[6] Data from 3 clinical trials revealed a reduction in RSV LRTI health care visits and hospitalizations by 60% to 80% compared with infants in the control arm through 150 days postdose.[7] A single, weight-based, intramuscular injection maintains a protective serum concentration (≥6.8 ug/mL) for at least 5 months.[7] For a small group of children between 8 and 19 months of age who remain vulnerable to severe RSV disease, a second dose is recommended at the onset of season 2.[7] Both A and B strains of RSV appear to be neutralized by this long-acting monoclonal antibody. For the first time, an intervention is available for the prevention of RSV illness in both healthy, term infants, as well as preterm infants and those with comorbidities, such as congenital heart disease and chronic lung disease of prematurity.

Of interest, specimens obtained during the clinical trial revealed the antibody response to the postfusion form of the viral RSV surface fusion glycoprotein did not reveal a statistical difference between nirsevimab recipients and placebo recipients, indicating RSV infection still may occur. This suggests that although it prevents most cases of symptomatic RSV illness, nirsevimab does not interfere with an active intrinsic immune response by an infant after a mild or asymptomatic RSV infection, perhaps resulting in disease attenuation in a subsequent season.[8]

A second advancement has enabled the prolongation of the immune globulin G (IgG) monoclonal antibody half-life. A substitution of 3 amino acids engineered in the constant region of the heavy chain (Fc fragment) of the antibody molecule results in more efficient binding to a receptor involved in the salvaging and recycling of IgG after the antibody has been taken up for intracellular degradation. This change extends the normal serum half-life of IgG from 20 days to 70 days, enabling the administration of a single dose near the start of the RSV season with protective concentrations of antibody lasting at least 150 days.

VACCINES

By the mid-1960s, clinical trials with a formalin-inactivated, whole-cell RSV vaccine were initiated. Results from this trial revealed that seronegative children <6 months of age who were immunized with this vaccine

did not derive protection against infection. Once infected with RSV, experimental vaccine recipients experienced enhanced disease and greater hospitalization rates than participants in the control arms. This tragic outcome inhibited RSV vaccine development for decades. However, now, progress in the development of RSV vaccines for active immunization for different age groups is progressing rapidly and a maternal vaccine for administration during pregnancy has been licensed by the FDA.

In May 2023, the FDA licensed, and in July 2023, the CDC recommended 2 stabilized recombinant preF RSV subunit vaccines (Abrysvo, Pfizer and Arexvy, GSK) to boost active immunity in adults >59 years of age using shared clinical decision making.[9] These vaccines take advantage of the increased antigenicity of the prefusion molecule to generate an anamnestic response because nearly every adult has been infected by RSV. In August 2023, the FDA licensed 1 of the 2 recombinant preF RSV subunit vaccines (Abrysvo, Pfizer) for use in pregnant individuals to boost maternal antibodies, increase transplacental transfer of protective antibodies, and reduce the risk of RSV LRTI in infants from birth through 6 months of age. A placebo-controlled clinical trial of this vaccine among 7392 pregnant subjects vaccinated at 26 to 36 weeks' gestation, reduced the risk of infant RSV hospitalization by 67.7% (99% confidence interval 15.9% to 89.5%) at 90 days and 56.8% (99% confidence interval 10.1% to 80.7%) at 180 days.[10] In this trial, a numerical imbalance in preterm births was observed among vaccinated mothers compared with placebo recipients, but the numbers were not statistically significant. To minimize the risk of preterm birth, the FDA licensed the vaccine for administration at 32 to 36 weeks' gestation because most of the imbalance in preterm births occurred among women who were vaccinated between 26 to <32 weeks' gestation. The second adult recombinant preF RSV (Arexvy, GSK) subunit vaccine was evaluated among pregnant individuals to protect newborns from RSV, but a statistically significant increase in preterm births was observed among vaccine recipients compared with placebo recipients in this trial. Thus, this vaccine is not approved for use in persons <60 years of age.[11] Individuals considered to have high-risk pregnancies were excluded from participation in both trials.

Nirsevimab and the licensed RSV vaccines are breakthroughs attributable to understanding the molecular biology of RSV, reminding us of the importance of research in basic virology.[12] The next step in childhood RSV control may be the availability of an intranasal, live attenuated vaccine developed using reverse genetics to delete certain viral proteins, such as those that suppress the immune response of the host. Ideally, this vaccine will be available for older infants and young children to induce a durable, adaptive immunity that is both local (mucosal) and systemic and includes both T-cell and humoral immunity.[13] In particular, the need is great for a safe, effective, stable, and inexpensive vaccine that can be used in low- and middle-income countries in which 99% of the >40 000 RSV-associated pediatric deaths occur annually.

The recent coronavirus epidemic emphasized the ability of respiratory RNA viruses to rapidly undergo mutation in critical proteins permitting the virus to escape vaccine and infection-induced immunity. Not surprisingly, a small number of RSV isolates with mutations in the nirsevimab binding site have been described, raising the specter of resistance after the widespread use of these interventions is initiated.[14] To enable the early recognition of resistant escape variants after the introduction of nirsevimab and the RSV vaccines, the CDC and the manufacturer are planning an RSV genomic surveillance program to examine isolates for resistance.

A final comment relates to the understanding that nirsevimab is a form of passive immunity and not a vaccine that induces active immunity. Despite this difference, recommendations for the use of nirsevimab will be included in the Childhood Immunization Schedule, and coverage for this drug will be included in the Vaccines for Children program to ensure equitable access to this important drug.

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
IgG: immune globulin G
LRTI: lower respiratory tract infection
preF: prefusion fusion protein
RSV: respiratory syncytial virus

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CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Older Infant-Young Child "Formulas"

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abstract

The category of "formulas" directed at older infants and toddlers 6 to 36 months of age has increased in prominence over the last years but is characterized by lack of standardization in nomenclature and composition as well as questionable marketing practices. There has been uncertainty and misperception regarding some of the roles of these beverages in ensuring adequate childhood nutrition. The aim of this clinical report is to review the context, evidence, and rationale for older infant-young child formulas, followed by recommendations.

INTRODUCTION

The first years of life are foundational for child growth and psychomotor development with lifelong influence and implications. Adequate nutrition in the early years is important for the developing brain as it relates to cognition and long-term brain function.[1] Additionally, these years represent a narrow window of time during which nutritional status and the right nutrients at the right time are primary determinants of health and disease and disease risk, including noncommunicable disease (eg, obesity, diabetes, metabolic syndrome, cardiovascular disease, allergy, and atopy), beginning in childhood and extending through adulthood.

The benefits of exclusive breastfeeding in the first 6 months of life are well documented and indisputable. However, there are a variety of sound reasons that certain infants must depend in part or entirely on iron-fortified infant formulas, the composition of which is relatively standardized based on decades of physiologic and food science evidence. After 6 months of age and with the introduction of complementary foods, human milk and formula constitute a progressively decreased proportion of total nutritional intake with advancing age. The American Academy of Pediatrics (AAP) supports continued breastfeeding along with appropriate complementary foods introduced at about 6 months, as long as mutually desired by mother and child for 2 years or beyond. If the infant is not breastfed, the AAP and others recommend whole cow milk as suitable for infants beginning at 12 months of age as part of a nutritionally complete, balanced diet.[2] More recently, a wide array of liquid nutritional products referred to as "formulas" have been developed for the older

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infant and toddler of separate age ranges and increasingly promoted by manufacturers in North America and elsewhere, with different identities including "transition formulas," "follow-on" or "follow-up formulas," or "weaning formulas," typically for children 6 to 24 months of age, and "toddler milks or formulas," "growing-up milks," or "young child milks" generally for children 12 to 36 months of age (Table 1).[3] The different names, compositions, and purported benefits of this group of formulas have resulted in questions and confusion among child caregivers, pediatricians and other pediatric health care professionals, and policy makers. Although medical or therapeutic formulas are indicated for a variety of conditions, such as chronic gastrointestinal diseases, metabolic disorders, food allergy, and others, such prescribed formulas are different from older infant-young child formulas (OIYCFs).

COMPOSITION

Infant formulas are required to be able to meet nutritional requirements as a sole liquid source of nutrition for infants through the first 12 months of life. All infant formulas sold in the United States, therefore, whether manufactured in the United States or imported, must meet the requirements of the Infant Formula Act enacted in 1980 and amended in 1986 and associated regulations, and facilities undergo annual inspections by the US Food and Drug Administration (FDA).[4,5] Unlike for standard infant formulas, the FDA does not have a distinct category of OIYCFs, and there are no US national or uniform international criteria for the composition or definition of formulas for children older than 12 months. Different international expert groups have developed composition recommendations; however, regulatory oversight in the United States to ensure formulas for this age group adhere to a standard does not currently exist.[6–8] It is perhaps not surprising, then, that the composition of this group of formulas is characterized by wide variation. Some of these formulas have been criticized as having elements considered to be unnecessary or potentially detrimental, including high or low protein, higher sodium content relative to cow milk, and added sweeteners, among others. Compared with cow milk, consumption of OIYCFs, which have been considered by some as "sugar-sweetened drinks," has been associated with greater intakes of sweetened beverages as well as sweetened dairy products, such as fruit yogurts and cream cheese desserts, perhaps because of an influence on taste preference.[9,10] OIYCFs are not nutritionally complete and are designed for healthy, normally growing children, specifically to replace or supplement the usual role of whole cow milk or human milk in the diet. Therefore, these formulas are not appropriate substitutes for medical nutritional therapy for older infants and children in states of deprivation or growth faltering (eg, malnutrition, so-called failure to thrive), with swallowing dysfunction, or with feeding aversions or conditions such as cerebral palsy, who similarly rely on them for a major proportion of their nutritional intake. They are also not adequate for those with disease-specific requirements (eg, celiac disease, gastrointestinal disorders, inborn errors of metabolism, food intolerance, or allergy).

POTENTIAL ROLE

The diets of US young children are generally adequate for most micronutrients, although possible gaps exist, especially for vitamins D and E and fiber.[11,12] Compared with unfortified cow milk, some children who consumed OIYCFs have demonstrated improved vitamin D and E intakes.[13,14] That nearly all store purchased cow milk in the United States is fortified with vitamin D generally obviates a potential need of OIYCFs for many in this regard. For breastfed infants, including those breastfed after 1 year of age, it is generally best to continue a vitamin D supplement, because other dietary vitamin D sources are minimal. Results of 1 study were interpreted to indicate a possible benefit of OIYCFs for children at nutritional risk because of an imbalanced diet.[15] OIYCFs with an appropriate composition and context can provide key nutrients and make an important contribution to support child health. However, the sum total of attributes of OIYCFs, including those that are undesirable in some, as described earlier, make them unnecessary for most; therefore, emphasis should be on consumer education, nutritionally balanced diets, consumption of fortified foods,

TABLE 1 Nomenclature of Older Infant-Young Child "Formulas"

Product[a]	Approximate Target Age	Comments
Infant formulas	0–12 mo	• Human milk substitute
Follow-up formulas; follow-on formulas	6–12 mo	• Human milk substitute; • manufacturers able to advertise in countries with laws against advertisement of infant formulas up to 6 mo of age
Transition formulas; weaning formulas	9–24 mo	• Human milk and cow milk substitute; • manufacturers able to advertise in countries with laws against advertisement of infant formulas up to 6 mo of age.
Toddler milks, formulas, and drinks; growing up milks; young child milks	12–36 mo	• Human milk and cow milk substitute

[a] Except for infant formula, terminology is largely at the discretion of manufacturers rather than universally accepted definitions.

and food security to ensure dietary adequacy. Further, OICYFs are more expensive than cow milk and can represent a significant cost burden to families, especially for a child consuming them daily.

A distinction should be made between OIYCFs and medically necessary pediatric formulas for oral or enteral use. For children at nutritional risk secondary to chronic gastrointestinal or neuromuscular diseases, medically necessary pediatric formulas (not OIYCFs) provide essential or supplemental nutrition. These pediatric formulas (polymeric, semielemental, and elemental) assist nutritionally to provide protein, cholesterol, and fat, when enteral support is required, and should be reserved for use when medically necessary.

NUTRITIONAL CLAIMS RELATED TO OIYCF PRODUCTS

In assessing nutritional claims, products designed for infants younger than 12 months need to be considered separately from those designed for children 12 months and older. For nonbreastfed infants younger than 12 months of age, nutritional intake is primarily provided by standard infant formula together with age-appropriate solid foods after about 4 to 6 months of age, and that provides goal intakes of key micronutrients including iron, calcium, and zinc.[16] For formula-fed infants, the formula provides most of these, even if solid foods are limited, but breastfed infants may fall short, especially for iron, vitamin D, and zinc.[17] The Pregnancy and Birth to 24 Months Project of the US Department of Agriculture concluded that complementary feeds introduced earlier than 6 months of age offer no benefit to the breastfeeding infant in growth or iron status but may be associated with an increased risk of being overweight or obese, especially if introduced before 4 months. The use of OIYCFs results in displacement of infant formula and has no essential role in providing micronutrients to this age group; infants should instead continue to receive both a healthy mixed diet and human milk or standard infant formula.

For children 12 months and older (toddlers), the situation is more complex. At this age, many toddlers will have begun consuming cow milk-based products, although some families may have switched to other liquids including almond beverages, soy "milk" or beverages, or goat milk. In general, with a nutritionally adequate solid food intake that includes sources of bioavailable iron and zinc, cow milk is entirely adequate to meet a toddler's needs. For breastfed toddlers in this age group, human milk is also adequate, although generally a vitamin D supplement should be provided. Caution should be exercised to limit cow milk intake to 16 to 17 ounces per day because of concerns regarding its negative effect on iron status.[18,19]

For toddlers receiving other milk type products, nutrient adequacy for calcium, phosphorus, magnesium, and vitamin D is less assured. Some commercial products are fortified with these micronutrients, especially calcium, whereas others may be severely limited in calcium. Some toddler formulas are marketed based on either hydrolyzed cow milk protein or soy protein. Families who, for medical or other reasons, wish to avoid cow milk products may use these toddler products after consulting with their pediatrician, although even then and in most cases, selecting a noncow milk standard product fortified with calcium and vitamin D and ensuring a sufficient solid food balanced intake will meet the toddler's nutritional needs.

Although micronutrients are provided in OIYCFs, the recommendation is for caregivers to provide a varied diet with fortified foods and supplements to optimize nutritional intake.[7,8] Therefore, for children consuming a diet of solid foods that provide sufficient iron and vitamin content, there is no advantage or need to consume OIYCFs.[7] The best approach is for the pediatrician to perform a focused nutritional assessment based on intake of mineral- and iron-rich solid foods and consider how best to counsel families. This assessment should consider intake of dairy and meat as well as fruits and vegetables. Families with very low intake of certain micronutrients may be counseled regarding these or referred to a pediatric dietitian. For most families, adjustment of solid food intake will be adequate. For others, consideration of a vitamin D, mineral, or iron supplement may be necessary. A diet-based approach is always preferred, and in the case of toddlers, developing taste preferences for a mixed diet is ideal.

MARKETING AND CONSUMER PERCEPTION

OIYCFs occupy an important business niche as a source of increased sales and revenue that have offset a decline in sales by volume of infant formula. Using Nielsen US retail scanner data, Choi et al observed a decrease in sales of infant formula by volume of 7% during the period 2006 to 2015 (30 to 28 million kg), compared with those of OIYCFs, which increased by more 158% (1 to 3 million kg).[20] This represented an increase in sales of OIYCFs (in US dollars) of $53 million ($39 to $92 million) associated with a fourfold increase in OIYCFs advertising, whereas that for infant formula declined.

Marketing of products in this age group potentially discourages continued breastfeeding and is often based on vague concerns parents have that their child is not getting some needed micronutrients and that these are uniquely provided by OIYCFs. Advertisement practices for OIYCFs often convey them as a necessary "next stage" or "next step" to ensure optimal nutritional intake after infant formulas or even human milk and on a formula

continuum from infancy through early childhood. Many infant formula and young child milk products are additionally sold in a manner to foster brand loyalty as a line of products, for example labeled as stages 1, 2, and 3. In contrast, the World Health Assembly in 1986 recognized specialty formula milks for older infants as unnecessary, and other expert organizations, including the AAP, have similarly recommended breastfeeding through 2 years of age or longer or whole cow's milk and other acceptable nonformula dairy sources in conjunction with appropriate complementary solid foods as nutritionally adequate.[21–23] OIYCFs frequently make structure-function health or expert-recommended claims on their packaging that are not required to be based on scientific evidence or be reviewed or approved by the FDA.[1,3] Experience with infant formula marketing is that many consumers mistakenly believe that promoted properties have been tested and scientifically proven.[24] Claims of improved brain development or immune function have incorrectly shown to influence parents' belief that OIYCFs are healthier than cow milk and promotes their intention to provide OIYCFs to their children.[25,26] Romo-Palafox et al observed that 60% of caregivers believed that OIYCFs provided nutrition that was not provided by foods.[26] Labeling and messaging of OIYCFs manufactured by infant formula companies commonly show evidence of cross-promotion with infant formula brands through the use of similar names, packaging (colors and designs), logos, pictures, and slogans or images of a child feeding from a bottle or who appears younger.[27,28] In 1981, the World Health Organization adopted the Code of Marketing of Breast-milk Substitutes with several updates over intervening years. The United States voted against adoption of the code in 1981 and has minimally recognized the rules, including those that have extended the guidance to products such as OIYCFs. Manufacturers have used direct-to-consumer marketing of OIYCFs in various countries, including the United States, in violation of the guidance of the codes.[29] Not surprisingly, this has resulted in confusion regarding these products by consumers who may not be able to identify often subtle marketing distinctions made by manufacturers.[30] As a result, child caregivers can be misled to understand that they are acceptable or beneficial for infants younger than 12 months, undermining breastfeeding or displacing infant formula by these nonrecommended products.[31,32]

RECOMMENDATIONS

- For infants younger than 12 months, the liquid portion of the diet should be provided by human milk or standard infant formula that has been reviewed by the FDA based on the Infant Formula Act.
- For toddlers (children 12 months and older), caregivers should provide a varied diet with fortified foods to optimize nutritional intake. OIYCFs can safely be used as part of a varied diet for children but do not provide a nutritional advantage in most children over a well-balanced diet that includes human milk (preferred) and/or cow milk, and these products should not be promoted as such. OIYCFs have no specific role in routine care of healthy children and are more expensive than cow milk.
- Marketing of OIYCFs should make the clear and unambiguous distinction from standard infant formula in promotional materials, logos, product names, and packaging. OIYCF product name should not be linked in any way to infant formula (numerical, steps, sequential name) and should be labeled as something other than formula—for example, follow-on or toddler "drink" or "beverage" rather than follow-on or toddler "formula." Product placement in store shelves of OIYCFs should not be alongside standard infant formulas.
- Education of families about OIYCFs by health care teams as part of well-child visits is encouraged.
- Medical providers and care teams should complete a focused nutritional assessment, with consideration of mineral- and iron-rich solid food consumption and offer adjustment of solid food intake and/or vitamin supplementation as needed.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
FDA: US Food and Drug Administration
OIYCF: older infant-young child formulas

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A Multisystem Approach to Improving Autism Care

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abstract

Children with autism face significant barriers to accessing evaluations and intervention services often because of confusing referral processes, lack of centralized coordination across organizations serving children with autism, insurance coverage gaps, multiyear waitlists for diagnostic services, and limited provider knowledge about autism. Racism and systemic inequities exist and persist in autism care across the United States. This article reviews targeted initiatives implemented by a multidisciplinary team to advocate for, and address barriers faced, by autistic children and their families in Washington, DC. We describe initiatives across multiple levels of the health care system including:

1. infrastructure-building initiatives (eg, coalition-building, policy, and advocacy);
2. enabling services (eg, population- and community-level supports that increase provider capacity to serve children's and families' needs); and
3. direct services (eg, innovative, gap-filling programs that directly serve children and families). We review outcomes and describe lessons learned.

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Autism* is increasingly prevalent in the United States, with rates rising from 1 in 1000 children in the 1980s to 1 in 44 children currently.[1] Children with autism are more likely to have unmet needs for both health care and family support services, higher rates of health care dissatisfaction, and greater family financial strain than children with other special health care needs.[2] Significant barriers exist to families accessing autism services, including a lack of knowledge about autism,[3,4] confusing referral processes, insurance coverage gaps,[5] and multiyear waitlists for diagnostic evaluations.[6] Racism and systemic inequities exist in autism care.[7] Black children are often diagnosed years after their parents first voice developmental concerns,[8] and Hispanic children are less likely than Black or white children to receive an autism diagnosis, impacting access to needed services.[1*]

Inequities and systems challenges exist in Washington, DC, where 19% of children experience poverty and 90% of those children are Black.[9] Like many other hospital systems in the country, Children's National Hospital (CNH), the largest provider of pediatric care in the District of Columbia, has been challenged by long and growing wait times in autism diagnostic clinics, limited coordination across different clinics providing services, and lack of centralized care coordination.[10] Concerns about autism care extend beyond CNH, such as lack of systems coordination locally for youth with increased likelihood of autism. To address these issues, a multidisciplinary team within CNH and stakeholders from the broader District of Columbia community (Table 1) united to address barriers faced by autistic children and their families, as described below.

*As individuals on the autism spectrum demonstrate a range of self-identification, we use both person-first and identity-first language in this manuscript (Kenny et al 2016).

TABLE 1 Key Stakeholders

Stakeholder Group	Divisions/Staff/Members
Internal partners	
CHAI	• Community Mental Health CORE
	• Government affairs
	• Advocacy education
	• Child health data laboratory
Goldberg Center for Community Pediatric Health primary care clinics	• PCPs
	• Clinical support team (nurses, operations)
	• Integrated mental health specialists
	• Social workers
	• Case managers and care coordinators
	• Quality improvement specialists
	• Pediatric and psychology, trainees
CASD and Division of Psychology and Behavioral Health	• Speech language pathologists
	• Neuropsychologists
	• Clinical psychologists
	• Neurodevelopmental pediatrics providers
	• Psychiatrists
	• Care coordinators and parent support members
Convening bodies	
Neurodevelopmental Workgroup (internal stakeholder group 50 members)	• Goldberg PCPs, social workers, integrated mental health specialists, and care coordinators
	• CASD psychologists, psychiatrists, and developmental neuropsychologists
	• CHAI advocates, public health practitioners, and clinicians
	• Neurodevelopmental pediatrics providers
	• Clinical psychologists
DC-AC (external stakeholder group 90 members)	• 4 CNH departments/divisions (CASD, CHAI, psychology, neurodevelopmental pediatrics)
	• 12 community organizations and districtwide convening bodies
	• 5 education sector groups (eg, IDEA part B and part C providers)
	• 4 health insurance groups (4 insurers)
	• 6 health care providers (5 large health care centers)
	• 4 legal organizations and advocacy groups
	• 6 local government organizations (eg, health care finance, public schools)
	• 6 parent advocacy groups and 10 parent professionals (eg, those with professional roles and whose child has autism or neurodevelopmental differences)

CHAI, Child Health Advocacy Institute; IDEA, Individuals with Disabilities Education Act.

METHODS AND PROCESS

Overview and Context for Autism Advocacy Efforts

We describe multiyear efforts (2017–2022) to improve autism care within CNH and the District of Columbia more broadly. Our advocacy efforts are aimed at multiple levels of the health care system and include:

1. infrastructure-building initiatives (eg, systems-level approaches);
2. enabling services that focus on population- and community-level services to build capacity and connect providers and families to needed resources; and
3. direct services that provide innovative, gap-filling services to children and families until such services can be more sustainably and broadly supported (Fig 1).

Our advocacy work has been guided by the collective impact framework,[11] which highlights the importance of a common agenda (including defining goals and priorities), shared measurement, mutually reinforcing activities, continuous communication, and infrastructure support. Although our core team provided the backbone support to move initiatives forward, our advocacy efforts were codeveloped and amplified by the larger group of stakeholder collaborators (Table 1). The smaller core group has more dedicated time to provide support, including meeting and communicating more frequently, and carrying a greater share of the workload. When referencing our team, we are referring to authors and core partners of our advocacy initiatives, including professionals from CNH's Child Health Advocacy Institute, Center for Autism Spectrum Disorder (CASD), Divisions of Psychology and Psychiatry, Goldberg Center for Community Pediatric Health primary care clinics, and a parent advocate. Our team's parent advocate has lived experience and professional experience, on both the local and national level. We began by deliberately strengthening partnerships

FIGURE 1
Community Mental Health Collaboration, Outreach, Research, Equity conceptual model.

between our advocacy team and CASD. Professionals from CASD were critical for providing autism expertise across advocacy objectives, including cocreating the model for service delivery in primary care and providing training and mentorship for our direct service and enabling service initiatives. The administrative and organizational home for many of our efforts has been in the Child Health Advocacy Institute's Community Mental Health Collaboration, Outreach, Research, Equity (CORE), a multidisciplinary team focused on improving mental health care access, equity, and sustainability. Together with this internal team, key stakeholders from across the District of Columbia, including education providers, health insurance groups, and legal and local government organizations, played a significant role in advancing advocacy initiatives (Table 1).

Several citywide collaborative initiatives also laid the groundwork for this work. An early example was the development of the DC Collaborative for Mental Health in Pediatric Primary Care, a citywide, public–private coalition that strengthened relationships with a range of stakeholders and garnered credibility across health, education, and government sectors.[12] Over time, the CORE increasingly integrated a focus on improving access to autism care in their work. Funding for these efforts has involved a mix of private (eg, philanthropy and hospital grants) and in-kind support. In this article, we describe our autism-focused advocacy methods across 3 levels of our work: Infrastructure-building, enabling, and direct services. We provide specific details on advocacy initiatives within each level in Table 2. We have created a timeline (Fig 2) and discuss key anchor points throughout, though acknowledge that events frequently overlapped and projects built off one another in a way that may not be fully captured in linear form.

Infrastructure-Building Initiatives

Our infrastructure-building initiatives facilitate sustainable systems-level solutions to promote accessible and equitable behavioral health care through coalition-building, policy, and advocacy. Our efforts include internal and external multidisciplinary partners from government, health care, education, advocacy, public health, and the community (Table 1). One example of an infrastructure-building advocacy initiative is the CNH Neurodevelopmental Workgroup, which was developed to address barriers to seamlessly caring for children with neurodevelopmental concerns across departments within CNH. Before the creation of this group, departments providing autism care often functioned independently, siloed in different locations and satellite clinics. Initially, the workgroup conducted a needs assessment of CNH providers to clarify the barriers preventing children from accessing autism diagnostic evaluations. Since 2017, the group has met quarterly to address strategic priorities by (1) better understanding the landscape of autism services, (2) identifying gaps or concerns, and (3) brainstorming and implementing solutions to clarify referral pathways.

Although the Neurodevelopmental Workgroup addresses concerns internal to CNH, the group could not sufficiently address citywide needs. To address these broader systemic concerns, our team identified barriers and community needs for children in the District of Columbia insured by Medicaid, shared priorities related to autism advocacy, and outlined 10 comprehensive recommendations, which were summarized in a thought paper.[10] This paper was used as an advocacy tool and resource with stakeholders and government agencies to promote awareness of systemic issues and collaboratively derive solutions. The paper included a recommendation to establish a citywide convening group focused on autism. In 2020, our team established the DC-Autism Collaborative (DC-AC), a multidisciplinary, public–private coalition of professionals, community leaders, and parents aiming to strategically address barriers to equitable access to high-quality autism diagnosis, treatment, and coordinated care. The DC-AC has quickly gained credibility and traction thanks to the extensive partnerships with a range of stakeholders. The DC-AC team conducted a citywide needs assessment to identify priority areas, which led to the development of 5 subcommittees: Developmental monitoring, screening, and evaluations; education, outreach, and engagement; early childhood transition points; policy; and data. Each subcommittee established goals and met regularly to develop initiatives related to improving autism care.[13]

TABLE 2 Specific Initiatives Across 3 Key Levels: (1) Infrastructure-Building, (2) Enabling, and (3) Direct Services

Project and Aim	Approach	Success
Infrastructure-building: Promote accessible and equitable care through sustainable systems-level approaches		
Autism policy-advocacy: Initiatives to develop and advocate for the implementation of comprehensive policy solutions to address barriers related to (1) network adequacy, (2) workforce gaps, (3) timely and equitable access to quality autism care for evaluations, diagnosis, and treatment, and (4) insurance challenges	• Tracked data and shared it with relevant stakeholders • Met with government agencies and elected officials to provide education and increase awareness of autism barriers and potential solutions • Provided testimony on relevant issues • Increased collaboration and coordination with District of Columbia state Medicaid office and public health insurance provider	• Published 1 white paper on the landscape of services for children with autism who are enrolled in Medicaid • Established a new districtwide convening body on autism (DC-AC) • Expanded access to the types of behavioral health providers who can be credentialed with District of Columbia Medicaid and bill for outpatient behavioral health services • Increased transparency of autism Medicaid managed care insurance requirements
Neurodevelopmental Workgroup: An interdepartmental and multidisciplinary group of CNH providers and staff focused on identifying and addressing barriers to caring for children with neurodevelopmental concerns at CNH	• Identified appropriate representatives to join the workgroup • Surveyed stakeholders to identify needs and barriers • Convened stakeholders regularly • Developed a workplan to advocate for and implement solutions	• Engaged 50 members from 13 departments or clinics • Conducted 2 needs assessments used to advocate for internal changes • Created a centralized website with standardized referral guidelines for clinics that see overlapping families (accessed on average 66 times per mo)
DC-AC: A public–private coalition of professionals, community leaders, and parents in the District of Columbia focused on identifying and addressing barriers to autism care, including policy and advocacy solutions to increase early and equitable access to high-quality autism diagnosis, treatment, and coordinated care	• Surveyed stakeholders • Convened stakeholders regularly • Summarized barriers across 5 priority areas • Developed products and recommendations to address areas of concern	• Engaged 90 members representing 45 organizations • Conducted 1 needs assessment • Developed 5 family and provider resources • Resource webpage accessed on average 200 times per mo
Enabling services: Build capacity at the population and community level by connecting providers and families to needed resources		
Autism Toolkit for Pediatric PCPs in DC: A toolkit to provide PCPs with the tools to identify children at increased likelihood of autism and help families navigate the complicated systems of care related to neurodevelopmental disabilities in Washington, DC	• Consolidated national recommendations regarding primary care management of children with or at increased likelihood of autism • Summarized practical and locally applicable information to support family navigation	• Toolkit accessed online on average 16 times per mo
Community trainings on autism: Trainings to provide early educators and interventionists with knowledge related to identifying concerns about autism and supporting families in navigating the next steps	• Interviewed community providers to identify needs • Provided community trainings • Provided technical assistance and support to facilitate a train-the-trainer model to encourage sustainability	• Conducted 4 sets of trainings reaching 340 participants • 93% of participants expressed high levels of satisfaction with the knowledge gained from trainings
ECHO Autism: A program to expand autism knowledge and self-efficacy in autism care among community providers, including medical, mental health, early educator, and intervention providers, across both professional and trainee levels, and across settings	• Leveraged expertise in autism care and services through a multidisciplinary hub team of autism experts • Used autism-focused curricula individualized for service providers • Recruited providers and trainees from the community and within our hospital system	• 535 providers participated across six 6-mo ECHO clinics. • In subsets of participants, 78% indicated improved autism-related knowledge, 100% noted improved competency in autism-related care, and 99% reported good satisfaction with the ECHO program as a mode of learning.
Direct services: Provide innovative, gap-filling services to children and families until such services can be more sustainably and broadly provided		
Integrated evaluations in primary care: A team of psychologists and care coordinators provide integrated autism evaluations in primary care with care coordination support and facilitate closed-loop communication with PCPs	• Designed and developed the program • Trained team of generalist psychologists in autism diagnostic evaluations • Provided evaluations and care coordination support to families	• 155 children evaluated • Expanded from 1 to 4 clinics • Staff expanded from 2 to 8 part-time clinicians • Decreased average wait time for autism evaluations (wait time for standard of care = 12 mo, intervention group = 1.3 mo) • High satisfaction with the program reported by providers (mean rating [1-5] = 4.43) and caregivers (mean rating [1-5] = 4.31)

Enabling Service Initiatives

Enabling services focus on population- and community-level supports that increase provider capacity and connect providers and families to needed resources.[6] Consultation with, discourse among, and education of frontline professionals such as health providers (eg, primary care providers [PCPs], general psychologists), early childhood educators (ECEs) and specialists (eg, early intervention providers), and support staff (eg, insurance-based care coordinators, clinic administrators) can improve care. These professionals have the potential to play a critical role in identifying autism in young children and connecting families to resources, but many report limited knowledge about autism and related resource navigation.[3,14,15]

To understand and address ECE providers' autism-related training needs, we conducted interviews with leaders from the District of Columbia's educational and early intervention agencies, as well as ECE mental health consultants. We then developed a set of replicable trainings to cover identified gaps in knowledge and skills, including general autism knowledge (eg, diagnostic criteria and tools, treatment), engaging families, and navigating local services. We used a train-the-trainer model to maximize sustainability and dissemination. To address PCP needs, we developed the "Autism Toolkit for Pediatric PCPs in DC."[16] The toolkit included District of Columbia-specific content on autism screening, diagnosis and treatment planning (including differences between educational classification of autism and medical diagnosis of autism), and resources.

Additionally, we amplified existing professional supports by connecting community champions to our hospital's ongoing Extension for Community Healthcare Outcomes (ECHO) Autism program. This program aims to build autism knowledge and competencies by establishing shared learning forums between community providers and a multidisciplinary group of autism specialists, to increase equitable access to autism services.[17] ECHO clinics occur virtually and target professionals in medical, community, and educational/early intervention settings.

