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Influenza Antivirals in Pediatrics: Why Aren't We Using All the Available Tools?

Pia S. Pannaraj, MD, MPH

Although attention to influenza was diverted during the coronavirus disease 2019 pandemic, it remains essential to ensure we are prepared to deal with upcoming influenza seasons. Four antiviral agents are now available for treatment and/or prophylaxis against influenza infection, including oseltamivir, zanamivir, peramivir, and baloxavir. Yet, these influenza antiviral agents remain significantly underutilized in children.

In this issue of *Pediatrics*, Antoon et al present contemporary findings on real-world outpatient prescribing of antiviral agents for the treatment and prevention of influenza infection in children.[1] The authors reviewed commercial insurance claims data for all outpatient and emergency department encounters in children from birth to 18 years across all 50 US states between 2010 and 2019. The results emphasize the under-prescribing of antiviral agents despite their proven importance in decreasing disease severity and accelerating resolution of influenza infections.

Both treatment and prophylaxis prescriptions varied widely by year and seasonal severity, age, and geographic location.[1] Rates encouragingly increased over the years of study, with the highest rate of antiviral agents dispensed during the most severe influenza season in 2017 to 2018. However, only 49.4% to 67.3% of children with an influenza diagnosis filled an antiviral prescription within 48 hours of diagnosis. A study of hospitalized children with laboratory-confirmed influenza in Canada over the same 9-year study period also showed under-utilization with only 41.3% receiving antiviral agents, whereas 72.8% received antibiotics.[2] National influenza guidelines from the Centers for Disease Control and Prevention, Infectious Diseases of America, and the American Academy of Pediatrics recommend treatment of all high risk individuals and any individual with severe, complicated, or progressive influenza disease in both outpatient and inpatient settings regardless of duration of symptoms.[3] In addition, treatment may be considered for any child with suspected or confirmed influenza disease, including those who are not at high risk for influenza complication, if treatment can be initiated within 48 hours of symptom onset.[3]

Of greatest concern, Antoon et al showed the lowest rate of antiviral treatment occurred in children <5 years of age, for whom only 37% of children <2 years and 34% of children 2 to 5 years with an influenza diagnosis received treatment.[1] Children <5 years are the pediatric age group who suffer the most influenza complications.[4] In particular, healthy children <2 years are at highest risk of developing complications with hospitalization rates similar to older children with chronic underlying conditions and adults >65 years of age.[4,5] For these reasons, the American Academy of Pediatrics guidelines identify children <5 years and especially those <2 years as high risk groups for whom antiviral treatment should be offered as early as possible, regardless of influenza vaccination status and duration of symptoms.[3]

The rationale for influenza treatment was recently reviewed and published in the Recommendations for Prevention and Control of Influenza in Children,

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Dr Pannaraj drafted the commentary and reviewed it critically for important intellectual content, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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2023 to 2024.[5] Cochrane reviews and meta-analyses of multiple randomized controlled trials to evaluate the efficacy of influenza antiviral agents for uncomplicated influenza in outpatients found that timely treatment within 48 hours of symptom onset shortens median duration of illness by 17.6 to 36 hours.[5–8] Treatment with oseltamivir also reduces incidence of otitis media.[7–9] Furthermore, an influenza transmission model projects that antiviral treatment of children aged 5 to 19 years has the highest impact on reducing community transmission.[10] Observational studies and clinical trial data suggest that prompt treatment with neuraminidase inhibitors may reduce transmission to close contacts.[11] A controlled trial to examine baloxavir efficacy to reduce transmission is currently underway.[11]

A greater understanding of the various factors contributing to suboptimal adherence to the antiviral treatment guidelines is urgently needed. Although hesitancy toward vaccines among providers and patients have been studied with resulting ongoing interventions, much less is known about provider and patient attitudes toward antiviral agents. A principal issue remains that providers and patients may perceive that influenza infection in children is not serious. Most healthy children experience 4 to 7 days of fever, cough, and coryza that spontaneously recover with rest and fluids. Unfortunately, not all healthy children can anticipate an uncomplicated course. Bacterial infections of the upper respiratory tract, such as otitis media and sinusitis, can occur in 20% to 50% of healthy individuals, and complications of the lower tract, including bronchitis and pneumonia, can lead to hospitalizations.[5] Importantly, it is underrecognized that 50% of pediatric influenza deaths occur in otherwise healthy children.[12]

Additional questions about antiviral utilization remain. What leads providers to prescribe antiviral agents more frequently in adolescents when younger children are more likely to present with symptoms and require hospitalization?[1,4,13] Are providers and parents concerned about adverse effects? Of note, the only reported adverse effect from clinical trials was vomiting in a small percentage above those who received placebo.[5] No link has been established between oseltamivir and neurologic or psychiatric events with ongoing surveillance despite initial reports in Japanese teenagers nearly 2 decades ago.[5] What are the reasons for the lowest prescribing rates in the Pacific region of the United States?[1] Are there factors related to cost, insurance coverage, knowledge of antiviral options, perception of benefit, antiviral shortages, regional climate, culture, media coverage, and/or social media on clinical practices? Do these factors also affect patient and parental acceptance? Studies are desperately needed to further evaluate the implementation of antiviral treatment and chemoprophylaxis for influenza in children. The use of antiviral agents against influenza and adherence to national treatment guidelines in both outpatient and inpatient settings must be highlighted as important targets for improvement.[5,14]

As life and human behavior have returned to prepandemic norms, influenza will circulate at higher rates in the community once again. Influenza vaccine effectiveness is known to vary greatly each season, and vaccination rates in children decreased during the coronavirus disease 2019 pandemic.[15] Thus, although we must improve influenza vaccination rates, antiviral agents also must play a larger role in the prophylaxis and treatment of influenza infection. When it comes to influenza, we should be using all the tools in our toolbox.

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Previous Infection and Effectiveness of COVID-19 Vaccination in Middle- and High-School Students

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abstract

BACKGROUND AND OBJECTIVES: Understanding the real-world impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mitigation measures, particularly vaccination, in children and adolescents in congregate settings remains important. We evaluated protection against SARS-CoV-2 infection using school-based testing data.

METHODS: Using data from Utah middle- and high-school students participating in school-wide antigen testing in January 2022 during omicron (BA.1) variant predominance, log binomial models were fit to estimate the protection of previous SARS-CoV-2 infection and coronavirus disease 2019 vaccination against SARS-CoV-2 infection.

RESULTS: Among 17 910 students, median age was 16 years (range: 12–19), 16.7% had documented previous SARS-CoV-2 infection; 55.6% received 2 vaccine doses with 211 median days since the second dose; and 8.6% of students aged 16 to 19 years received 3 vaccine doses with 21 median days since the third dose. Protection from previous infection alone was 35.9% (95% confidence interval [CI]: 12.9%–52.8%) and 23.8% (95% CI: 2.1%–40.7%) for students aged 12 to 15 and 16 to 19 years, respectively. Protection from 2-dose hybrid immunity (previous SARS-CoV-2 infection and vaccination) with <180 days since the second dose was 58.7% (95% CI: 33.2%–74.4%) for students aged 12 to 15 and 54.7% (95% CI: 31.0%–70.3%) for students aged 16 to 19 years. Protection was highest (70.0%, 95% CI: 42.3%–84.5%) among students with 3-dose hybrid immunity, although confidence intervals overlap with 2-dose vaccination.

CONCLUSIONS: The estimated protection against infection was strongest for those with hybrid immunity from previous infection and recent vaccination with a third dose.

WHAT'S KNOWN ON THIS SUBJECT: Waning immunity from coronavirus disease 2019 vaccines against infection has been documented; however, protection of hybrid immunity against infection is not well-described. During omicron BA.1 emergence, the rates of infection among children and adolescents increased substantially, leading to widespread seroprevalence.

WHAT THIS STUDY ADDS: In this study, we evaluate the protection of coronavirus disease 2019 vaccination and previous SARS-CoV-2 infection among students attending school: a congregate setting with limited data. Protection against SARS-CoV-2 infection was strongest among those recently vaccinated and with hybrid immunity.

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Ms Almendares and Ms Ruffin conceptualized and designed the study, conducted analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript; Ms Collingwood and Ms Dash collected data and critically reviewed and revised the manuscript; Drs Avrich Ciesla and Wiegand critically reviewed and revised the manuscript; Drs Nolen, Lanier, Tate, and Kirking conceptualized and designed the study 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.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of Utah Department of Health, or the Centers for Disease Control and Prevention.

Mental Health of Youth With Autism Spectrum Disorder and Gender Dysphoria

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abstract

BACKGROUND AND OBJECTIVES: Youth with either autism spectrum disorder (ASD) or gender dysphoria (GD) alone have also been shown to be at greater risk for mental health (MH) concerns; however, very little research has considered how cooccurring ASD and GD may exacerbate MH concerns. The purpose of this study was to examine associations between ASD, GD, and MH diagnoses (anxiety, depression, eating disorder, suicidality, and self-harm) among US adolescent populations.

METHODS: This is a secondary analysis of a large administrative dataset formed by 8 pediatric health system members of the PEDSnet learning health system network. Analyses included descriptive statistics and adjusted mixed logistic regression models testing for associations between combinations of ASD and GD diagnoses and MH diagnoses as recorded in the patient's electronic medical record.

RESULTS: Based on data from 919 898 patients aged 9 to 18 years, adjusted mixed logistic regression indicated significantly greater odds of each MH diagnosis among those with ASD alone, GD alone, and cooccurring ASD/GD diagnoses compared with those with neither diagnosis. Youth with cooccurring ASD/GD were at significantly greater risk of also having anxiety (average predicted probability, 0.75; 95% confidence interval, 0.68–0.81) or depression diagnoses (average predicted probability, 0.33; 95% confidence interval, 0.24–0.43) compared with youth with ASD alone, GD alone, or neither diagnosis.

CONCLUSIONS: Youth with cooccurring ASD/GD are more likely to also be diagnosed with MH concerns, particularly anxiety and depression. This study highlights the need to implement developmentally appropriate, gender-affirming MH services and interventions for youth with cooccurring ASD/GD.

WHAT'S KNOWN ON THIS SUBJECT: Youth with either autism spectrum disorder (ASD) or gender dysphoria (GD) alone have been shown to be at greater risk for mental health concerns. However, very little research has considered cooccurring ASD/GD and further associations with mental health.

WHAT THIS STUDY ADDS: Building on recent research on cooccurring autism spectrum disorder (ASD) gender dysphoria (GD), this study illustrates the increased risk for anxiety and depression that youth with cooccurring ASD/GD experience and highlights the need for developmentally appropriate, gender-affirming mental health services and interventions for these youth.