Direct Service Initiatives

The foundation and partnerships established through the aforementioned enabling services and infrastructure-building methods encouraged us to develop, refine, and scale promising direct services. In our Autism in Primary Care (APC) Program, embedded psychologists are trained and subsequently supervised by a psychologist specializing in autism to provide diagnostic evaluations for young patients (aged <5 years) referred by their PCP with high concern for autism. The Goldberg Center for Community Pediatric Health primary care clinics (where our APC program is housed) are the largest provider of pediatric primary care in the District of Columbia, serving high percentages of youth who are publicly insured. Through APC, families receive care coordination after evaluation, and PCPs receive direct feedback about the case. This initiative, which focuses on targeted use of scarce specialty resources through mentoring and triage of patients with high concern for autism, facilitates more streamlined and equitable access to a comprehensive evaluation, which is often a critical preliminary step in obtaining autism services. Our ultimate goal is to scale up APC to other primary care clinics regionally over time. We also encourage all community PCPs and integrated behavioral health providers to use ECHO to support their ability to diagnose autism.

Outcomes

Working collaboratively on the infrastructure-building, enabling, and direct service advocacy initiatives outlined above and described in Table 2 allowed us to support several changes to autism care in the District of Columbia, including the following:

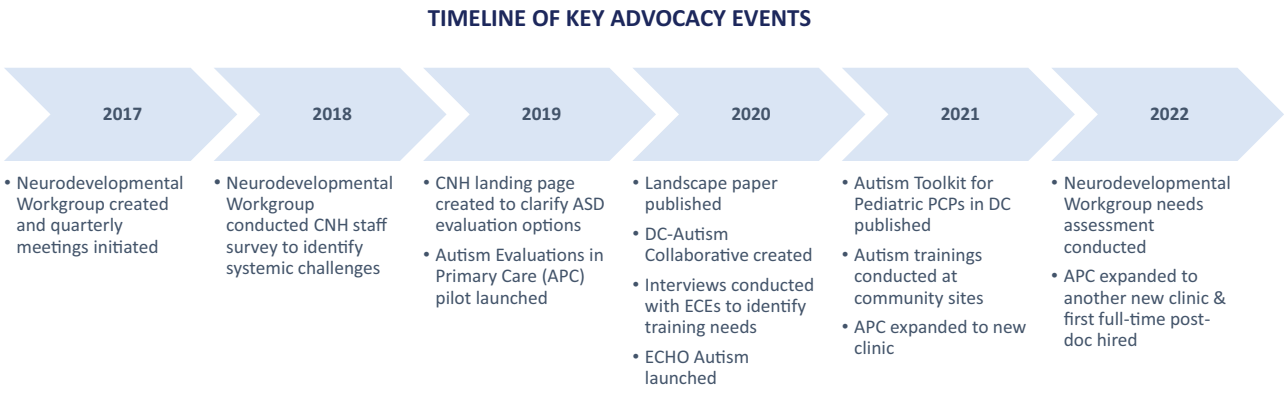

FIGURE 2
Timeline of key advocacy initiatives.

- Surveyed stakeholders (in health care and education/early intervention) and synthesized findings (including barriers and proposed solutions) in a policy paper[10] and in hospital-specific memos. The goals were to create a shared understanding of the issues (eg, barriers to care faced by families and providers, such as long wait times and the need for more coordination) and potential solutions (eg, increased autism navigators and autism education, such as ECHO). Summary documents developed have been used to advocate to leaders within the hospital and across the District of Columbia about needed improvements like staff increases and program expansions.
- Decreased regulatory barriers by contributing to advocacy for changes to local policies that had previously limited access to autism care for some children. This included successfully expanding the types of behavioral health care providers (eg, psychologists) who can be credentialed with District of Columbia Medicaid and bill for outpatient behavioral health services; advocating for policy changes and funding in the District of Columbia's budget to improve access to autism services; and advancing policies that support integration of behavioral health services within local managed care organizations without subcontracting, that may support more effective and efficient care delivery. We continue to provide input on and monitor implementation of the policy changes, which would include a Medicaid state plan amendment that would permit reimbursement for a more comprehensive range of services.
- Coordinated efforts among multiple partners within the hospital (eg, Neurodevelopmental Workgroup) and across the District of Columbia (eg, DC-AC) to break down siloes and increase collaboration and relationship-building across groups in tackling autism-specific concerns. For example, we collectively developed web-based resources to clarify different autism assessment options locally.
- Disseminated autism-related information, including clinical information (eg, diagnostic criteria and procedures) and systems navigation information, through the creation of provider- and family-facing resources (eg, what to do while awaiting an autism diagnostic evaluation) and trainings (eg, toolkits,[16] train-the-trainer modules), and leveraging existing professional mentoring programs (ECHO clinics). Resources were made freely available and were disseminated at meetings, electronically (eg, newsletters), and on websites targeting families and providers (eg, PCPs) across the District of Columbia.
- Increased access to care for children and families facing significant barriers by developing and implementing CNH's APC program that has served >150 children and their families in primary care to date. Wait times for evaluations through APC were less than wait times at local specialty clinics, and children were diagnosed younger than the national average of >4 years. Moreover, patients served were primarily those who had historically faced more barriers to accessing case (Black and Latinx families and those who speak a language other than English).

Barriers and Lessons Learned

We hope that other institutions and coalitions can learn from our efforts in the District of Columbia, including from the barriers we have faced and from the following lessons learned:

- Identify clear guiding principles for the work: A deliberate focus on access, equity, and sustainability underlies all our efforts. For example, our policy efforts focus largely on children insured through Medicaid, whereas our enabling and direct service work focuses on families who face barriers to accessing care (eg, difficulty accessing services because of insurance barriers and wait times). Similarly, we intentionally developed partnerships with community stakeholders who serve underresourced families to build their capacity to address autism-related needs.
- Start small to ensure initial success and momentum. This can be challenging when the systems issues are large and when demand for autism services far outpaces the supply. For example, our APC program started at 1 primary care site with a focus on children aged <5 years with high likelihood of autism despite the pull to make the service available to a wider range of children from the start. However, starting small (eg, encouraging a student volunteer to help gather and summarize information) helps to encourage measured progress, build momentum, and avoids overwhelm, especially when resources and time are limited.
- Work across different levels of the health care and educational system. Working with children and families informed our educational and policy efforts by providing specific examples of barriers to and facilitators of care. Systems-level work improves direct patient care because it helps to address systems inefficiencies and gaps and gives providers an outlet to advocate for factors that may impact their burnout, increasing their agency. Working simultaneously across systems also maintains momentum and engagement, because there may be progress happening in 1 area even if progress is stalled elsewhere.
- Prioritize coalition-building from the start. Engagement with stakeholders from various disciplines, sectors, and agencies has facilitated problem-solving to address complex yet universal areas of concern and to amplify our collective voice. For those in institutions with limited resources, starting with even 1 connection internally or externally can prove fruitful. We are actively working to enhance the role that families can play in this work. Although we have >10 family members of children with neurodevelopmental differences

(including autism) who participate in our coalitions in a professional capacity, we continually seek ways to increase parent involvement (eg, presenting information and soliciting input at parent forums, interviewing families who have participated in our APC program) and aim to do so more in the coming year. Coalition-building takes time and can be challenging given that stakeholders have different priorities and constraints. Balancing the needs of continuing to move the work forward while ensuring agreement and engagement is difficult, though we have been impressed by the level of stakeholder engagement toward common goals related to improving autism care.

- While supporting broad participation, identify champions across groups (eg, individuals who can promote efforts and disseminate information within their organizations). Despite strong interest, many professionals have limited time for efforts that are not directly part of their professional duties. Identifying champions can enhance accountability and keep progress moving forward despite these challenges.
- Consistent with a collective impact framework, obtain backbone infrastructure support from individuals with dedicated time to communicate more frequently, carry a greater share of the workload, and make key decisions. We have been challenged by not always having sufficient backbone support, which can slow progress for periods of time. We recognize that identifying backbone support is especially challenging in underresourced institutions and may require external partnerships. However, even in a setting of limited resources, small incremental changes and development of stronger partner relationships can be very impactful in the long term.
- Diversify financial and in-kind support to ensure sustainability of the efforts and prevent dependence on a single source of funding. Philanthropic funds (often relatively small amounts) gave us the flexibility to address areas that are traditionally not supported through research or operational funding (eg, piloting new initiatives, developing and disseminating resources). Sustainable funding remains challenging because it can be difficult to balance funders' desire to support new and innovative ideas with the need to sustain enduring efforts. However, we encourage consideration of ways in which impacts can be made without financial supports within the context of standard clinical practice (eg, through quality improvement processes).
- Systematically gather and report on quantitative and qualitative data. Such data (eg, tracking provider concerns, supplementing themes with specific examples) has been helpful in deconstructing silos to document the nature and pervasiveness of challenges. We have built evaluation and continual improvement into our activities, including evaluating the effectiveness and functioning of our collaborative teams. Relatedly, it is important to synthesize and highlight the needs and business case for funders, hospital leadership, and other key stakeholders. We have faced challenges in accessing data (eg, population-level electronic health record data) and in soliciting regular feedback from stakeholders about barriers to autism care. Even once data are synthesized and presented, leaders face competing demands on their time and on resources they can allocate to address concerns.
- Identify and celebrate small wins. Advocacy work takes time to pay off and may come with unexpected obstacles. Recognizing small steps along the way encourages momentum, enthusiasm, and reflections on the progress being made.

CONCLUSIONS

We have begun to address clinical and access challenges in autism care through multidisciplinary collaboration and education across our hospital system and the District of Columbia, though we face continued challenges and much work remains. We aim to sustain this work by building on our initial success and using braided funding wherever possible. We are eager to explore federal advocacy efforts that align with our goals and work. Although each state and jurisdiction will face unique challenges, we hope that others can learn from our efforts to improve autism care for children and their families.

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ABBREVIATIONS

APC: Autism Evaluations in Primary Care
CASD: Center for Autism Spectrum Disorder
CNH: Children's National Hospital
DC-AC: DC-Autism Collaborative
ECE: early childhood educator
ECHO: Extension for Community Healthcare Outcomes
PCP: primary care provider

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Trends in Pediatric Nonfatal and Fatal Injuries

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Recent trends in pediatric injury-related fatalities are alarming,[1] with increases in homicides, suicides, and poisonings in the past decade. However, it is difficult to accurately assess the root cause of these trends in pediatric injury-related deaths without placing them in the context of all childhood injuries (ie, inclusive of nonfatal injuries). The analysis of nonfatal injuries can provide valuable insights into the circumstances and mechanisms of injury, which can help further develop effective preventive strategies to reduce both fatal and nonfatal injuries. Most studies to date have compared fatal and nonfatal injuries related to a specific mechanism such as firearm-related injuries[2] or intent such as self-harm.[3] Although these studies are informative, a broader lens is also useful to accurately predict general trends of pediatric injury. Here, we compared trends in fatal and nonfatal injuries in children, across intent and mechanism of injury.

METHODS

Fatal (2011–2021) and nonfatal injury (2011–2020) data for children aged <18 years were derived from the Centers for Disease Control and Prevention, the National Center for Health Statistics' Web-based injury statistics query and reporting system (WISQARS). Fatal injury data in WISQARS are based on death certificates from the National Vital Statistics System. WISQARS provides exact death counts and death rates for the United States by age, intent, and mechanism. Nonfatal injuries presented in WISQARS provide national estimates on the basis of weighted data from the US Consumer Product Safety Commission's National Electronic Injury Surveillance System. Case fatality rates were calculated as the percentage of injuries that were fatal for each intent or mechanism. Linear regressions were used to evaluate time trends in fatal and nonfatal injury rates on the basis of intent and mechanism. The study is exempt from the institutional review board.

RESULTS

At the beginning of the study period in 2011, fatal injury rates were 14.07 per 100 000 children and increased to 17.30 per 100 000 by 2021 ($P = .006$ for linear trend). In contrast, nonfatal injuries decreased from 11 592.56 per 100 000 to 5359.73 per 100 000 in 2020 ($P < .0001$) (Fig 1A). Nonfatal unintentional injuries and assaults decreased (54.9% and 59.8%, respectively, $P < .0001$), whereas nonfatal self-harm injuries increased by 57.1% ($P < .0001$) (Fig 1B). Firearm fatalities increased by 87.1%, drug poisoning fatalities increased by 133.3%, and suffocation-related fatalities increased by 12.5% (Fig 1C). At the same time, although the leading causes of nonfatal injuries decreased across most mechanisms (52.8% decrease in injuries from falls, $P < .0001$; a 66.7% decrease in injuries from overexertion, $P < .0001$; a 63.0% decrease in struck by against injuries, $P < .0001$; a 47.3% decrease in motor vehicle occupant injuries, $P = .005$; a 36.7% decrease in cut pierce injuries, $P < .0001$), nonfatal injuries

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Ms Mannix and Dr Mannix conceptualized and designed the study, collected the data, analyzed the data, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr Neuman critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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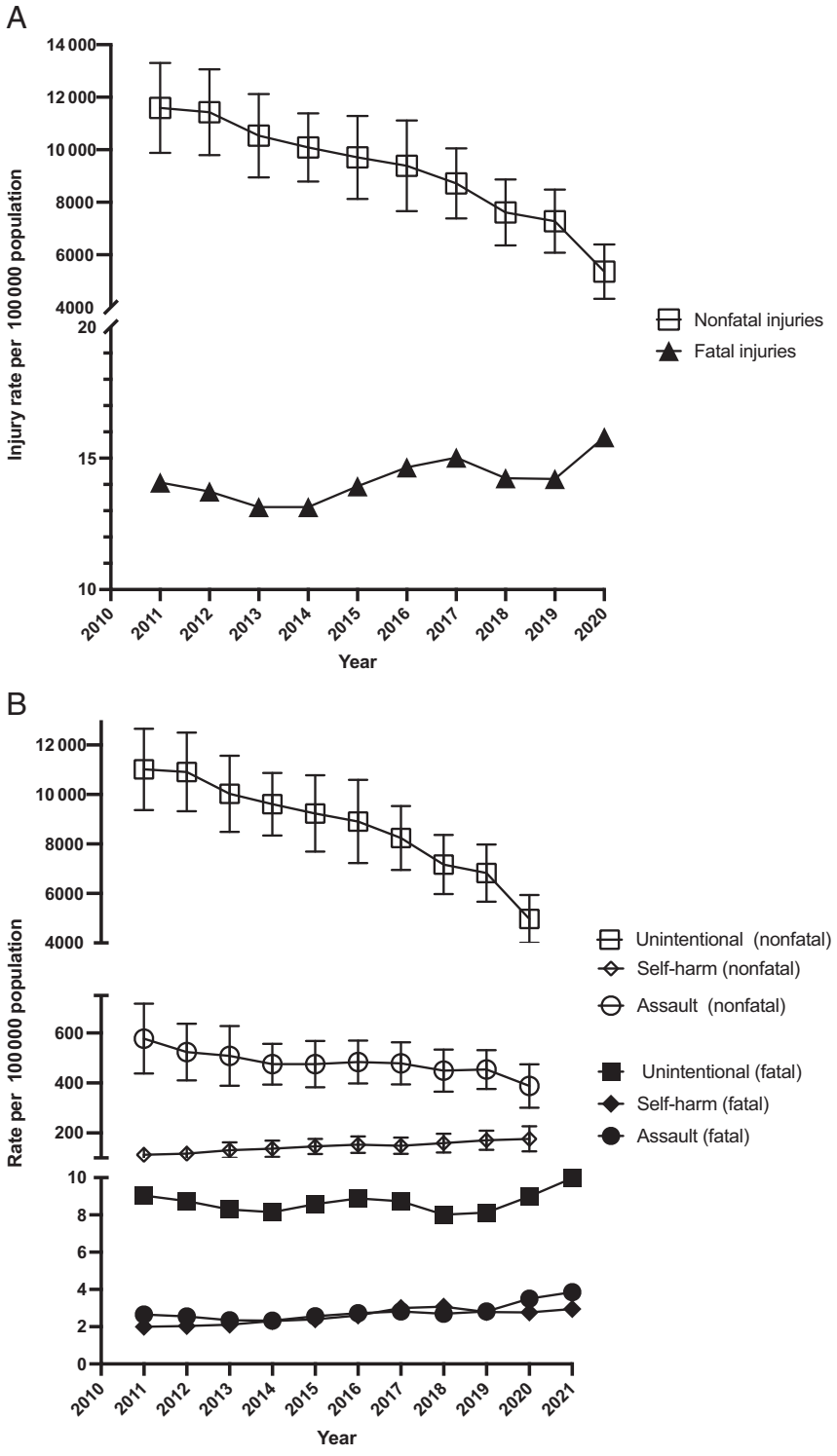

FIGURE 1

1A, Increasing case fatality rate from 2011 to 2020. Nonfatal injuries decreased substantially from 2011 to 2020 ($P < .0001$ for trend), whereas fatal injuries increased ($P = .006$). Error bars are 95% confidence intervals, based on nonfatal injuries rate estimates in WISQARS. B, Increasing fatal injuries are demonstrated for self-harm ($P = .0002$) and assault ($P = .0039$). Unintentional and assault nonfatal injuries decreased substantially from 2011 to 2020 ($P < .0001$), whereas self-harm nonfatal injuries increased ($P < .0001$) over the same time period. Error bars are 95% confidence intervals, based on nonfatal injuries rate estimates in WISQARS. C, Increasing trends in fatal injuries occurred for suffocation/hanging ($P = .0252$), poisonings ($P = .0121$), and firearms ($P < .0001$). Nonfatal injuries for those same mechanisms showed increases in poisonings ($P = .0126$) and firearms ($P = .0150$), but not suffocation/hanging ($P = .4445$). Error bars are 95% confidence intervals, based on nonfatal injuries rate estimates in WISQARS. D, Case fatality rates increased from 0.12% in 2011 to 0.30% in 2020 ($P < .0001$ for trend). E, Case fatality rates across mechanisms.

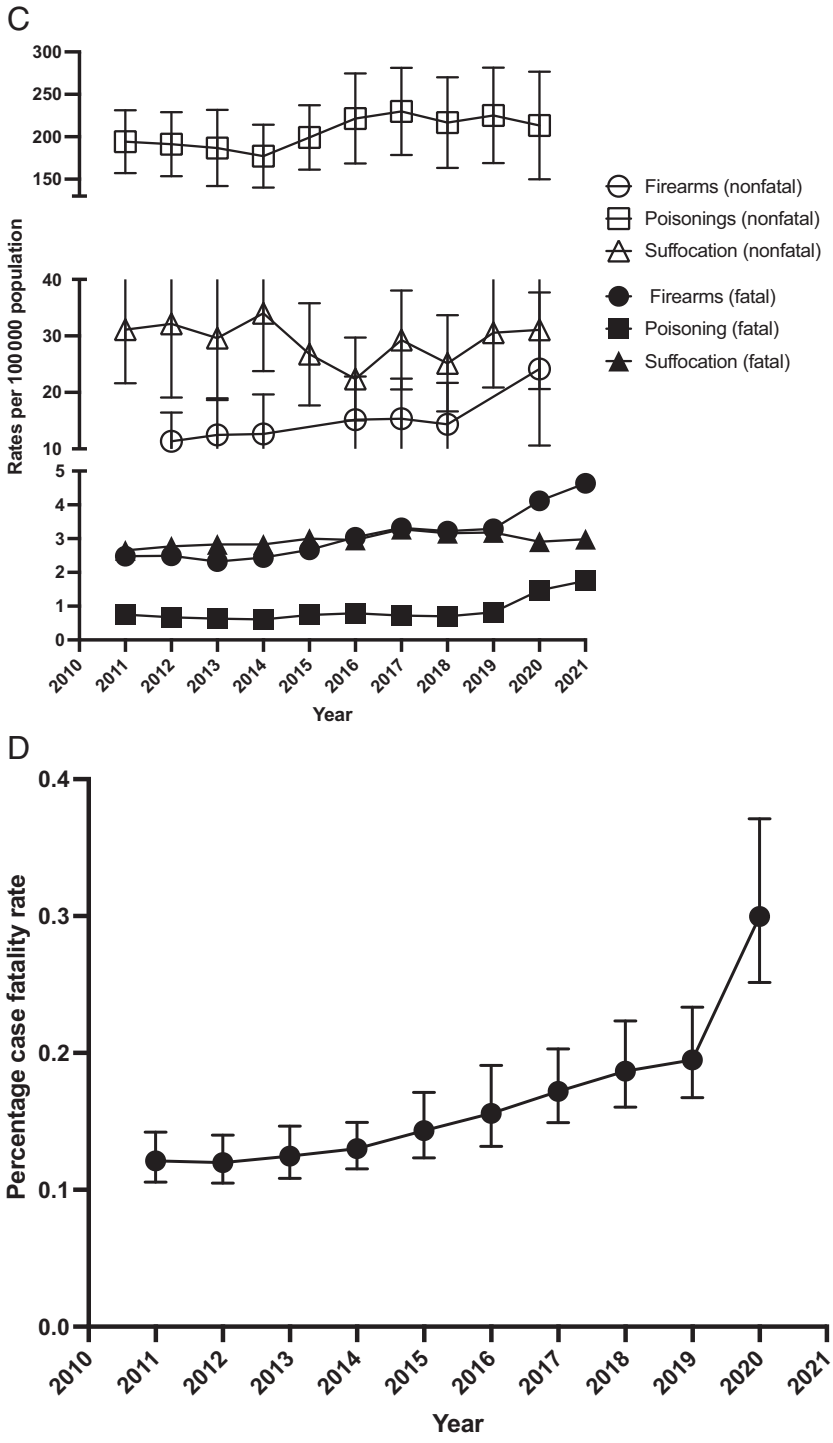

FIGURE 1
Continued

from drowning did not change (P = .715) and nonfatal firearm- and poison-related injuries increased (113.1%, P = .015 and 9.9%, P = .013, respectively) (Fig 1C). From 2011 to 2020, the overall case fatality rate increased by 250% (P = .0012) (Fig 1D), with the highest case fatality rates in firearm, drowning, and suffocation (Fig 1E).

DISCUSSION

Over the past decade, we observed dramatic increases in pediatric case fatality rates, driven both by declining nonfatal injuries and increasing fatal injuries. The divergent trends between fatal and nonfatal injuries highlight the need for a comprehensive approach to childhood injury prevention.

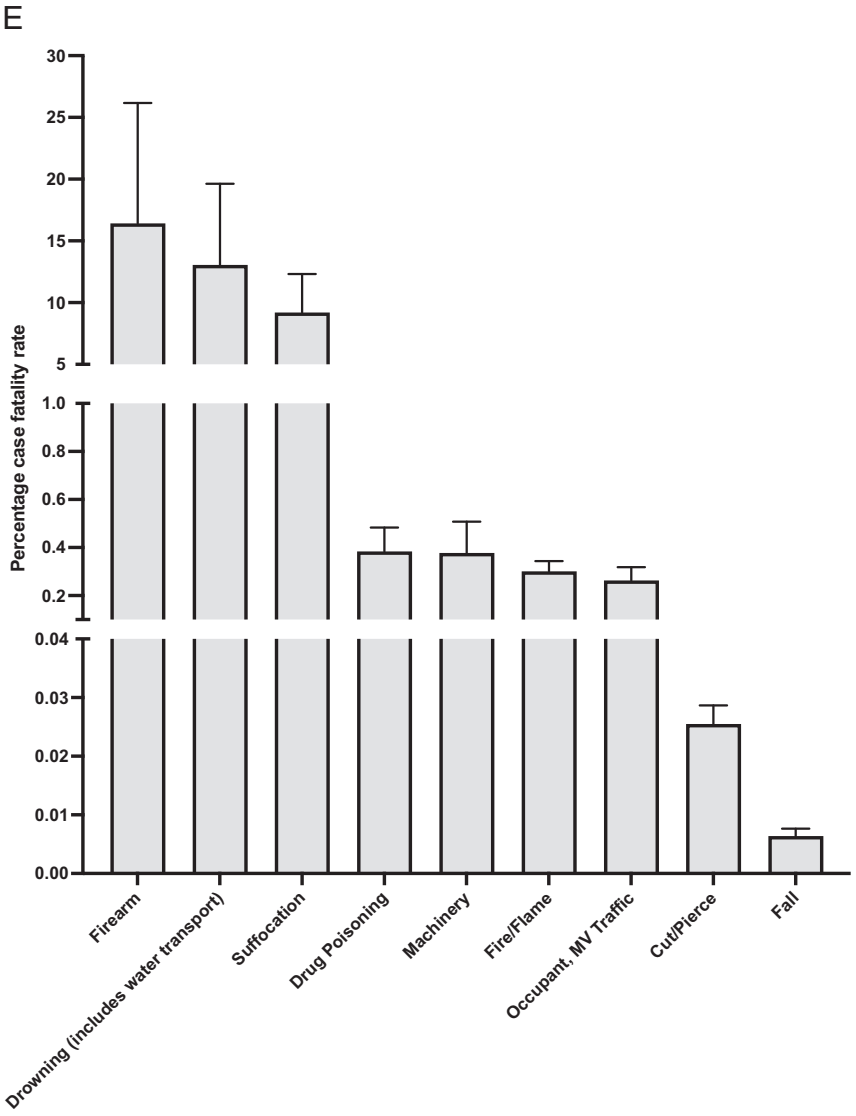

FIGURE 1
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Notably, pediatric injury fatalities sharply increased in the pandemic years of 2020 to 2021, and it remains unclear whether these trends will continue. In contrast, nonfatal injuries showed a steady declining trend throughout the study period, driven largely by decreases in falls (3564 per 100 000 in 2011 vs 1682 per 100 000 in 2020) and struck by/against (2945 per 100 000 in 2011 vs 1088 per 100 000 in 2020) mechanisms. The decrease in nonfatal injuries may also be driven, in part, by recent public health interventions targeting pediatric safety partnered with technological advancements and legislative requirements. For example, improved booster seat technology has been paired with effective legislative and education campaigns.[4] Yet, despite the progress in reducing most nonfatal injuries, the trends in increasing nonfatal firearm and poisoning injuries defy the overall trend in nonfatal injuries, in part because public health legislative support has lagged in these critical injury mechanisms. This is especially concerning given the high case fatality rate of these injury mechanisms in children. Targeted interventions, such as strengthening legislation, enhancing public awareness, and improving health care systems are needed to address both fatal and nonfatal injuries among children, but these efforts alone are likely not sufficient, given the myriad societal forces that impact pediatric injuries. Continued research and surveillance are crucial to monitor trends, evaluate interventions, and inform evidence-based strategies for effective injury prevention and mitigation.

ABBREVIATION

WISQARS: Web-based injury statistics query and reporting system

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Management of Discharge Instructions for Children With Medical Complexity: A Systematic Review

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abstract

CONTEXT: Children with medical complexity (CMC) are at risk for adverse outcomes after discharge. Difficulties with comprehension of and adherence to discharge instructions contribute to these errors. Comprehensive reviews of patient-, caregiver-, provider-, and system-level characteristics and interventions associated with discharge instruction comprehension and adherence for CMC are lacking.

OBJECTIVE: To systematically review the literature related to factors associated with comprehension of and adherence to discharge instructions for CMC.

DATA SOURCES: PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials, PsycInfo, Cumulative Index to Nursing and Allied Health Literature, Web of Science (database initiation until March 2023), and OAIster (gray literature) were searched.

STUDY SELECTION: Original studies examining caregiver comprehension of and adherence to discharge instructions for CMC (Patient Medical Complexity Algorithm) were evaluated.

DATA EXTRACTION: Two authors independently screened titles/abstracts and reviewed full-text articles. Two authors extracted data related to study characteristics, methodology, subjects, and results.

RESULTS: Fifty-one studies were included. More than half were qualitative or mixed methods studies. Few interventional studies examined objective outcomes. More than half of studies examined instructions for equipment (eg, tracheostomies). Common issues related to access, care coordination, and stress/anxiety. Facilitators included accounting for family context and using health literacy-informed strategies.

LIMITATIONS: No randomized trials met inclusion criteria. Several groups (eg, oncologic diagnoses, NICU patients) were not examined in this review.

CONCLUSIONS: Multiple factors affect comprehension of and adherence to discharge instructions for CMC. Several areas (eg, appointments, feeding tubes) were understudied. Future work should focus on design of interventions to optimize transitions.

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Although all children are at high-risk for adverse outcomes (eg, unplanned emergency department visits and readmissions, medication errors) after the transition from hospital to home,[1–4] children with medical complexity (CMC) are particularly susceptible. The Pediatric Medical Complexity Algorithm (PMCA) defines this high-risk group as children with multiple chronic conditions, technology dependence, progressive conditions associated with decreased life expectancy, and metastatic malignancies.[5] Despite comprising only 1% of children in the United States, CMC account for 25% of hospital days and 33% of hospital expenditures for children.[6,7] Readmissions and other adverse outcomes are more likely in children with greater complexity.[8,9] Across pediatric populations, parents and other caregivers (referred to subsequently as caregivers) face challenges related to comprehension of and adherence to their child's discharge instructions,[10] potentially contributing to adverse outcomes.[1,2,11–13] Discharge instructions that are more complex are associated with higher error rates,[14–16] although the reasons why these errors are more prevalent for some caregivers of CMC are less understood.[17,18]

Recent research and initiatives have focused on improving outcomes for CMC.[19–21] Prior reviews about CMC have summarized studies examining how to prevent health care utilization,[22,23] have focused on care of CMC in general but not the inpatient to outpatient transition,[24] or have focused on specific populations (eg, children with cancer).[17,18] Other reviews have examined caregiver experiences with the hospital to home transition.[25,26] Prior reviews have not specifically focused on patient-, caregiver-, family-, provider-, and system-level characteristics (as outlined by frameworks such as the Pediatric Self-Management Model)[27] that are associated with discharge instruction comprehension and adherence. Our objective was to systematically review the literature related to factors, including interventions, associated with caregiver or patient comprehension of and adherence to discharge instructions for CMC.

METHODS

The protocol for this review was registered (PROSPERO ID: CRD42020214393) and is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=214393.

Search Strategy

A medical librarian (J.M.) searched PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials, PsycInfo, Cumulative Index to Nursing and Allied Health Literature, and Web of Science from database initiation until March 7, 2023 (Supplemental Table 3). Studies identified as part of this search strategy included Medical Subject Headings (MeSH) and keywords representing 4 key concepts: children, caregivers, discharge OR transition of care, and medical complexity. The medical complexity concept was defined based on the PMCA[5]; for example, this included terms related to multiple chronic conditions, decreased life expectancy, or technology dependence.[28] The search strategy was iteratively refined by J.M. and A.F.G. through preliminary searches. Of note, a concept related to comprehension/adherence was not included in the search strategy because its inclusion led to exclusion of key articles; instead, comprehension/adherence was examined manually in the title/abstract and full-text screenings described later. We also searched the database OAIster (Open Archives Initiative) for these concepts to identify nonpublished studies (eg, the gray literature), as well as the table of contents from 2016 to 2021 for the following journals (given relevant articles identified in a preliminary search and as per the Cochrane Handbook[28]): *Academic Pediatrics*, *BMC Pediatrics*, *Contemporary Pediatrics*, and *European Journal of Pediatrics*. Two authors (A.F.G. and M.T.) identified other potential articles by examining references of included studies, references of relevant review articles, and studies that cited included articles.

Study Selection

We followed a 2-step screening process as recommended by Cochrane[28] and the Agency for Healthcare Research and Quality[29] to select studies for inclusion and used a web-based tool (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; www.covidence.org) to organize studies. First, 2 authors (A.F.G. and either A.V.S., J.S.F., M.T., or R.H.R.) independently examined the titles and abstracts identified in the literature search for relevance to our research question; we expected that many studies may clearly not be relevant in this screen given our broad search strategy. A third author from this group settled any disagreements.

For studies identified as potentially relevant in this screen, 2 authors (A.F.G. and either A.V.S., J.S.F., or M.T.) independently reviewed the full article text against inclusion and exclusion criteria; a third author resolved disagreements. We included studies that: (1) were original interventional or observational research studies (eg, not review articles, commentaries); (2) primarily focused on children (aged 0–18 years) with medical complexity (defined by the PMCA[5]) and/or their caregivers; (3) examined discharge to home from the general inpatient (ie, acute care) unit or PICU; and (4) examined factors (including patient-, caregiver-, family-, and system-level factors, as well as interventions) impacting comprehension of or adherence to discharge instructions overall or related to specific discharge instruction domains (ie, medications, appointments, return precautions, restrictions, equipment). We excluded studies that: (1) focused on patients from other settings (eg, newborn nursery, NICU, ambulatory, emergency department); (2) focused on oncology patients (medically complex,[5] but covered in other systematic reviews[17,18]); or

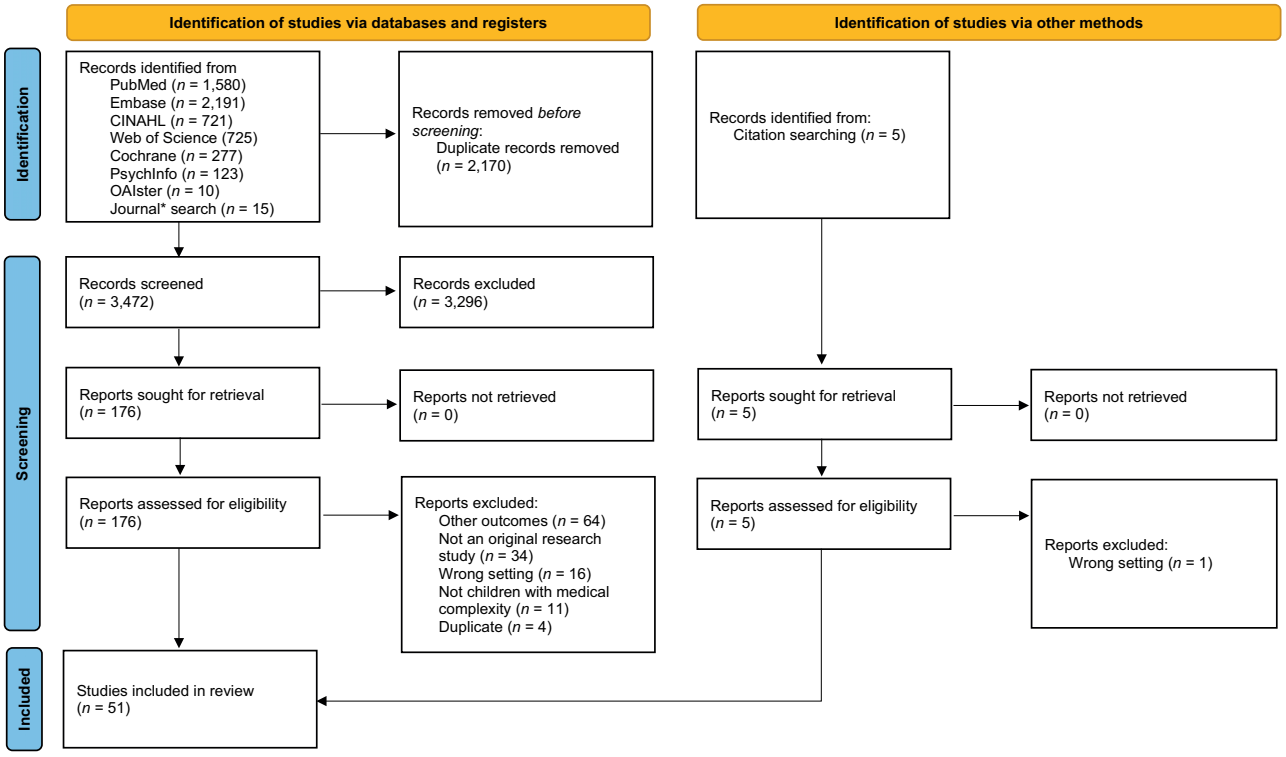

FIGURE 1
PRISMA flow diagram.