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Dr Kahn conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Sequeira, Garrison, Orlich, Christakis, and Richardson and Mx Reyes assisted in conceptualizing the study and reviewed and revised the manuscript; Drs Aye, Conard, Dowshen, Kazak, Nahata, Nokoff, and Voss 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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Further Insights Into Cord Management

Roger F. Soll, MD

Management of the umbilical cord at birth has changed dramatically during the past decade. In both term and preterm infants, the previous standard of immediate early cord clamping has been shown to be inferior to a variety of other umbilical cord management techniques.[1–3]

Delayed (or deferred) cord clamping (DCC) (for anywhere from 30 seconds to minutes of life) is the most extensively tested approach to optimizing placental transfusion. In preterm infants, delayed umbilical cord clamping is associated with improved transitional circulation, improved hematologic measures, and lower incidence of mortality and major disability.[2,4]

However, there are concerns regarding DCC for a critical group of infants: those thought to be in need of immediate resuscitation. Two additional approaches have been suggested in these circumstances: umbilical cord milking (UCM) and DCC with resuscitation with an intact cord.[5] Umbilical cord milking allows for more rapid placental transfusion by "milking" the umbilical cord in the direction of the infant before clamping the cord. Delayed cord clamping with resuscitation is a more complex intervention, allowing for resuscitation with the cord intact. Although delayed cord clamping with resuscitation has been shown to be feasible for providing placental transfusion in preterm neonates in need of respiratory support,[6] the relative ease of performing UCM leads many to assume that this approach should be preferred.[5]

Early studies of cord milking seemed safe and effective in providing placental transfusion to preterm infants.[7] Many centers adopted UCM as part of routine practice. A survey of obstetricians and perinatologists in the United States reported 39% provide UCM in healthy term and preterm infants.[8] However, more recent studies have raised the concern of increased risk of intraventricular hemorrhage (IVH) in extremely preterm infants.[9,10]

In this issue of *Pediatrics*, Katheria et al report a randomized controlled trial of UCM versus DCC in infants 28 to 32 weeks' gestation.[11] This study is the extension of a previous study in a broader population that was halted early because extremely preterm infants (23 to 27 weeks' gestation) in the UCM arm had increased risk of IVH compared with infants in the DCC group.[10] Given that the concern for IVH was seen only in the lowest gestational age range, the authors decided to continue enrollment only of mothers at risk for delivering between 28 and 32 weeks' gestation.

The authors enrolled a total of 1019 infants. For the primary outcome, 7/511 (1.4%) infants randomized to UCM developed severe IVH or died compared with 7/508 (1.4%) infants randomized to DCC (rate difference, 0.01%; 95% confidence interval, –1.4% to 1.4%). Although the authors could not demonstrate noninferiority at a 1% margin, the authors conclude that UCM may be a safe alternative to DCC in preterm infants born at 28 to 32 weeks' gestation who require resuscitation.

The authors discuss several limitations of the trial, including not recalculating the sample size to account for the lower incidence of severe IVH and/or death in the more mature infants being enrolled. The recalculated sample size suggests that a threefold increase in enrollment would be required to avoid missing a real difference in the 2 interventions.

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The authors' conclusions are in keeping with the recommendations of authoritative groups such as International Liaison Committee on Resuscitation, who state that UCM is "a reasonable alternative to deferring cord clamping (weak recommendation, moderate-certainty evidence), in infants born between 28 and 34 weeks' gestational age, not requiring immediate resuscitation."[12]

Although the study seems to support these recommendations, it is worth taking a step back to understand the underpinning of the trial and our approach to UCM. Why is UCM "noninferior"? It certainly is easier to accomplish quickly and without changes in equipment or processes. However, it assumes that there is pressing need to deliver the preterm infant to an open warmer where resuscitation can begin. This argument falls prey to a series of misbeliefs about the ability of the preterm infant to make an adequate transition. There are lessons we learned from our evolving approach to respiratory management in the delivery room, where less invasive approaches to support are clearly gaining ground. In studies that have examined our approach to "resuscitation," preterm infants frequently receive positive pressure ventilation or other respiratory support even though most were breathing and no attempt was made to assess heart rate.[13,14]

Does UCM in preterm infants without significant signs of fetal distress feed into this paradigm? Is our assumption that all these infants need immediate resuscitation as opposed to allowing for a more physiologically appropriate transition, potentially causing more harm than good? Certainly, Katheria and colleagues have shown that we can achieve effective placental transfusion in moderately preterm infants with umbilical cord milking, but other more subtle outcomes, such as parental/maternal attitudes and experience are missing from these analyses. The authors of this study clearly understand the commitment to examining all the nuances of cord management and are committed to follow-up of the infants in this study as well as leading a variety of other studies evaluating different cord management techniques. We frequently make the mistake of losing impetus to continue trials once some, but not all, of the answers have emerged. We can thank these and other investigators for continuing to evaluate these issues that surely affect the health of every newborn worldwide.

ABBREVIATIONS

DCC: delayed cord clamping
IVH: intraventricular hemorrhage
UCM: umbilical cord milking

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Preterm Birth and Infantile Appendicitis

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abstract

OBJECTIVE: To investigate the potential association between preterm birth and infantile appendicitis.

METHODS: We conducted a retrospective, multicenter, matched case-control study. This study included consecutive patients <1 year of age with surgery- or autopsy-confirmed appendicitis, admitted between December 2007 and May 2023. For each case, 10 healthy infants were randomly selected and matched by age. Infants were categorized as neonates (0 to 28 days) or older infants (>28 days and <1 year).

RESULTS: The study included 106 infants diagnosed with appendicitis (median age 2.4 months) and 1060 age-matched healthy controls. In the univariate analysis, preterm birth was significantly associated with the development of appendicitis within the first year of life (odds ratio [OR], 4.23; 95% confidence interval [CI], 2.67–6.70). Other factors associated with a higher risk of infantile appendicitis included being male (OR, 1.91; 95%CI, 1.25–2.94), weight-for-age *z*-score (OR, 0.72; 95%CI, 0.64–0.81), and exclusively fed on formula (OR, 2.95; 95%CI, 1.77–4.91). In multivariable analyses, preterm remained significantly associated with appendicitis (adjusted OR, 3.32; 95%CI, 1.76–6.24). Subgroup analysis revealed that a preterm birth history increased the risk of appendicitis in both neonates (adjusted OR, 4.56; 95%CI, 2.14–9.71) and older infants (adjusted OR, 3.63; 95%CI, 1.72–7.65). However, preterm did not significantly influence the incidence of appendiceal perforation.

CONCLUSIONS: Preterm infants have an increased risk of appendicitis during the first year of life. A preterm birth history may help improve the timely diagnosis of infantile appendicitis.

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Drs Liu and Yu designed the study, performed the research, analyzed the data, and wrote the manuscript; Drs Zhang, Xie, Li, and Mu performed the research and edited the paper; Dr Chen contributed to data interpretation and critically revised the manuscript for important intellectual content; Drs Chen and Huang designed the study and edited 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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WHAT'S KNOWN ON THIS SUBJECT: Infants with appendicitis exhibit high mortality rates, yet early diagnosis remains a challenge. Limited studies have been conducted on appendicitis in infants <1 year old, particularly those focusing on its risk factors.

WHAT THIS STUDY ADDS: Our research establishes preterm birth as a significant risk factor for the development of infantile appendicitis without elevating perforation rates. Preterm might serve as an essential clue for early suspicion and the promotion of timely diagnosis of infantile appendicitis.

To cite: Liu Y, Yu X, Zhang G, et al. Preterm Birth and Infantile Appendicitis. *Pediatrics.* 2023;152(6):e2023063815

Rehydration Rates and Outcomes in Overweight Children With Diabetic Ketoacidosis

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for the Pediatric Emergency Care Applied Research Network Diabetic Ketoacidosis FLUID Study Group*

abstract

BACKGROUND AND OBJECTIVES: The Pediatric Emergency Care Applied Research Network Fluid Therapies Under Investigation in Diabetic Ketoacidosis (DKA) (FLUID) Trial found that rapid fluid infusion does not increase the risk of cerebral injury. Concern persists, however, whether fluid rates should be adjusted for overweight or obese patients. We used the FLUID Trial database to evaluate associations between fluid infusion rate and outcomes in these patients.

METHODS: We compared children and youth who were overweight, obese, or normal weight, in regard to protocol adherence, mental status changes, time to DKA resolution, and electrolyte abnormalities. We investigated associations between outcomes and the amount of fluid received in these groups.

RESULTS: Obese children and youth were more likely to receive fluids at rates slower than dictated by protocol. Overweight and obese children and youth in the fast fluid arms, who received fluids per the study protocol based on their measured weight, had similar rates of mental status changes or clinically apparent cerebral injury as those with normal weights. Risk of hypophosphatemia was increased in those receiving larger initial bolus volumes and reduced in those receiving higher rehydration rates. No other metabolic outcomes were associated with rehydration.

CONCLUSIONS: Protocol adherence data in the FLUID Trial suggest that physicians are uncomfortable using weight-based fluid calculations for overweight or obese children. However, higher rates of fluid infusion were not associated with increased risk of mental status changes or cerebral injury, suggesting that physicians should not limit fluid resuscitation in obese children and youth with DKA.

NIH

WHAT'S KNOWN ON THIS SUBJECT: A recent clinical trial by our group found that rapid fluid rehydration did not increase the risk of cerebral injury in children with DKA, however, there were no specific analyses of data for overweight or obese children.

WHAT THIS STUDY ADDS: Our analysis suggests that physicians are uncomfortable with weight-based fluid rates in overweight children with DKA. However, higher infusion rates did not increase risk of cerebral injury in this group, suggesting fluid rates should not be limited based on weight.

To cite: Brown KM, Glaser NS, McManemy JK, et al. Rehydration Rates and Outcomes in Overweight Children With Diabetic Ketoacidosis. *Pediatrics*. 2023;152(6): e2023062004

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Diabetes in Pregnancy, Neonatal Morbidities, and Early Growth in Moderate or Late Preterm Infants

Catherine O. Buck, MD,[a] Veronika Shabanova, PhD,[a] Reese H. Clark, MD,[b] Sarah N. Taylor, MD, MSCR[a]

abstract

OBJECTIVES: To compare differences in short term morbidities and early growth among moderate and late preterm infants of mothers with and without diabetes (DM) in pregnancy.