(3) focused on other single chronic conditions (not considered CMC[5]). Full-text articles not written in English were translated by a native speaker or professional translation service (Datagain, Secaucus, NJ; https://datagainservices.com/).

Data Extraction and Assessment of Quality and Risk for Bias

Information related to study characteristics, study design, methods, subject characteristics, and results were extracted independently by two authors (A.F.G. and either A.V.S., M.T., R.H.R., or V.Z.) using a structured form, similar versions of which were piloted and used previously (Supplemental Table 5).[10,30]

Two authors from this same group independently assessed study quality and risk of bias using the Mixed Methods Appraisal Tool (MMAT).[31] The MMAT was chosen because multiple study types were included in this review. In addition to assessing 2 screening questions for all study types (if there are clear research questions and if data are collected to address the research questions), the MMAT examines 5 criteria for each study type. Examples include whether methods were appropriate to address the research question (qualitative studies) and whether analyses accounted for confounders (quantitative nonrandomized studies). Questions are answered with "yes," "no," or "can't tell." Disagreements were resolved by consensus discussion.

RESULTS

Article Selection

The 5642 articles identified in the initial search represented 3472 unique studies (Fig 1). We screened the titles and abstracts of these studies; 3296 were excluded from a lack of relevance. We screened the full text of the remaining 176 articles. Forty-seven met inclusion criteria with 4 additional studies identified through reference review and citation tracking.

Quality Assessment

All 51 studies had clear research questions with data collected to adequately answer these questions (MMAT screening questions) (Supplemental Table 4). For MMAT questions assessing study type–specific metrics, 24 studies met criteria (ie, a "yes" answer) for all 5 questions; 18 studies met criteria for 4 questions. The remaining 9 studies met criteria for between 1 and 3 of 5 questions.

Characteristics of Included Studies

Of the 51 included studies, 5 were conference abstracts[32–36] and 1 was a doctoral thesis[37]; the remainder were journal

articles. Zero studies were randomized controlled trials (RCTs). The study types included 18 qualitative,[32,38–54] 14 nonrandomized interventional,[34,36,55–66] 12 mixed methods,[33,37,67–76] 3 cross-sectional,[77–79] 3 quality improvement,[35,80,81] and 1 prospective cohort.[82] Most (n = 40) studies were from the United States; the remainder were conducted in Brazil (n = 4),[43,49–51] Turkey (n = 2),[55,61] the United Kingdom (n = 1),[76] Republic of Korea (n = 1),[64] Ireland (n = 1),[39] Canada (n = 1),[67] or China (n = 1).[45] All studies were published in English.

Study findings are summarized in the following sections, organized by domain of care. Some studies covered multiple domains of care and are referenced in multiple sections. Key findings for each study are represented in Table 1. A summary of study findings is presented in Table 2.

Equipment/Supplies

Respiratory Equipment/Tracheostomy

Respiratory equipment was the focus of 25 studies, with 22 on tracheostomies. Nine qualitative or mixed methods studies assessed caregiver views on barriers and facilitators to comprehension of and adherence to tracheostomy instructions[33,38–40,45,52,54,69,76]; 1 study examined barriers to completion of a discharge education program as assessed by provider survey and chart review.[78]

Several barriers were identified, many of which were at the system level. Barriers related to home care services included delayed start of services, issues with insurance approval, and poor staff availability and training.[38–40,45,69,76,78] Barriers related to the equipment and supplies included not being delivered,[38–40,69] not understanding how to set up equipment,[38] and equipment being different in the home and hospital.[40] Caregivers also experienced challenges related to care coordination (eg, hospital training and equipment delivery at same time)[38,40,69] and communication (eg, poor communication among providers, having limited English proficiency [LEP]).[38,54,69,78] Caregiver- and family-level barriers included lack of funding for equipment,[78] difficulty traveling with equipment,[40] mental and emotional health,[38,39,45,52,78] not feeling prepared for emergencies or malfunctions,[38,69,76] and family dynamics.[78]

Several studies assessed interventions that aimed to improve adherence. One of the most frequently cited intervention elements that led to improvements in objective measures of knowledge or skills was hands-on experience with equipment.[36,56,59–61,64] After staff demonstrated how to perform a task (eg, changing tracheostomy tubes), caregivers demonstrated the skill for staff to assess competency (ie, showback). In some cases, caregivers progressively worked toward taking on all aspects of their child's care in the hospital before taking on these responsibilities at home.[56,59–61] Additional intervention elements included provision of visual (eg, video, pictographic) materials[60,61,64] and training with home equipment.[60]

Intervention elements and other facilitators that caregivers believed improved their ability and confidence to care for respiratory equipment were staff demonstration and hands-on training,[33,38–40,52,56,57,59,63,65,69–72] watching videos,[45,52,54,72,76,79] debriefing/feedback,[63–65,70,71] teachback,[72] comprehensive written materials,[52,79] telehealth visits after discharge,[35,81] additional caregiver support,[45] meeting with another experienced family,[54,69] tailored education,[52] experience caring for CMC,[52] social support,[54,76] and proper coordination of home care.[69]

Gastrostomy Tube

Two nonrandomized interventional studies found improvement in subjective (eg, caregiver confidence) and objective (eg, knowledge) measures after receipt of an intervention related to gastrostomy tube (GT) management. Intervention components included a standardized checklist,[55,58] demonstration,[55] educational materials (eg, booklet, video),[58] showback,[58] a postdischarge phone call,[58] and staff ordering supplies.[58]

Multiple/General

Equipment and supplies management in general (ie, not focusing on specific equipment types) were examined in 6 studies, including 5 qualitative/mixed methods and 1 interventional study. Potential factors that may impact comprehension and adherence included appropriate access to equipment and supplies (eg, set up/delivered before discharge),[47,68,74,75] timely communication between providers and equipment company,[48] and differing practices for equipment use in-hospital versus at home.[48]

An intervention for caregivers of technology-dependent children that used education tailored toward gaps in their knowledge related to emergency preparedness during a power outage led to increased preparedness (eg, having emergency kit).[62]

Medications

Ten studies examined medications, including 9 qualitative/mixed methods studies[41,42,44,46,47,50,68,74,75] and 1 prospective cohort study using subjective measures of adherence.[82] Objective measures of adherence (eg, actual medication dosing) or knowledge (eg, caregiver report of side effects) were not assessed.

Facilitators of adherence were generally at the system level, with coordination of and access to medications before discharge (eg, dispensing from a hospital-based pharmacy) being critical.[42,47,68] Inability to access medications was a common barrier,[41,46,74,75] often because of insurance issues.[74,75] Additional adherence facilitators included a method for tracking when medications are given,[50,74] provision of a detailed medication schedule (eg, frequency, dose),[68] and providing prefilled medication syringes.[50] Families also desired that education was

TABLE 1 Characteristics of Included Studies

Citation	Study Design	Domains Addressed	Interventions (When Applicable) and Key Findings
Acorda (2022)[52]	Qualitative interviews (n = 23 caregivers of children with trach)	Equipment (trach)	Barriers included feeling overwhelmed, delaying learning from HCP, and illness severity/acuity. Facilitators included hands-on teaching, simulation, videos, demonstration, comprehensive education, positive reinforcement, education tailored to caregiver learning style, transparency from HCPs, sharing information, early caregiver engagement in teaching, goal-oriented approach, and experience caring for CMC.
Amador (2022)[36]	Pre and postintervention (n unavailable [abstract only], caregivers of children with trach)	Equipment (trach)	Intervention focused on simulation using a low-fidelity manikin and trach equipment. There was an increase in skill scores, but not knowledge or attitude scores, after the simulation.
Amar-Dolan (2020)[38]	Qualitative interviews and focus groups (n = 13 caregivers of child with trach)	Equipment (trach)	Barriers included issues with home nursing (eg, insurance approval, nurse availability and turnover, trusting nurses, loss of control/privacy, training nurses), poor coordination (eg, hospital training and equipment delivery at same time), not enough supplies, lack of guidance on equipment setup, poor communication among providers, not clear who to contact, and feeling overwhelmed. Facilitators included hands-on training (eg, on manikin and then child, with home equipment, supervised full care of child in hospital).
Antolick (2020)[80]	QI (n = 40 CMC) examining intervention feasibility/acceptability	General	Intervention focused on standardized process including family engagement in postdischarge goal identification and documentation with Posthospitalization Action Grid (used during rounds and families brought home). Action grids completed for 11/40 (28%) patients. Five of 11 discussed on daily rounds (45%), 9/11 (92%) sent to outpatient provider. Staff (n = 6) generally felt that the action grid would be helpful, but responses varied about having time to use or if would be best tool to use.
Antoniou (2022)[76]	Mixed methods (caregivers of children with trach: n = 5 semistructured interviews, n = 35 questionnaires)	Equipment (trach)	Barriers included limited education before trach placed, limited education on emergencies/complications, staff with competing priorities, inconsistent training times due to lack of qualified staff, need for refresher training after discharge, lack of emotional support, and lack of community services/support. Facilitators included videos/podcasts.
Bravo (2020)[77]	Cross-sectional (n = 32 CMC and their caregivers)	General	Higher child and caregiver self-efficacy associated with higher self-management. Higher child HRQOL level (and physical and social subscores) associated with higher self-management. Caregiver physical HRQOL correlated with self-management.
Brenner (2015)[39]	Qualitative interviews (n = 15 caregivers of children with trach)	Equipment (trach)	Barriers included feeling overwhelmed, not having everything in place, homecare (eg, delayed, limited availability, lack of competence, not equitable), and suboptimal care available at local hospitals. Facilitators included gradually taking over more responsibility for care of child.
Brooks (2022)[63]	Pre and postintervention (n = 44 caregivers of children with trach)	Equipment (trach)	Intervention consisted of a course (including didactics, a video, and demonstration) and high-fidelity simulation of an emergency situation, and postsimulation debriefing. There was variability in caregiver skills demonstrated in the simulation. Mean caregiver comfort increased from preintervention (2.09; SD 0.74) to postintervention (2.5; SD 0.63; $Z = -3.28$, $P = .001$). Caregivers were satisfied and rated hands-on practice as most useful.
Callans (2016)[40]	Qualitative focus groups (n = 18 caregivers of child with trach)	Equipment (trach)	Relevant challenges identified included poor care coordination, new home care providers not comfortable with trach care routines, equipment not delivered, equipment different in home and hospital, and having to travel with equipment outside of home. Nurse confidence lead to caregiver confidence, learning by being involved in care in the hospital.
Canary (2017)[41]	Qualitative interview/focus groups (n = 32, caregivers of CMC and non-CMC, PCPs, hospitalists)	General (1 theme related to medications)	Barriers included delays obtaining medications, delayed discharge, poor communication among providers, lack of postdischarge resources/support, caregiver emotions, lack of comfort, and lower level of care at home compared with hospital. Facilitators included teamwork, access to hospitalist after discharge, early discharge planning, discharge checklist, assessing discharge readiness, postdischarge phone call, and improved written instructions (eg, formatting, clear/detailed instructions [eg, follow-up plan]).

TABLE 1 Continued

Citation	Study Design	Domains Addressed	Interventions (When Applicable) and Key Findings
Connelly (2022)[35]	QI (n = 10 caregivers of children on home mechanical ventilation)	Equipment (home mechanical ventilation)	Intervention incorporating telemedicine visit within 48 h of discharge. Telemedicine visits identified issues with supplies (eg, not delivered/unsuitable/needing adjustments), home set up, and need for more education.
Curran (2020)[67]	Mixed methods: (1) case studies (n = 6), (2) interviews (n = 9 HCPs), (3) multidisciplinary stakeholder meeting	General	Phases 1 and 2: Themes included trust with HCPs, community resources, care coordination, communication among HCPs, written care plans, access to HCPs and online resources, HCP expertise and confidence, and caregiver confidence. Phase 3: Key priorities: build on existing programs, develop new and accessible resources, care coordinators as a resource/liaison, comprehensive written plans codesigned by stakeholders (eg, advanced practice nurse, caregiver, discharge coordinator), system for storing and organizing informational resources, and educational strategies to address HCP skills and knowledge.
Desai (2016)[42]	Qualitative interviews (n = 18 caregivers of CMC and non-CMC)	General (theme related to medications)	Barriers included worry, lack of clear expectations, lack of self-efficacy, competing priorities (eg, work). Facilitators included access to provider knowledgeable about their child, access to pharmacy/prescriptions, transportation, home care, support groups with other families with CMC, school informed about child's needs, comprehensive verbal and written discharge instructions, practicing with equipment before discharge, and planning for setup and logistics of equipment.
Frush (2023)[53]	Qualitative interviews (n = 12 caregivers of CMC)	General	Caregivers believed that telemedicine visits promoted self-efficacy, independence, were convenient and cost effective, can serve in place of in-person visits, provided direct access to the care team (providing an alternative to an ED visit), and helped with problem-solving.
Gillen (2019)[62]	Single arm, pre and postintervention (n = 50 caregivers of technology-dependent children)	Equipment (including feeding pump, suction, oxygen monitor, respiratory support)	Intervention consisted of educational materials tailored to gaps in preparedness for 72-h power failure at home noted on baseline assessment. Subjects were prepared for a median of 3 of 8 checklist items on admission compared with 4 at discharge and 7 at the 2-wk follow-up, representing significant increases. Preparedness for individual items also increased.
Goes (2017)[43]	Qualitative interviews (n = 6 clinicians), caregiver interview/drawing sessions (n = 11)	General	The ability of caregivers to learn how to manage their child's care at home was facilitated by nurses explaining and demonstrating how to do so with the caregiver then practicing tasks with supervision and subsequent feedback on performance.
Gold (2020)[44]	Qualitative focus groups (n = 24 CMC caregivers)	Medications	Caregivers wanted medication education that was complete, clear, in their preferred language, consistent (eg, between hospital and pharmacy), early in hospitalization, performed by someone knowledgeable about their child, and personalized (eg, with color coding and graphics if needed).
Gong (2019)[45]	Qualitative interviews (n = 13 caregivers of children with trach)	Equipment (trach)	Barriers to learning and adherence included lack of access to timely community nursing, anxiety, and depression. Facilitators included planning and scheduling, having additional caregiver support, and watching videos.
Graf (2008)[78]	Cross-sectional (n = 11 HCP of children with trach), chart review (n = 70 children)	Equipment (trach)	Education program included meeting with physicians and nurse specialist, video, trach care performed by caregiver with supervision, education course (eg, practice on manikin then child), training with home equipment, and 24 h of caring for child in hospital. Barriers included lack of transportation, other children in the home, language, anxiety, fear, home water/electricity, and funding for DME and home care.
Kim (2022)[64]	Nonrandomized interventional (n = 18 caregivers of children on home ventilation)	Equipment (home mechanical ventilation)	Intervention consisted of 5 sessions, including videos and 1:1 bedside teaching (with subjects receiving feedback after practicing tasks). Caregivers receiving the intervention had better observed suctioning and trach management skills, as well as measures of self-efficacy, compared with the control group.
Leary (2020)[46]	Qualitative interviews (n = 20 CMC caregivers)	General (theme related to medications)	Barriers included symptom confusion, poor inpatient continuity, medication challenges (not available in pharmacy [eg, certain formulations, complex medicines], obtaining refills), and delayed delivery of DME.
Lerret (2015)[82]	Prospective cohort (n = 51 caregivers of children with transplant)	General, medications, appointments	Caregiver perception of care coordination and quality of discharge teaching associated with discharge readiness. Discharge readiness not associated with medication adherence at 3 wk after discharge.

TABLE 1 Continued

Citation	Study Design	Domains Addressed	Interventions (When Applicable) and Key Findings
Leyenaar (2017)[47]	Qualitative interviews (n = 39 caregivers and HCP of CMC)	General (themes related to medications, equipment/supplies, appointments)	Facilitators included family engagement, establishing discharge readiness, care coordination (eg, medications, DME setup before discharge; transportation; knowing who to call with questions), discharge timing, setting expectations, clarifying home routine, and individualized education.
Leyenaar (2018)[68]	Mixed methods, Delphi process (n = 29 caregivers of CMC, 37 HCPs)	General (themes related to feeding, medications, supplies, activity, school return)	Important/feasible interventions included goal setting, aligning schedule with family routine, care coordination (eg, medications, DME), assessing discharge readiness, addressing social concerns, optimizing verbal (eg, teachback, language, key topics discussed [return to school/activities, return precautions]) and written (eg, timing/locations of all appointments, provider contact information, plain language summary of hospital course, medication/treatments schedule) education, and transportation needs.
Licon (2019)[37]	Mixed methods (n = 90 nurses caring for CMC)	General (themes related to medications, equipment)	Barriers included extensive time needed for education (especially teachback and "show me"), lack of communication, unclear discharge plan early in admission, family language (eg, timely interpreter access, quality of phone interpreter), and family feeling fatigued/overwhelmed.
McCormick (2015)[69]	Mixed methods (n = 220 patients with trach or caregiver)	Equipment (trach)	Barriers included poor care coordination, not enough supplies, poor communication, and inexperienced home nurse. Facilitators included standardized teaching, meeting with another family, practicing with equipment, observing trach care, and involving home care in discharge process.
McCoy (2022)[65]	Pre and postintervention (n = 18 caregivers of 10 children with trach)	Equipment (trach)	Intervention included a simulation program with high-fidelity manikin focused on emergency scenarios and a debriefing. Caregiver self-reported knowledge, confidence, and comfort taking care of their child at home improved pre to postintervention. Caregivers felt positively about the program.
Ming (2022)[66]	Nonrandomized interventional (n = 48 caregivers of CMC)	General	Intervention consisted of weekly telemedicine visits for first 4 wk after discharge. The visits were feasible (82% completed $\geq$1 visit, median connection time of 1 min). Caregivers rated them highly in acceptability, usability, functionality, and experience. Caregiver self-efficacy and family self-management were similar for experimental and control groups.
Moreno (2020)[81]	QI (n = 2 patients with trach, retrospective review of n = 10)	Equipment (trach)	Intervention included standardized discharge protocol and a postdischarge telehealth visit (which allows for discussion of caregiver concerns, review of treatment plan, and demonstration of trach skills). Caregivers satisfied with intervention, which was feasible.
Musial (2020)[75]	Mixed methods (n = 67 caregivers of CMC)	General (return precautions, appointments, medications, equipment and supplies)	Common challenges identified related to appointments (eg, large quantity, difficulty scheduling, lack of transportation), medications (eg, not having all medicines, not covered by insurance), home nursing (eg, limited availability), and DME and supplies (eg, needing supplies).
Nageswaran (2020)[48]	Qualitative focus groups (n = 32 stakeholders, home nurses)	General (feeding, equipment and supplies, return precautions)	Potential strategies included accurate home health orders prepared in advance, comprehensive care plans, ensuring appropriate communication with home care/outpatient providers, home care receives child-specific training and has inpatient provider to contact as a resource, caregiver preparation (eg, setting expectations about home care services/staffing), and standardized educational process.
Nageswaran (2022)[54]	Qualitative interviews (n = 56 caregivers of 41 CMC with trach, 5 focus groups of 33 clinicians)	Equipment (trach)	Facilitators included access to social support, health care providers, and experienced parents, as well as use of language concordant print materials, videos, simulation, and internet resources.
Olson (2022)[34]	Postinterventional chart review (n = 118 encounters of CMC)	General	The intervention consisted of a predischarge visit between the telehealth nurse and family, a telehealth visit $\leq$7 d postdischarge, and additional contact as needed. 54.2% of visits identified new issues or barriers to discharge plan adherence (related to prescriptions, medication administration, coordination of services, and obtaining supplies); all issues were addressed by the nurse.
Pars (2020)[55]	Nonrandomized, pre and postinterventional (n = 30 caregivers of children with GT)	Equipment (GT)	Intervention included standardized discharge training using guide and checklist reviewed with caregiver ($\sim$90 min) with demonstration for caregiver. Objective measures and caregiver self-report of knowledge related to GT care increased after receiving the intervention.

TABLE 1 Continued

Citation	Study Design	Domains Addressed	Interventions (When Applicable) and Key Findings
Poeppelman (2019)[33]	Mixed methods ($n = 24$ caregivers of patients with trach)	Equipment (trach)	Barriers included inconsistent education. Caregivers reported that hands-on practice with trach care is beneficial, so they can make mistakes with hospital staff.
Precce (2020)[49]	Qualitative focus groups ($n = 9$ caregivers of CMC)	General (medications, feeding, technology/ gastrostomy)	Barriers included following the hospital schedule at home. Involving caregivers of other children in the education process was a facilitator.
Precce (2020)[50]	Qualitative focus groups ($n = 9$ caregivers of CMC)	General (technology and supplies, feeding, return precautions)	Barriers included large amount of information, limited caregiver participation in care in hospital, and challenges with access (eg, to special formula, school, special benefits, transportation). Potential facilitators included gradual presentation of education, tracking timing of medications on the phone, preparing medications in syringes advance, experience caring for CMC, and educational videos.
Prickett (2019)[57]	Nonrandomized, pre and postinterventional ($n = 39$ caregivers of children with trach)	Equipment (trach)	Intervention included standard training (classroom didactics, bedside teaching, caregiver demonstration of skills) and additional simulation with high-fidelity manikin allowing caregiver to practice skills in 3 emergency scenarios (desaturation, mucus plugging, accidental decannulation). Mean caregiver confidence (10-cm visual scale) increased from pre- to postintervention for managing emergencies related to desaturations (9 mm; 95% CI, 3.0–14 mm), mucus plugging (16 mm; 95% CI, 8.0–23 mm), and decannulation (10 mm; 95% CI, 3–17 mm). Caregivers believed training was helpful.
Pritchett (2016)[79]	Cross-sectional ($n = 19$ children with trach)	Equipment (trach)	Most caregivers rated the following as moderately or very helpful: an educational DVD (80%) and educational binder (100%). Twenty-two percent felt neutral or disagreed that teaching was consistent; 11% felt too little time for teaching; 12% did not know who to contact with concerns.
Schweitzer (2014)[58]	Nonrandomized pre and postinterventional ($n = 26$ caregiver/ child with GT dyads, 12 providers)	Equipment (GT)	Intervention included preprocedure educational materials (eg, DVD, booklet), postprocedure staff identification and ordering of home supplies, education check list (includes booklet, DVD, return demonstration), postdischarge phone call, and multidisciplinary teaching at 3-mo follow-up. Mean confidence (100-point scale) in managing emergencies preprocedure ($M = 42.5$, $SD = 35.4$) to postprocedure ($M = 88.6$, SD 20.5; $P < .05$); no overall increase in confidence. Overall knowledge increased from preprocedure ($M = 5.8$, $SD = 1.8$) to postprocedure ($M = 7.9$, $SD = 2.1$; $P < .001$).
Silva (2020)[51]	Qualitative interviews ($n = 15$ caregivers of CMC)	General	Assessed caregiver views on individualized training program: low-fidelity simulation (procedural skills training), medium-/high-fidelity simulation (management of complications in simulated home environment) and debriefing after simulations. Caregivers felt simulations were helpful and led to increased confidence. Training led to anxiety for some. Caregivers also felt other family members should be trained.
Sobotka (2018)[32]	Qualitative interviews ($n = 15$ care coordinators)	General	Themes related to family experiences caring for technology-dependent children included family stress/feeling overwhelmed, finding home nursing in a timely manner, caregiver employment, and family functioning.
Tearl (2006)[59]	Nonrandomized, pre- and postinterventional ($n = 74$ respiratory technology-dependent children, 17 providers, 19 DME companies)	Equipment (trach)	Intervention included dedicated RT discharge coordinator and development of pathway to guide discharge planning, with progression in training based on family comfort, demonstration of knowledge and skills, and 24 h of supervised care performed by family. After implementation, DME company noted fewer family requests for assistance with DME, improved family knowledge and performance, and that home equipment was better suited for the patient. Intervention led to higher multidisciplinary team satisfaction with discharge process.
Tearl (2007)[60]	No-randomized pre and postinterventional ($n = 20$ caregivers of children with trach)	Equipment (trach)	Intervention personalized for caregiver (based on demonstration of skills and knowledge) and included illustrated manual, training with home respiratory equipment, practice with manikin, and checklist of objectives. Knowledge scores increased pre to post (Wilcoxon signed rank $Z = -3.84$, $P = .001$; pretraining mean 35.3 [SD 13.2]) % vs. posttraining 91.1 [SD 4.9] % posttraining with $P = .001$). Caregivers believed the training was timely, thorough, easy to understand, and allowed for questions.

TABLE 1 Continued

Citation	Study Design	Domains Addressed	Interventions (When Applicable) and Key Findings
Tofil (2013)[70]	Mixed methods ($n = 7$ families of children with trach)	Equipment (respiratory technology support)	Evaluation of caregiver views on ventilator training, including new predischarge simulation with high-fidelity manikin in home environment including common scenarios, debriefing, and practicing skills. Training allowed for hands-on learning and practice. A total of 71% strongly agreed they were better prepared to care for child, 86% felt like confidence was improved, and 100% thought training was helpful.
Tofil (2018)[71]	Mixed methods ($n = 7$ caregivers of children with trach)	Equipment (trach)	Evaluation of caregiver views on training including didactic, hands-on training, and session with high-fidelity simulator focusing on 4 common emergencies followed by debriefing. More than 90% felt prepared to take care of child, confident in their abilities, knew what to do in an emergency, and would recommend other caregivers undergo training. Overall, caregivers felt the training was helpful.
Thrasher (2018)[72]	Mixed methods, postsimulation survey (caregivers of $n = 47$ children with LTMV)	Equipment (trach)	Intervention included handouts, videos, hands-on bedside training (including teachback or showback of each concept/skill), high fidelity simulation of emergencies, and caregiver cares for child in hospital for 1–3 d. All intervention components perceived as helpful. Caregivers perceived that the intervention improved self-confidence, increased preparedness, and presented real-life scenarios.
Van Orne (2018)[56]	No-randomized pre and postinterventional ($n = 68$ caregivers of child with trach)	Equipment (trach)	Intervention included progressive training sessions (eg, observing care, practicing care on a doll, providing care independently). Subjects receiving the intervention had a lower mean number of discharge training days compared with standard care (16.4 [SD 7.0] vs. 60.0 [SD 58.3], $P < .001$). Caregivers found the intervention helpful, and 94% felt prepared to care for their child.
Wells (2017)[74]	Mixed methods ($n = 36$ CMC and caregivers)	General (medications and technology)	Assessed utility of postdischarge home visit (reinforce discharge plan, assess home environment, and address problems). At least 1 problem identified in each visit; 72% of visits identified ≥3 problems (eg, lack of caregiving support, funds for appointments and transportation, medication access, misunderstanding how to administer medications, DME not delivered). Caregivers were satisfied with home visit.
Williams (2021)[73]	Mixed methods ($n = 6$ caregivers of CMC, $n = 24$ HCP/nurses)	General	Barriers included difficulty coordinating multiple teams, caregivers with different availability and goals than HCPs. Facilitators included being proactive about care coordination (eg, ordering supplies, inpatient/outpatient team coordination, early discharge planning), ensuring collaboration among team members, and family inclusion (eg, listening to families, ensuring their circumstances are accounted).
Yegit (2022)[61]	Nonrandomized pre and postinterventional ($n = 62$ caregivers of child with trach)	Equipment (trach)	Intervention including provision of information on routine trach care and emergencies (includes videos and pictures), practical training (eg, trach tube change) using manikin, and access to online materials. For knowledge assessment, median number of questions right (of 23) increased from 12 to 18 ($P < .001$). Steps performed properly for trach tube change and suctioning also improved after training.

CI, confidence interval; CMC, children with medical complexity; DME, durable medical equipment; GT, gastrostomy tube; HCP, health care provider; HRQOL, Health Related Quality of Life; LTMV, long-term mechanical ventilation; PCP, primary care provider; QI, quality improvement; trach, tracheostomy

presented in their preferred language, consistent between hospital and pharmacy, provided early in the child's hospitalization, and personalized.[44] A prospective cohort study found perceived discharge readiness on the caregiver level was not associated with medication adherence at 3 weeks after discharge.[82]

Appointments

Three qualitative/mixed method studies had themes related to appointment instructions. Facilitators included comprehensive written information (eg, with time, location).[68] Barriers included issues with the number of,[47,75] timing of,[47,75] and transportation to appointments.[75] No objective measures of appointment-related knowledge (eg, report of reasons for appointments) or adherence (eg, appointment attendance) were assessed.

Return Precautions and Who to Call With Questions

Six studies used subjective measures to review system-level factors that may impact caregiver comprehension of symptoms to be aware of and the action to take should these symptoms arise. Potential facilitators included an explicit verbal discussion of these symptoms before discharge,[68] provision of detailed written instructions (ie, actions to take for

TABLE 2 Summary of Key Factors That Impact Comprehension of and Adherence to Discharge Instructions for Children With Medical Complexity

Category	Factors
System level	• Access to formulas/special diets • Access to support groups or other families of CMC • Access to pharmacy and needed medications • Access to school • Care coordination (eg, designated care coordinators, timing of hospital training and equipment delivery) • Community resources/services/support • Equipment/supplies (ability to travel with equipment, amount of supplies, guidance about equipment setup, delivered in a timely manner, same equipment in hospital and home) • Home care/nursing (availability and turnover of staff, insurance approval, involvement in discharge process, loss of control/privacy, qualified/trained staff, timeliness of setup, trust in staff) • Insurance • Level of care in local hospitals • Mechanisms to track medications (eg, on phone, paper) • Prefilled medication syringes • Online resources • Transportation
Provider level	• Access o Home visits o Postdischarge phone call o Telemedicine visits o To hospitalist after discharge o To primary care provider • Assessment of caregiver discharge readiness • Appointment scheduling process/navigation • Competing priorities (eg, care for other patients, time needed for education) • Confidence and expertise • Consistency in education (eg, between hospital and pharmacy) • Continuity among inpatient providers • Communication and collaboration among providers • Discharge checklists • Educational/communication strategies o Demonstration o Education/resources related to emergencies o Gradual presentation of information throughout hospitalization o Hands-on teaching/showback/simulation (low and high fidelity manikins, on manikin and then on child, with home equipment, followed by debriefing and feedback, supervised gradual takeover of care in the hospital) o Language concordant verbal and written communication (including availability and quality of interpreters) o Limiting information o Plain language o Tailored/personalized education o Teachback o Videos/podcasts o Visuals/pictographic instructions o Written instruction (clear, comprehensive, formatting) • Level of engaging caregivers • Knowledge of/familiarity with patient • Multidisciplinary involvement • Number of teams/specialties involved in care • Positive reinforcement • Setting goals/expectations with caregivers • Standardized discharge processes • Timing of discharge planning and teaching (eg, in advance of procedure or discharge, refresher training after discharge) • Transparency • Trustworthiness
Family level	• Family functioning • Finances • Home utilities • Home/family routines and alignment with hospital schedule • Family dynamics (eg, other children in the home) • Social concerns/determinants of health • Support from other caregivers (eg, emotional support logistical support to care for child)

TABLE 2 Continued	
Category	**Factors**
Caregiver level	• Competing priorities (eg, work) • Engagement and involvement in care in hospital • Experience caring for patient/CMC • Mental health and emotions (anxiety, depression, fatigue, fear, feeling overwhelmed, stress) • Self-efficacy/comfort/confidence
Patient level	• Discharge instruction complexity (eg, number of appointments) • Health-related quality of life • Illness severity/acuity • Self-efficacy

symptoms and provider contact information),[42,68] postdischarge phone calls,[41,42,75] and home visits.[74] Barriers included a lack of clarity in whom to contact or need for access to providers able to answer their questions (eg, primary care provider not comfortable caring for CMC).[41,42,47]

Restrictions

Three qualitative/mixed method studies discussed factors associated with comprehension of and adherence to instructions related to restrictions in activity, feeding, and return to school. Facilitators included ensuring specific discussions and goal setting about these ideas (eg, when to return to school),[68] provider communication with school about child's needs,[42] access to school,[50] ensuring feeding schedule fits into family routine,[68] and access to specialized dietary needs.[50]

General

Twenty-two studies included information about factors associated with comprehension of and adherence to the discharge plan overall, including 3 examining perceptions of interventions,[51,66,80] 1 examining the impact of an intervention via chart review,[34] 1 cross-sectional study,[77] and 1 prospective cohort study[82]; the remainder of the studies used qualitative/mixed methods.[32,37,41–43,46–50,53,67,68,73–75]

Several system- and provider-level factors were identified that may impact overall comprehension and adherence. Factors influencing the discharge education process included communication among team members and care coordination,[41,46–48,67,68,73,82] family inclusion in discharge planning (eg, engaging and listening to families, accounting for home schedules),[32,47,49,68,73,80] planning for discharge early in the hospitalization,[41,50,73] competing provider priorities,[37,42] discharge timing,[41,47] and provider expertise.[67] Factors that may impact adherence postdischarge included transportation,[42,47,50,68,74] postdischarge resources and social/community support,[41,42,67,68,74] access to a knowledgeable provider after discharge,[41,42,67] telemedicine visits,[34,53,66] and timeliness of home care setup.[32,42,75]

Caregiver-level factors believed to be associated with comprehension of and adherence to discharge instructions included emotions (eg, stress, fatigue, anxiety),[32,37,41,42] comfort or self-efficacy,[41,42,67,77] experience caring for CMC,[50] employment,[32] financial concerns,[74] and health-related quality of life.[77]

Recommended provider communication techniques included high-quality written instructions (eg, comprehensive, plain language,),[41,42,48,67,68] goal/expectation setting,[42,47,48,68] assessing discharge readiness,[41,47,68] standardized discharge processes (eg, a checklist),[41,48] communicating in the caregiver's preferred language,[37,68] teachback,[68] demonstrating how to perform a task with showback by caregiver,[43] educational videos,[50] limiting amount of information provided,[50] simulation/debriefing,[51] and engaging caregiver participation in care during the hospitalization.[50]

DISCUSSION

In this systematic review, we identified 51 studies that discussed child-, caregiver-, family-, provider-, and system-level characteristics, as well as interventions that may impact caregiver comprehension of and adherence to discharge instructions for CMC. Many studies focused on equipment, medication management, and caring for CMC in general. Qualitative and mixed method studies were the most common study types. There were few interventional studies, and few studies overall examined objective measures of caregiver comprehension or adherence.