METHODS: In a longitudinal analysis using data from the Pediatrix Clinical Data Warehouse of preterm infants (born 32 0/7 to 36 6/7 weeks) discharged from neonatal intensive care units from 2008 to 2019, health characteristics were compared between DM exposure groups. Change in growth from birth to discharge were compared using linear mixed effects modeling.

RESULTS: Among 301 499 moderate and late preterm infants in the analysis, 14% ($N = 42\,519$) were exposed to DM in pregnancy. Incidence of congenital anomalies, hypoglycemia, and hyperbilirubinemia were higher in DM-group ($P < .001$), and DM-group was more likely to need respiratory support in the first postnatal days ($P = .02$). Percent weight change from birth differed by gestational age, such that 36-week DM-group infants remained on average 2% (95% confidence interval [CI]: 1.57 to 2.41) below birth weight on day 14, whereas 32-week DM-group infants were on average 2.1% (95% CI: 1.69 to 2.51) above birth weight on day 14. In the regression analysis, DM-group had faster weight loss in the first postnatal week when stratified by gestational age. The adjusted difference in weight velocity (g per day) from days 0 to 3 was −4.5 (95% CI: −5.1 to −3.9), −6.5 (95% CI: −7.4 to −5.7), and -7.2 (95% CI: −8.2 to −6.2) for infants born 34-, 35-, and 36-weeks, respectively.

CONCLUSIONS: In moderate or late preterm infants, diabetes in pregnancy is associated with common neonatal morbidities. Examination of intensive care nutritional practices may identify reasons for observed differences in weight trajectories by gestational age and diabetes exposure.

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Dr Buck conceptualized and designed the study and drafted the initial manuscript; Drs Clark and Taylor supervised the design of the study and the data analysis; Dr Shabanova conducted the statistical analysis; and all authors 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: Diabetes in pregnancy is associated with adverse maternal and infant health outcomes, including prematurity and common neonatal morbidities. Few studies of preterm infants exposed to diabetes in pregnancy have focused specifically on growth and nutritional outcomes.

WHAT THIS STUDY ADDS: In a large, multicenter cohort of moderate or late preterm infants admitted to newborn intensive care units, diabetes in pregnancy is associated with common neonatal morbidities and gestation age specific differences in early growth trajectories.

To cite: Buck CO, Shabanova V, Clark RH, et al. Diabetes in Pregnancy, Neonatal Morbidities, and Early Growth in Moderate or Late Preterm Infants. *Pediatrics.* 2023;152(6): e2023061285

Measurement of Ambulatory Medication Errors in Children: A Scoping Review

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abstract

BACKGROUND AND OBJECTIVES: Children use most medications in the ambulatory setting where errors are infrequently intercepted. There is currently no established measure set for ambulatory pediatric medication errors. We have sought to identify the range of existing measures of ambulatory pediatric medication errors, describe the data sources for error measurement, and describe their reliability.

METHODS: We performed a scoping review of the literature published since 1986 using PubMed, CINAHL, PsycINFO, Web of Science, Embase, and Cochrane and of grey literature. Studies were included if they measured ambulatory, including home, medication errors in children 0 to 26 years. Measures were grouped by phase of the medication use pathway and thematically by measure type.

RESULTS: We included 138 published studies and 4 studies from the grey literature and identified 21 measures of medication errors along the medication use pathway. Most measures addressed errors in medication prescribing ($n = 6$), and administration at home ($n = 4$), often using prescription-level data and observation, respectively. Measures assessing errors at multiple phases of the medication use pathway ($n = 3$) frequently used error reporting databases and prospective measurement through direct in-home observation. We identified few measures of dispensing and monitoring errors. Only 31 studies used measurement methods that included an assessment of reliability.

CONCLUSIONS: Although most available, reliable measures are too resource and time-intensive to assess errors at the health system or population level, we were able to identify some measures that may be adopted for continuous measurement and quality improvement.

WHAT'S KNOWN ON THIS SUBJECT: The majority of pediatric medications are utilized in the ambulatory setting where most errors are not intercepted before reaching the patient. There is no established set of measures to continuously measure and reduce harm due to pediatric outpatient medication errors.

WHAT THIS STUDY ADDS: We have comprehensively described existing measures of pediatric outpatient, including home, medication errors and evaluated measure quality. This study identifies a set of measures that may be adopted at the health system level for continuous measurement and quality improvement.

To cite: Rickey L, Auger K, Britto MT, et al. Measurement of Ambulatory Medication Errors in Children: A Scoping Review. *Pediatrics*. 2023;152(6):e2023061281

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Dr Rickey conducted analysis and drafted the initial manuscript; Dr Walsh conceptualized and designed the study and coordinated and supervised data collection and analysis; Drs Auger and Britto conceptualized and designed the study and performed data analysis; Ms Rodgers, Ms Field, Ms Odom, and Ms Lehr performed the data collection; Ms Cronin performed data collection and contributed to the writing of the manuscript; and all authors 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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Risk of Developmental Disorders in Children Born at 32 to 38 Weeks' Gestation: A Meta-Analysis

Katherine J. Pettinger, MSc,[a] Clare Copper, MEd,[b] Elaine Boyle, PhD,[c] Sarah Blower, PhD,[a] Catherine Hewitt, PhD,[a] Lorna Fraser, PhD[a,d]

abstract

CONTEXT: Very preterm birth (<32 weeks) is associated with increased risk of developmental disorders. Emerging evidence suggests children born 32 to 38 weeks might also be at risk.

OBJECTIVES: To determine the relative risk and prevalence of being diagnosed with, or screening positive for, developmental disorders in children born moderately preterm, late preterm, and early term compared with term (≥37 weeks) or full term (39–40/41 weeks).

DATA SOURCES: Medline, Embase, Psychinfo, Cumulative Index of Nursing, and Allied Health Literature.

STUDY SELECTION: Reported ≥1 developmental disorder, provided estimates for children born 32 to 38 weeks.

DATA EXTRACTION: A single reviewer extracted data; a 20% sample was second checked. Data were pooled using random-effects meta-analyses.

RESULTS: Seventy six studies were included. Compared with term born children, there was increased risk of most developmental disorders, particularly in the moderately preterm group, but also in late preterm and early term groups: the relative risk of cerebral palsy was, for 32 to 33 weeks: 14.1 (95% confidence intervals [CI]: 12.3–16.0), 34 to 36 weeks: 3.52 (95% CI: 3.16–3.92) and 37 to 38 weeks: 1.44 (95% CI: 1.32–1.58).

LIMITATIONS: Studies assessed children at different ages using varied criteria. The majority were from economically developed countries. All were published in English. Data were variably sparse; subgroup comparisons were sometimes based on single studies.

CONCLUSIONS: Children born moderately preterm are at increased risk of being diagnosed with or screening positive for developmental disorders compared with term born children. This association is also demonstrated in late preterm and early term groups but effect sizes are smaller.

Full article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2023-061878

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Dr Pettinger conceptualized and designed the study, performed the literature search, data extraction and data analysis, drafted the initial manuscript, and revised the manuscript; Mrs Copper participated in the literature search and data extraction and critically reviewed the manuscript; Drs Blower, Boyle, Hewitt, and Fraser supervised the study design, the literature search, data extraction and analysis, 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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Transcutaneous Bilirubin Accuracy Before, During, and After Phototherapy: A Meta-Analysis

Lisa ten Kate, MD,[a] Tiemen van Oorschot, MD,[b] Jessica Woolderink, MD,[c] Sarah Teklenburg-Roord, MD, PhD,[d] Jolita Bekhof, MD, PhD[d]

abstract

CONTEXT: Transcutaneous bilirubinometry (TcB) is used as a valid screening to identify neonates requiring measurement of total serum bilirubin (TSB) before phototherapy. Its use during and after phototherapy is not advised yet because of unknown reliability.

OBJECTIVES: To determine the agreement of TcB and TSB measurements before, during, and after phototherapy.

DATA SOURCES: PubMed Medline, Cochrane Library, and references of eligible studies were searched.

STUDY SELECTION: Prospective and retrospective cohort and cross-sectional studies reporting Bland-Altman statistics of paired TcB and TSB measurements in term and preterm newborns.

DATA EXTRACTION: Meta-analysis was performed using the Mantel-Haenszel weighted approach. The agreement between TcB and TSB in μmol/L was described by pooled mean differences (MDs) and limits of agreement (LoA).

RESULTS: Fifty-four studies were included. The pooled MD before phototherapy is 2.5 μmol/L (LoA −38.3 to 43.3). The pooled MD during phototherapy is −0.3 μmol/L (LoA −34.8 to 34.2) on covered skin and −28.6 μmol/L (LoA −105.7 to 48.5) on uncovered skin. The pooled MD after phototherapy is −34.3 μmol/L (LoA −86.7 to 18.1) on covered skin and −21.1 μmol/L (LoA −88.6 to 46.4) on uncovered skin. Subgroup analysis revealed the best agreement at the forehead. We did not find any difference in agreement between term and preterm neonates.

LIMITATIONS: Language restriction.

CONCLUSIONS: TcB measurements before and during phototherapy on covered skin show good agreement compared with TSB in term and preterm newborns. More studies are needed to evaluate the accuracy after phototherapy.

Full article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2023-062335

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Dr ten Kate conceptualized and designed the study, collected and extracted data, conducted the initial analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr van Oorschot conceptualized and designed the study, and collected and extracted data; Dr Woolderink conceptualized and designed the study, and conducted the initial analyses; Dr Teklenburg-Roord reviewed and revised the manuscript; Dr Bekhof conceptualized and designed the study, coordinated and supervised data collection and initial analyses, drafted the initial manuscript, 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.

This study is registered at PROSPERO, CRD42022361932. Deidentified data will not be made available. All data, including the calculations concerning the pooling of data, are available upon reasonable request. Please use the contact information below.

To cite: ten Kate L, van Oorschot T, Woolderink J, et al. Transcutaneous Bilirubin Accuracy Before, During, and After Phototherapy: A Meta-Analysis. *Pediatrics.* 2023;152(6): e2023062335

Innovations in Cancer Treatment of Children

Lauren Helms, MD,[a,*] Allison E. Guimera, MD,[b,*] Katherine A. Janeway, MD,[c] Kelly M. Bailey, MD, PhD[d]

Pediatric cancer outcomes have significantly improved, and yet this success is not spread equally across cancer types or patients. Disparities data in pediatric oncology highlight needed improvements in access to care, including clinical trials and advanced testing for all patients. For cancers such as brain tumors and sarcomas, continued advancement in understanding the biology of tumor heterogeneity is an essential step toward finding new therapeutic combinations to improve outcomes. Pediatric cancer survivors need access to emerging technologies aimed at reducing or better managing toxicities from therapy. With advances in treatment and survival, pediatric oncology patients continue to need longitudinal, multidisciplinary subspecialty care. Refining the communication between pediatric oncologists, primary pediatricians, survivorship clinics, and adult primary care is key in ensuring the best lifelong care of pediatric cancer survivors. In this State-of-The-Art review, we discuss 5 major domains in pediatric oncology: reducing toxicity, cancer biology, novel therapies, detection and monitoring, and access to care, to highlight recent advances and areas for continued improvement.

Full article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2023-061539

abstract

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Drs Helms and Guimera contributed to the manuscript draft and figure editing; Drs Janeway and Bailey conceptualized the article and contributed to the manuscript draft; 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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A Quality Improvement Initiative to Reduce Necrotizing Enterocolitis in Very Preterm Infants

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abstract

OBJECTIVE: To reduce the incidence of necrotizing enterocolitis (NEC) among very preterm infants in the Calgary Health Region to ≤2% within 2 years.

METHODS: A multidisciplinary team developed key drivers for NEC. Targeted interventions included strategies to increase mothers' own milk (MOM), improve compliance with feeding regimens, standardize management of feeding intolerance, prevent intestinal microbial aberrations, and feed conservatively during blood transfusion and the treatment of patent ductus arteriosus. The outcome measure was NEC (≥ stage 2). Changes in NEC rates were examined among racial and ethnic groups. Process measures included MOM feeding at discharge, the difference between actual and expected time to reach full feeds, lowest hemoglobin, and the duration of empirical antibiotics. Growth, the rate of blood transfusion, and the duration of parenteral nutrition were balancing measures. The preintervention, intervention, and sustainment periods were January 2013 to June 2016, July 2016 to December 2018, and December 2018 to December 2021, respectively.

RESULTS: We included 2787 infants born at $\leq 32^{6/7}$ weeks' gestation (1105 preintervention, 763 during intervention, and 919 in sustainment). NEC decreased from 5.6% to 1.9%. Process measures indicated increased MOM feeding at discharge, improved compliance with feeding regimens, increased lowest hemoglobin levels, and shorter durations of empirical antibiotics. Balancing measures revealed improved weight *Z*-scores, shorter durations on parenteral nutrition, and increased rates of blood transfusion.

CONCLUSIONS: Quality improvement initiatives to increase MOM, improve compliance with feeding regimens, feed conservatively during blood transfusion and treatment of patent ductus arteriosus, and prevent intestinal microbial aberrations were associated with reduced NEC.

Full article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2023-061273

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Dr Alshaikh conceptualized and designed the project, drafted the initial manuscript, and supervised data collection; Ms Wood, Ms Spence, Ms Knauff, and Ms Hamilton contributed to the implementation of this project; Drs Sproat and Roy designed the educational materials, followed quality improvement measures, and obtained ethics approval; 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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CONFLICT OF INTEREST DISCLOSURES: The authors have indicated they have no potential conflicts of interest to disclose.

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CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Supporting the Family After the Death of a Child or Adolescent

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COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, SECTION ON HOSPICE AND PALLIATIVE MEDICINE

Whether death occurs in the context of a chronic illness or as the sudden loss of a previously healthy infant, child, or adolescent, the death of a child is a highly stressful and traumatic event. Psychosocial support for families after the death of a child embodies core medical values of professional fidelity, compassion, respect for human dignity, and promotion of the best interests of a grieving family. The pediatrician has an important role in supporting the family unit after the death of a child through a family-centered, culturally humble, trauma-informed approach. This clinical report aims to provide the pediatrician with a review of the current evidence on grief, bereavement, and mourning after the loss of a child and with practical guidance to support family caregivers, siblings, and the child's community. Pediatricians have an important role in helping siblings and helping families understand sibling needs during grief. Ways for pediatricians to support family members with cultural sensitivity are suggested and other helpful resources in the community are described.

INTRODUCTION

The death of a child, no matter what the cause, is devastating.[1] The pediatrician is positioned to help family members adjust to the loss of a child and adapt to the ongoing effects of the child's death. This clinical report identifies the key considerations for pediatric care teams supporting family caregivers and siblings through grief and suggests ways that pediatricians can commit to joining with grieving families.

Throughout this report, the term "family" is used to be inclusive of whomever the child and caregiver consider to be "family." Additionally, throughout this report, the term "child" is used to be inclusive of pediatric and young adult patients from birth into early adulthood with recognition of the relational role of child to family caregiver. The term "caregiver" recognizes the unique special bonds with parents while inclusively honoring whether a guardian, step-parent, same-sex partner,

abstract

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foster parent, or grandparent serves in caregiver role. Specific age and developmental groups or relationships are highlighted where relevant.

INCIDENCE OF PEDIATRIC DEATH

Although childhood is generally presumed to be a time of health and development, the reality of pediatric death rates cannot be ignored and should not be minimized (Table 1).[2] Each of these stark statistics represents not just a number but the loss of a loved child and a family grappling with grief.

The coronavirus disease 2019 pandemic revealed the vulnerability of even pediatric patients. By March 2022, approximately 355 children ages 0 through 4 years and 737 ages 5 through 18 years died of severe acute respiratory syndrome coronavirus 2 infection and related causes in the United States.[3] Although American Indian/Alaska Native, Black, and Hispanic children represent 41% of the US population under age 20, they accounted for 78% of coronavirus disease 2019-related deaths in this age cohort.[4]

GRIEF AND BEREAVEMENT

Grief reactions may include waves of sadness or sorrow, anguish, anger, emotional numbness, anxiety, and guilt for caregivers and siblings.[5,6] Because of the unpredictable and intense nature of grief, these emotions may be experienced less like waves and more like tsunamis by a grieving family. Grief impacts physical, existential or spiritual, psychological, social, cognitive, and behavioral domains.[7] Grief is a natural reaction to the loss of a loved one that is unique to each individual and family, and it is important not to pathologize it, particularly in the early phases.[8] Trauma can complicate grief, warranting attentiveness to trauma symptoms as well as grief symptoms. Families are often in need of both practical and emotional support at each stage of their grief journey.[9] The pediatrician and the pediatric practice can be an important source of support and linkage to additional community resources as indicated.

A pediatrician can support families after the loss of a child by being present for the family in the time surrounding loss. Hospital staff should consider suspending visitor restrictions to accommodate family members being with the child during the time of death and surrounding death. The family may benefit from a private space and additional time to remain with their child and welcome loved ones (such as siblings or grandparents) after the death. Pediatricians may recognize the child by name and acknowledge the family's grief. Depending on the relationship with the child and family, a pediatrician may consider inquiring about the family's traditions for remembering loved ones, verbalizing ways that the child will be remembered, and considering ways caring for the child or family may impact future care efforts. A quiet presence and actively listening ear may also be appropriate. Expressions of sympathy are always appropriate even when there is concern for malpractice (the American Academy of Pediatrics policy statement on disclosure of adverse events in pediatrics[10] serves as a further guide for conversations contextualized to scenarios of medical liability).

The timing of conversations about an autopsy requires personalization for each family and the circumstances surrounding the child's death. Suggestions to improve autopsy discussions include having a trusted professional sensitively broach the topic through preparatory guidance and education.[11,12] Some bereaved caregivers report that having a first conversation about the clinical, emotional, or research domains of an autopsy before death would help with decision-making.[13] The pediatrician may consider obtaining a copy of the autopsy report and offering to review it with the family to help discern how much or how little information would be preferred, to interpret the medical language, and to keep the lines of communication open. Follow-up conversations regarding autopsy results provide care teams the opportunity to create a safe space for processing the medical facts surrounding the child's death while supporting emotions and remaining available for questions.

In the initial days after the child's death, families will be faced with practical decisions to be made regarding the final disposition of the child's body, funeral or memorial plans, communicating news of the child's death with family and friends, and managing activities of daily living for themselves and any surviving children. The preferences of adolescents to serve as organ donors as they

TABLE 1 United States Pediatric Death Rates and Leading Causes in 2020

Age Cohort	Deaths	Mortality Rates	Leading Causes
Infant	19 582	541.9 (per 100 000 live births)	Congenital and chromosomal; disorders related to short gestation and low birth wt; sudden infant death syndrome
1–4 y	3529	22.7 (per 100 000 population)	Injuries; congenital and chromosomal; assault (homicide)
5–14 y	5623	13.7 (per 100 000 population)	Ages 5–9 y: injuries; cancer; congenital and chromosomal; ages 10–14 y: Injuries; Intentional self-harm (suicide); cancer
15–19 y	12 278	58.6 (per 100 000 population)	Injuries; homicide; suicide

Source: National Vital Statistics System – Mortality data (2020) via CDC WONDER.

indicated at informed consent times, such as on their driver's license, should be honored.

Families will have varying levels of social support networks.[14] The pediatric practice can be helpful in reminding families about the importance of reaching out to resources in their lives, such as clergy, family, friends, neighbors, the child's school community, work colleagues, medical providers, grief counselors, and others either in-person or via telehealth modalities. These resources are the "front line" of support for families and can be extremely helpful in managing the initial phase after the death.[15] Pediatricians practicing in areas with significant gaps in support resources may wish to foster a staff member becoming familiar with online or written grief resources (see Resources section for a starting list) and access to telehealth subject matter expertise.

As the weeks and months after the child's death pass, families absorb the inevitable shock of the death and move into new phases of their grief that are more emotionally laden and existential.[16,17] This process is rarely linear and instead occurs via a waxing and waning of experiences and an evolution of emotions over time. Pediatricians can be helpful in preparing the family to expect changes in their reactions to the child's death over time and to expect that it will be a long and difficult process during which it will be important for them to be emotionally gentle with themselves and each other.[18] It is during this time that some families are interested in being connected to bereavement support systems. The array of grief supports that are available is unique to each community. Hospitals, hospice and palliative care programs, funeral homes, social workers, community centers, support groups, and organizations focused on chronic illness can be excellent sources of information on bereavement support offerings.

Some communities experience disproportionate burden in the type of death a child experiences. In 2019, Black youth had a firearm mortality rate 4.3 times higher than that of white youth and a firearm homicide rate over 14 times higher than that of white youth.[19] Public health disparities in the burden of preventable deaths warrant consideration of strategic policy, coordinated advocacy, and increased access to support specific to particular types of death within communities. It can be helpful for pediatric practices to maintain a list of advocacy groups, support services, and bereavement resources for families. There are also online resources to include diagnosis-specific organizations (muscular dystrophy, sickle cell disease, etc) that some caregivers may prefer to access, rather than attending in-person supports.