Equipment-related instructions were addressed in more than half of the studies in this review, including 22 studies specifically examining tracheostomy care. This emphasis on technology-dependent children is not surprising because they experience disproportionate readmissions compared with those not dependent on technology.[83] Children with tracheostomies are particularly vulnerable to poor outcomes; 1 study of a national claims database found that within 5 years of tracheostomy placement, 25% of patients died and 53% had a complication.[84] Our review found that caregivers face several barriers related to home care services for their child's respiratory technology,[38–40,45,69,78] as well as issues with the equipment itself.[38–40,69] We found that many interventions focused on teaching families to use these types of equipment; future interventions should improve access and coordination given the commonality of these barriers.

Our review found less emphasis on other types of equipment. One may have expected additional focus on

feeding tubes, which were examined in just 2 studies,[55,58] given their association with complications and morbidity.[85,86] Other common types of equipment (eg, central lines, airway clearance devices)[87] were not the focus of any of the studies from our literature search, although these may be more commonly studied in the context of specific diagnoses outside of the scope of this review. For example, adherence to airway clearance devices have been examined in the setting of cystic fibrosis and similar diagnoses. Factors that impact adherence mirror those relevant for the general CMC population, including those on the patient/family (eg, competing priorities, funding, social support) and system (eg, staff availability for counseling, consistency of training) levels.[88] Additional research is likely needed to determine how to optimize the transition from hospital to home for caregivers managing understudied equipment types in the general CMC population.

Most articles examining caregiver comprehension of and adherence to medication instructions were qualitative/mixed methods studies, many of which described care coordination and access to medications as being key factors perceived to influence adherence.[41,46,47,68,74,75] Medication adherence for caregivers of children with cancer can also be influenced by medication side effects, prognosis, disease-related perceptions, and patient personality traits,[17] in addition to factors relevant to the general CMC population identified by our review. Additional work is needed to objectively measure the types of medication errors that caregivers of CMC make and factors that may influence these errors. Future studies should examine whether established interventions and strategies that improve dosing and adherence to individual pediatric medications (eg, plain language, pictographic dosing diagrams, teachback[89,90]) or for single chronic conditions[91,92] can be applied to medication-related counseling for CMC.

Some domains of care were understudied. For example, few studies examined types of factors that may lead to challenges caregivers have with instructions related to appointments or restrictions (eg, diet, activity). Clearly designed and action-oriented written instructions,[42,68] coordination of care,[47,75] easy access to providers (eg, transportation, phone calls),[41,42,47,74,75] and consideration of the family's schedule[68] were common ideas identified as being potentially helpful. Next steps would include design and study of interventions to determine which elements are most helpful for caregivers managing these domains for their CMC after discharge.

Several broader themes emerged, including optimizing communication and educational modalities to ensure caregiver learning. Some included studies discussed the importance of communicating with patients and families in their preferred language[37,44,54,68]; this theme may have been even more prevalent if a greater number of studies included LEP families as subjects. Other studies have found that compared with English-speaking families, LEP families are more likely to experience adverse events,[93] receive less detailed discharge counseling,[94] and have more difficulty following discharge instructions.[10] Language is also a key barrier that impacts education for caregivers of patients not included in our review, such as those with cancer.[95] Future work is needed to determine whether the mechanisms for overcoming the barriers to provision of language-concordant discharge education in the general LEP population[96,97] can be adapted to CMC and their caregivers.

Additional educational strategies discussed in the included studies were informed by health literacy principles and are recommended for use as part of communicating with all families.[98] Teachback, or having caregivers repeat in their own words how they would perform a task, was recommended in 2 studies we reviewed.[68,72] A more common strategy incorporated into studies in this review, especially for equipment such as tracheostomies, was the use of hands-on training.[33,36,38–40,43,52,54–61,63–65,69–72] This type of training allowed the medical team to demonstrate how to perform a task and then caregivers would practice performing (or showback) the task and receive feedback. Because most identified studies focusing on these educational strategies were qualitative/mixed methods or examined intervention impact immediately after intervention completion, next steps would be to incorporate RCTs to study intervention impact. Furthermore, as several different types of interventions have been designed incorporating hands-on training, future studies comparing their effectiveness are necessary.

Our review identified that most studies used subjective measures of comprehension, such as confidence, self-efficacy, or views on helpfulness when examining the impact of interventions.[51,53,57,65,66,70–72,79–81] Using objective assessments to ensure that caregivers understand instructions are crucial because comprehension of instructions is a major contributor to adherence.[14,99] Given the high levels of stress, anxiety, and overwhelmed feelings reported in several studies included in this review,[32,37–39,41,42,45,52,76,78] confirming comprehension is important because the ability to understand and process information is affected by high stress.[100] Measurements of perceived ability to manage instructions may not translate to more objective measures of comprehension and adherence,[101] so the overall utility of many of the interventions studied should be assessed further in a more objective manner.

In addition to the communication techniques identified by studies included in this review, a family-centered approach was described as being essential to ensuring adherence. Studies emphasized the importance of engaging and listening to families,[47,73,80] as well as accounting for family functioning, schedules, learning styles, and competing priorities (eg, other children).[32,42,47,49,52,68,78] This type of family-centered approach has been emphasized in interventions to improve adherence to instructions for other diagnoses that were not the focus of this review, such as cancer.[95] Future interventions targeting CMC should incorporate a patient- and family-

centered approach to ensure family dynamics are accounted for, and therefore may need to be more intricate than those targeting caregivers without CMC.

There were limitations to this review. Given the recent increased focus on CMC,[19–21] the vast literature on this topic, and the heterogeneity of the CMC population and study designs, it was necessary to limit the scope of this review, leading to potential limitations in generalizability. A strength of this review was that it allowed for a broad understanding of patient-, caregiver-, provider-, and system-level characteristics and interventions that may impact caregiver comprehension and adherence across domains of care that would not be possible, for example, by examining single outcomes from quantitative interventional studies or focusing on individual domains of care (eg, medications). However, multiple study types and outcomes measured in several different ways were examined, precluding the possibility of a meta-analysis and posing challenges to a quantitative comparison of findings across studies. A major limitation of this review is that it excluded patients discharged from the NICU, emergency departments, and ambulatory settings. In particular, interventions effective in promoting optimal care after a NICU discharge may also be relevant to discharges from the acute and pediatric intensive care settings. Although inclusion of NICU studies was outside the scope of this review given its already broad focus and unique features of NICU discharges (eg, difference in caregiver presence/involvement during the hospitalization, timing/preparation [ie, after a pregnancy]), future reviews should focus on this distinct population, as well as specific outcomes/interventions that may be relevant to all settings (eg, impact of telemedicine visits, use of showback and demonstration). This study also excluded caregivers of patients with cancer, which have been the subject of other systematic reviews,[17,18] and other single isolated chronic diagnoses, which do not qualify as CMC per the PMCA.[5] On the other hand, a great deal of overlap exists in factors identified as impacting treatment regimen comprehension and adherence in our review and those in studies examining specific individual chronic diagnoses and equipment types.[17,18,88,102,103] Provider perspectives, although captured in some of the literature examined,[32,37,41,43,47,48,54,59,67,68,73] were not the focus of this review and may differ from those of caregivers, for example, when it comes to feasibility of interventions related to incorporation of system-level changes. Despite our broad search criteria, it is possible that our search may have missed relevant studies. Although inclusion of gray literature in this review was a strength in that it limited publication bias, fewer details can be provided within the space constraints of conferences abstracts. This led to less available information on study design and results, contributing to some of the lower MMAT ratings observed. Although no studies were excluded from this review because of low MMAT ratings,[31] one must be cautious in interpreting results from studies with lower quality.

CONCLUSIONS

Caregiver comprehension of and adherence to instructions for their CMC after discharge from the inpatient setting can be affected by several system-level barriers, which may be mitigated by improving coordination of and access to care. A health literacy–informed and family-centered approach to the transition from hospital to home may help alleviate barriers. Gaps in the literature include examination of several domains of care (eg, appointments, restrictions, nonrespiratory equipment), assessment of objective measures of comprehension and adherence as primary outcomes, use of RCTs, and assessment of longer term outcomes measures (eg, days or weeks after intervention exposure). Future studies can apply lessons learned from the qualitative/mixed methods literature to intervention design and testing. Because several interventions incorporating hands-on practice/showback have been designed, future studies can incorporate comparative effectiveness designs to determine which to use in practice.

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ABBREVIATIONS

CMC: children with medical complexity
GT: gastrostomy tube
LEP: limited English proficiency
MeSH: Medical Subject Headings
MMAT: Mixed Methods Appraisal Tool
PMCA: Pediatric Medical Complexity Algorithm
RCT: randomized controlled trial

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Updates in Food Allergy Prevention in Children

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Although significant evidence exists that feeding early has a role in the prevention of food allergy, this intervention in isolation may not be sufficient. Recent evidence highlights that early introduction of peanut specifically has had no significant impact on the populational prevalence of peanut allergy. Other factors that may contribute to food allergy prevention include regularity of ingestion once an allergen is introduced and consideration to the form in which the allergen is introduced (such as baked versus cooked egg). There are also many practicalities to early feeding and some discrepant viewpoints on these practicalities, which has led to poor implementation of early feeding strategies. In general, preemptive screening before food introduction is not recommended by most international allergy societies. Although there is little guidance to inform early introduction of allergens other than milk, egg, and peanut, the mechanism of sensitization is thought to be similar and there is no harm to early introduction. In terms of frequency and duration of feeding, there is little evidence to inform any concrete recommendations.

It is now widely accepted that early food introduction has a role in the prevention of food allergy, especially in higher-risk infants. Seven years ago, the Learning Early About Peanut (LEAP) study was a literal "leap" forward as the first randomized controlled trial to demonstrate a significant (81%) relative risk reduction in the development of peanut allergy with early (age 4–11 months) versus delayed (age 5 years) peanut introduction in atopic infants.[1] The LEAP study found a preventive effect in both peanut skin test-negative (13.7% vs 1.9%; $P < .001$) and skin test-positive infants (35.3% vs 10.6%; $P = .004$), which supported early peanut introduction as a means of both primary and secondary prevention. Since the LEAP study, there have been several randomized controlled trials demonstrating a preventive effect with early introduction for several different allergens including cow's milk,[2] egg,[3] and multiple allergens.[4] A systematic review and meta-analysis noted moderate certainty evidence that both early peanut and egg ingestion had a role in food allergy prevention.[5] Multiple international guidelines published over the past several years have uniformly adopted early food introduction as a means of food allergy prevention.[6–12]

Despite the significant evidence that early introduction plays a role in food allergy prevention, increasingly, it has become evident that this is only part of the solution. A recent populational study by Soriano et al in Australia demonstrated that, although peanut introduction in the first year of life has increased more than threefold (21.6%–85.6%) from 2007 to 2018 (before and after early introduction guidelines), there has only been a nonsignificant decrease in peanut allergy in the population over this time (3.1%–2.6%; difference −0.5% [95% confidence interval (CI) −1.4% to 0.4%]; $P = .26$).[13] The authors of this population-level study concluded that "the high prevalence of peanut allergy … despite early peanut introduction, suggests an important contribution of other … factors.

abstract

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An increase in less-researched environmental factors, potentially interacting with genetic susceptibility, could have masked the protective association with earlier peanut introduction."[13] In addition, although there has been near-uniformity in guideline uptake of early food introduction, there remains controversies around its implementation. There are discrepant viewpoints regarding which infants (eg, all infants versus only high-risk ones) should be targeted for early introduction strategies, and whether any infants should be preemptively screened before food introduction.[14–16] Perhaps as a result of these controversies, there has been variable acceptability of early feeding strategies among key stakeholders, including both patients and physicians.[17–19]

The goal of this article is to review what remains less well understood regarding food allergy prevention. Because food allergy is common, often lifelong, and has increased in prevalence over time,[20] a secondary goal is to provide some key strategies to clinicians in navigating this ever-evolving landscape with their patients.

DOES QUANTITY MATTER: THE ROLE OF "REGULAR" ALLERGENIC SOLID FOOD INGESTION AND FOOD ALLERGY PREVENTION

The Soriano et al study has highlighted that, although there is a role for early food introduction, feeding early alone may not be sufficient. In examining the sentinel studies on food allergy prevention, a key component of all study protocols was regularity of allergen ingestion, in addition to early food introduction. As 1 example, in the most effective egg prevention randomized controlled trial to date, the PETIT study, 147 infants with eczema were introduced to heated egg powder at 6 months of age (or avoidance until a year of age), but also were required to eat the heated egg powder at least daily, resulting in such a significant protective effect with early introduction (8% in the early introduction had egg allergy compared with 38% in the placebo group) that the trial was halted prematurely.[3] Similarly, in the LEAP study, infants in the early introduction group ate peanut at least 3 times a week (6 g per week) until 5 years of age.[1] In keeping with this hypothesis, Soriano et al highlighted in their populational study that, although early peanut introduction had increased dramatically in Australia, <30% of infants were eating peanut 2 or more times per week and >20% had only eaten peanut <5 times.[21] It is possible that the lack of change in prevalence of peanut allergy that was demonstrated may be partially explained by lack of regularity of peanut ingestion. However, no early introduction study has shown that a specific allergen quantity was necessary for successful early introduction.

Perhaps the best illustration of the potential importance of regularity of ingestion as a means of food allergy prevention stems from the cow's milk allergy prevention literature. There have been several observational and randomized controlled trials that have consistently demonstrated that delayed ingestion and/or irregularity of ingestion increase the risk of cow's milk allergy. In a 2010 prospective study of 13 019 general population infants, delayed (after 14 days) and/or irregular (<1 per day) cow's milk ingestion significantly increased the risk of cow's milk allergy compared with introduction in the first 14 days of life with regular daily exposure thereafter (odds ratio [OR] 19.3; 95% CI 6.0–62.1).[22] In a case control study of 51 patients with confirmed cow's milk allergy compared with matched controls, as well as unmatched patients with egg allergy, there was a significantly increased risk of cow's milk allergy among infants with delayed (>1 month after birth) and/or irregular (<1 per day) cow's milk exposure (adjusted OR 23.74; 95% CI 5.39–104.52 compared with control, adjusted OR 10.16; 95% CI 2.48–41.64 compared with egg allergy group).[23] In a prospective study of 1992 general population (eg, "standard risk") infants who were recruited on the basis of parental feeding preference to either exclusive breastfeeding or at least 1 meal of cow's milk formula per day (with or without breastfeeding) for the first 2 months of life, there was a significantly reduced prevalence of cow's milk allergy at a year of age among those infants who were regularly exposed to cow's milk formula (relative risk 29.98, $P < .001$).[24] In a recent randomized controlled trial of early cow's milk exposure, subgroup analysis of infants who ingested cow's milk formula in the first 3 days of life found a significantly higher incidence of cow's milk allergy among any infant in whom cow's milk formula was discontinued (<1 month, 1–2 months, 3–5 months) compared with continuous ongoing ingestion until 6 months of age ($P < .001$ for all groups).[25]

There is also emerging, although limited, evidence that the preventive effect of regular ingestion may persist into later childhood, in particular among at-risk children. In a follow-up study of 146 siblings of peanut allergic children (aged 3.4–7.5 years) who had tolerated peanut a median of 2.9 years earlier, the risk of peanut allergy was 0% (95% CI 0–6) among those patients eating peanut at least once monthly, 3% (95% CI 0.5–15) in patients eating peanut less than monthly, and 18% (95% CI 5–48) for children who had not eaten peanut at all.[26]

The Canadian Society of Allergy and Clinical Immunology (CSACI) is the first allergy society internationally that has recently released a statement reiterating the importance of regular ingestion of common allergens, recommending that both early introduction and regular ingestion of age-appropriate amounts of allergens multiple times per month (with a goal of at least once weekly) are likely to be useful in food allergy prevention.[27] The CSACI further recommends that, once introduced, single or occasional exposures to an allergen could be detrimental and, if an allergen is not a common component of the diet

(and hence regular ingestion not feasible), avoidance may be preferable to intermittent ingestion.

FORM FOLLOWS FUNCTION: IS PREVENTION BECAUSE OF THE FORM OF THE ALLERGEN ITSELF?

For some common allergens such as egg, the degree of allergenicity can vary with the method of preparation (Fig 1). Egg and milk are heat-labile allergens, where the proteins creating the allergen are mainly the result of 3-dimensional protein folding and can be denatured with increasing temperature (eg, conformational epitopes), whereas with peanut, tree nut, and seed, the allergenic proteins are the result of contiguous linear areas (eg, linear epitopes) and are not heat-labile. There is some evidence that the form in which egg is introduced (eg, baked versus cooked versus raw) may influence its tolerability and effectiveness at food allergy prevention, given that a higher cooking temperature can denature the primarily conformational epitopes, and reduce the allergenicity.[11] There are 5 randomized controlled trials on early egg introduction as a means of egg allergy prevention which had very discrepant results with respect to safety and effectiveness, and it has been hypothesized that this is related to the form in which egg is introduced in these studies.[11] The most effective study, the previously described PETIT study, used gently heated egg (eg, poached) as its study protocol, a form subjected to a mild degree of heat denaturing. In contrast, the other 4 randomized controlled trials used raw pasteurized powdered egg and demonstrated either no significant protective effect with early egg introduction[28–31] and/or significant safety concerns.[30,31] Pragmatically, it is unlikely that raw egg from a culinary standpoint would be introduced outside a study protocol, and the choice of a raw egg was because of ease of use in a study protocol (crystallized form), but this trend in the literature suggests that the form of allergen itself may influence the effectiveness of early introduction.

There may be a further protective effect based on the way egg is heated (cooked versus baked), although evidence is limited to 1 study. A 2010 population-based cross-sectional study of 2589 infants demonstrated that, among infants with diagnosed egg allergy, in addition to a protective effect with early introduction, first exposure to cooked egg (egg cooked on a stove) reduced the risk of egg allergy compared with first exposure to egg in baked goods (egg baked into goods in the oven) (OR 0.2; 95% CI 0.06–0.71).[32] Joint guidance on prevention through the American Academy of Allergy, Asthma, and Immunology (AAAAI), the American College of Allergy, Asthma, and Immunology (ACAAI), and the CSACI recommends that egg be introduced in cooked forms only, avoiding any raw, pasteurized egg-containing products where possible.[11] The British Society of Allergy and Clinical Immunology specifies that, when egg is introduced at ~6 months of age, it should be introduced in a cooked form (scrambled egg, omelet, soft- or hard-boiled egg).[7] Further studies on this topic are needed, and it is not known to what degree this applies to the literature regarding other allergens such as cow's milk.

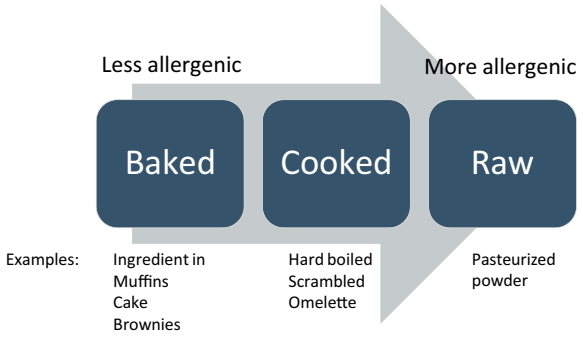

FIGURE 1
Various preparations of egg and impact on allergenicity.

TO SCREEN OR NOT TO SCREEN FOR PEANUT ALLERGY, THAT IS THE QUESTION

Largely as a result of a priori decisions made in the LEAP study, the National Institute for Allergy and Infectious Diseases (NIAID) released an addendum guideline in 2017 for the prevention of peanut allergy in the United States, which recommended that infants with LEAP risk criteria (egg allergy and/or severe eczema) be strongly considered for preemptive testing before peanut introduction.[10] The American Academy of Pediatrics (AAP) supports this recommendation, although notes that "it is hoped that the screening process for the infants at highest risk will not be a deterrent or generate 'screening creep' for infants not in the high-risk category. Furthermore, these guidelines may be difficult to follow in communities where there is no access to the medical care needed for their implementation."[9]

Although targeted screening was supported by the NIAID in 2017, these recommendations are not in keeping with other international guidelines published since the LEAP study such as the Australasian Society of Clinical Immunology and Allergy, the British Society of Allergy and Clinical Immunology, the AAAAI, the ACAAI, or the CSACI. None of these societies recommend routine preemptive screening in infancy before allergenic solid food introduction (Fig 2).[7,11,33] The CSACI has strongly advocated against screening, noting that screening testing in infants is not recommended, irrespective of level of risk.[12] Health economic modeling has shown that screening is most likely to overestimate the rate of allergy, leading to cost accumulation because of false-positive testing being considered as a surrogate for allergy.[34]

There are several limitations to screening on a population level before peanut introduction (Table 1). Firstly,

Professional Organization	Last Updated (Year)	Summary of Recommendations
National Institute for Allergy and Infectious Diseases	2017	For infants 4–6 months of age with existing egg allergy and/or severe eczema, strongly consider skin prick and/or serum IgE testing before introduction.
Australasian Society of Clinical Immunology and Allergy	2017	Introduce without testing for all infants between 4 and 12 months of age, including those with severe eczema and/or existing food allergy.
American Academy of Pediatrics	2019	For infants 4–6 months of age with existing egg allergy and/or severe eczema, skin prick test by an allergist is preferred or serum IgE testing, followed by referral to allergist if positive.
British Society for Allergy and Clinical Immunology	2019	Systematically screening all infants with severe eczema is not currently available in most areas and may not be effective. Introduce without testing for all infants, including those with severe eczema and/or existing food allergy.
American Academy of Allergy, Asthma and Immunology American College of Allergy, Asthma and Immunology Canadian Society for Allergy and Clinical Immunology	2021	No routine screening. When deemed appropriate, medical providers should discuss the role of IgE testing before introduction of foods as a method to determine whether the food will be introduced at home or under supervision in the office setting.
Canadian Society of Allergy and Clinical Immunology	2021	Preemptive screening is not recommended.

FIGURE 2
Differences in screening recommendations from various professional organizations.

although all allergy testing, whether skin prick testing or peanut-specific immunoglobulin E (IgE) testing, is safe, sensitive, and widely available, it is poorly specific and will result in overdiagnosis of peanut allergy.[16] The specificity of skin prick testing and peanut-specific IgE testing is <50%, and most infants with positive allergy tests can tolerate the food of concern when such IgE is identified, meaning the presence of the antibody is not pathognomonic for disease.[35–37] For example, a retrospective chart review of 125 children, of whom 96% had eczema, noted that 80% to 100% of foods which were avoided because of positive allergy testing could be reintroduced into the diet after an oral food challenge.[38] Secondly, preemptive screening on a populational level is not feasible, or actually necessary to promote safe early introduction. HealthNuts, an Australian prospective population-based cohort study, demonstrated that screening all infants with early onset eczema and/or egg allergy would require screening 16% of the population, and would still miss 23% of cases of peanut allergy.[39] In addition, in this study, 29% of infants would require follow-up because of positive testing. The resource limitations associated with a screening approach, resulting in delays in infant ingestion of peanut pending allergy assessment, could inadvertently negate the benefits of early peanut ingestion supported by the LEAP study, with infants missing the window of opportunity for allergy prevention with early ingestion of peanut. Thirdly, although the AAP cautioned against a potential screening creep, the reality of the increased nondiscriminant testing has emerged as a major concern. In 1 recent real-life study, only 48% of patients screened for peanut sensitization fit the NIAID criteria.[40] Another post-NIAID report demonstrated a significant increase in the number of nonhigh-risk infants that were inappropriately screened, receiving testing for a median number of 10 foods.[41] Finally, peanut screening has been shown to be poorly cost-effective, and the Soriano et al study has clearly demonstrated that there can be uptake of early peanut ingestion on a population level in the absence of screening.[13,42]

It is also important to highlight that feeding infants common allergens such as peanut (in an age-appropriate way) is safe, and the process to do so should not be overmedicalized. There has never been a fatality on first ingestion of a food in infancy, even in infants at high risk for food allergy.[43,44] In the LEAP study, for example, of those infants randomized to the early introduction group,

TABLE 1 Pitfalls of Population-Level Screening Before Introduction of Allergenic Foods

Caregiver	Clinician	Systemic Issues
Undue anxiety regarding safety of introduction without testing	Improper interpretation of results	Delay in introduction while waiting for testing or referral
Request for testing before introduction	Inaccurate diagnosis	Not cost-effective
Distrust in changing and contradictory guidelines	Time constraints to discuss during clinical encounters	Disparities in timely access to specialists

only 2.2% had a positive oral food challenge (observed ingestion) at baseline; none required epinephrine and symptoms were predominantly cutaneous.[1] Australian data at a population level have noted that <5% of early peanut introduction has resulted in a severe reaction.[39]

There is always a role for shared decision-making, especially in the context of a family who is not comfortable feeding an allergen such as peanut in the absence of screening testing.[11] However, the ultimate goal in such high-risk infants is early peanut ingestion, and such early introduction is the only identified measure that reduces the risk of peanut allergy. The associated negative impact peanut allergy has on long-term quality of life can be devastating for some families. Fundamentally, LEAP demonstrated the significant protective effect of early peanut introduction in a screened population, but not that screening was preventive or necessary for safe implementation. Furthermore, screening, because of access to care issues, may result in prolonged delays pending timely assessment, which also may paradoxically increase the burden associated with peanut allergy.

WHAT ARE THE PRACTICALITIES OF EARLY FEEDING?

Although the LEAP study and subsequent guidelines have helped forward the narrative that early introduction of allergenic solids is safe and effective at preventing certain food allergies, how to optimally advise and implement this is still uncertain in many areas. These areas include which allergens to focus on as a priority for early introduction, how often to advise allergenic solid foods are fed, how much quantity of allergen to feed, and how long feeding is required for a full preventive effect.

The bulk of the evidence for benefit of early allergenic solid introduction exists for peanut,[1,5] egg,[5,29–32] and cow's milk.[22–24,45] There are no randomized controlled trials focused exclusively on tree nut, soy, grains, seeds, legumes, finfish, or shellfish (although 2 randomized controlled trials have examined multifood ingestion early in life with discrepant results).[4,46] Some of the lack of data for other allergens may be a pragmatic limitation; given that some investigators consider the effects of early introduction to likely generalize across allergens, further trials with groups randomized to avoidance or delayed introduction may no longer be ethical. There is no evidence of harm from early feeding of other common allergens (in an age-appropriate way), and the mechanism of sensitization is thought to be similar for all common allergens.[12] There is also some observational evidence that dietary diversity early in life may help in the prevention of food allergy.[11,47,48] Guidance on the prevention of food allergy endorsed by the AAAAI, ACAAI, and CSACI recommends specifically egg and peanut introduction at ~6 but not before 4 months of life, but notes no evidence of harm with introduction of other allergens in this time interval and recommends no "deliberate delay" for the introduction of other potentially allergenic complementary foods.[11] The AAP focuses specifically on early peanut introduction because the most conclusive data were available for peanut, but notes no evidence that delaying introduction of other common allergens prevents atopic disease.[9]

In terms of frequency and duration of feeding, there is little evidence to inform any concrete recommendations other than that regularity of ingestion appears to play some role, but it may not be the sole factor. A per-protocol secondary analysis of the Inquiring About Tolerance study, a randomized controlled trial of early (3 months) versus standard (6 months) introduction of 6 common allergens, suggested that a dose of ~2 g of peanut protein and egg white protein per week (~1 boiled egg and 1.5 tsp of peanut butter) was sufficient for maintenance of tolerance, although further studies are required.[3,46] However, a recently published, multicenter, cluster-randomized trial of early (3 months) versus standard introduction of milk, egg, wheat, and peanut found a significant protective effect with early introduction, with no specific dosing requirements in the study (pragmatic design).[4] AAAAI, ACAAI, and CSACI guidance notes "insufficient evidence to support a precise dose and frequency necessary to support tolerance," recommending feeding amounts and types of allergens that the child enjoys in an age-appropriate way with some regular frequency. Similarly, the duration of ingestion required to maintain tolerance is unknown, although a follow-up to the LEAP study, the LEAP-On study, demonstrated that ongoing regular ingestion until 5 years of age was protective against development of peanut allergy in children who then underwent a full year of subsequent avoidance.[49] Although further studies are required, this study does suggest that regular ingestion through toddlerhood can help augment long-term protection, at least for peanut, though it remains unclear if such augmentation is truly necessary.

HOW DO WE OVERCOME BARRIERS?

To effectively implement widespread early introduction of allergenic foods to all infants on a population level, it will require buy-in from caregivers, primary care pediatricians, professional and advocacy organizations, and allergists/immunologists. Caregivers can lose confidence when guidelines change, and particularly when new recommendations contradict previous advice.[50] For almost 20 years before these new recommendations, parents were specifically told to avoid giving their infants any of the "top 8" allergenic foods.[51] This was on the basis of expert opinion at the time and not evidence or studies demonstrating protection through avoidance. However, to now implement a paradigm shift that contradicts previous advice, clinicians and guidelines need to address why the advice has changed, why we can trust this new approach, and why

TABLE 2 Examples to Overcome Barriers to Implementation of Food Allergy Prevention Discussions in the Primary Care Office

Time in the Office	Discussion Points	Parental Concerns
Incorporate into well-child visits at every age.	Proactively address in a positive manner; don't wait for families to ask.	Do not rub the food on your child's skin before letting them eat it.
Use preformed smartphrases in the electronic medical record.	Introducing peanut and other allergenic foods in age-appropriate forms is safe for infants.	Food allergy reactions occur within 1–2 h of ingestion and typically cause hives, swelling, or vomiting. If this does not occur, that is reassuring and can keep in their diet.
Have ancillary staff provide written handouts.	The benefit of preventing food allergy outweighs the risk for severe allergic reaction.	Address common childhood conditions unrelated to food allergy that may wax and wane as new foods are introduced (ie, gastroesophageal reflux, constipation or loose stools, and eczema).
	Testing before introduction can cause a delay in ingestion and false-positive results.	Offer to be available for follow-up questions or concerns.
		You do not need to have epinephrine prescribed or available before introducing foods to infants (unless they have existing food allergy).

it's important to consider. This requires humility, proactive discussion, and time to address parental concerns (Tables 2 and 3). A survey of 2000 soon-to-be or current parents of infants was conducted 1 year after the NIAID addendum guidelines were published, and only 31% of respondents were willing to introduce peanut before 6 months of age.[17] Although current parental attitudes toward early introduction have not been formally studied in recent years, this still warrants time and explanation to families during individual patient encounters. As addressed earlier, the current inconsistency in screening recommendations across various guidelines is only perpetuating the confusion regarding food allergy prevention.

Consistent positive messaging surrounding the safety and benefits of introducing allergenic foods during early infancy is important. This requires clinicians to understand the evidence, commit to proactively discussing during patient encounters, and incorporate this within existing time constraints on patient care. Some practical advice includes not rubbing food on the skin before feeding, reviewing time to onset of food reactions (1–2 hours), discussing other common childhood conditions that wax and wane with food introduction (such as constipation), and offering to be available for follow-up questions (Table 2). Little data exist on how well this is being done by clinicians, but surveys suggest ongoing hesitancy and need for further education.[19] Incorporation into the electronic medical record is 1 method to help standardize and increase the consistency of these conversations. Australia adopted widespread public health messaging surrounding food allergy prevention and has demonstrated increased acceptance and introduction of peanut over the past few years.[21]

Soon after the NIAID addendum guidelines were published in 2017, various companies started producing commercial products containing multiple allergenic foods in palatable forms for infants, such as powders, puffs, cereals, and cookies.[52] These commercial products are marketed directly to consumers and also pediatricians in an effort to have them recommend to families. Aside from the cost associated with these products, there is significant inter- and intraproduct variability in regard to the amount of protein included for each allergen.[53,54] In addition, none of these products have evidence demonstrating that they can prevent food allergy development through their use. With these marketed across the world, caregivers may be led to believe that these commercial products are necessary to prevent food allergy, or that they are safer than giving actual food to their infants. This adds a layer of confusion and mixed messaging that parents have to navigate as they try to understand and incorporate food allergens into their infant's diet.