Grief theories have matured to recognize that grief is not a linear process that goes through predictable stages.[20] Rather, the different emotions associated with grief, such as denial, depression, anger, bargaining, and acceptance, may appear at any time and with varying combinations in different individuals and families. It is important to recognize that not all grief is expressed in the same manner or timeline. The diagnosis of "prolonged grief" is a formal diagnosis according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* criteria[21] and entails loss over a year (may be longer based on social, cultural, or religious norms) with at least daily occurrence of 3 of the following symptoms during the prior month: identity disruption, marked sense of disbelief about the death, avoidance of reminders, intense emotional pain related to the death, difficulty with reintegration, emotional numbness, feeling that life is meaningless, and intense loneliness.[22] It is important to stress that sibling and caregiver grief does not carry a predictable timeline and that care should be taken to not pathologize continued grief in caregivers of children who have died, especially when considering grief after the death of a child.[23] Occasionally, the grief reaction causes continued or prolonged functional impairment or intense emotional suffering, including not being able to sleep and eat, work, care sensitively for their surviving children, maintain or regain social connections, and imagine a future. In these situations, referral to professional support, such as counseling, is indicated.[24,25] Consider early counseling for surviving siblings to address survivor's guilt about being alive (particularly pertinent in acute causes of death occurring after the family experienced a shared traumatic event such as a natural disaster, gun violence, motor vehicle crash, etc).

In some communities, there are grief counselors specially trained to support grief processes. Many mental health specialists (psychiatrists, psychologists, couples and family therapists, social workers, and counselors) have some foundational knowledge in supporting people through the grief process and can assess the extent to which there is a need for more specific mental health focused interventions. In resource-limited settings, telehealth support options may be considered. The physician should recognize when the grieving process has started (realizing anticipatory grief often begins before the child's actual death for families experiencing the loss of a child from a chronic or prolonged terminal illness) and make a careful suggestion to the family about a counselor while remaining sensitive to the family's preference on the timing and acceptance of counseling support.

Family members cannot be expected to "move on" or "get over" the death of a child; instead, families benefit from receiving compassionate and comprehensive support as they attempt to adjust to the physical absence of their child while maintaining a sense of continued connection.[26–28] The process of living with the grief of losing a child has been described by bereaved families as learning to live with an empty seat at the table and a hole in the heart.[29]

Death as the Result of Chronic Illness or Disability

Racial and socioeconomic disparities in health outcomes and mortality exist for many pediatric chronic illnesses,

including cardiomyopathy[30] and childhood cancer,[31] among others.[32] Cancer is the leading disease-specific cause of death in older children and adolescents.[2]

Congenital and chromosomal diagnoses are the leading biomedical causes of death for children ages 0 through 4 years. Grief often begins at diagnosis for families of children born with congenital diagnoses. Improved understanding about genetic transmission of some diagnoses has revealed unique grief support needs for families who may experience guilt surrounding heritable conditions or face multiple losses within one family unit.[33]

Pediatric palliative care represents an essential early intervention to support quality of life for children, to help families find meaning in each day, and to offer a safe space for processing emotions and existential concerns. The palliative care team may serve as an additional form of interdisciplinary support specialized in grief principles and in helping to connect the family with additional resources, such as hospice services. For pediatric patients with an anticipated survival of 6 months or less if the diagnosis were to take a natural course, enrollment in the hospice benefit would avail continued curative or disease-directed treatments (concurrent care). Hospices are required to provide a minimum of 1 year of bereavement support after death occurs.

Anticipatory grief may occur before an expected death occurs.[34] The "anticipatory" descriptor applies to the timing of grief before death and does not necessarily translate into a caregiver feeling more prepared for or accepting of the child's death.[35] In the setting of a child's illness, parental grief often begins long before the actual moment of death as part of ongoing adaptation to daily losses. Grief fluctuates throughout the illness and wellness trajectory as the child's condition changes over time, warranting early support for families.[36] A family experiencing the death of a child with a chronic condition may have already experienced a significant amount of chronic grief before the child's death. Ambiguous loss is a type of loss that occurs when a loved one is physically present but increasingly absent (because of illness trajectory, decline in alertness, or psychologic or developmental regression) and, thus, grief is experienced as perpetual and painful.[37,38]

When a child or adolescent's death results from a chronic illness or complex medical condition, it is likely that the pediatrician and other members of the care team have been involved in the patient's care and may have a long-standing relationship with the family. Although the family may have been medically advised to anticipate a child's shortened life span because of the medical condition or prognosis, the weight and profound heaviness of grief at the time of death is not lessened or diminished. Depending on the duration and proximity of the therapeutic relationship with the family surrounding the child's illness or disability, the family also may suffer from the loss of the relationship with the pediatrician and other members of the care team and risks feeling abandoned. Under these circumstances, the pediatrician's continuing involvement with the family may be especially meaningful and a form of professional fidelity.

Sudden, Unexpected Death

Unexpected deaths often can cause sudden, intense feelings of anguish for families with significant lasting effects.[39,40] Sudden and unexpected infant deaths, including sudden infant death syndrome, accidental suffocation deaths, and ill-defined deaths, represent 3400 deaths per year in the United States and are the largest category of sudden and unexpected deaths in childhood.[41] Motor vehicle crashes were cited as the leading cause of pediatric deaths for over half a century.[42] Beginning in 2017, firearms now represent the number one cause of death among persons ages 1 to 19 years.[43] Overall firearm-related fatalities involving children and adolescents in the United States increased 29.5% between 2019 and 2020.[42] Drug overdose and poisoning increased by 83.6% in this same time frame among children and adolescents, now representing the third leading cause of pediatric death.[42]

Pediatricians may not immediately be aware of the death in sudden circumstances. If there is a brief period of survival after the event, the pediatrician may be involved; however, unexpected deaths often occur at the scene, in transport, the emergency department, or in the ICU. In these situations, the emergency or critical care physician can inform the pediatrician of the death, including the details of the last hours of care. These details will often be what haunts the caregivers' thoughts in the months after the death.[44,45] Pediatricians may hear about the death of a child or adolescent who was one of their patients from the news or community members. Pediatricians may be asked to complete the child's death certificate. Even if the pediatrician was not involved in the care of the child at the time of the death, they can still play an important role in supporting the family.

When death occurs by suicide[46] or the use of alcohol or drugs,[47] the emotions experienced by caregivers can be particularly strong and complicated. When death occurs in the context of medical error or malpractice, mistrust of the health care system may further complicate acceptance of hospital-relevant bereavement support. Homicide or injuries that are caused by negligence, such as by drunk driving, often produce intense anger and may overwhelm a prior sense of justice, security, or peace. Pediatricians may consider additional thoughtfulness toward families' mourning or guilt experiences after sudden and unexpected death as law enforcement, death scene investigation, and courts may be involved. Pediatricians can be prepared to help connect families in these complex circumstances to specialized help to include focused support groups and professional

counseling services.[48,49] If the cause of a child's death is concerning for nonaccidental trauma, special considerations beyond the scope of this statement must be addressed.[50,51]

In honor of children as vulnerable community members, pediatricians maintain a duty to continue advocating for public health measures that protect the lives of children and adolescents and subsequently decrease the number of grieving families.

Fetal and Infant Death

Physicians often fail to appreciate the deep feelings of loss and sadness experienced by caregivers and families after fetal loss or miscarriage.[52] Part of recognizing the potential depth of these feelings includes providing support for pregnancy losses and stillbirths for families with whom the pediatrician has an existing relationship.[53,54]

Infant mortality, recognized as death of a child younger than 1 year of age, accounts for more than half of all childhood deaths in the United States. In 2020, infant mortality rates (IMRs) in the United States reached a record low of 5.4 deaths per 1000 live births.[4] Glaring IMR inequity exists across racial and ethnic groups, with an IMR of 4.5 for non-Hispanic white infants, 5 for Hispanic infants, 7.9 for non-Hispanic American Indian/Alaska Native infants, 8.2 for Pacific Islander infants, and 10.6 for Black infants born in the United States in 2019.[55] Pediatricians ought to be cognizant of these inequities and understand the role that social drivers of health and structural racism have in driving these inequities, recognizing how these realities can complicate grief reactions.[56,57]

FAMILY CONSIDERATIONS

Guidance regarding grief is ideally individualized, with attention to relational context and roles within family units.[58] Often parents, aunts, uncles, cousins, and grandparents experience grief warranting inclusive support. Pediatricians may help families explore ongoing meaning making within and across generations,[59] particularly for grandparents and other members of extended families who experience the confounding grief of losing a child and deep care for additionally grieving relatives.[60,61]

SIBLING CONSIDERATIONS

Research has shown that how caregivers cope with the loss of a child has a direct correlation to how well their other children will fare over time.[62–64] Caregivers will understandably feel the burden of managing the normal responsibilities of caregiving, helping their surviving children manage grief, and at the same time processing their own grief. Some caregivers may start to have excessive worry about the well-being of the surviving children. Some report that their grief is so overwhelming that they feel unable to provide the surviving siblings with the attention they need. Thus, helping caregivers get support helps the surviving siblings.[65]

Parts of the sibling's routines, such as school or sports or community events, can provide some familiar structure to the sibling's day in the midst of family change and transition. Returning to routines can help children feel more safe and secure; spending time with family in fun activities or routine activities they previously enjoyed does the same. It might also be important, depending on the circumstances of the child's death, for parents to reassure the child they are safe, that their sibling's death is not their fault, and that the parent and trusted adults are there for them. Children often process feelings through play and so families should recognize that playfulness is not disrespectful or failure to grieve and instead may be cherished as a restorative part of life even during loss. Creating space where children can talk about their sibling, recall memories of their sibling, and look at pictures of their sibling can be helpful. Listening in an attuned way and validating the sibling's feelings represent important components of trauma-informed care for siblings.

The pediatrician is in a unique position to screen for grief impact and provide direct support to the siblings, both immediately after the child's death and in subsequent years as they follow and care for the siblings' health.[66] The bereavement experience of siblings may be long lasting.[67,68] The loss of the sibling is absolute, and its effect ripples through virtually every aspect of the siblings' lives: family, school, social interactions, extracurricular activities, and inner emotional life. Grief may present as anger outbursts, sleep disruption, behavioral issues at school, and/or social withdrawal.[69] It is also common for children to move back and forth frequently between expressions of grief within a single day, and even within a single hour.[70,71] Research has shown that during the first year after the child's death, there are increases in anxiety, depression, and illicit substance use in the siblings before returning to baseline.[72,73] Adolescent-specific bereavement needs may be additionally exacerbated by the high level of identity transition already occurring as part of adolescence.[74,75] An extended period in which an adolescent sibling loses interest in daily activities and events, is unable to sleep or fears being alone, repeats statements of wanting to join the dead sibling, withdraws from peers, experiences a sharp decline in school performance, or refuses to attend school warrant heightened concern.

Initially, and especially if the death of the child has been sudden and unexpected, the caregivers may be overwhelmed by their own grief and, thus, less able to tend to each surviving sibling's physical and emotional needs. Younger children requiring more intensive day-to-day care for things such as feeding and clothing may be especially at risk, but the needs of older children, who may be experiencing untended emotional needs, also warrant attention. Regardless of the age of the siblings,

care from extended family or close friends can be a short- or medium-term bridge while the caregivers absorb the initial shock. When family or friends are not available, other social services may need to be recruited to provide support.

The way siblings respond to the death of a sibling of any age varies depending on the developmental stage of the sibling, including how they understand the concept of death. This response changes as the sibling matures (Table 2)[76] and may also be influenced by the personality of the sibling, the sibling's preexisting mental health, family life stability after the loss, how the sibling's needs are met, parental coping styles with stress, and any experience with prior loss.[77] Additional issues relevant to siblings include survivor guilt, overprotection of the surviving child, the "replacement" or subsequent children, parentification of the surviving child, becoming an only child, new responsibilities for the surviving child, and risk of parent-child role reversal.[78,79] If the death is attributable to a genetic diagnosis and the sibling has not been tested, the pediatrician can discuss testing with the family with sensitive timing. Pediatricians may caringly watch for and even inquire about surviving sibling experiences as part of pediatrician-family interactions (Table 3). Pediatricians can also provide grieving parents with anticipatory guidance on

TABLE 2 Sibling Developmental Stage, Concept of Death, and Supportive Interventions

Age	Development	Concept of Death	Supportive Interventions
Infancy: 0–2 y	• Sensorimotor; • dependent	• Death is perceived as separation or abandonment	• Maximize physical relief and comfort through sensory input (eg, touch, rocking, sucking); • provide comfort with familiar people and transitional objects (eg, toys); maintain routine
Early childhood: 2–6 y	• Preoperational; • imaginative and intuitive	• Highly attuned to caregivers' emotional status and responsiveness; • death is reversible or temporary; • may equate death with sleep or long journey; • may have magical thinking about death; • may associate death with the sorrow of others	• Minimize the child's separation from usual caregivers or provide reliable and consistent substitutes; provide routine and stability; offer reassurance in simple terms; • ask open-ended questions about feelings and experiences; acknowledge sadness; • dispel misconceptions about death as punishment; • provide concrete information about state of death (eg, a "dead person no longer breathes or eats"); • families may consider sharing language and concepts from their spiritual or faith tradition (as relevant)
Middle childhood: 7–12 y	• Concrete; • logical	• Death is irreversible but is unpredictable; • aware that death is personal and can happen to them; • may be interested in what happens after death; • can understand the biological essentials of death (heart stops, etc)	• Foster opportunities for questions and answers; listen actively; • may benefit from specifics about the illness; reassurance that they did not cause the death; • maintain the child's access to trusted loved ones and routines to include opportunities for fun and play; • foster sense of connection and validate feelings; encourage remembering the sibling who died and offer opportunities to talk about memories and feelings
Adolescence: 13+ years	• Identity formation; • abstract considerations with advancing logical functions	• Death is irreversible, universal, personal, but distant; • has the ability to develop physiologic and spiritual explanations of death	• Reinforce formation of meaning, purpose, hope, and value; • allow expressions of anger; • provide privacy while also remaining available; • maintain access to peers; • acknowledge and validate feelings to include sadness, guilt, confusion, etc; • foster routines and also allow for moments of fun together (it's okay to still try to enjoy life)

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TABLE 3 Exemplar Support Questions for Family Members
Exemplar Support Questions
• It's been 6 mo since Sam[a] died, how are you doing?
• Do you talk about Sam[a] at home?
• It's normal when someone you love dies to have all kinds of feelings. How has that been for you?
• When you think about Sam[a], are you able to think about the happy memories, or does it only make you feel sad, scared, or angry?
• Grief can impact every part of our daily lives, how are you doing with your sleep, appetite, and concentration?
• I remember what a great sense of humor Sam[a] had, is that something you think about when you remember him?
• How have things been at work, school, or with friends since Sam's[a] death?
• How have your peer friendships changed since Sam[a] died? (Note: Acknowledge that peer friends don't always know what to say and some friends may drift away because of discomfort with not knowing how to act or interact. If the child knows what would help [like playing video games together and riding bikes without necessarily talking about the loss], they can be encouraged to consider telling a friend that. Or, a trusted adult can help guide the parent of a friend on helpful behaviors.)
• What do you remember about spending time with Sam[a] at this time of the year?
• Do you know any other caregiver or child who has had a child or sibling die? Have you talked with them? How did that go?
• Who can you talk to when you feel really sad or upset about Sam's[a] death? Who can you talk to when you feel numb or disassociated from remembering the fullness of Sam's[a] life?
• How do you think your caregiver or child is doing since Sam[a] died? Are you worried about them?
[a] Insert personalized name.

how to identify and address present and future grief reactions that can occur among their surviving children.

Survivor Guilt

One of the most common responses to the death of a sibling is survivor guilt, especially in situations of unexpected death.[80] It can be beneficial for the pediatrician to reassure and gently explain to the sibling (aged preschool and up) how their thoughts, words, or actions in no way caused their sibling's death. Fear may occur in accidental or abusive deaths if the sibling feels they "didn't do enough" to save their sibling. Sibling guilt is also common and especially problematic if the sibling was a donor (eg, bone marrow) and the treatment was not successful.[81] Again, in these situations, it can be beneficial to reassure the sibling about the lack of responsibility regarding the child's death. All these associated thoughts and memories have the potential to become emotionally crippling unless talked about and processed in counseling or psychotherapy.[82]

Overprotection

Caregivers commonly fear that their surviving child or children will also die.[83] These fears and the associated anxiety may lead to an atmosphere of anxiety in the home as well as problematic overprotection of surviving siblings, such as restricting age-appropriate activities.[84] Behavior problems in these siblings may stem from a fear that they may also die or from the feelings of the need to break free from stifling overprotection. The pediatrician can be sensitive to these possibilities and assess the situation as able, through conversations with the sibling directly and/or with the caregivers. If significant overprotection is suspected, the pediatrician can help the caregiver understand that although fearful overprotection may be part of the coping process, it can be harmful to siblings. The pediatrician can then help families access support through professional counseling.

Idealization and the Replacement Child

After the death of a child, caregivers and extended family may speak often of the child, put up many photos around the house, leave the child's bedroom untouched, and/or develop rituals to honor the child. These activities may help caregivers process grief and honor the child who is now missing. Surviving children benefit from open conversations about memories and special family moments with opportunity for them to ask questions and participate without feeling pressured. Siblings may worry that they do not measure up to the child who has died, or they may feel neglected or experience feelings of jealousy or resentment.[85] In instances when an infant is born after the death of the child, existing siblings may also worry that they were not enough, and the newest child may grow to believe that they were born to replace the sibling who died.[86,87] Such feelings may impact one's sense of identity and may lead to behavioral problems in the siblings.[88] The pediatrician can be aware of these potential dynamics, vigilantly assess for their presence, and offer counsel to the family when guidance is needed. With time and helpful support, the desire to honor the loved one who is gone can be balanced with attention and care for the surviving siblings in a way that is healing and healthy.

Assuming the Parental Role

Older siblings commonly assume a parental role when caregivers are absorbed with their own grief.[84] Although this reaction may be adaptive in the early months of the caregivers' grief journey, it may become maladaptive if it continues. The pediatrician can look for situations of

parentification of older siblings and help the caregiver and surviving sibling to relinquish this distortion of family roles.[89]

Providing Sibling Support

The loss of a sibling includes loss of the roles inherent in the relationship the surviving children had with their sibling.[90] For example, if the child had been living with illness, the surviving siblings may have played roles as helping caregivers. It is important to note that the children may not be sharing their feelings of loss or sadness with their caregivers because they do not want to burden the caregivers further.[91] With the understanding of the family structure and dynamics, the pediatrician is well-positioned to assess for those relationships. The pediatrician can also assess for prior experiences with loss that the sibling may have—the death of a grandparent or pet, a divorce, or a move—that may inform the reaction to this new loss.

Providing support to siblings shortly after the death of their sibling will also include assessing the child's understanding of what has happened.[76,89] The pediatrician may feel equipped based on their training in child development and communication to talk with children about death or to advise the caregivers in how to talk to the children about death and to support ongoing sibling sense of connection.[92] At a minimum, the pediatrician can be a bridge to help find professional support for the children so that they have a safe place or way to express their feelings.

As the sibling matures and develops, the pediatrician can track emotional development and inquire specifically about how the sibling is experiencing the grief over time.[93] A pediatrician may consider placing a reminder message of a deceased sibling in the electronic or paper medical record as a reminder to the care team whenever a patient is being seen. The well-child visit is an especially appropriate time to communicate care and assess for grief. It is important that pediatricians gently invite siblings and caregivers to share about how they are currently experiencing their grief. Sensitive questions can begin these conversations (Table 3). Even if a sibling or caregiver of the deceased child chooses not to respond at length, they may appreciate having their child or sibling remembered and the questions clearly demonstrate that the provider is a caring resource. Cultivating compassion via active listening to the family members and acknowledging their grief is important for healing.

Although the child may not wish to discuss their sibling who has died, this reaction may change over time.[94] It is always a good idea to name the loss gently and give the child permission to speak about their feelings and struggles. A prompt from a trusted person normalizes the grief and opens the door, in a safe place, for the child to process a life-changing event for which the impact shifts over time.[95]

In addition to the clinical encounter, pediatricians may recommend professional grief support for the siblings. This support may be in the form of one or more of the following: one-on-one work with a professional therapist, summer camps, one-on-one work with a school counselor, or a support group with other bereaved siblings, which helps the child see that they are not alone. The pediatrician can be an effective resource by facilitating referral and linkage for families to have access to the appropriate and available mental health providers and support groups and organizations in the community. Peer support groups are preventive in nature and appropriate for most bereaved siblings, whereas psychosocial treatments by professionally trained personnel are appropriate to address severe or persistent grief experienced by a subset of the bereaved.[96] Research has shown that children are resilient and that with effective grief supports—family, community, professional—they can process the loss and adapt to life without their sibling.[69] There are many excellent children's books as well as adolescent and young adult or teen books that deal with the death experience that may be helpful.[97,98]

CULTURE AND COMMUNITY CONSIDERATIONS

Grief is both a universal and deeply personal phenomenon; however, culture influences all aspects of the grief experience in fundamental ways.[5] Cultural differences exist not only between religions and cultures, but also within subgroups of the same culture or religion. Knowledge of all the different variations in the meaning and practices surrounding bereavement is not possible, but an understanding of the different dimensions of the grief process may be helpful to guide the clinician in navigating this subject with families of diverse cultural and religious backgrounds.[99] The following are aspects of grief and bereavement that are influenced by culture.