It may seem like an insurmountable task, but these challenges can hopefully be overcome through dedicated and consistent effort across multiple levels.

TABLE 3 Take-Home Points

Take-Home Points
Introduce all allergenic foods in age-appropriate forms once your infant has shown interest and has tolerated other solids such as purees and cereals.
Once they've tried a new food, it is most important to keep it in their diet consistently, ideally several times each wk.
Infants with higher risk for developing food allergy likely benefit the most from early introduction, but it can help all children.

CONCLUSIONS

Although early introduction has been demonstrated to be a highly effective intervention in the prevention of food allergy, it may not be enough. There may be a role for ongoing regularity of ingestion in the prevention of food allergy, and in fact, regularity of ingestion may play as significant a role as timing of introduction. For some allergens such as egg, the form in which the allergen is introduced may play a role. There is still much to learn about the practicalities of early feeding, although guidance largely applies to peanut, and potentially egg and cow's milk at this time. There are significant harms to a preemptive screening approach for any common allergen, and in general, testing before food introduction is not recommended.

ABBREVIATIONS

AAAAI: American Academy of Allergy, Asthma, and Immunology
AAP: American Academy of Pediatrics
ACAAI: American College of Allergy, Asthma, and Immunology
CI: confidence interval
CSACI: Canadian Society of Allergy and Clinical Immunology
IgE: immunoglobulin E
LEAP: Learning Early About Peanut Study
NIAID: National Institutes of Allergy and Infectious Diseases
OR: odds ratio

honoraria – American Academy of Pediatrics, American College of Allergy, Asthma and Immunology; member – Joint Task Force on Practice Parameters for Allergy/Immunology; and Board of Regents for the American College of Allergy, Asthma, and Immunology. Dr Greenhawt has received past research support to his institution from DBV Technologies and the Agency for Healthcare Research and Quality; receives current research support from Novartis and Silota; is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Nutricia, Novartis, Aquestive, Allergy Therapeutics, AstraZeneca, ALK-Abello, and Prota; is an unpaid member of the scientific advisory council for the National Peanut Board and medical advisory board of the International Food Protein Induced Enterocolitis Syndrome Association; is a member of the Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group; is the senior associate editor for the *Annals of Allergy, Asthma, and Immunology*; and is a member of the Joint Task Force on Allergy Practice Parameters. He has received honorarium for lectures from ImSci, RMEI Medical Education, MedLearningGroup, and multiple state/local allergy societies.

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Early Peanut Introduction in Infants: Improving Guideline Adherence With EMR Standardization

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abstract

OBJECTIVES: Peanut allergy in children is a population health problem. Evidence suggests early peanut introduction (EPI) for infants can reduce the development of peanut allergy. Primary care settings have not widely adopted guidelines recommending EPI. Peanut allergy prevention depends on primary care providers incorporating EPI guidelines into well-child check (WCC) encounters. We aimed to improve guideline adherence in a primary care setting by implementing a bundle of clinical decision support (CDS) tools.

METHODS: Using quality improvement methodology, the team developed a standardized work protocol and CDS tools within an electronic medical record (EMR) at 4, 6, and 9-month WCC encounters. The team executed changes and modifications through plan-do-study-act cycles and analyzed results with statistical process control charts.

RESULTS: We collected data from 445 WCC encounters from baseline through sustainability. EMR documentation of EPI guidance at 4, 6, and 9-month WCCs shifted from 13.9% to 83.5% over 12 months. Provider adoption of smart lists and templates increased from 2% to 73%, the distribution of home peanut introduction handouts increased from 5.2% to 54.1%, and caregiver-reported peanut ingestion increased from 0% to 34.6%. Diphtheria-tetanus-acellular pertussis vaccination rates remained at 100% for 6-month visits, and patient in-room time remained at 65 minutes.

CONCLUSIONS: Quality improvement methodology improved documentation of EPI guidance and increased reported peanut ingestion at routine WCC encounters without impacting other measures. Broader use of bundled CDS tools and EMR standardization could further improve guideline adherence and increase early peanut introduction to prevent peanut allergy in infants.

Peanut allergy is a common problem among children. Its prevalence in children has increased by more than 50% from 2001 to 2017 in the United States.[1] Allergic reactions to peanuts are the leading cause of anaphylaxis in children.[2] Families living with peanut allergies can suffer financial and psychological burdens.[3]

Early exposure to allergens through disrupted skin barriers, as in infants with eczema, can lead to the development of food allergies.[4] Evidence from the Learning Early About Peanut (LEAP) study suggests that early peanut introduction (EPI) for infants, especially those with eczema, can reduce the risk of developing peanut allergy.[1,2,5,6] This was a large shift in practice for pediatricians and families from prior American Academy of Pediatrics (AAP) guidelines that recommended that high-risk infants avoid peanuts until 3 years of age. Current AAP guidelines, updated in 2019 after the initial release in 2017, recommend early introduction of peanuts but have not been widely adopted in primary

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Dr Herlihy conceptualized and designed the project, designed the data collection instruments, collected data, conducted the initial analyses, and drafted the initial manuscript; Dr Walters advised Dr Herlihy throughout the project design and implementation and aided in data analyses; Dr D'Auria advised Dr Herlihy throughout the project design and implementation; Dr Orgel collaborated on the standard work protocol's design and rollout; Dr Jordan oversaw project implementation and sustainability efforts and aided in data analysis; and all authors critically reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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care settings. Currently, clinicians, caregivers, and policymakers struggle to optimize the guidelines' implementation strategies.[7,8]

Cost, time, resource utilization, and practice infrastructures are documented barriers to EPI guideline adherence.[9–11] Lack of provider confidence, time, willingness, and knowledge around screening procedures, interpretation of serum immunoglobulin E, skin prick tests, and oral food challenges to peanuts are common obstacles throughout the literature.[9,12,13] Eczema severity classification can be challenging in the primary care setting.[14–16] There is also concern that guidance around EPI might result in overmedicalization of food introduction and delayed introduction of other foods.[17,18] It is also important to note that although our clinical setting is in the United States and follows guidance from the AAP, screening for peanut allergy varies between national allergy societies. Societies recommend EPI, but there is variability in recommendations for screening and some do not recommend any standard screening or endorse precautions around introduction.[5]

Eczema remains the highest risk factor for developing IgE-mediated food allergies.[5] The LEAP study found an 86.1% relative reduction in the prevalence of peanut allergy among infants randomized into either a peanut consumption group or a peanut avoidance group through age 60 months.[2] However, a gap remains in incorporating this new knowledge in primary care settings. Results from a retrospective chart review conducted by other researchers at The University of North Carolina (UNC) several years before our baseline data collection found that only 0.8% of clinical encounters for infants under 12 months of age presenting for either a well-child check (WCC) or eczema-focused visit had documentation of EPI guidance.[19]

Peanut allergy prevention success in infants depends on primary care providers (PCPs) incorporating the addendum guidelines into routine WCC encounters at 4 and 6 months of age.[20,21] Even infants with mild to moderate eczema should receive guidance on EPI.[13,18,22,23] Evidence shows that primary care settings using clinical decision support (CDS) tools, electronic medical record (EMR) prompts, order sets, and best practice alerts for infants with eczema or egg allergy had better guideline adherence rates than clinics without these tools.[20]

Baseline documentation of EPI guidance and caregiver-reported peanut ingestion in our clinic were 13.9% and 0%, respectively. We aimed to increase the documentation of clinically appropriate EPI to 50% and caregiver-reported peanut ingestion to 50% at 6 and 9-month WCC encounters from the project's launch through sustainability.

METHODS

Context

This quality improvement (QI) initiative targeted all infants seen for routine care at 4, 6, and 9-month WCC encounters. The intervention occurred in an off-site, academic, residency continuity clinic at UNC serving several counties in North Carolina. The clinic serves a large population of patients on Medicaid or self-pay (66%) and patients experiencing food insecurity. Spanish is the preferred language for approximately a quarter of the population.

Baseline Data

During the baseline period, the clinic conducted 134 WCC encounters for 4, 6, and 9-month-old infants between January 1, 2022, and March 31, 2022. The average in-room time for patients was 63 minutes, and diphtheria-tetanus-acellular pertussis (DTaP) vaccination rates for the 6-month WCC encounters were 100%. Providers documented EPI guidance during 13.9% of these visits. Home peanut introduction handouts and smart lists were unavailable during baseline data collection. There was no documentation of reported peanut consumption in any patients' EMR during chart review at baseline.

Interventions

This QI initiative lasted from April 2022 to August 2022, when a leadership handoff occurred. The project leader collected sustainability data through December 2022. Using QI methodology, the QI team developed a standardized work protocol and CDS tools within the EMR, including smart lists (a predefined list of text choices), visit templates, and patient education handouts for home peanut in English and Spanish. The team executed modifications through plan-do-study-act (PDSA) cycles to improve guideline adherence.

Stakeholder Engagement

The project lead identified a firm commitment from the clinic director regarding the importance of EPI and standardizing an approach to implement the guidelines. Other stakeholders for the project included the clinic staff, pediatric residents, and other clinical faculty in practice.

Practice Facilitation

Primary care practices often lack the resources to invest in infrastructure and training. Practice facilitation increases the likelihood of success in QI initiatives, increases provider adherence to evidence-based guidelines, and improves care quality metrics in many clinical settings.[24] The project lead served as the practice facilitator and engaged in QI activities, such as kickoff meetings, goal setting, maintaining momentum, and planning for leadership handoff.

Standard Work Protocol

The team streamlined and standardized eczema classification based on physical exam findings, body surface area affected, and topical steroid use. Thereafter, we

directed the provider to follow the work protocol for the appropriate EPI guidance. The eczema classification and the EPI guidance resulted in 1 unified standard work protocol for providers (Fig 1).

Home Peanut Introduction Handout

The QI team determined that the instructions in the addendum guidelines, as written, were complex and might deter caregivers. The addendum guidelines offer 3 different types of peanut-containing foods.[1] The team felt using peanut butter was most practical and accessible to families, and thus we removed other forms of peanut-containing foods from our handout. PORCH, a community organization collecting food donations, supplies the clinic with food, including peanut butter, ensuring access to those families with food insecurity.

Given the site-specific needs assessment, the project lead simplified the instructions for home introduction of peanuts. The new handout captures similar safety guidance and simplifies feeding directions (Fig 2). Providers electronically inserted the handout in the patients' after-visit summary. The clinic used UNC translation services for a Spanish-translated version of the handout to serve the clinic's Spanish-speaking families.

EMR Changes

There were 3 changes to the clinic's provider templates for 4, 6, and 9-month WCC encounters. Members of the

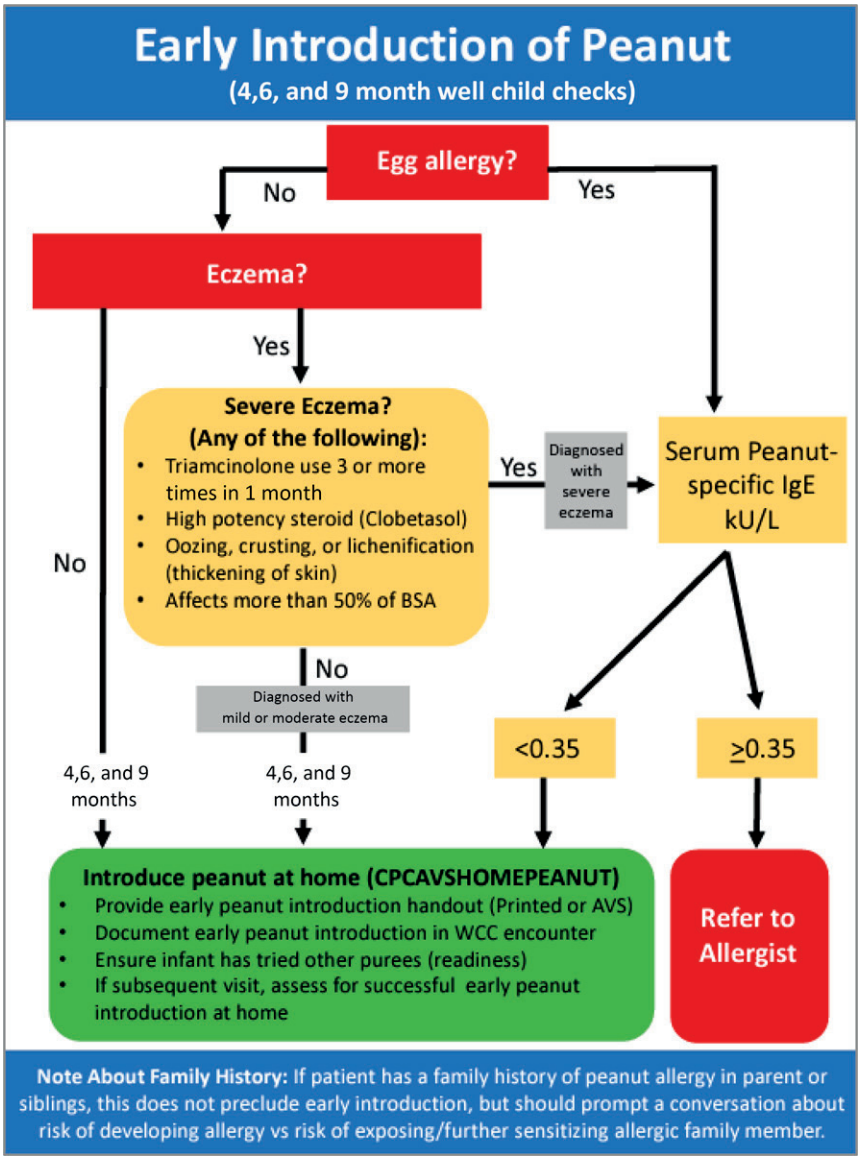

FIGURE 1
Standard work protocol for provider use during 4, 6, and 9-month WCC encounters. The tool aids in determining appropriate EPI guidance for infants.

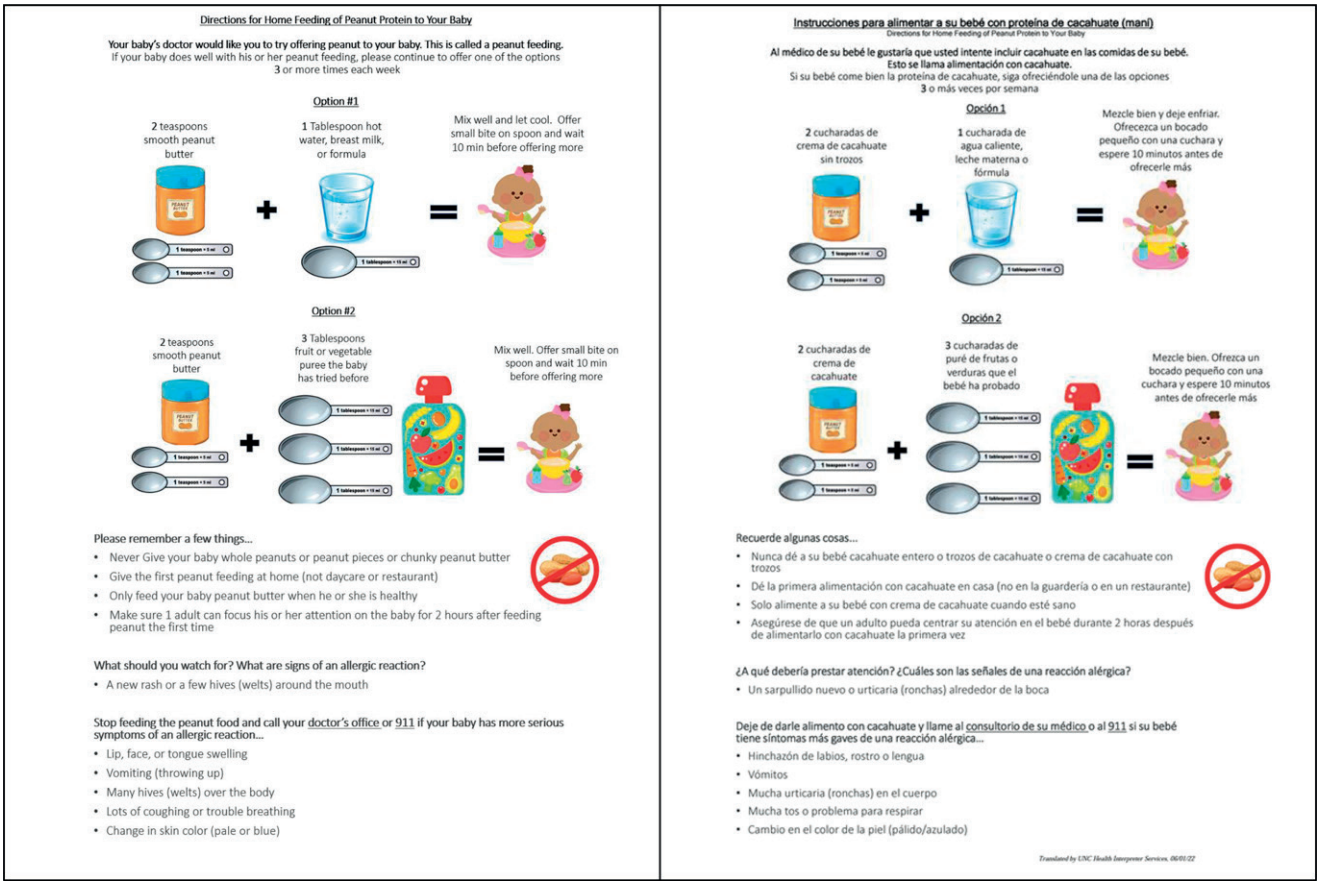

FIGURE 2

Home peanut introduction handouts (English and Spanish) for distribution in infants' printed AFVs. AFVs are also available electronically through patients' health portals.

QI team adapted the note templates for these WCC encounters in the EMR to remove redundant elements in the existing note templates. The sections of the note template addressing peanut introduction were designed to be easy and quick to use.

Second, the QI lead included an anticipatory guidance section for EPI screening for each 4, 6, and 9-month WCC visit template for the associated visit. The EPI screening tool involved multiselect drop-down lists for solid food introduction, peanut introduction, and assessment of other risk factors for the development of peanut allergy. The template then prompted the provider to select a low or high-risk level for the infant related to the development of peanut allergy. Based on the risk stratification, the provider chose from another drop-down list to guide the family toward home introduction or direct the provider to order a serum immunoglobulin E to peanut. In rare cases, the work protocol prompted the provider to recommend peanut avoidance when there is a history of allergic reactions consistent with the diagnosis of peanut allergy. At 6 and 9-month WCC visits, the templates prompted providers to ask about peanut consumption since the infant's last visit.

Third, we modified the physical skin exam findings on the EMR template to a specific detailed skin assessment drop-down list detailing the presence or absence of typical morphologic features of eczema on specified areas of the infant's body. This focus on standardizing and improving eczema classification is essential to adequately stratify infants into the correct risk category for the development of peanut allergy. Screenshots of EMR changes appear in Fig 3.

STUDY OF THE INTERVENTIONS

Using tailored EMR reports and manual chart reviews, the project lead compiled data from baseline through 6 PDSA cycles (Table 1) and 5 months of sustainability after the project for all 4, 6, and 9-month WCCs in the clinic.

MEASURES AND ANALYSIS

This project included 2 primary outcome measures, 1 focused on EPI documentation and the other on caregiver-reported peanut ingestion. An additional outcome and single process measure targeted provider behaviors in

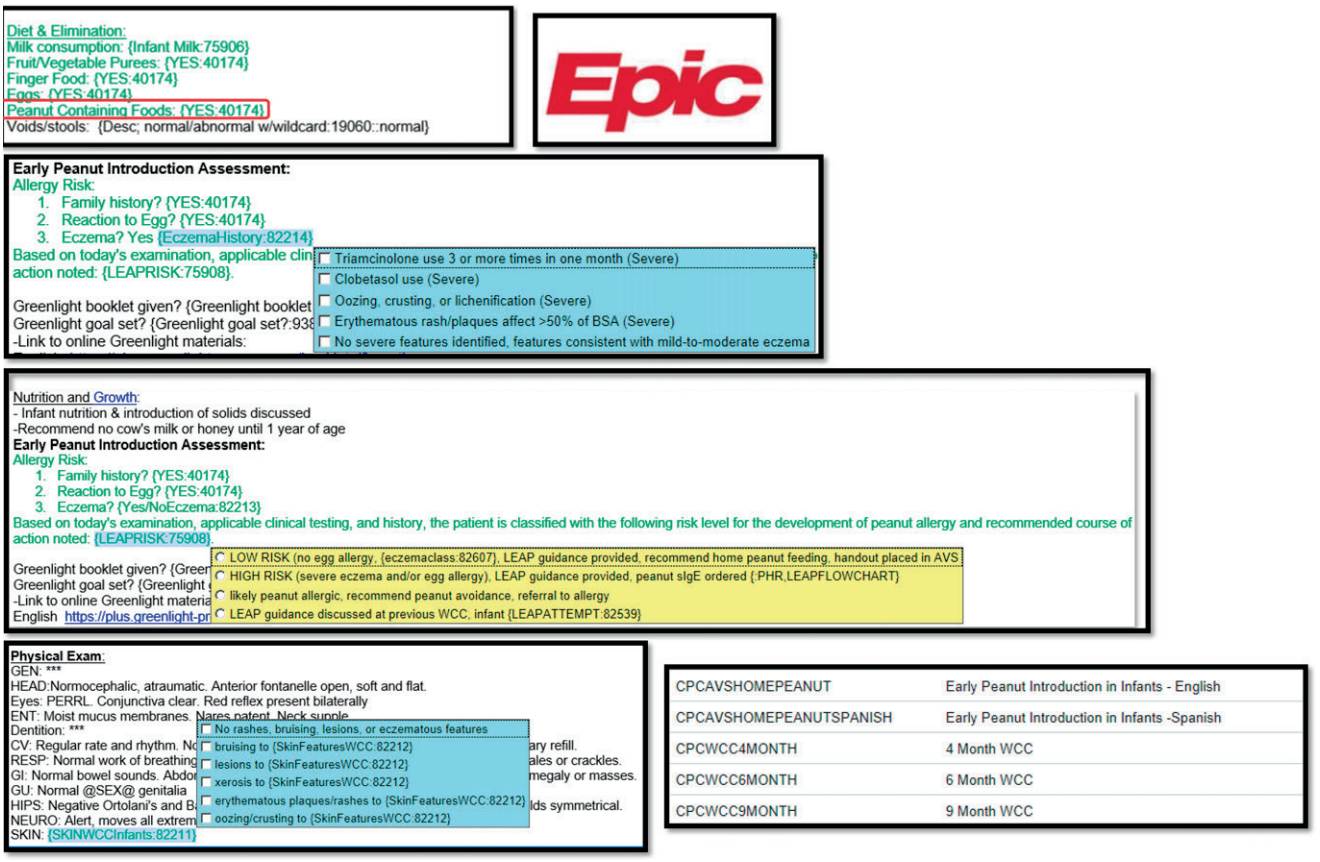

FIGURE 3

Screenshots of EMR features. Green text indicates a change to the existing note template with our intervention. Blue lists are multiselect, and yellow lists are single-select tools.

response to our QI initiative. Two balancing measures tracked the project's impact on vaccination rates and patient in-room time. The QI team used control charts for the measures analyses, observing the Shewhart Rules in determining clinical and statistical significance (Table 2). The project lead used QI macros for Excel (KnowWare International Inc., Denver, Colorado; Version 2018) to generate statistical process control charts (SPCCs) and analyze data. We collected and reported data for all infants seen for their routine 4, 6, and 9-month WCC encounters over a period of 12 consecutive months.

ETHICAL CONSIDERATIONS

The UNC institutional review board (IRB) found this QI initiative was an internal improvement project and exempt from IRB oversight. IRB #22-0559.

RESULTS

The average number of 4, 6, and 9-month infant visits in each biweekly period was 19 (ranging from 8 to 28). The workflow prompted providers to insert the home peanut introduction handout for infants with no or mild-moderate eczema at 4, 6, and 9-month WCCs. The home introduction handout was not expected for infants not yet developmentally ready for solids or infants already eating peanuts. The distribution rate of the home peanut introduction handout into the patients' after-visit summary (AVS) increased from 5.2% at baseline to 54.1% during sustainability (Fig 4).

The EPI guidance documentation increased from 13.9% at baseline to 83.5% during sustainability (Fig 5). Reported peanut consumption by caregivers during 6 and 9-month WCCs increased from 0% at baseline to 34.6% during sustainability (Fig 6).

The adoption rate of the EMR templates, smart lists, and phrases increased from 2% at baseline to 73% during sustainability (Fig 7).

There were no significant changes to balancing measures during the project. DTaP vaccination rates remained at 100%. There was no significant shift in the patient time in-room of 65 minutes during the project (Fig 8).

DISCUSSION

We significantly improved measures to increase early peanut introduction in infants using QI methodology and

TABLE 1 PDSA Cycles

Date	PDSA Cycle	Changes to Improve Outcomes
4/1/22–4/28/22	#1	Clinic residents and faculty piloted the EMR templates and smart lists or phrases for user and logic errors. Minor adjustments to smart phrase logic and usability in response to piloting feedback.
4/29/22–5/19/22	#2	Project lead provided education to residents and faculty on the background of peanut allergy, LEAP guidelines, and QI project CDS toolkit and aims.
5/20/22–6/2/22	#3	Project lead launched the approved EMR templates and CDS tools for 2 uninterrupted weeks to allow interface with the smart lists or phrases, home peanut introduction handout, and standard work protocol by multiple providers in the clinic.
6/3/22–6/16/22	#4	UNC interpreter services translated the home peanut introduction handout into Spanish for AVS. Modified work protocol to tighten classification of 'severe' eczema to exclude recurrent hydrocortisone use after feedback from faculty providers. Expanded EMR accessibility to home peanut introduction handout through the EMR permissions feature.
6/17/22–7/7/22	#5	Project lead visited the clinic weekly to answer questions and boost engagement with the project by providing candy and printed peanut allergy comic strips. Laminated computer tags with visual text reminders of smart phrases for the English and Spanish home peanut introduction handout to increase distribution in AVS.
7/8/22–8/11/22	#6	Placed in-text reminder embedded in the LEAP risk smart phrase or list section reminding provider to put home peanut introduction handout in the patient AVS for low to moderate-risk infants.

interprofessional collaboration. Using a standardized EMR bundle of CDS tools, engagement, facilitation, and feedback to providers conducting the targeted WCC encounters helped achieve project aims.

Before this project, discussing EPI guidance between providers and caregivers under the 2017 and updated 2019 guidelines was a reasonable expectation in the primary care setting. Given the rationale for our project was that implementation of these guidelines was low, this particular outcome measure's improvement from 13.9% to 83.5% throughout the project and, into 5 months of sustainability, shows the powerful impact of our intervention.

For the other measures analyzed with SPCCs, we exceeded our goals of 50% for the documentation of EPI

TABLE 2 Project Measures

Measure Type	Description	Measure	Significance	Analysis
Outcome	EPI guidance from providers to patient caregivers	Documentation of clinically appropriate EPI guidance at 4, 6, and 9-mo WCCs in patient EMR	Measurement of QI initiative on provider behavior	SPCC with statistical significance using Shewart rule for Significance
Outcome	Caregiver-reported peanut consumption by infants	Reported consumption of peanut by caregivers at 6 and 9-mo WCCs	Measurement of QI initiative on caregiver behavior in response to provider guidance	SPCC with statistical significance using Shewart rule for Significance
Outcome	Distribution of home peanut introduction handout	Percentage of expected home peanut introduction handout inserted in AVS for infants with no eczema or mild to moderate eczema	Measurement of QI initiative on provider behavior	SPCC with statistical significance using Shewart rule for Significance
Process	Provider adoption of revised 4, 6, and 9-mo WCC templates and smart lists	Percentage of provider use of templates, smart lists, and documentation features as intended without deletions or substitutions at 4, 6, and 9-mo WCCs	Measurement of QI initiative on provider behavior	SPCC with statistical significance using Shewart rule for Significance
Balancing	Patients receiving 6-mo DTaP vaccine (expected)	Rate of vaccination for DTaP at 6 mo of age (EPIC dashboard data)	Measurement of QI impact on immunization compliance	Descriptive statistics
Balancing	Average visit length (min) for 4, 6, and 9-mo WCCs	Patient time in-room (min)	Measurement of QI impact on length of provider-parent interaction	SPCC with statistical significance using Shewart rule for Significance

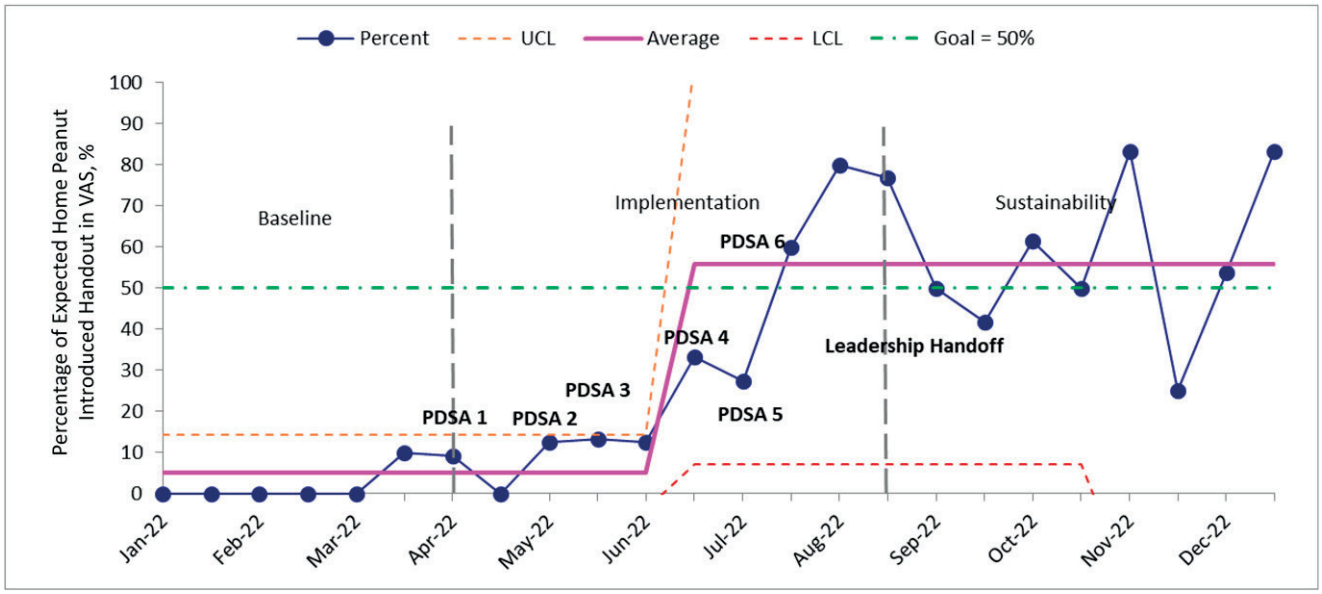

FIGURE 4
Distribution of home peanut introduction handout at expected visits. Blue dots are data points in relation to the mean, goal, and upper control limit/lower control limit (UCL/LCL) lines. PDSA numbers refer to PDSA cycles from Table 1. Vertical lines separate baseline, implementation, and sustainability phases, with a notation of leadership handoff occurring in early sustainability.

guidance and distribution of the handout in the AVS. We fell just short of our goal for provider adoption of the templates and smart lists, but the measure improved from baseline with a statistically significant shift in the mean.

We tracked caregiver-reported peanut consumption at 6 and 9-month WCC visits through all project phases. We observed shifts in the percentage of reported ingestion between baseline, implementation, and sustainability as template use gained momentum. Most infants had not

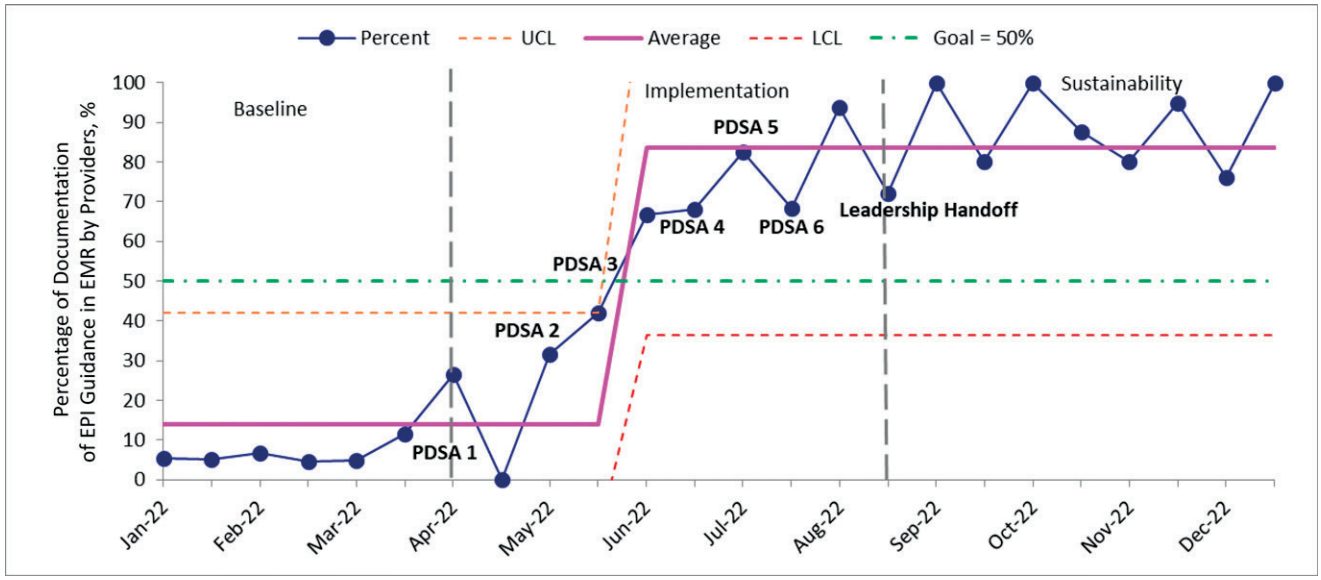

FIGURE 5
Documentation of EPI guidance in EMR by providers. Blue dots are data points in relation to the mean, goal, and UCL/LCL lines. PDSA numbers refer to PDSA cycles from Table 1. Vertical lines separate baseline, implementation, and sustainability phases, with a notation of leadership handoff occurring in early sustainability.