The Meaning of Death

Different cultural groups often have common understandings of the meaning of death. These are often heavily influenced by religious, spiritual, or existential beliefs.[100] Although a belief in the immortality of the soul and a life after death is a common theme, the emphasis and details of what happens after death vary significantly between religions.[101] Additionally, some religions posit that all life events, including death, are predetermined and, therefore, could not have been prevented. This belief tends to reduce the prominence of guilt as an emotion observed among mourners. Little is known about whether and how these beliefs influence the internal experience of grief.[102]

Expressions of Grief

Some cultures may allow, normalize, or encourage the outward expression of emotional pain as a healthier alternative to "bottling" up of emotions and suffering internally.[103] In these cultures, the outward expression of grief may be expected and lack thereof may be interpreted as apathy or as a sign of not caring about the person who died. Other cultures value restraint in the expression of emotions and value "stoicism." Again, little is known about the corresponding internal cognitive or emotional experiences associated with loss in different cultures.

The Role of Hospital Clergy and Community Leaders

Hospital chaplains may be offered as a resource in helping families facing loss. Chaplains can help provide access to cultural practices surrounding terminal diagnoses or religious traditions such as last rites. Hospital chaplains may serve as a direct support for caregivers and may additionally help connect interested families with members of communities with which the family identifies.

The role of religious figures in the practices surrounding death and in the spiritual care of the bereaved varies across cultures and religions. For example, Islamic religion has no priesthood and religious leaders do not have a spiritual authority. Their role tends to be restricted to knowledge and implementation of the religious laws and traditions. In Christianity, priests or pastors may be viewed as being endowed with spiritual insight or authority. In Judaism, the rabbi may serve as a spiritual leader and religious teacher. Religious leaders may have varying levels of involvement or engagement in providing spiritual guidance and comfort for the bereaved based on spiritual role within the community and family preference. Cultural factors may significantly influence practices and traditions among groups even within the same religion.

Burial and Postdeath Physical Care

Traditions associated with burial are also influenced by religious traditions. Rituals surrounding the timing of burial and the treatment of the deceased body, including washing, embalming, and viewing of the deceased vary widely between religious and cultural groups.[104] For example, although in some cultures cremation is the norm for treatment of the body, other cultures consider cremation as mutilation of the body. In some cultures, all medical equipment, such as breathing tubes or intravenous lines, are required to remain with the body for burial rather than to undergo removal after time of death.[105]

Mourning

Mourning traditions may also be culturally driven and often impact the societal expectations of acceptable behavior of the bereaved.[106] The amount and quality of emotional and material support provided to the bereaved may vary, with some societies providing the bereaved with traditionally set periods of companionship, food, and other material support.[107] Cultural traditions may also govern the length of mourning period and assign different mourning roles and periods to family members.

Gender Roles

Gender differences in the expression of grief is present across societies, with men often expected to show more restraint in the expression of pain than women in certain cultures and communities.[108] Additionally, the gender of a deceased child may have special implications in certain societies. For example, in some patriarchal societies, a male child provides an important economic advantage for families. In some matriarchal societies, a female child may be valued for future caregiving roles for aging relatives. Therefore, the loss of a child can have a social or relational significance extending beyond what is customarily observed during bereavement.

Nature of Relationships

Culture determines the nature of relationships between individuals and often the strength of the emotional attachment within these relationships. Most cultures acknowledge the strong attachment that caregivers have with their children. However, in some societies in which infant and child mortality is high and children are not uniformly expected to survive, caregivers may intentionally avoid strong emotional attachment with young infants and children to protect themselves from the intense emotions associated with bereavement. This may be perceived as abnormal or callous in other cultures in which the loss of a young infant or a child is a rare and unexpected occurrence.

Cause of Death

Cultural and religious attitudes toward suicide may complicate the bereavement process. These may include the heightened social stigma associated with mental illness and suicide in some cultures.[109] Death attributable to mass casualties, such as school shootings,[110] war,[111] or political conflict, may also be associated with a unique set of complex emotions including guilt at having survived or having been positioned in a place of conflict, or at delaying grief because of preoccupation with one's own survival. Also, grief for death by war can be exacerbated by multiple deaths and by the loss of social and material support systems. In addition to religion, tradition, and geography, cultural variations based on political history and collective trauma of a people may influence their concept of death and grieving. Acute loss and bereavement may be compounded by the historical trauma

and continuing inequities, marginalization, and dispossession. Social and structural inequities exist in access to bereavement support according to racial and ethnic, rural and urban, socioeconomic, and educational domains.[112]

PEDIATRIC ROLE

The death of an infant, child, or adolescent is a devastating and traumatic experience for a family. The pediatrician can consider tangible forms of care, such as writing a personalized condolence letter or making a phone call to acknowledge the family's loss, affirm the dignity of the patient, and share empathy.[113] Content may be personalized with the child's name and a special memory of the child.[114] The pediatrician may consider offering continued ongoing correspondence with the family at special times, such as the child's birthday, the anniversary of the child's death, or special holidays for the family. Pediatricians may consider attending a celebration of the child's life or funeral service in honor of the child based on existing relationship with the family.[115]

Pediatricians have a special role in honoring culture as part of grief care.[98] Welcoming a conversation with the family about their traditions and preferences may be helpful and appreciated by the family. Showing respectful and sensitive interest in the cultural traditions of families is not only helpful in improving the clinician's knowledge and cultural competence and awareness but can also be helpful in building trust with the family.[104] Although it may feel awkward, humbly and sensitively asking families directly about their preferences is recommended and usually well received.[116]

Pediatricians may be in a unique position to offer grief resources to the child's school through child life services or social work or other interdisciplinary expertise. Pediatricians may consider extending support to other families or children at the pediatric practice who may know the child or family as well as office staff. Pediatricians benefit from acknowledging the impact of a child's death on their own well-being with attentiveness to caring for oneself and one another as a professional community.

SUMMARY

The pediatrician is in a special position to help families through their grief experience and can partner with interdisciplinary colleagues and community resources to maximize support for families.[117] The ultimate goal of such support is to help bereaved families realize they are not alone, to foster a culturally sensitive, trauma-informed approach to grief, to maximize adjustment and adaptation after the death of a child, and to promote the best interests of a grieving family.[118]

Recommendations

Pediatricians should consider the following regarding this support:

1. Respect that compassion is a universal language of care and can be expressed through taking the time to listen and provide emotional support to a family.
2. Realize how knowledge about the structure of a family and their intrafamilial and extrafamilial support systems may be important in recognizing each family's unique needs and may be helpful in understanding some of the cultural aspects of the family's concept of health and illness as well as death and dying.
3. Consult with resources to learn about the cultural and religious traditions surrounding death and bereavement to include culturally appropriate parental roles of grieving.[106]
4. Become aware of personal beliefs, values, and practices about grief and death and reflect on how these may bring implicit and explicit biases; consider opportunities for formal training in cultural humility, cultural sensitivity, and implicit bias.[119]
5. Recognize that failing to acknowledge the death of an infant, child, or adolescent who was a patient can contribute to the family's pain. Pediatricians should consider visiting their seriously ill or dying patients in the emergency department or PICU, as able. A telephone call or a face-to-face visit with the caregiver(s) of a patient who has died is encouraged.
6. Follow-up with and provide guidance to surviving siblings who are still patients. Providing guidance to siblings requires recognition of the special issues experienced by grieving siblings.
7. Recognize the potential of support groups in helping caregivers adapt to grief after their child's death to include substance misuse resources, as may be relevant. Be aware of the presence of such groups in the community and provide this information to families, support families in finding support groups and organizations with their permission, and if families initially decline, then gently reassess whether they are interested in this information in the future.
8. Be aware that when the death of a child or adolescent is unexpected or sudden, such as by suicide, through the use of alcohol or drugs, from sudden and unexpected infant deaths, in a motor vehicle crash, or through homicide, the grief for caregivers may be especially intense and accompanied by guilt and/or anger.
9. Consider referral for counseling or psychotherapy as additional layers of support for families experiencing the death of a child.

10. Understand that the duration of grieving within a family after the loss of a child is longer than many expect, and families often hold a cherished, forever connection to the child.

RESOURCES

- The American Academy of Pediatrics Resilience Curriculum: Resilience in the Face of Grief and Loss. Web site: https://www.aap.org/en/learning/resilience-curriculum-resilience-in-the-face-of-grief-and-loss/
- The Compassionate Friends. A national self-help support organization with >600 local chapters. Many local chapters have special groups for siblings. Web site: http://www.compassionatefriends.org
- Courageous Parents Network. A nonprofit organization with resources – including professionally produced videos of bereaved parents – for families caring for children living with serious illness, including bereavement materials for parents, grandparents, and siblings. Web site: https://courageousparentsnetwork.org/
- The Dougy Center. A nonprofit providing support to grieving children. Web site: https://www.dougy.org/
- Family to Family Health Information Centers. Family-led centers funded by the Health Resources and Services Administration (HRSA) staffed by knowledgeable, skilled family members with first-hand experiences and understanding of challenged faced by families of children with complex, diverse needs. Web site: https://familyvoices.org/lfpp/f2fs/
- First Candle. Support for families who have experienced a stillbirth or the loss of an infant. Web site: http://firstcandle.org
- National Alliance for Children's Grief. Feature enables a search of individual and group support by state. Web site: http://www/nacg.org/find-support
- National Alliance for Grieving Children. A nonprofit organization that raises awareness about the needs of children and teens who are grieving a death and provides education and resources for anyone who supports them. The search feature enables a search for support groups by state. Web site: https://childrengrieve.org/find-support
- Missing Pieces. A coalition to support the availability and quality of resources for those impacted by pediatric deaths through education, program development, and collaboration. Web site: https://www.missingpiecesgrief.org/
- National Alliance on Mental Illness (NAMI). A grassroots organization dedicated to building better lives for those affected by mental illness. Web site: https://nami.org/Home
- SHARE. Support for those touched by the death of an infant through miscarriage, stillbirth, or newborn death. Web site: http://www.nationalshare.org
- Sudden Unexplained Death in Childhood (SUDC) Foundation. Foundation with a mission to promote awareness, advocate for, and support those affected by sudden unexpected or unexplained death in childhood. Web site: https://sudc.org/#
- Survivors of Suicide. Support for those who have lost a loved one to suicide. Web site: http://www.survivorsofsuicide.com
- Camps for grieving siblings such as Bereavement Camps, Siblings Grief Camps at Sudden Unexplained Death in Childhood Foundation, or Military One Source. Web site: https://www.militaryonesource.mil/casualty-assistance/grief-support/bereavement-camps-a-place-to-grieve-and-heal
- Hotline – 988 Suicide and Crisis Lifeline – Available 24 hours per day in English and Spanish