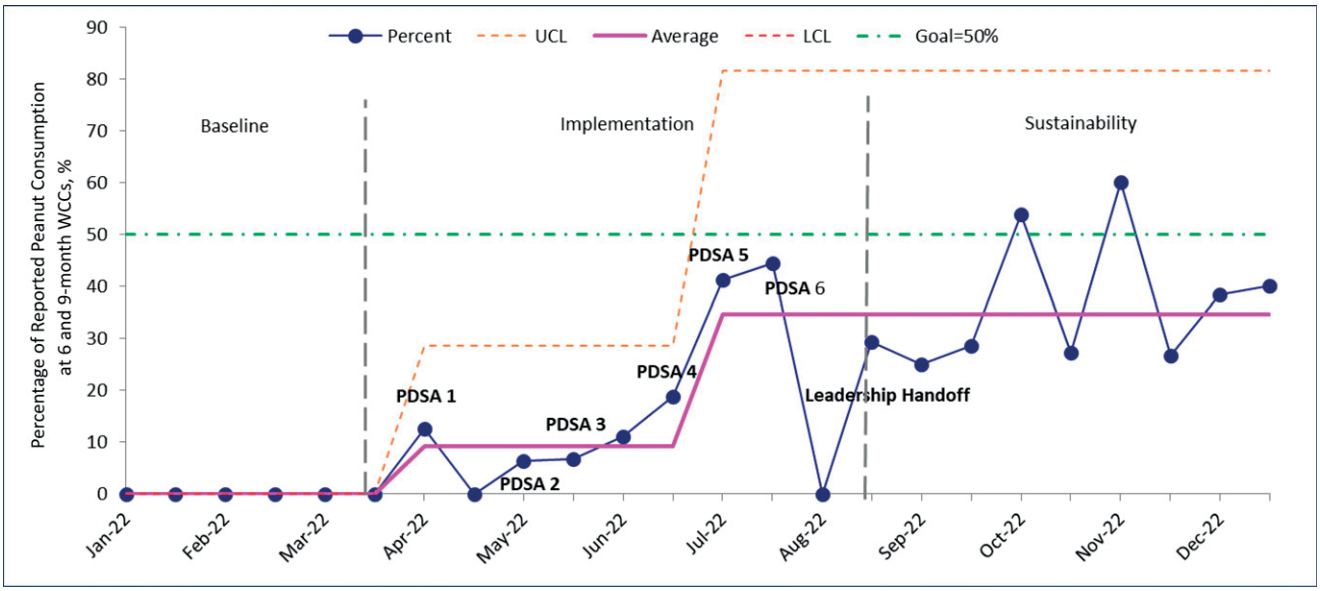

FIGURE 6
Reported peanut consumption by caregivers. Blue dots are data points in relation to the mean, goal, and UCL/LCL lines. PDSA numbers refer to PDSA cycles from Table 1. Vertical lines separate baseline, implementation, and sustainability phases, with a notation of leadership handoff occurring in early sustainability.

yet introduced solids by 4 months, but EPI guidance is still important during these early infant WCCs. We did not find any documentation of reported peanut consumption during our baseline review of charts. Though we did not reach our goal of 50% peanut consumption at 6 and 9-month WCCs during the project, 34.6% reported consumption in this age group by the end of sustainability speaks to the efficacy of our CDS bundle on patient-

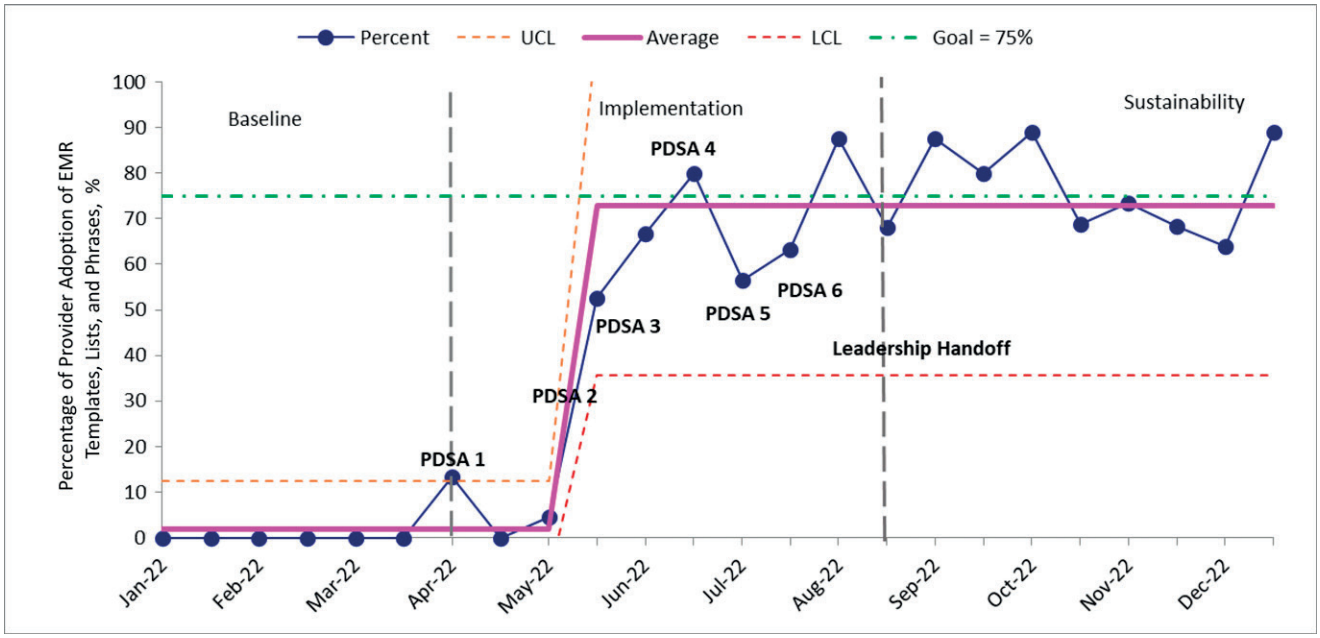

FIGURE 7
Provider adoption of EMR templates, lists, and phrases. Blue dots are data points in relation to the mean, goal, and UCL/LCL lines. PDSA numbers refer to PDSA cycles from Table 1. Vertical lines separate baseline, implementation, and sustainability phases, with a notation of leadership handoff occurring in early sustainability.

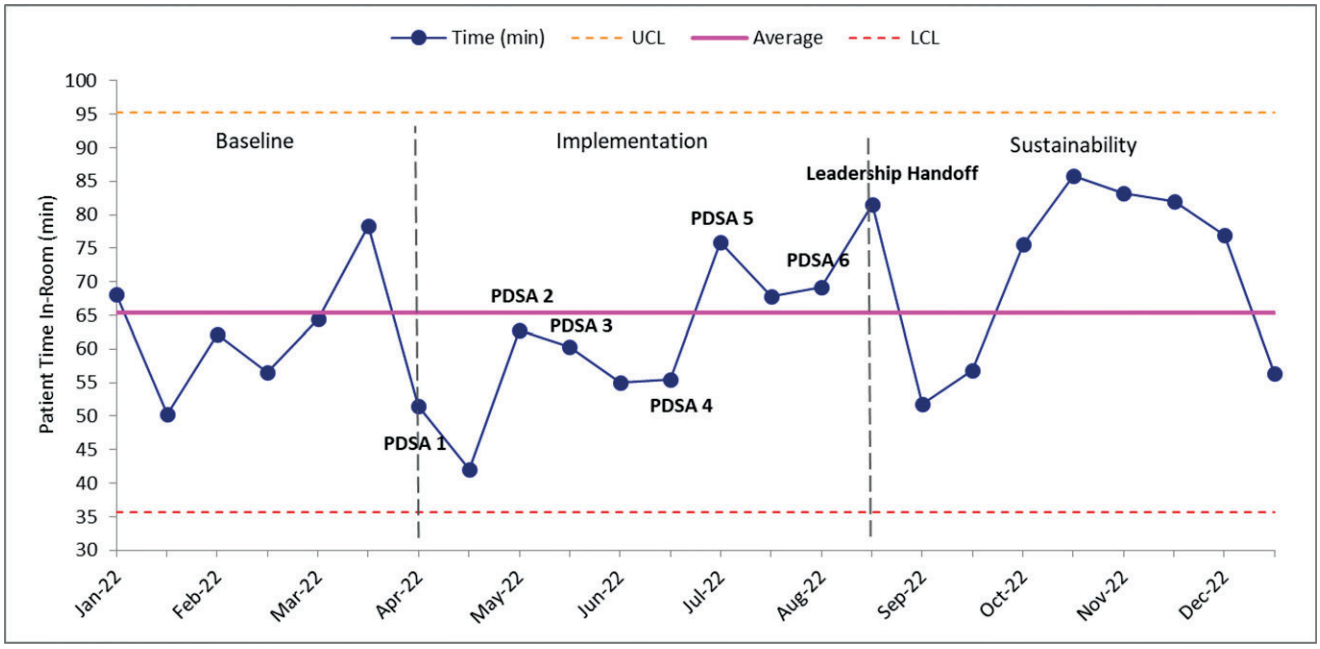

FIGURE 8

Patient in-room time. Blue dots are data points in relation to the mean and UCL/LCL lines. PDSA numbers refer to PDSA cycles from Table 1. Vertical lines separate baseline, implementation, and sustainability phases, with a notation of leadership handoff occurring in early sustainability.

centered outcomes. Caregivers who reported no peanut consumption at the 6 and 9-month WCC visits allowed providers to reinforce EPI guidance.

Identifying and tracking balancing measures remain essential parts of QI work. Overall, we made significant changes to the context of these WCC visits with minimal disruption to these other visit aspects. Although in-room time did not significantly change throughout the project, we observed the beginnings of a data shift above the average in-room time during early sustainability, which coincided with the start of a new academic year and a surge of influenza, coronavirus disease 2019, and respiratory syncytial virus in the Fall of 2022. The clinic experienced increased visits during this time and had challenges with staffing because of illness. In addition, we suspect that many new resident providers forget to document when the patient visit is complete, which alters the recorded in-room time.

The availability of the coronavirus disease 2019 vaccine for infants in our target population, new residents starting with the academic year, and surges of respiratory illness coincided with a decrease in our measures tracked with SPCCs. These findings were not unexpected, but revamping toward education, engagement, and facilitation showed these measures rebounded quickly, and during the second half of sustainability, in-room time showed recovery, evidenced by consecutive decreases in the final 3 months of the project.

A particular strength of this QI project was the use of the EMR to make counseling about EPI easier for providers. The prompt in the note template reminded providers to counsel about this topic in our clinic, where many resident physicians rotate through without consistent presence to learn new processes. In addition, the patient education materials were easily inserted into the after-visit materials for patients, allowing a tool to guide a conversation with families and materials for the family to take home. Lastly, our process-driven CDS tools captured reported peanut consumption by caregivers at 6 and 9-month WCCs.

Other published QI work aiming to improve EPI guideline adherence discusses projects that used education sessions and pre and postassessments but did not incorporate CDS tools.[13,25] Although these projects documented increased provider awareness and knowledge about EPI guidelines, the projects lacked supporting data that increased knowledge translated into practice changes during WCC encounters. One QI project used emails to providers, small group education sessions, reminder cards at workstations, home introduction sheets, and onsite assistance by an allergist to improve guideline adherence.[26] Guideline adherence did not exceed 17% during the intervention cycles. Although these interventions represent CDS tools, they were neither standardized nor inclusive of EMR templates or smart phrases.

The most similar effort to improve EPI guideline adherence is the iREACH program, a CDS bundle utilizing EMR features and handouts to aid providers in EPI in primary care settings. In a sample of 143 WCC encounters at 4 and 6 months, results showed better adherence to guidelines (52.4%) with the use of the iREACH bundle compared with the control clinic (14.1%) without the bundle ($P < .001$).[20]

Koplin et al showed that guideline adherence might only prevent up to 44% of peanut allergy diagnoses if providers restrict interventions to high-risk infants.[11] Therefore, continuing to use the home peanut introduction handout in infants with no eczema may be beneficial in preventing unnecessary peanut avoidance. PCPs are most likely to interface with otherwise healthy infants, and assessing infants for early atopy offers a unique opportunity to practice primary and secondary prevention. Most infants observed during this QI project met the criteria for immediate home introduction of peanuts and were able to avoid unnecessary allergy referrals. PCPs should confidently promote broad EPI and diet diversification in patients showing developmental readiness for solid food introduction.

Although this project at a single site showed improvements in early peanut introduction, the goal of generalizability of this QI initiative to the broader population remains an unmet need. Moving the needle on this initiative will require working with more primary care clinics. One barrier to generalizability is that some offices do not use EMR systems, making the reproducibility of these interventions more challenging. However, the handouts can serve as stand-alone documents for printing and distribution to families. Additionally, CDS tools could include modifying prompts about EPI guidance on paper charting systems in place of EMR accessibility.

Another limitation of our study is that there are significant anticipatory guidance recommendations for WCCs. Our study examined several balancing measures but could not capture the full complexity of WCCs and aspects of the visit that may have been lost because of adding in this counseling. Future projects should assess caregiver understanding and knowledge of EPI guidelines after visits, as this was beyond the scope of our project.

CONCLUSIONS

Peanut allergy in children is a population health problem affecting families and healthcare systems. Research shows EPI can reduce the incidence of peanut allergy, but adoption of this practice remains low in primary care settings. QI methodology improved documentation of EPI guidance at routine WCC encounters and reported rates of peanut consumption without impacting other measures at our site. Broader PCP use of CDS tools and EMR standardization could improve guideline adherence to prevent peanut allergy in infants.

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Thank you to the providers and staff at the UNC Children's Primary and Specialty Care Clinic for engaging with this project. Thank you also to Dr. Edwin Kim for his mentorship.

ABBREVIATIONS

AAP: American Academy of Pediatrics
AVS: after visit summary
CDS: clinical decision support
EMR: electronic medical record
EPI: early peanut introduction
IRB: Institutional Review Board
LEAP: Learning Early About Peanuts
PCP: primary care provider
PDSA: Plan Do Study Act
QI: quality improvement
SPCC: statistical process control chart
UNC: University of North Carolina
WCC: well child check

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13-Year-Old Female With New Onset Multifocal Pulmonary Ground-Glass Opacities

Dawn Janysek, MD, Sharanya Joginpalli, MD, Mitali Thanawala, MD, Ankhi Dutta, MD, MPH, Manuel Silva-Carmona, MD, Maria Pereira, MD

abstract

A 13-year-old female who recently emigrated from Honduras presented to an emergency department in Texas with a 2-month history of weight loss, fatigue, cough, and progressive shortness of breath. Her symptoms started with a nonproductive cough, and she later developed dyspnea on exertion and orthopnea. On physical examination, she was tachycardic and tachypneic. She had a thin, emaciated body habitus. She was visibly in respiratory distress with nasal flaring, tracheal tugging, and intercostal and subcostal retractions. She had diminished breath sounds at the bases and bibasilar crackles. A computed tomography scan of the chest revealed multifocal ground-glass opacities throughout all lobes of both lungs with small bilateral pleural effusions and prominent bilateral hilar lymph nodes. We will discuss the approach to the initial evaluation and subsequent diagnosis.

Baylor College of Medicine, Houston, Texas; and Texas Children's Hospital, Houston, Texas

Drs Janysek, Joginpalli, and Thanawala contributed to the project's conception, design, and acquisition of data and drafted the initial manuscript, tables, and figures; Drs Dutta, Silva-Carmona, and Pereira participated in the interpretation of data and critically reviewed and revised the manuscript; and all authors approved the final manuscript and agree to be accountable for all aspects of the work.

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HISTORY OF PRESENT ILLNESS

Dr Janysek, Pediatric Resident, Moderator

The patient is a 13-year-old female who was admitted to our institution for evaluation of progressive shortness of breath and abnormal chest imaging. The onset of her symptoms occurred 2 months before presentation with a nonproductive cough and poor appetite. The symptoms progressed to dyspnea on minimal exertion, such as taking a shower, and orthopnea, in which she required several pillows to sleep at night. She reported subjective fevers but was afebrile on arrival. She denied chest pain, wheezing, or hemoptysis. She had no history of recurrent infections or similar symptoms. She had immigrated from Honduras 6 months ago. She spent 1 month traveling to the United States and stayed a few weeks at a shelter in California that her mother reported was crowded. She had no known tuberculosis (TB) contacts but reported that she had been exposed to many people in close quarters with chronic cough. When she lived in Honduras, she had a cat, a dog, and 3 pet parakeets. Her mother reported that she did not notice any changes in her health after adopting the birds. She did not have any known arthropod bites. She was not aware of any raw meat or unpasteurized dairy consumption. She reported drinking bottled water but was unable to confirm whether well or creek water was consumed during her travel to the United States. She had updated her immunizations at a local health center but had not received her coronavirus disease 2019 vaccine. She had no known drug allergies. Her past medical and surgical history were negative. Family history was noncontributory. She denied the use of cigarettes, e-cigarettes, or vaping.

Vitals revealed a heart rate of 119 beats per minute, blood pressure of 95/55 mmHg, temperature of 36.4°C, respiratory rate of 25 breaths per minute, and

saturation of peripheral oxygen of 99% on room air. On physical examination, she had a thin body habitus and was less than the third percentile for weight and less than the first percentile for height (using the World Health Organization girls [5–19 years] growth chart). Her conjunctivae were clear, and no nasal or oral ulcers were seen. No enlarged cervical lymphadenopathy was detected. She was visibly tachypneic with tracheal tugging and intercostal and subcostal retractions. She had diminished breath sounds at the lung bases and bibasilar crackles. A cardiac examination was notable for tachycardia but otherwise normal with no peripheral cyanosis or clubbing. Abdominal examination was normal without organomegaly. Her proximal and distal muscle strength was normal in all extremities. A joint examination was negative for effusion, synovial tenderness, or synovial thickness. She had scattered hypopigmented macules noted on her left temporal area near her left eye and streaks of white hair seen on her scalp, which her mom reported was stable since the initial onset ~1 year before. This was presumed to be due to vitiligo. She did not have any unusual skin tightness, telangiectasias, livedo, or subcutaneous nodules. There was no peripheral discoloration or signs suggestive of Raynaud's phenomenon. She was noted to have periungual erythema in all fingers and dilated nailfold capillaries on the left third and fourth digits. Erythema was present on the extensor surfaces of the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints (Fig 1), as well as on the extensor surfaces of the bilateral elbows (Fig 2) and left knee. No malar rash or heliotrope rash was noted. She had normal visual acuity on ophthalmologic examination.

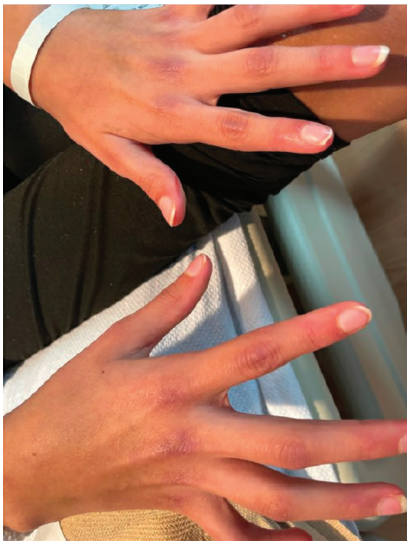

FIGURE 1
Dorsum of hands. Erythema of the extensor surfaces of the MCP, PIP, and DIP joints.

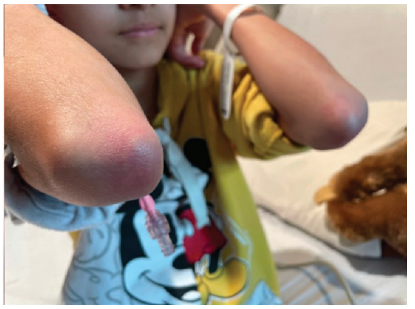

FIGURE 2
Bilateral elbows. Erythema of the extensor surfaces of bilateral elbows.

Laboratory monitoring revealed a normal comprehensive metabolic, as well as a normal blood cell count with differential (Table 1). Peripheral smear was normal with unremarkable morphology of blood cells and no blasts. Inflammatory markers were normal. Urinalysis was positive for trace leukocytes but otherwise negative for proteinuria or hematuria. Chest radiograph revealed patchy bilateral airspace opacities, most confluent at the left lung base, and bilateral pleural effusions (Fig 3). A computed tomography (CT) scan of the chest with contrast was notable for multifocal ground-glass opacities throughout all lobes of both lungs with small, non-septate bilateral pleural effusions and prominent bilateral hilar lymph nodes. There were no discrete areas of consolidation, and no bronchiectasis was seen (Fig 4).

DR DUTTA, WHAT INFECTIOUS DISEASES ARE ON THE DIFFERENTIAL FOR A TEENAGE PATIENT WITH PROGRESSIVE SHORTNESS OF BREATH AND GROUND GLASS OPACITIES?

Dr Dutta, Pediatric Infectious Disease

In any child with progressive shortness of breath, weight loss, chronic cough, and ground glass opacities, it is imperative to rule out infections first. It is even more important in this setting with a travel history and animal exposure. The infectious differential diagnosis of this is broad but crucial to rule out before considering other noninfectious diagnoses. Highest on the differential, especially because this patient is from Honduras, are pulmonary tuberculosis and endemic mycoses like histoplasmosis, blastomycosis, coccidioidomycoses, and paracoccidioidomycoses. Given her pet exposure, psittacosis should be considered as well. *Mycoplasma pneumoniae* and *Legionella* species should also be considered. We would also need to rule out HIV and other underlying immunosuppressed states because atypical pathogens like nontuberculous mycobacteria, *Pneumocystis jirovecii, Nocardia*, *Actinomyces*, gram-negative pathogens, and *Bartonella*, given cat exposure, could cause ground glass opacities in an immunocompromised host. Routine bacterial pathogens like *Staphylococcus aureus, Streptococcus pneumoniae,*

TABLE 1 Laboratory Markers at Initial Presentation

Clinical Variables, Units	Value	Reference Range
Complete blood count with differential		
White blood cell count, x10*3/μL	10.19	4.19–9.43
Hemoglobin, g/dL	14.4	10.8–13.3
Hematocrit, %	43.0	33.4–40.4
Platelet count, x10*3/μL	306	194–345
Absolute neutrophil count, x10*3/μL	5.92	1.82–7.47
Absolute lymphocyte count, x10*3/μL	3.54	1.16–3.33
Absolute monocyte count, x10*3/μL	0.46	0.19–0.72
Absolute eosinophil count, x10*3/μL	0.21	0.02–0.32
Absolute basophil count, x10*3/μL	0.04	0.01–0.05
Immature granulocytes, %	0.2	0.0%–0.3%
Complete metabolic panel		
Sodium, mmol/L	139	136–145
Potassium, mmol/L	3.8	3.5–5.5
Chloride, mmol/L	103	95–105
Carbon dioxide, mmol/L	26	20–28
BUN, mg/dL	6	2–23
Creatinine, mg/dL	0.38	0.50–0.80
Calcium, mg/dL	9.6	8.8–10.6
Phosphorous, mg/dL	4.4	2.5–5.0
Alkaline Phosphatase U/L	114	93–386
ALT, U/L	11	11–28
AST, U/L	29	10–30
GGT, U/L	12	14–25
Albumin	4.6	3.7–5.0
Inflammatory markers		
C-Reactive protein, mg/dL	<0.5	<1.0
Sed rate, mm/hr	8	<1–20
LDH, U/L	213	169–285
Uric acid, mg/dL	3.1	2.0–6.2
Urinalysis		
Spec gravity	1.016	1.001–1.035
pH	7.0	5.0–8.0
Blood	Negative	Negative
Protein	Negative	Negative
Urobilinogen, mg/dL	2.0	<2.0
Bilirubin	Negative	Negative
Glucose	Negative	Negative
Ketone	Negative	Negative
Nitrite	Negative	Negative
Leukocytes	Trace	Negative

or S*treptococcus pyogenes* are less likely given the chronic nature of her illness. Lastly, viral causes like cytomegalovirus, adenovirus, Epstein-Barr virus, severe acute respiratory syndrome coronavirus 2, or other respiratory viruses can cause this constellation of symptoms.

Dr Janysek

The patient had an extensive infectious workup. Viral test results for severe acute respiratory syndrome coronavirus 2, respiratory syncytial virus, rhinovirus, influenza, parainfluenza, and human metapneumovirus were negative. Severe acute respiratory syndrome coronavirus 2 anti-nucleocapsid protein immunoglobulin G and total spike protein antibodies were elevated, but spike protein immunoglobulin M was negative, indicating previous infection. No organisms were isolated in the blood culture, including anaerobic bacteria, aerobic bacteria, or mycobacteria. Karius testing of blood for pathogen genetic material also yielded negative results. Fungitell serum assay and *Aspergillus* galactomannan antigens produced negative results. Fungal complement fixation revealed negative results for coccidioides, blastomycosis, histoplasmosis, and *Aspergillus* titers. QuantiFERON gold TB, enzyme-linked immuno-spot test of TB-associated T cells TB, and purified protein derivative testing results were negative. Epstein-Barr virus, cytomegalovirus, HIV, and syphilis screening results were negative. *C. pneumoniae, C. trachomatis,* and *C. psittaci* serum immunoglobulin G level results were negative. Urine *legionella* antigen was not detected. Stool evaluation results for ova and parasites were negative. Transthoracic echocardiogram results were negative for vegetations. A right upper quadrant ultrasound to evaluate for organomegaly or other liver or spleen abnormalities was also normal. A bronchoscopy with bronchoalveolar lavage (BAL) revealed a predominance of macrophages (38%), the most common cell type in alveoli, and foamy cells, which are lipid-laden macrophages that can be a marker of generalized inflammation.[1] The BAL also revealed a mixed inflammatory infiltrate (31% neutrophils, 16% lymphocytes, and 15% eosinophils) but was otherwise unrevealing for infection. A wedge biopsy of the left upper lung lobe revealed nonspecific cellular and fibrosing patterns consistent with interstitial pneumonia, multifocal organizing pneumonia, and lymphocytic and constrictive bronchiolitis. The patient had significant weakness and was unable to adequately perform the maneuvers of pulmonary function testing (PFT) before her wedge biopsy. However, with clinical improvement post-biopsy, she was able to perform the PFT maneuvers adequately. Her PFT revealed a forced expiratory volume in 1 second (FEV_1) of 0.32 L (13.7% of predicted value for age), a forced vital capacity (FVC) of 0.37 L (14.3% of predicted value for age), and an FEV_1/FVC ratio of 86 (normal range >80). These findings are highly suggestive of restrictive lung disease in the setting of reduced FEV_1 and FVC but normal FEV_1/FVC ratio. Total lung capacity and diffusion capacity of the lungs for carbon monoxide were unable to be performed. The diffusion capacity of the lungs for carbon monoxide is decreased in interstitial lung disease because of impaired diffusion from inflammation and scarring of lung tissue. A 6-minute walk test was performed, and the patient was able to ambulate 373 m, ∼58% of the distance predicted for her age, and maintained a saturation of peripheral oxygen of 93% and above, although she had associated dyspnea and tachycardia. The 6-minute walk test

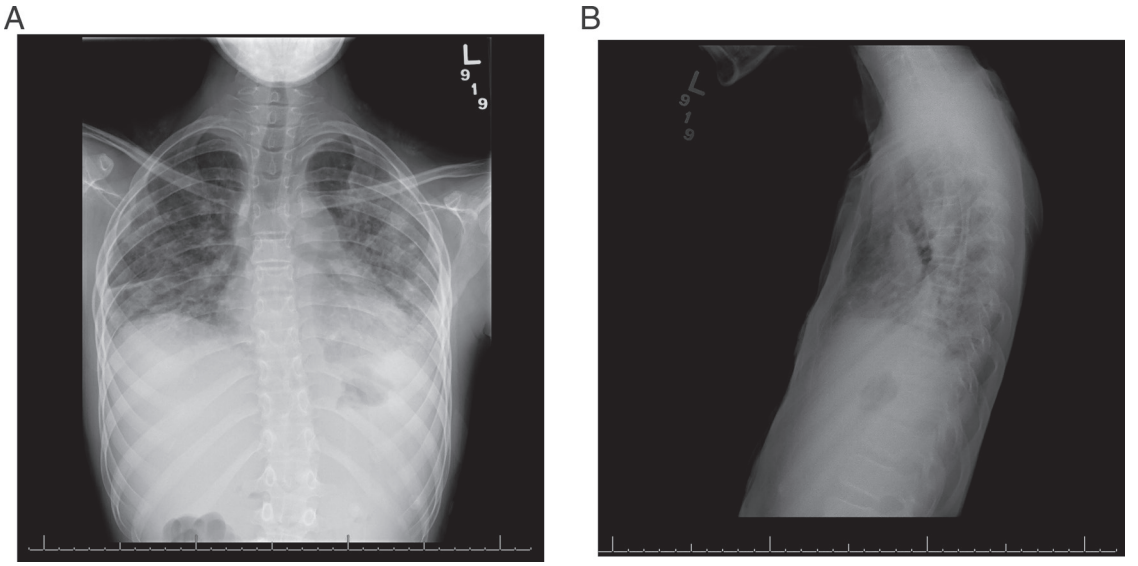

FIGURE 3
Initial chest radiograph (A) AP and (B) lateral views. Patchy bilateral airspace opacities and bilateral pleural effusions.

was informative of her decreased endurance and muscular weakness in the setting of her severe lung disease.

DRS THANAWALA AND SILVA-CARMONA, HOW DO YOU APPROACH THE EVALUATION OF A PATIENT WITH INTERSTITIAL LUNG DISEASE?

Drs Thanawala and Silva-Carmona, Pediatric Pulmonology

The initial findings of diffuse ground-glass opacities on chest imaging are nonspecific with a broad differential in which infectious etiology is often most common. However, the differential also can include alveolar hemorrhage, noninfectious pulmonary inflammation, substance use from vaping and e-cigarette-related injury, and more. For this patient, her extensive evaluation did not reveal an infectious etiology, bronchoscopy and BAL studies were not consistent with diffuse pulmonary hemorrhage, and the history was otherwise negative for substance use. In the setting of her periungual changes, tortuous nailfold capillaries, skin hyperpigmentation, and vitiligo, we had a higher clinical suspicion of underlying rheumatologic disease. With suspicion of rheumatologic process, the ground glass opacities and associated significant increased work of breathing brought interstitial lung disease higher on our differential.

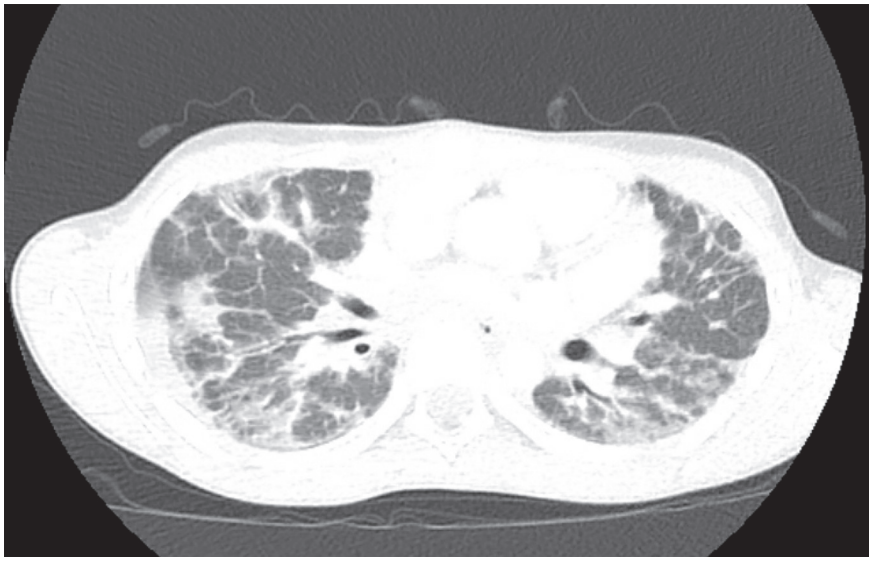

FIGURE 4
Chest CT with contrast. Multifocal ground-glass opacities with small bilateral pleural effusions and prominent bilateral hilar lymph nodes.

Interstitial lung disease (ILD) in children is a rare group of pulmonary diseases that result in impaired gas exchange due to changes in the lung interstitium and airspaces.[1] Patients with ILD can present with cough, exercise intolerance, dyspnea, hypoxemia, crackles, and tachypnea. As the disease progresses, patients can develop failure to thrive, increased work of breathing with retractions, hemoptysis, and pulmonary hypertension. Workup for ILD may include a CT scan of the chest, a flexible bronchoscopy with BAL to exclude infection, an echocardiogram to rule out pulmonary hypertension and cardiac disease, genetic testing, and lung biopsy.[2,3]

It is important to consider more common diffuse lung diseases before narrowing the differential to interstitial lung disease. Diffuse lung diseases include pulmonary infections, recurrent aspiration, cystic fibrosis, primary ciliary dyskinesia, immunodeficiencies, congenital heart disease, and more.[3] If these diseases have been excluded, or if the patient is initially diagnosed with one of these diseases but is clinically presenting with respiratory symptoms that seem out of proportion to the diagnosis, then further evaluation for ILD is recommended.

In children <2 years of age (Fig 5), the differential for noninfectious causes of diffuse lung disease include developmental disorders, pulmonary growth abnormalities with alveolar simplification, neuroendocrine cell hyperplasia of infancy, pulmonary interstitial glycogenosis, and surfactant protein disorders, including genetic mutations in surfactant protein-B gene, surfactant protein-C gene, and ATP binding cassette subfamily A member 3 that encode the proteins surfactant protein-B, surfactant protein-C, and ATP binding cassette subfamily A member 3.[4] If the ILD is severe and leads to chronic respiratory failure and end-stage lung disease, these patients may be considered for lung transplantation.

In our patient's case, the differential for noninfectious causes of diffuse lung disease is broad and is typically divided into large subgroups, including interstitial pneumonias, lymphoproliferative disease, small airway disease, vascular disorders, and other systemic diseases (Fig 6).[4] Patients with interstitial disease can be further categorized on histopathology as organizing, fibrinous, desquamative, or unspecified pneumonia, or from diffuse alveolar damage. Immunocompromised patients may develop ILD secondary to treatment such as chemotherapy, radiation, drug hypersensitivity, or transplant rejection. A wide spectrum of disorders presents similarly to ILD; however, they have more diffuse airway and parenchymal involvement and include underlying bronchiolitis, lymphatic and vascular disorders, thromboembolic disease, granulomatous diseases, and more. In our patient's case, we classified her lung disease as an ILD related to systemic disease from an immune-related disorder that will be revealed in the discussion below. Her PFT was concerning for severe restrictive ILD, with significantly diminished lung mechanics, and her BAL and lung biopsy samples revealed significant signs of inflammation without infection or diffuse hemorrhage. These findings of severe interstitial lung disease can be found without significant elevation of markers of systemic inflammation.

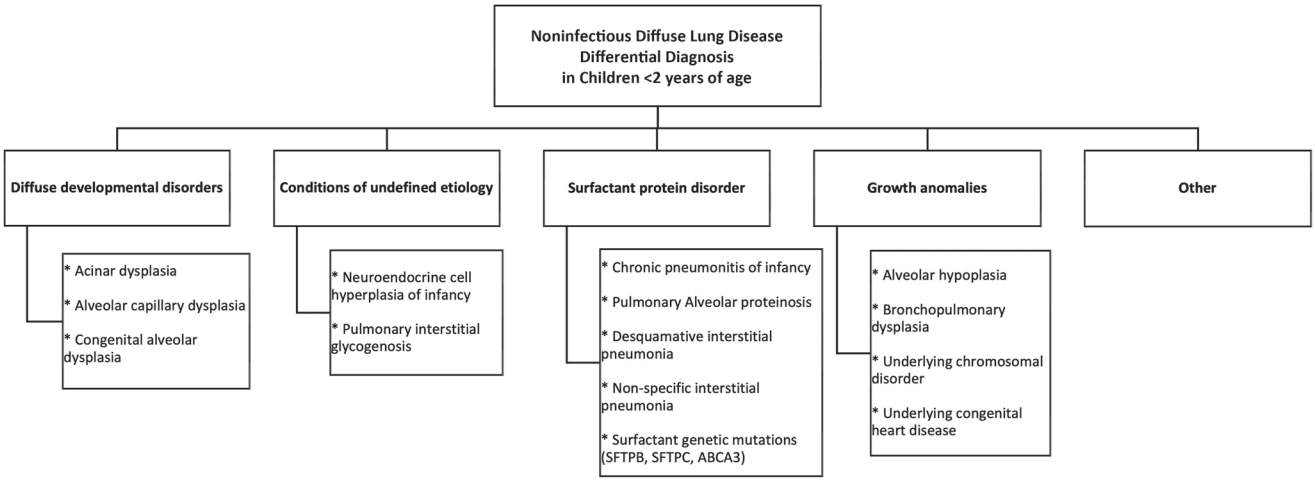

FIGURE 5

Differential diagnosis for noninfectious diffuse lung disease in children <2 years of age. Figures 5 and 6 exclude more common causes of diffuse lung disease, including chronic aspiration, cystic fibrosis, primary ciliary dyskinesia, and have been adapted from Figure 7 of the following publication*: Rice A, Tran-Dang MA, Bush A, Nicholson AG. Diffuse lung disease in infancy and childhood: expanding the chILD classification. Histopathology. 2013 Dec;63(6):743-55. doi: 10.1111/his.12185. Epub 2013 Oct 9. PMID: 24117670.*

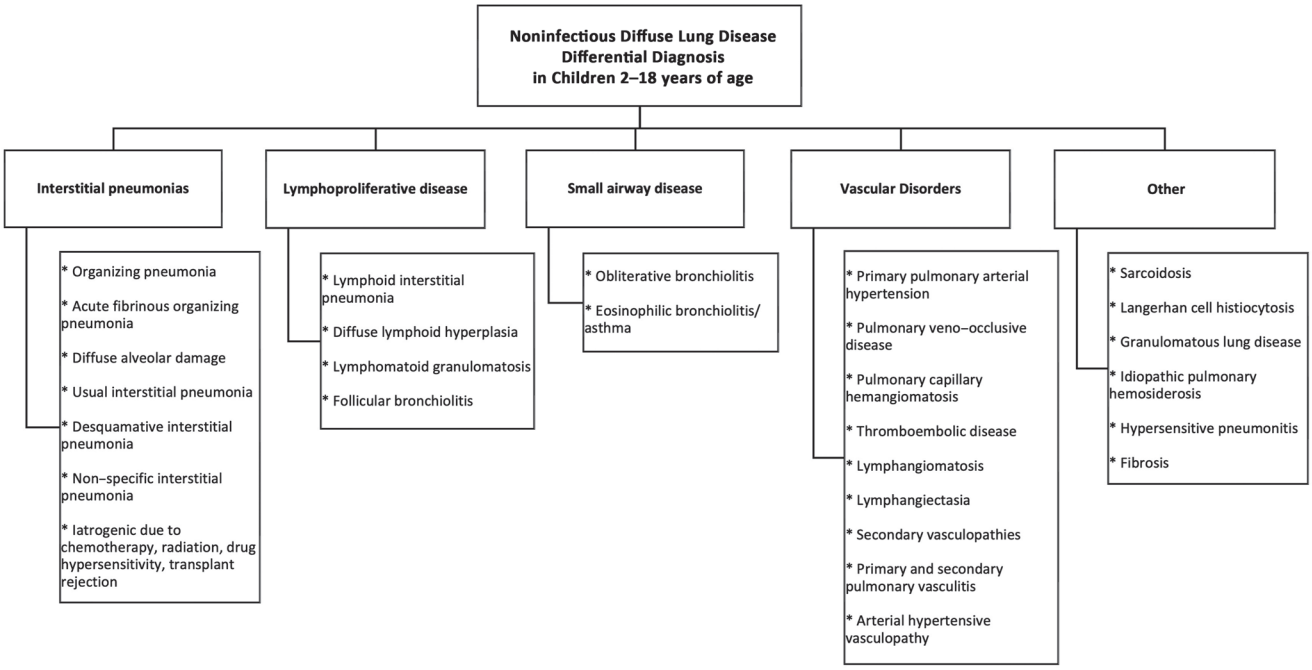

FIGURE 6

Differential diagnosis for noninfectious diffuse lung disease in children 2 to 18 years of age. Figures 5 and 6 exclude more common causes of diffuse lung disease, including chronic aspiration, cystic fibrosis, primary ciliary dyskinesia, and have been adapted from Figure 7 of the following publication: *Rice A, Tran-Dang MA, Bush A, Nicholson AG. Diffuse lung disease in infancy and childhood: expanding the chILD classification. Histopathology. 2013 Dec;63(6):743-55. doi: http//doi:10.1111/his.12185. Epub 2013 Oct 9. PMID: 24117670.*

DRS PEREIRA AND JOGINPALLI, WHAT RHEUMATOLOGIC PROCESSES DO YOU INITIALLY CONSIDER IN A PATIENT WITH PULMONARY GROUND GLASS OPACITIES?

Drs Joginpalli and Pereira, Pediatric Rheumatology

There are many rheumatologic disorders or autoimmune diseases that can affect the lung. Most patients develop a restrictive pattern in the PFTs with radiologic findings of interstitial lung disease. Other lung manifestations, such as diffuse alveolar hemorrhage and pulmonary hypertension are less common. The etiologies to consider include systemic lupus erythematosus, Sjogren's disease, mixed connective tissue disease, systemic scleroderma, sarcoidosis, idiopathic inflammatory myositis (including juvenile dermatomyositis), systemic-onset juvenile idiopathic arthritis, systemic vasculitis, and most recently described, coatomer protein complex subunit α syndrome.

Dr Janysek

The patient's autoimmune evaluation revealed an elevated antinuclear antibody of 1:1280 with a speckled pattern and an elevated histidyl transfer RNA synthetase antibody (anti-Jo1) of >1147.2 (reference range ≤20.0). Double-stranded DNA, Sjogren syndrome A Ro52, Sjogren syndrome A Ro60, Sjogren syndrome B, ribonucleoprotein, and anti-topoisomerase 1 antibody test results were all negative. A myositis extended antibody panel revealed again a positive anti-Jo1 result. Anticyclic citrullinated peptide and rheumatoid factor results were negative. Thyroid peroxidase antibody and thyroglobulin antibody results were negative. Thyroid function was normal. Antineutrophil cytoplasmic antibodies and perinuclear antineutrophil cytoplasmic antibodies screening results were negative. Immunoglobulins G, A, and M were at normal levels. Serum angiotensin-converting enzyme level was mildly low at 11 U/L (normal range 13–100 U/L). Creatinine kinase was <20 U/L. There can be variability in the degree of elevation of serum muscle enzymes in patients with idiopathic inflammatory myopathies, and up to 33% of these patients have normal muscle enzymes.[5] MRI is a nonspecific method of assessing muscle inflammation and may support the diagnosis of myositis, especially in the absence of elevated muscle enzymes.[6] For this reason, MRI was indicated to further evaluate for myositis in the absence of muscle enzyme elevation or musculoskeletal examination abnormalities. The patient's MRI of the bilateral lower extremities without contrast revealed normal and symmetric muscle bulk without fatty infiltration, atrophy, or edema, confirming the absence of myositis.

DRS JOGINPALLI AND PEREIRA, BASED ON OUR PATIENT'S CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP, WHAT DO YOU THINK IS THE MOST LIKELY DIAGNOSIS?

Drs Joginpalli and Pereira

This patient presents with evidence of interstitial lung disease and marked elevation of the Jo-1 antibodies. Her physical examination is remarkable for Gottron's sign, characterized as erythematous to violaceous colored papules and plaques overlying the extensor surfaces of the MCP, DIP, and PIP joints, elbows, and knees. Abnormal nailfolds with erythema and prominent dilated tortuous blood vessels were present, which are a sign of vasculopathy. These findings are commonly seen in idiopathic inflammatory myositis; however, our patient did not have evidence of muscle inflammation by examination, laboratories, or imaging studies. She did not have other classic cutaneous manifestations that can be seen in juvenile dermatomyositis, such as the heliotrope rash, shawl sign, or holster sign. Given her pulmonary manifestations in the setting of a positive anti-Jo1, her diagnosis is consistent with anti-synthetase syndrome. A positive Jo-1 antibody result is highly specific for anti-synthetase syndrome alone.

DRS JOGINPALLI AND PEREIRA, WHAT IS ANTISYNTHETASE SYNDROME AND WHAT IS THE TREATMENT?

Drs Joginpalli and Pereira

Anti-synthetase syndrome is an idiopathic inflammatory myopathy characterized by a triad of interstitial lung disease, myositis, and arthritis.[7–10] This syndrome is more prevalent in the adult population with rare incidence in children. Anti-synthetase antibodies, including Jo-1, have been described in 2% to 5% of juvenile idiopathic inflammatory myopathies.[11] Anti-Jo-1 is the most common anti-synthetase antibody, accounting for 60.3% of anti-synthetase antibodies. Although clinically, anti-synthetase syndrome may share features with dermatomyositis and polymyositis, it has unique serological and pathologic features that indicate it represents its own separate disease entity within the idiopathic inflammatory myopathies.[8]

Most patients do not have the full triad on presentation but progress to develop the complete clinical picture over time. ILD is the hallmark pulmonary manifestation and the major contributor to morbidity and mortality.[12,13] In 15 to 30% of anti-synthetase syndrome patients, ILD is the presenting disease manifestation. Various studies have revealed the prevalence of ILD in anti-synthetase syndrome to range from 69% to 100%. Seventy-eight to 100% of patients will have nonspecific interstitial pneumonia or organizing pneumonia pattern on high-resolution CT scans, and pulmonary function tests reveal restrictive physiology. Approximately one-half of patients present with a gradual onset of progressive dyspnea and cough and one-half with an acute onset. The characteristic cutaneous lesions are "mechanic hands," which are fissured, erythematous, and hyperkeratotic eruptions on the lateral edges of the fingers that resemble the type of occupational dermatosis of a manual laborer. Similar findings on the toes are described as "hiker's feet." More than one-half of patients develop Raynaud's phenomenon.[7–10] Other classic cutaneous findings, such as Gottron's sign, heliotrope rash, and abnormal nailfold capillaroscopy may also be present. Myositis is typically symptomatic with significant weakness and myalgias. Proximal muscle groups are affected, primarily the legs more often than the arms or neck. Articular manifestations include polyarthralgias and symmetric polyarticular arthritis seen in 58% to 70% of patients. Myocarditis and pericardial effusions are much less common.[8] Many patients present with only a single disease manifestation but often go on to develop additional features with time.[12,13]

Our patient was treated with immunosuppressive therapy with a combination of high-dose intravenous methylprednisolone, intravenous immunoglobulin, rituximab, and mycophenolate mofetil with gradual improvement in her respiratory symptoms. Systemic corticosteroids are the mainstay in the management of inflammatory idiopathic myopathies, followed by methotrexate as the most commonly used steroid-sparing agent. However, methotrexate was not used in this case for its potential to cause lung toxicity. Mycophenolate mofetil was added as a preferred option for treating pulmonary involvement. Intravenous immunoglobulin is commonly used in inflammatory myositis with vasculopathy (abnormal nailfold capillaries correlate with severity), and rituximab is used as an adjunctive treatment in severe presentations with lung involvement. Steroid-sparing medications have been proven to stabilize lung function, improve long-term outcomes, and reduce the need for corticosteroids.[8,11]

Dr Janysek

Seven months after her diagnosis, the patient tolerated a corticosteroid wean. She currently participates in regular activities with minimal oxygen supplementation during exertion and uses a wheelchair for long distances. Although minimal, she has shown some improvements in her pulmonary function testing as well.

In summary, anti-synthetase syndrome is an associated idiopathic inflammatory myopathy characterized by the presence of an anti-transfer RNA synthetase antibody, predominantly anti-Jo1. Clinical features of this disease may include acute or gradual onset ILD, myositis, arthritis, Raynaud's phenomenon, or mechanic's hands.

Although this syndrome is rare in children, autoimmune causes such as anti-synthetase syndrome should be considered in pediatric patients who present with interstitial lung disease of unknown etiology.

ABBREVIATIONS

Anti-Jo1: histidyl transfer RNA synthetase antibody
BAL: bronchoalveolar lavage
CT: computed tomography
DIP: distal interphalangeal
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
ILD: interstitial lung disease
MCP: metacarpophalangeal
PFT: pulmonary function testing
PIP: proximal interphalangeal
TB: tuberculosis

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The Role of Primary Care in Bridging Adolescents Awaiting Eating Disorder Treatment

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The striking rise in adolescent eating disorders since the severe acute respiratory coronavirus syndrome 2 pandemic has amplified demands for specialty eating disorders services and contributed to protracted delays in care. In the context of these delays, patients are at risk for increased weight loss, medical instability, escalating disease progression and poor prognosis. Primary care providers (PCPs) are frequently the first point of contact for young patients with eating disorders and are often left to bridge the gap while families struggle to establish specialty care. Yet, beyond case detection and medical comanagement, there are no evidence-based guidelines that can assist PCPs to prepare families for treatment, halt disease progression, and begin the lengthy process of weight and nutritional restoration in efforts to reduce medical complications and support a favorable prognosis. We present the case of a 13-year-old girl with a restrictive eating disorder to illustrate how PCPs can use intervention principles and strategies derived from evidence-based eating disorder treatment to successfully manage adolescent patients until they can access specialty treatment. We offer concrete guidelines for decision-making, as well as suggested behavioral and medical interventions for the PCP. With evidence-based tools, PCPs are well-positioned to support young patients with restrictive eating disorders and their family members as they begin the process of recovery from an eating disorder.

Adolescent eating disorders are life-threatening conditions associated with a protracted course and diminished quality of life and functioning.[1] Timely intervention is critical to improve prognosis.[2] Unfortunately, there is a well-established shortage of mental health providers with eating disorder expertise.[3,4] This scarcity of trained providers has become even more pronounced with the severe acute respiratory syndrome coronavirus 2 pandemic, which has strained the American mental health system and left many patients with eating disorders on waitlists or unable to find care entirely.[5] This has distinct implications for primary care providers (PCPs), who are frequently the first point of contact for patients with eating disorders and are often left to bridge the gap while families struggle to establish specialty care.[6]

This paper describes a case where a PCP implemented behavioral eating disorder interventions alongside medical management. Specifically, the PCP used strategies informed by Family-Based Treatment (FBT), an evidence-based treatment for adolescent eating disorders that empowers caregivers to take charge of weight restoration,[7] and that has a precedent for use in bridging programming (eg, programming that spans the period between referral to and initiation of specialty

abstract

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Dr Partain conceptualized and drafted the initial manuscript and drafted clinical tools included as Figures 2 and 3; Drs Lebow and Sim conceptualized and drafted the initial manuscript and provided input into behavioral management recommendations; Ms Fladager Muth provided background on the case example; Drs Billings, Mattke, and Jacobson provided input into clinical recommendations; Dr Le Grange provided guidance on incorporating Family-Based Treatment principles into behavioral recommendations; and all authors critically reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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services).[8] Consent and assent was obtained from the patient and her parents for this case report.

CASE: "ARIANA"

Ariana, a 13-year-old cisgender female, was generally healthy aside from a history of peanut allergy. She presented to her PCP with concerns about weight loss, worsening anxiety, and increased rigidity around food preferences. At this visit, she had lost 6 kg from her peak weight from her 11-year-old well child visit, dropping from the 91st to the 55th percentile, with a concurrent decline in BMI percentile from the 84th to the 44th percentile (Fig 1). A complete blood count revealed mild anemia (hemoglobin = 10.5 g/dL) and leukopenia (total white blood cell count = 3.0 x 10^9/L), and a complete metabolic profile demonstrated a mild elevation in creatinine (0.9 mg/dL, ref range 0.35–0.86 mg/dL). Other testing was negative, including inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), celiac serology, thyroid stimulating hormone, transaminases, and blood glucose. Her electrocardiogram showed mild bradycardia (heart rate 53) but was otherwise normal. Hospitalization was considered but not pursued because the patient did not present with severe bradycardia (heart rate <50 awake or <45 sleeping), or laboratory abnormalities that met criteria for admission.

After her initial workup, Arianna was referred for specialty eating disorder treatment. Her parents contacted two treatment centers, each of which offered a continuum of eating disorder services. Both centers placed Ariana on a waitlist and told parents that the first available appointment would be in 3 to 4 months. Parents contacted Ariana's PCP to inquire about what they should do in the meantime to help their daughter. To provide a bridge until she was able to begin specialty treatment, Ariana's PCP arranged weekly follow-up visits.

Ariana's PCP was a pediatric nurse practitioner who had been working with children and adolescents for 16 years. She had no prior eating disorder training, other than a 1 hour-long continuing education lecture she had attended 3 years previously. Several of her primary care colleagues provided outpatient care for eating disorders, using an FBT-informed approach,[9] so she was able to receive point-of-care consultation and recommendations from these individuals as needed.

Week 1: Weight 48.6 kg (± 0.5 kg)

The PCP spent this first visit emphasizing the seriousness of Ariana's weight loss. The PCP framed Ariana's laboratory abnormalities and bradycardia as physical consequences of malnutrition that would resolve with weight gain. The PCP discussed that because of the impact of starvation on her cognitive processes, Ariana was less able to make good choices about her health and required her parents to take charge by selecting and monitoring all meals and snacks. To improve Ariana's iron deficiency anemia, the PCP prescribed an iron supplement.

Week 2: Weight 49.3 kg (± 0.7 kg)

Ariana's parents reported that they were able to gently encourage her to eat more but that she continued to be very rigid about food choices. Ariana reported feeling full all the time. The PCP praised the progress made with meals and commended the parents for prioritizing food as medicine. The PCP highlighted that Ariana's rigidity about specific foods represents eating disordered thinking rather than oppositional behavior and that early satiety was expected given her degree of malnutrition.

Week 3: Weight 49.0 kg (−0.3 kg)

Because of parents' work schedules, Ariana had several unmonitored meals. The family asked if Ariana could participate in soccer. The PCP empathized with how difficult it can be to implement meal monitoring and engaged in joint problem-solving to ensure Ariana was getting consistently monitored meals and snacks. The PCP discussed that return to sports would require increased calories given the associated increase in metabolic demands. Parents made the collaborative decision to delay sports for Ariana until she consistently showed weight gain.

Week 4: Weight 48.5 kg (−0.5 kg)

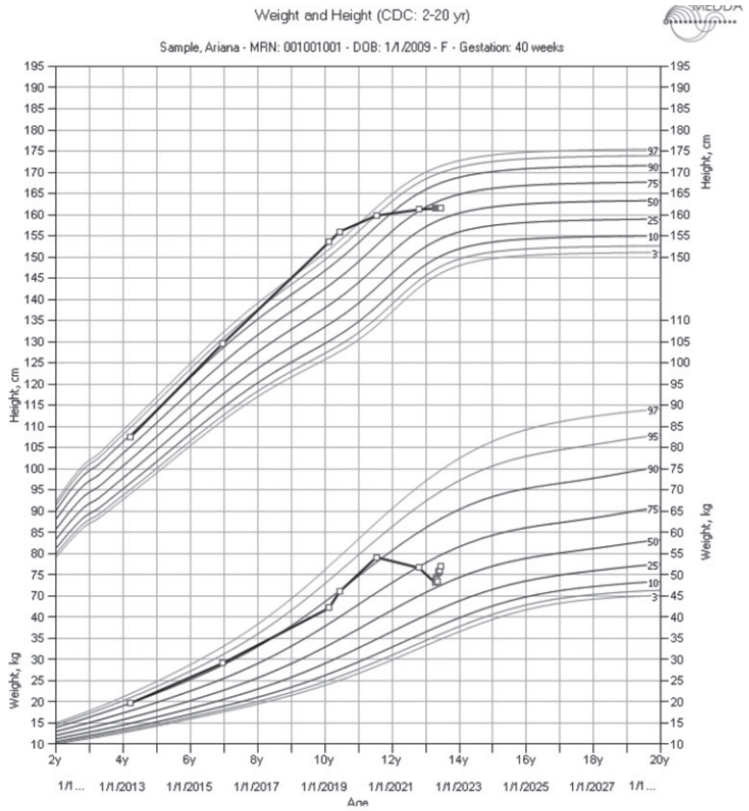
Despite eating regular meals and snacks with improved monitoring, Ariana's weight decreased. The PCP explained the high metabolic demands of an underweight patient. The PCP discussed the importance of prioritizing foods that increase calorie density without enlarging volume and helped the parents brainstorm concrete strategies to supplement meals and snacks.

Week 5: Weight 50.4 kg (± 1.9 kg)

Ariana and her parents all felt the prior week went well. They reported that Ariana was still uneasy about certain foods but was able to eat everything chosen for her regardless. The PCP recognized this excellent progress and encouraged continued diligence with meals. The PCP rechecked the complete blood count and comprehensive metabolic panel to follow up on prior leukopenia and creatinine elevation. Both had resolved.

Week 6: Weight 50.7 kg (± 0.3 kg)

The family reported that they had found a regular rhythm with meals and snacks. Given ongoing progress, the PCP and parents determined that sports clearance was reasonable. However, they collaboratively established clear expectations for Ariana's ongoing sports



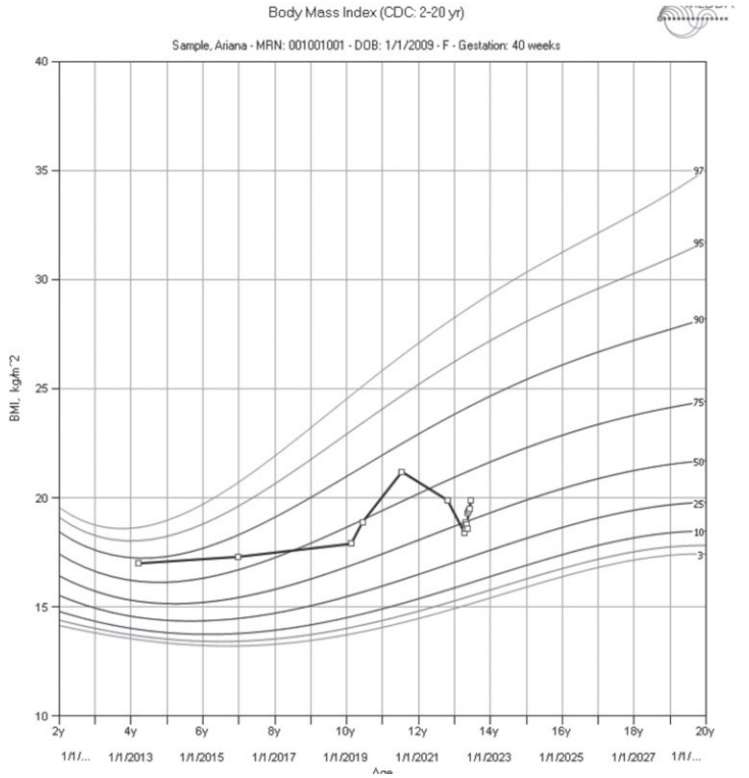


FIGURE 1
(A) Weight, height, and (B) BMI chart for Ariana.

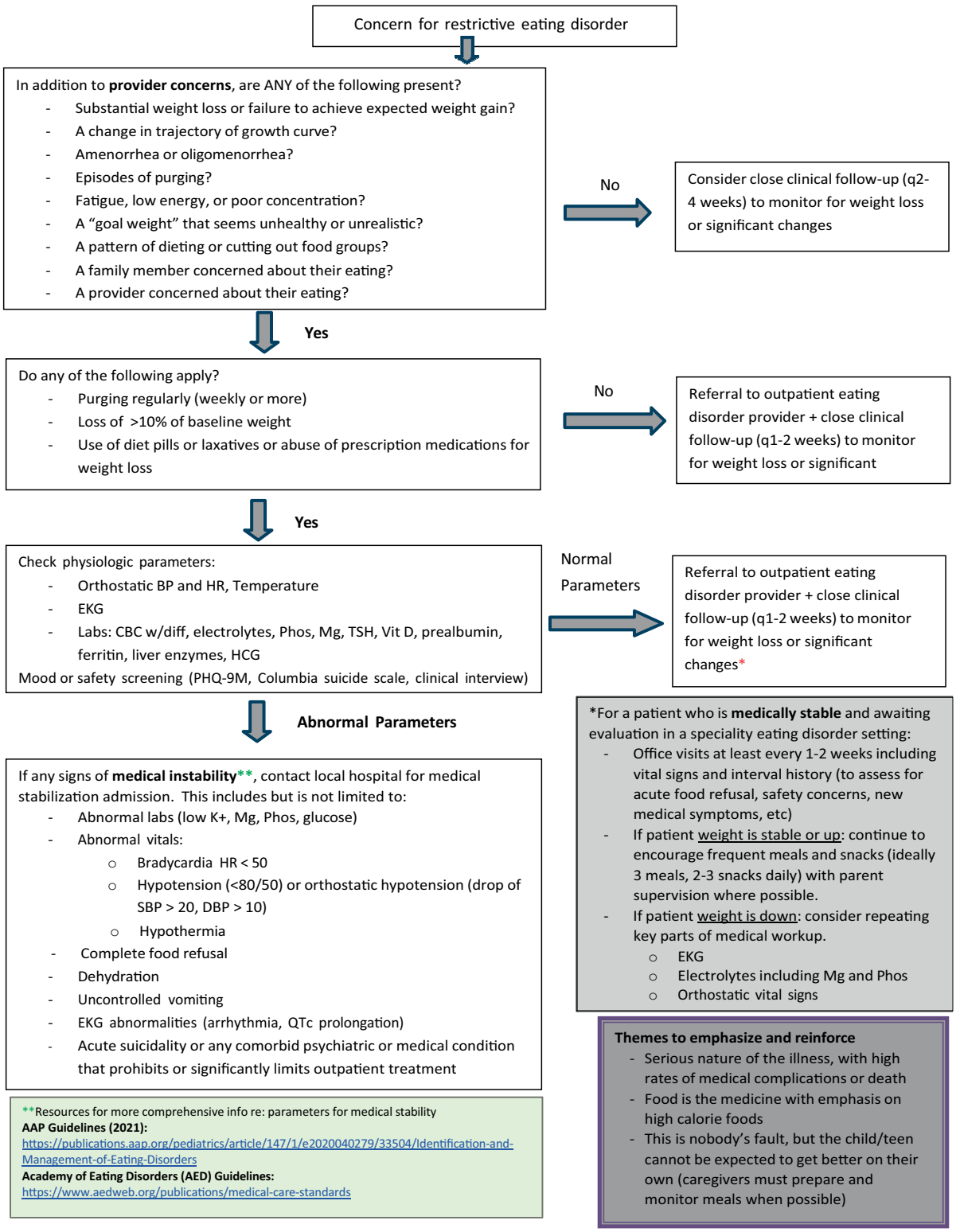


FIGURE 2
Recommendations for medical evaluation and follow-up in patients with suspected eating disorder awaiting specialty care. CBC, complete blood count; EKG, electrocardiogram; HCG, human chorionic gonadotropin; HR, heart rate; Phos, phosphorous; PHQ-9M, The Patient Health Questionnaire-9 Modified; mg, milligram; TSH, thyroid stimulating hormone.

participation contingent on continued progress with eating and weight restoration.

Week 7: Weight 50.9 kg (± 0.2 kg)

Even though her eating continued to improve, parents noticed that Ariana experienced significant distress about not being in control of her meals. The PCP emphasized that despite Ariana's improvements so far, the eating disorder still appeared to be present during many meals and that parents still needed to be in charge of all meals and snacks.

Week 8: Weight 52.0 kg (± 1.1 kg)

Ariana and her parents received a last-minute cancellation spot for an intake for an eating disorder clinic. Because of the strong partnership and follow-up she had with her PCP, Ariana entered this visit with a weight almost 4 kg higher than at initial presentation and thus, had progressed toward weight restoration to her prior growth trajectory, one of the main goals of her eating disorder treatment. She no longer exhibited signs of acute medical instability.

DISCUSSION

In the context of the current eating disorder crisis, cases like Ariana's are increasingly common. Given the dearth of eating disorder treatment options, PCPs often must independently manage the care of young patients with restrictive eating disorders for lengthy periods of time. Though guidelines are available to support PCPs in the identification of eating disorders and the management of their physical health complications, these resources do not provide recommendations for PCPs managing eating disorders independently, without the support of an eating disorder specialty team.[7,10,11] Without guidance on how to improve patients' eating and weight while they await specialty care, patients can become medically unstable and more difficult to treat. As Ariana's case illustrates, PCPs have potential to help caregivers begin the process of weight restoration for their

Behavioral Interventions	
Follow up frequently	Weekly or bi-weekly visits in primary care until established in specialty care
Communicate the diagnosis	When possible, use specific diagnoses: --"Eating disorder" instead of "disordered eating" --"Anorexia nervosa" instead of "unexplained weight loss"
Provide education	--Emphasize the impact of malnutrition (physical, cognitive, social-emotional) --Draw a parallel between eating disorders and medical conditions like cancer: cite the high mortality rate, significant morbidity, crucial need for care, no one's "fault"
Prioritize weight gain	--Weight restoration is essential for physical and psychological recovery --Food is the medicine --Encourage caregivers to decide what/how much the patient eats (taking into consideration high caloric needs) --Maximize calorie dense foods --Reduce opportunities for energy expenditure (limit physical activities or pause sports clearance until weight loss stops and trend of weight gain is established)
Reduce guilt and blame	--Caregivers do not cause eating disorders --Eating disorders are not willful gestures on the part of the patient --Separate the patient from the illness *(ex: "It sounds like the eating disorder was making meals hard this week.")*
Medical Management	
Monitor vital sign stability	Every visit to include: --Weight (gowned or light clothes, no shoes) --Height --Temperature --BP, HR (consider orthostatics in initial visits)
Monitor labs and electrocardiograms (EKGs)	--Follow up any abnormal labs from initial workup (especially looking for hyponatremia, hypokalemia, hypomagnesemia, hypophosphatemia, metabolic acidosis or alkalosis, and hypoglycemia) --Serial EKGs for any initially diagnosed bradycardia or conduction abnormalities --With normal findings and weight maintenance or improvement, ongoing labs or EKGs could be paused
Refer for stabilization (as needed)	--Medical instability --Acute suicidality or safety concerns (*note: although patients with eating disorders frequently report depressive or anxious symptoms, typical interventions like medication and psychotherapy are not likely to be successful until weight restored. We recommend waiting to initiate these interventions if possible to avoid dilution of treatment effects and emphasize the importance of weight restoration as a necessary precondition for psychiatric recovery*)
Replete where necessary	Multivitamin Vitamin D Iron Calcium

FIGURE 3
Clinical pearls to assist PCPs in bridging patients until specialty care for eating disorder becomes available. HR, heart rate; EKG, electrocardiogram.

child, prepare the family for eating disorder treatment, mitigate disease progression, and move the patient toward recovery.

Ariana's case illustrates recommendations for PCPs who must provide bridging care for young patients with eating disorders who are waiting to access eating disorder treatment (Fig 2). First, we recommend that PCPs schedule regular follow-up visits at a frequency of weekly or every other week. This level of oversight allows providers to track symptom progression, maintain an emphasis on the severity of the illness, and bolster caregivers' efforts to address weight suppression. Though this schedule of follow-up is initially more time-intensive than the average primary care treatment plan, it has potential to prevent acute medical and psychiatric instability that leads to extensive medical workups, emergency hospitalization or crisis interventions, which ultimately are a greater burden on the healthcare system.

Second, PCPs must provide ongoing medical management. This includes monitoring vital sign, laboratory, and electrocardiogram stability, managing supplementation where necessary (eg, iron, vitamin D, calcium), as well as assessing for changes to medical or psychiatric acuity, and triaging referrals for stabilization through medical or psychiatric hospitalization as needed (Fig 3).[12]

Third, we recommend that PCPs take advantage of the opportunity during follow-up appointments to deliver behavioral interventions to halt weight loss and begin the process of weight restoration. As in the case of Ariana, PCPs can implement behavioral strategies similar to those delivered via FBT, an evidence-based intervention for adolescent eating disorders that empowers caregivers to take charge of eating and weight restoration.[7] There is precedent for using FBT principles in bridging programming[8] and for the delivery of these principles by a pediatric generalist practitioner.[9,13] We suggest PCPs deliver these strategies in conjoint visits with at least one caregiver present, as efforts to address low weight with patients individually are generally unsuccessful because of the impact of malnutrition on decision-making around eating and weight.[14,15] These strategies include directly conveying to families that their child has an eating disorder diagnosis and providing education on the impact restrictive eating has on cognitive and physical functioning. As part of this education, PCPs should focus on reducing caregiver and patient guilt and blame by sharing the well-established fact that caregivers do not cause eating disorders.[16] It is also imperative to convey that eating disorders are not willful or intentional behavior on the part of the patient, rather they are biologically-based conditions that are driven by starvation-related changes to the brain.[17] Most importantly, the PCP must emphasize the seriousness of eating disorders and empower caregivers to take charge of selecting and monitoring meals, emphasizing that food is medicine and that weight gain and return to the patient's prior growth trajectory are the primary targets of the intervention.[18,19]

The specific interventions described in this case, and further detailed in Figs 2 and 3, provide a framework for PCPs to use when bridging young patients with eating disorders. Using these principles and strategies, Ariana's PCP was able to have a meaningful impact on Ariana's weight and symptoms. Despite her lack of expertise in eating disorders, the PCP had access to colleagues who had such knowledge, allowing for peer consultation and support. We recognize that this is not available in most primary care practices and thus highlights the need for more primary care-specific resources to support and bolster the skills of PCPs providing bridging care for young patients with eating disorders awaiting specialty treatment. Training and guides for eating disorder identification and medical management are available. However, these educational resources are often not designed for PCPs, who have limited time and resources.[20] Consequently, brief, accessible, tailored resources are needed to support PCPs in providing eating disorder management over longer periods of time in their context.

In the case of Ariana, in addition to ensuring she remained medically stable while she waited for admission to specialty practice, her PCP was able to use their visits to lay the groundwork for future treatment, mobilize parents to begin to reverse Ariana's weight loss, and reduce the family's guilt and blame, all of which serve to increase caregiver self-efficacy, a proposed mechanism of change for improving young patients' eating disorder symptoms. Though a PCP-led bridging intervention is not always possible, this case offers a model for PCPs to initiate symptom management in what may be a prolonged although finite time before a patient can access specialty care for eating disorders.

ABBREVIATIONS

FBT: Family-Based Treatment
PCP: primary care provider

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Urine Toxicology Test for Children With Altered Mental Status

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abstract

The rate of unintentional ingestion of edible cannabis products in young children is rising rapidly as laws decriminalizing both recreational and medical marijuana in the United States become more widespread.[1] Cannabis poisoning in children can lead to a myriad of symptoms, most notably neurologic changes. The abrupt onset and severity of signs and symptoms after ingestion can cause diagnostic uncertainty for practitioners in the emergency department. Here, we present a case series of 5 children, 6 years of age and younger, who initially presented with altered mental status and were ultimately diagnosed with acute δ-9-tetrahydrocannabinol toxicity after cannabis ingestion confirmed by urine toxicology testing. Although urine toxicology testing is not routinely used as a diagnostic tool in pediatrics, the increasing accessibility of edible cannabis products suggests that more widespread urine toxicology testing in children with undifferentiated altered mental status is warranted.

The growing legalization of recreational cannabis and the increasing accessibility of edible cannabis have been accompanied by a rapid increase in the number of unintentional ingestions in young children.[1,2] The inappropriate storage of edible cannabis places young children at risk for unintentional or exploratory ingestions.[3] Edible cannabis products are manufactured by infusing food items with cannabis extract containing cannabinoids, including δ-9-tetrahydrocannabinol (THC), the primary psychoactive cannabinoid from marijuana. Other cannabinoids, cannabidiol, and δ-8-tetrahydrocannabinol, and synthetic cannabis products, have also recently gained popularity and become more available to consumers. These products are sold in a variety of forms, and some are packaged so that they are nearly indistinguishable from common household snacks.

Because of the lack of standardized dosing and serving sizes of edible cannabis products, the ingestion of a package in its entirety can cause life-threatening toxicity due to THC.[1] Signs of THC toxicity in children include altered mental status (AMS), ataxia, tachycardia, mydriasis, seizures, hypotonia, and respiratory depression.[1] Despite other popular cannabinoids and synthetic cannabinoid products, THC is the only cannabinoid present on a standard urine toxicology test. This case series focuses on pediatric edible cannabis exposures containing THC, although depending on the clinical scenario, health care professionals should also consider other cannabinoids and synthetic cannabinoid substances.

Obtaining urine toxicology testing early in the evaluation of a pediatric patient with undifferentiated altered mental status has been suggested in recent literature in an effort to expedite diagnosis and minimize invasive and costly interventions.[4–8] Traditionally, urine toxicology testing has been recommended in only select cases because its use has generally not been shown to alter management.[9–13] Because of this, clinicians may not routinely order urine toxicology in cases of undifferentiated

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AMS in young children despite the widespread availability of a reliable qualitative urine test for identifying THC. As a result, THC toxicity may be missed or the diagnosis may be delayed, leading to extensive evaluations, unnecessary interventions, and/or prolonged hospitalizations.

CASE REPORT

The objective of this case series is to describe the clinical course of young children with edible cannabis ingestion containing THC and the utility of the urine toxicology screen as a diagnostic test. We present 5 cases of children 6 years of age and younger who presented to a pediatric emergency department (ED) for neurologic changes and were ultimately found to have THC toxicity confirmed by positive urine toxicology (Table 1). The data presented were compiled by the New York City Poison Control Center and the associated Toxicology fellowship programs at New York University Grossman School of Medicine and North Shore University Hospital & Long Island Jewish Medical Center between the years 2021 and 2022. It should be noted that recreational cannabis has been legal in the state of New York since 2021. Consent for publication was obtained from the caregivers of all 5 children.

CASE 1

A 6-year-old healthy transgender male presented to a community ED with unresponsiveness. The patient's mother reported that he felt dizzy and vomited once after his 3-year-old sibling struck him in the head with an empty metal water bottle. The injury had not been witnessed by the parent. His initial vital signs were notable for tachycardia. On physical examination, he was pale and limp. There were no external signs of trauma. He was intubated for airway protection. A computed tomography (CT) scan of the head, cervical spine, and chest did not reveal any acute injury. Initial serum laboratory studies were reassuring. The patient was transferred to a pediatric trauma center, in which further laboratory studies were obtained, including a urine toxicology test. Two hours after the patient's arrival at the trauma center, the urine toxicology test was reported to be positive for THC. Toxicology and Social Work were consulted, and he was admitted to the PICU for further management. The patient was extubated ~24 hours after initial presentation. On further investigation, the patient reported eating a "gummy candy" at a neighbor's house.

CASE 2

A 3-year-old healthy female presented to a community ED with lethargy. The patient was at her aunt's home before arrival and had depressed mental status after waking from a nap. On physical examination, she had normal vital signs. She responded to verbal stimuli but was noted to have decreased tone and was unable to sit without support. A CT scan of the head did not reveal any acute changes and serum laboratory studies were within normal range. The patient was transferred to a tertiary pediatric hospital. Urine toxicology was sent after admission to the pediatric hospital and resulted positive for THC. Toxicology, Neurology, Child Protective Services, and Social Work were consulted. On further investigation, the patient's aunt reported having THC-containing gummies in the home. The patient returned to her baseline mental status 36 hours after presentation and was discharged from the hospital after 3 days.

CASE 3

A 2-year-old healthy female presented to a community ED for unresponsiveness. Her parents reported that shortly after waking in the morning, she "giggled" and then became unresponsive. On physical examination, she had normal vital signs. She did not open her eyes spontaneously and was noted to have a clenched left hand and plantar flexion of the left foot. A CT scan of the head revealed no acute injuries. A urine toxicology test was obtained ~1 hour after arrival at the ED and was positive for THC. Toxicology, Child Protective Services, and Social Work were consulted. On further investigation, the parents reported having edible cannabis in the house. Approximately 7 hours after initial presentation, the patient returned to her baseline mental status and was discharged from the hospital from the ED.

CASE 4

A 2-year-old healthy female was brought to a community ED for somnolence after visiting her grandparents. On arrival, her vital signs were normal. On physical examination, she was drowsy but rousable. Additional history revealed she had slurred speech and an episode of nonbloody, non-bilious emesis before arrival. Serum laboratory studies were normal, and a CT scan of the head without contrast was reassuring. She was transferred to a Pediatric ED for further evaluation and management. Once the patient arrived at the Pediatric ED, urine toxicology testing was obtained and reported to be positive for THC. Further discussion with the family revealed that edible cannabis gummies belonging to a family member were missing. Toxicology and Social Work were then consulted. She had an episode of oxygen desaturation to the 80s while asleep but required no respiratory intervention. She was observed in the ED for 12 hours and discharged from the hospital to her parent's care.

CASE 5

A healthy 4-year-old male was brought to a community ED by his mother after she noticed that he had become less responsive. On arrival at the ED, he was sleeping but

TABLE 1 Summary and Features of Patient Presentations

Case	Patient Demographics (Age/Sex)	Cannabis Product Ingested, Source	Chief Complaint	ED Vital Signs	Physical Examination Findings	Urine Toxicology Test (Qualitative)	Diagnostic Tests	Imaging	Interventions	Disposition	Hospital Length of Stay
1	6-y-old male	Gummy candy, Outside of home	Altered Mental Status, Tachycardia	BP 96/53, HR: 135, RR: 20, Temp: 36.4°C, O2 Sat: 100%, Tachycardic	Limp, pale appearing, unresponsive	THC Detected	POC glucose, VBG, CBC, CMP, EKG	CT head and cervical spine CT chest XR chest	Transferred to Pediatric Trauma Center Consulted Toxicology, Social Work	Admitted to PICU	48 h
2	3-y-old female	Gummy candy, family member's home	Altered Mental Status, Hypotonia	BP 92/58, HR: 109, RR: 20, Temp: 36.6°C, O2 Sat: 100%, Normal	Arouse to verbal stimuli	THC Detected	CBC, CMP, EKG	CT head	Consulted Toxicology, Neurology, Child Protective Services, Social Work	Admitted to the pediatric floor	72 h
3	2-y-old female	THC-infused candy, patient's home	Altered Mental Status	BP: 105/54, HR: 122, RR: 26, Temp: 37.1°C, O2 Sat: 100%, Normal	Minimally responsive to verbal stimuli. Patient had a clenched left hand and plantar flexed left foot	THC Detected	CBC, CMP, EKG	CT head	Consulted Toxicology, Child Protective Service, Social Work	Observed in ED	7 h
4	2-y-old female	THC-infused candy, family member's home	Altered Mental Status	BP: 96/46, HR: 104, RR: 20, Temp: 36.9°C, O2 Sat: 99%, Normal	Sleepy, rousable to stimuli	THC Detected	CBC, CMP	CT head	Transferred to Pediatric Emergency Department Consulted Toxicology, Social Work	Observed in ED	12 h
5	4-y-old male	THC-infused candy, patient's home	Altered Mental Status	BP: 106/48, HR: 76, RR: 18, Temp: 36.9°C, O2 Sat: 98%, Normal	Sleeping, rousable to tactile stimuli	THC Detected	CBC, CMP, Acetaminophen, Salicylate, Ethanol, TSH		Transferred to Pediatric Emergency Department Consulted Toxicology Child Protective Services, Social Work	Admitted to PICU	12 h

BP, blood pressure; HR, heart rate; RR, respiratory rate; O2 Sat, oxygen saturation; CBC, complete blood count; CMP, complete metabolic panel; VBG, venous blood gas; POC glucose, point-of-care glucose; IV, intravenous; THC, δ-9-tetrahydrocannabinol; US, ultrasound.

responsive to tactile stimuli. Urine toxicology obtained on arrival resulted positive for THC. On further questioning, the patient's mother reported having THC edibles in the home. The patient was then transferred to a tertiary children's hospital for admission to the PICU. While in the PICU, Toxicology, Social Work, and Child Protective Services were consulted. He was observed for 12 hours and was discharged from the hospital in the care of his mother.

DISCUSSION

Cannabis use is on the rise worldwide, and unintentional pediatric cannabis exposures are increasing rapidly.[2,14–16] A study of children presenting to a Pediatric ED for unintentional edible cannabis ingestion revealed that there was a >1000% increase in cases between 2017 and 2021. In addition, 97.7% of ingestions occurred in a residential setting.[17] Other data reveal that, since 2016, the number of pediatric edible cannabis exposures reported to America's Poison Centers has increased by 23-fold.[18] Because young children with acute THC toxicity can have many different signs and symptoms, the diagnosis may not be immediately obvious. In fact, a recent study revealed that the time to diagnose marijuana ingestion was 5 times longer in children than in adolescents. The delay in diagnosis can lead to a 3-fold increase in potentially avoidable diagnostic tests and a 4-fold increase in medical costs per patient.[7] To address these concerns, urine toxicology testing in children presenting with AMS has been recommended.[4–8]

We presented 5 cases of undifferentiated AMS caused by THC toxicity that were ultimately diagnosed with the aid of urine toxicology testing. In each of these cases, there was no initial history to suggest cannabis ingestion, although further questioning revealed sources of potential exposure.

At our institutions, a urine toxicology test assesses for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinoids. The urine toxicology tests provide semiquantitative results in which any THC concentration >50 ng/mL is reported as "detected," and any level below that is resulted as "not detected." Initial testing is done by urine immunoassay with confirmation of positive results by gas chromatography/mass spectrometry, the gold standard. The immunoassay has a sensitivity of 92.5% and specificity of 92.4% after the acute ingestion of edible cannabis.[19] Quantitative serum testing for THC is available if there is question in the patient's history and, therefore, the accuracy of the urine toxicology test result. However, the results of serum testing often return hours to days after the patient's initial presentation and, because of the delay, do not typically alter acute clinical management.

Unlike adolescents and adults who intentionally smoke cannabis and possibly have a positive urine toxicology test for THC in the absence of acute intoxication, a positive urine toxicology test for THC in a child should prompt concern because secondhand smoke has been rarely shown to produce positive urine drug tests.[20,21] An additional consideration for providers regarding edible cannabis ingestion is that, although THC can be detected by the standard urine toxicology assay, other pharmacologically active cannabinoids (eg, cannabidiol) do not typically cause a positive THC result and can be associated with significant toxicity.[22] As always, providers must carefully consider the patient's presentation and history when interpreting a urine toxicology test. For all the above cases, further discussion with the families revealed that the child had access to edible cannabis products and given the presenting signs and positive THC, unrecognized ingestion of cannabis best explained their clinical presentations.

Time to urine toxicology testing results was variable in our patients, ranging from immediately on presentation in the ED to 24 hours after hospitalization. Notably, in case 5, the positive result for THC on the urine toxicology test obtained immediately after presentation to the ED in conjunction with targeted family discussion obviated the need for further invasive diagnostic procedures or imaging. In contrast to the other cases, case 5 illustrates that prompt urine toxicology testing in patients with undifferentiated AMS may decrease the need for unnecessary diagnostic evaluation.

Pediatric providers are in the midst of a public health crisis because, with greater access to edible cannabis, young children are increasingly at risk for exploratory ingestions. The American College of Medical Toxicology and the American Academy of Pediatrics have both released position statements addressing pediatric cannabis exposures that emphasize the need for regulated packaging and labeling, education on safe storage, and prevention strategies.[23,24] Education on safe storage practices, signs of toxicity, and resources is needed for both caregivers and practitioners. In addition, it is crucial to involve the regional Poison Control Center (or local Toxicologist) and Social Work in the management of these patients. Injury prevention research and advocacy to change legislation regarding THC potency, packaging, and available forms must be prioritized so that we may best address this public health crisis.[25]

CONCLUSION

The unintentional ingestion of edible cannabis containing THC in children is a serious and growing public health concern. Given the national trend to legalize cannabis, there is potential for an even steeper rise in the number of unintentional pediatric ingestions. Providers must have a high index of suspicion for edible THC toxicity in young patients who present with undifferentiated abnormal neurologic findings or AMS, even when caregivers do not initially report a

potential cannabis exposure. A urine toxicology test is critical for this diagnosis and may both change management and minimize further unnecessary testing in these patients.

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ABBREVIATIONS

AMS: altered mental status
CT: computed tomography
ED: emergency department
THC: δ-9-tetrahydrocannabinol

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Diagnostic Approach to Recurrent Intracardiac Masses That Present With Systemic Symptoms

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Cardiac masses are difficult to diagnose in the pediatric population, especially in the setting of systemic symptoms. Although multiple imaging modalities are available to characterize cardiac masses, it is important to consider a different diagnostic approach in the setting of recurrent cardiac masses and nonspecific systemic symptoms. We present a case involving a previously healthy adolescent with multiple hospitalizations because of persistent fevers, cachexia, and recurrent cardiac masses. Echocardiography and cardiac computed tomography imaging suggested endocarditis, but the patient failed to respond to multiple intravenous antibiotic treatments. He developed recurrent cardiac masses in the right atrium and right ventricle that were debulked and biopsied. The biopsy did not yield a conclusive diagnosis. The patient returned to the hospital with hemoptysis and large pulmonary pseudoaneurysms that had to be occluded during cardiac catheterization. Given his constellation of symptoms and improvement with steroids during surgical procedures, he was ultimately diagnosed with a variant of Behcet's disease known as Hughes-Stovin syndrome. His symptoms resolved completely with steroids and immunosuppression therapy. Our report reveals the limitations of the standard diagnostic approach toward cardiac masses and the importance of considering response to treatment as a clue to the etiology of an unusual cardiac mass.

Cardiac masses are rare within the pediatric population, with an incidence of 0.17%.[1] Although the majority of cases are benign, the recurrence of cardiac masses in the setting of systemic symptoms such as recurrent fevers requires a different diagnostic approach. It may be difficult to differentiate inflammatory and infectious causes of cardiac masses on the basis of the current available imaging modalities, which include echocardiography, computed tomography (CT), and MRI. In this report, we present the management of a previously healthy 16-year-old male patient who presented with recurrent intracardiac masses in the setting of fevers and cachexia.

CASE

A 16-year-old previously healthy male presented to the emergency department with persistent fevers, chills, and an unintended 15-lb weight loss over a period of 3 weeks. Other than fever (38.5°C) and sinus tachycardia, his initial physical exam was unremarkable. His inflammatory markers showed an elevated C-reactive protein of 18.7 mg/L (normal range 0–10 mg/L), an erythrocyte sedimentation rate of 53 mm per hour (normal range 0–15 mm per hour), and an elevated white count of 16.6×10^9 cells per liter (normal range $3.4–10.8 \times 10^9$ cells per liter) with neutrophil predominance. He was admitted for further management of a suspected infectious process and started on vancomycin and ceftriaxone to provide board

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Dr Slesnick conceptualized the study, supervised the study, and critically reviewed the manuscript; Dr Shaw collected the data, supervised data collection, and critically reviewed and revised the manuscript; Dr Hashemi collected the data and critically reviewed and revised the manuscript; Dr Ro conceptualized the study, collected and reviewed the data, wrote the initial draft, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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spectrum coverage. Although hospitalized, he developed new onset of left-sided pleuritic pain and had a chest CT to rule out pulmonary emboli. There was evidence of multiple pulmonary emboli in both lungs. An incidental right ventricular cardiac mass and bilateral lung nodules were also found. An echocardiogram revealed that he had developed cystic masses in the right ventricle (RV) (Fig 1A). To further characterize the ventricular masses, a cardiac MRI was performed, which showed multiple pedunculated masses attached to the basal inferior RV wall. These demonstrated high signal intensity on T2-weighted images and did not perfuse after contrast administration, findings that are consistent with an infectious process with abscesses or with newly formed wet thrombi (Fig 2). The decision was made at that time to surgically debulk the RV mass and obtain a tissue biopsy, but the pathologic analysis was inconclusive because of insufficient sampling. Full resection of the mass was unable to be completed because of its proximity to the tricuspid valve. Yet, the patient's symptoms, including his fever, resolved after the surgical procedure. On the basis of the modified Duke criteria, the patient fulfilled the criteria for possible infectious endocarditis on the basis of his cardiac vegetations and a blood culture which yielded cutibacterium acnes.[2] He was discharged from the hospital on intravenous vancomycin and ceftriaxone for suspected bacterial endocarditis.

The patient returned to the emergency department 6 weeks later because of fevers that returned the day before admission despite being on intravenous antibiotics. A repeat echocardiogram revealed a new mobile mass in the right atrium and multiple masses in the RV (Fig 1B). In addition, ultrasound examination identified multiple thrombi in his left iliac vein, right subclavian, and right axillary veins. Given this apparent prothrombotic state, he was started on anticoagulation and specialist teams were consulted. His rheumatologic and hematologic workup was unrevealing. A repeat cardiac MRI was performed, which showed cardiac mass tissue characteristics similar to the previous study, and the RV masses were noted to have irregular borders that were infiltrated into the RV myocardium. We broadened the differential diagnosis to include a possible atypical sarcoma, intramyocardial teratoma, myxoma, or an inflammatory/infectious process. The decision was made to return to the operating room for further debulking of the cardiac mass in the right atrium and RV. A repeat tissue biopsy revealed inflammatory infiltration, with fibropurulent exudate noted on pathologic examination. After this procedure, the patient's fevers improved and concentrations of inflammatory markers fell. The patient was discharged on intravenous penicillin and levofloxacin, as well as anticoagulation with apixaban.

The patient returned a third time after 2 weeks because of persistent fevers, poor appetite, and new onset of hemoptysis while on antibiotic and anticoagulation therapy. A repeat echocardiogram revealed recurrence of a right ventricular mass. For hemoptysis workup, a chest CT with contrast was performed and revealed 2 large distal right pulmonary artery mycotic pseudoaneurysms distal to the site of pulmonary emboli seen on the previous chest CT (Fig 3). The patient first required device closure of the pseudoaneurysms via catheterization, and subsequently a right lower lobe lobectomy. Given the continued fevers despite multiple antibiotic treatments, we revisited the possibility of a rheumatologic process. Over the course of his multiple hospitalizations, it was noted that his fever curve improved after each surgical intervention. After further investigation, we associated the decrease in his fevers and fatigue after each surgery

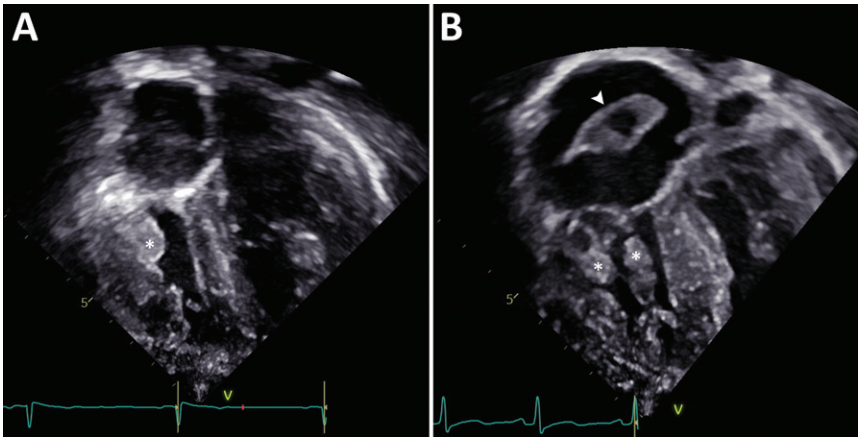

FIGURE 1
A, Initial echocardiogram revealing cystic masses in the right ventricle (*); B, follow-up echocardiogram 6 weeks later revealing a highly mobile, pedunculated mass attached to the right atrial appendage wall and multiple large masses along the RV free wall (arrow).

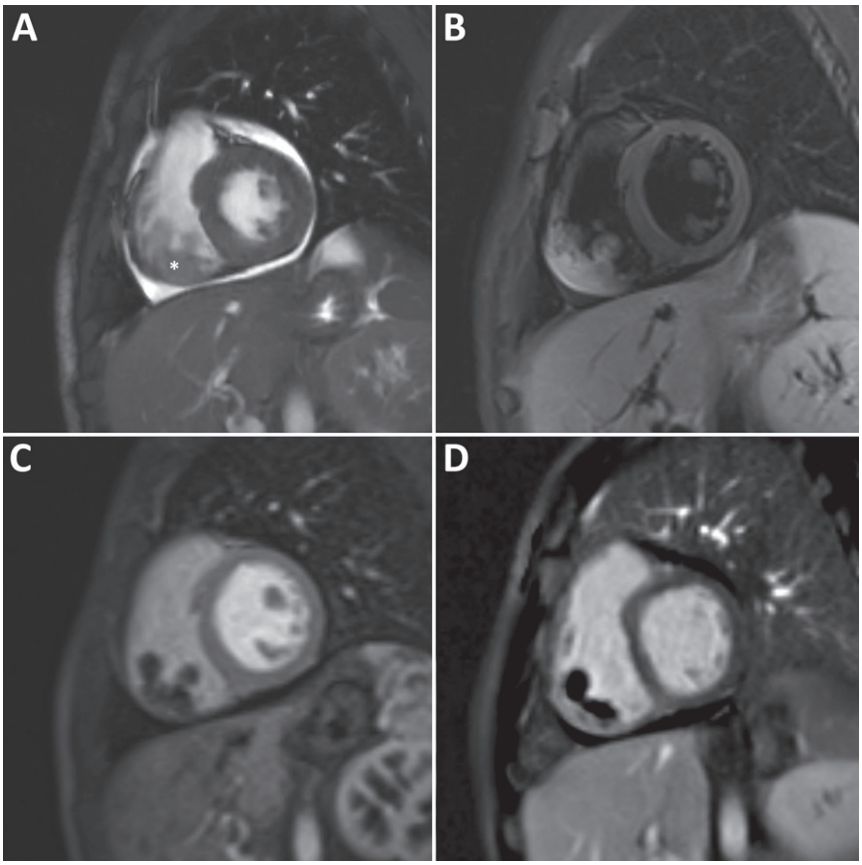

FIGURE 2
Initial cardiac MRI showing multiple masses along the inferior RV free wall.

with the standard protocol of administering high-dose steroids during cardiopulmonary bypass to reduce inflammatory responses during cardiac surgery. Given the new sign of pulmonary pseudoaneurysms in the context of fevers and thromboembolism, we considered a variant of Behcet's disease without mucocutaneous findings, also known as Hughes-Stovin syndrome. Although this was a diagnosis of exclusion, we decided to initiate corticosteroid

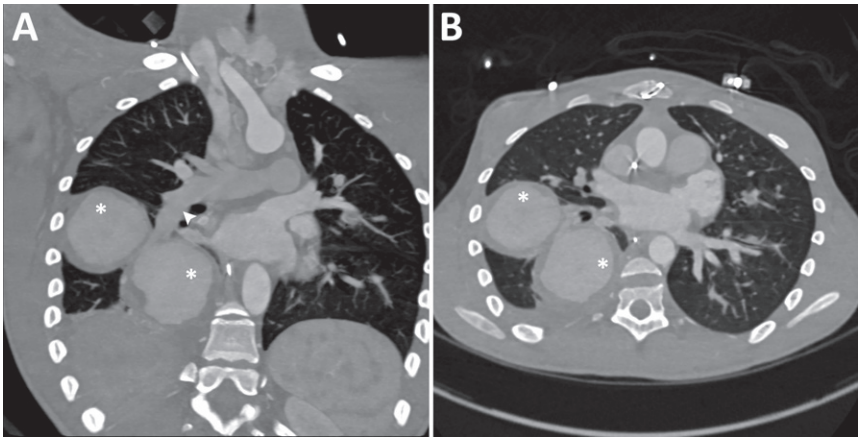

FIGURE 3
Repeat chest CT 2 months later revealing 2 large right pulmonary artery pseudoaneurysms (seen by *) in a coronal view (A) and axial view (B).

therapy and evaluate the patient's response. After 1 week of treatment with high-dose corticosteroids, the patient's fevers and fatigue resolved and his appetite improved. He was transitioned to cytotoxin 2 weeks later and has remained afebrile with no recurrence of cardiac wet thrombi on immunosuppression therapy.

DISCUSSION

Hughes-Stovin syndrome is a rare clinical diagnosis that occurs predominantly in young males and is characterized by fevers, thrombophlebitis, and multiple pulmonary aneurysms.[3,4] It is considered to be a variant of Behcet's disease. The etiology is unknown but there is consensus that vasculitis is the primary pathologic process.[5] Hughes-Stovin syndrome has only been described in a total of 90 cases reported in the literature, so the incidence of this disease is unknown.[4,6] Intracardiac masses present rarely in Hughes-Stovin syndrome and are thought to result from endomyocardial fibrosis, a sequela of vasculitis involving the myocardium.[7]

Characterization of cardiac masses in the pediatric population can be approached in a systematic way. However, even with the gold standard of cardiac biopsy, the utility of various diagnostic modalities may not prove to be helpful for recurrent cardiac masses. As highlighted in this case, it is as important to assess the trend and response to different treatment approaches. The goals of diagnostic evaluation of any pediatric cardiac mass are to understand its location within the heart, characterize the tissue, and evaluate its growth over time. Echocardiography is an important noninvasive modality to confirm the presence of a cardiac mass and understand its relation to other cardiac structures. This case highlights the utility of echocardiography in assessing the growth and recurrence of intracardiac masses over a period of several months. When surgical intervention is considered for cardiac masses, it is crucial to understand how it may cause obstruction to circulation. In this case, the knowledge that the cardiac mass was close to the tricuspid valve also helped assess the risks and benefits of surgical debulking. The shape, location, and mobility of the cardiac mass are often a clue into the type of tumor it may be. Myxomas are typically found in the left atrium, whereas rhabdomyomas are seen in the ventricular walls or atrioventricular valves.[8] Therefore, echocardiography is important for the initial evaluation of any cardiac mass, but delineating morphologic features of the mass does not necessarily allow an accurate diagnosis.

Cross-sectional imaging helps to provide high-resolution images of intra- and extracardiac structures to delineate the cardiac mass and its extension with more precision. Cardiac MRI is the modality of choice to evaluate intracardiac masses. MRI provides the ability to characterize the tissue on the basis of its water and fat content and how it perfuses with contrast.

These indicators can be helpful in distinguishing whether a cardiac mass is benign or malignant.[9] In this specific case, the presence of multiple pedunculated masses which did not perfuse with administration of contrast suggested abscesses or newly formed thrombi as a result of either an inflammatory or infectious process rather than a cardiac tumor. Chest CT with contrast is a highly sensitive modality for proximal and distal pulmonary vasculature evaluation. In this case, it revealed distal right pulmonary thrombi, and later, mycotic pseudoaneurysms.

Finally, cardiac biopsy offers histologic evaluation, but does not always produce a definite diagnosis. Often, an incisional biopsy has limited utility unless it is part of a total surgical resection. Although pathologic examination of a cardiac mass can reveal the type of cardiac tumor, it may not elucidate the etiology of infectious or inflammatory masses. This case demonstrates the importance of considering noninfectious causes in the presence of intracardiac masses that present with systemic symptoms consistent with infectious endocarditis that are unresponsive to antibiotics and anticoagulation.

In the setting of a systemic inflammatory disorder, a multimodality approach is needed to distinguish thrombi from cardiac tumors or vegetations. The reoccurrence of cardiac masses in any patient requires a thorough and reflective approach to assess the evolution of symptoms and response to each treatment. In this specific case, the observation that intraoperative high-dose steroids consistently improved the patient's symptoms was a key determinant in arriving at the diagnosis.

ABBREVIATIONS

CT: computed tomography
RV: right ventricle

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