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CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Fecal Microbiota Transplantation: Information for the Pediatrician

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abstract

Fecal microbiota transplantation (FMT) involves the delivery of an entire microbial community from a healthy donor to a recipient with the intention of ameliorating or curing a specific disease. Current evidence strongly supports a role for FMT in the treatment of *Clostridiodes difficile* infection, with cure rates of approximately 80% to 90%. This success has led to increasing attention for FMT as a potential therapeutic intervention for other conditions associated with disturbances of the intestinal microbiome, including inflammatory bowel diseases, autism spectrum disorder, and obesity. This clinical report endorses the joint society statement by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition and is meant to provide the general pediatrician with a broad overview to enable appropriate guidance to families seeking FMT as treatment of a child's condition.

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Dr Oliva-Hemker conducted the literature search, conceptualized, wrote, and revised the manuscript, and considered input from all reviewers and the board of directors; Drs Kahn and Steinbach assisted with the conceptualization, writing, and revisions; and all authors approve of, and take responsibility for, the final publication.

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INTRODUCTION

The past 2 decades have led to an explosion of interest and research into the gastrointestinal microbial environment, which consists of 500 to 1000 bacterial species in addition to viruses, archaea, fungi, bacteriophages, and other unicellular organisms.[1] The number of bacterial cells in the body is similar to the number of human cells, approximately 3×10^{13} (30 trillion), with the greatest abundance of bacteria residing in the colon.[2] The composition of the gut microbiome is unique in each individual. Most of the colonization occurs in the first few years of life, but subsequently the microbiota remains relatively stable and distinct to each person into adulthood, even if transient changes occur with diet and medications.[3] The gut microbiota has far-reaching impact on health and disease, playing an important role in metabolism, protecting the intestinal barrier, and maintaining immune homeostasis.[1] Disturbances in the composition of microbial communities have been associated with a broad array of autoimmune, metabolic, cardiovascular, and gastrointestinal disorders, and there are multiple reviews available on these topics.[4–6]

Fecal microbiota transplantation (FMT) is typically defined as the transfer of stool from a "healthy" donor to another individual with the intent of restoring the recipient's imbalanced microbiome to a "healthy" one, thereby ameliorating or curing a specific disease.[7] FMT is not itself a new concept. Documentation by the Chinese medical practitioner, Ge Hong, in the fourth century describes the use of human fecal suspensions called "yellow soup" for the treatment of diarrheal diseases.[8] The first reported use of FMT in modern medical literature, from 1958, describes 4 adults with severe pseudomembranous enterocolitis who were cured after receiving fecal retention enemas.[9] Since that initial case series, there have been thousands of patients reported in the medical literature who have been cured of *Clostridioides difficile* (formerly *Clostridium difficile*) infection (CDI) after FMT, and this success has led to increasing accounts in the media and greater public interest in this procedure. This clinical report highlights the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition joint position paper with the purpose of summarizing current evidence and providing expert opinion regarding the use of FMT in the management of CDI.[10]

The purpose of this clinical report is to present a broad overview of FMT to enable pediatricians to identify those patients who might benefit from timely referral for recurrent CDI and may be considered candidates for this procedure. Clinicians should also be aware of other forms of microbial therapies on the horizon. It should be noted that in the United States, fecal microbiota is classified as both a biological agent and drug and, therefore, subject to regulation by the US Food and Drug Administration (FDA). FMT has not been given market approval for a specific clinical indication and is still considered investigational. There have been no controlled trials of FMT in the pediatric population. However, in 2013 the FDA announced that it would exercise "enforcement discretion" for FMTs being performed for the treatment of CDI.[11] This means that if a health care provider believes that it is clinically indicated, FMT can be administered to patients with CDI without the need for an investigational new drug application (IND). However, an investigational new drug application is required when FMT is used for research purposes or to treat conditions other than CDI. Even though health insurance plans do not, as a matter of course, cover treatments without FDA approval, providers with specialty expertise can work with payers in certain circumstances when such treatments appear promising.

FMT IN THE MANAGEMENT OF CDI

C difficile is a spore-forming Gram-positive anaerobe that is a major cause of hospital-associated diarrhea and is the most common infectious cause of antibiotic-associated diarrhea.[12] It is a serious public health challenge with an estimated annual national burden of more than 476 000 cases and an increasing incidence since 2000 that has only recently begun to stabilize in the hospital setting but continues to rise in the community.[13] In hospitalized children with symptomatic CDI, two-thirds have complex chronic conditions such as malignancy, hematologic, immunologic, cardiovascular, neuromuscular, gastrointestinal, and respiratory conditions.[14] Children with inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis, have rates of CDI that far exceed those seen in the general population.[15]

Symptomatic CDI is typically defined as 3 or more liquid stools in a 24-hour period with *C difficile* toxins identified in the diarrheal stool specimen. Clinical manifestations can vary from mild diarrhea and abdominal discomfort to severe bloody diarrhea with pseudomembranous colitis to toxic megacolon and peritonitis, which, fortunately, are extremely rare in children. Although most patients will have resolution of symptoms, *C difficile* spore production can make the organism difficult to eradicate, and up to 30% of patients treated for CDI experience a recurrence after discontinuation of *C difficile*-directed antibiotic therapy. In those with a recurrence, the rates of further occurrences can be as high as 65%.[16] Risk factors for recurrent CDI in children include prior use of antibiotics and acid suppression medications, recent surgery, malignancy, solid organ transplantation, and presence of tracheostomy or gastrostomy tube.[17–19]

After the initial case series reported in 1958, global experience with FMT for treating CDI developed in the adult population based on case reports and case series that included hundreds of patients.[20] Then in 2013, the first adult open-label randomized controlled trial comparing FMT delivered via nasoduodenal tube with vancomycin therapy showed superiority of short-course oral vancomycin followed by FMT over vancomycin alone in the treatment of recurrent CDI (81% vs 31%, $P = .008$).[21] The pediatric experience began in 2010 with the case report of a 2-year-old child with CDI refractory to multiple courses of antibiotics and probiotics. FMT delivered via nasogastric tube led to symptom resolution and stool testing negative for *C difficile* toxin 6 months after the procedure. Two years later, a 16-month-old received the first successful pediatric FMT delivered via colonoscopy.[22,23] Subsequently, numerous adult studies, including large observational studies, randomized controlled trials, and registries have now established that FMT is 80% to 90% effective in curing CDI in adults and has a significant advantage over vancomycin and fidaxomicin.[21,24–26] Although controlled trials are not available in pediatric patients, a large multicenter cohort of 372 children reported CDI eradication rates of 81% after a single

FMT and 86.6% after 1 or 2 FMTs.[27] These positive outcomes have led to the inclusion of FMT in therapeutic algorithms and guidelines throughout the life span, including the clinical practice guidelines for CDI by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America.[28] In most cases, cure of CDI—typically defined as resolution of symptoms without recurrence within 2 to 3 months after the procedure, can be achieved with only 1 FMT, although some patients may require a second FMT or further treatment with antibiotic therapy.

Indications for consideration of FMT in pediatric patients with CDI have been recommended by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition.[10] These include a history of recurrent CDI within 8 weeks of receiving treatment, moderate CDI not responsive to standard treatment, or severe or fulminant CDI not responsive to therapy, which is, fortunately, rare in pediatric CDI. It is recommended that a pediatrician consider referring a patient at the time of the first (or second) CDI recurrence to a center with specialists, such as pediatric infectious disease or gastroenterology providers who are experienced with the FMT procedure.

Given that antibiotic use has been identified as the most common associated risk factor for CDI, disruption of the health intestinal microbiota, also called "intestinal dysbiosis," appears to be at the core of disease pathogenesis.[29,30] Although the mechanisms by which FMT resolves CDI remain unclear, the procedure has been shown to (1) result in durable restoration of normal gut microbial environment as manifested by increased relative abundance of *Bacteroidetes* (phylum containing multiple symbiotic, beneficial bacterial species) and decreased abundance of *Proteobacteria* (phylum including many pathogenic bacteria); (2) increase bacterial diversity; (3) result in a microbiome composition more similar to the donor profile; and (4) restore normal fecal bile acid composition.[31–33]

BRIEF OVERVIEW OF FMT

A detailed discussion regarding the FMT procedure itself is beyond the scope of this report but can be found in multiple publications both for adults and children.[10,34] Patients should be referred to centers that have experience with this procedure and are familiar with best practices, including the handling of the fecal suspension, delivery modalities, informed consent, and patient follow-up. Although national guidelines have been developed to standardize FMT, including donor screening and selection, this is a procedure that still contains variability across institutions.[10]

The process of FMT involves the selection and screening of an appropriate "healthy" donor and then the administration of the fecal material into the recipient's gastrointestinal tract. Donor screening requires a rigorous process to evaluate risk of infectious diseases and a history of disorders potentially associated with perturbation of gut microbiota, such as chronic gastrointestinal diseases, autoimmune disorders, and obesity. Recommendations from various medical groups and experts employ a combination of screening questionnaires to exclude high-risk donors, donor blood, and stool tests to evaluate for enteric pathogens and serologic evidence of infections.[34]

Donors can be known or unknown to the recipient. Typically, donors are requested to complete an extensive questionnaire similar to that administered for blood donation, undergo health evaluation by their primary care provider, and submit blood and stool samples to evaluate for transmittable infections. With the increasing need to screen for more infectious agents, the ability for individual clinicians to maintain a robust screening process and keep up with regulatory and safety concerns has become more difficult. This has led to an emergence of both institutional and third-party stool banks, typically operating under the regulatory authority of the FDA in the United States, to facilitate a more cost-effective, standardized, and traceable process in the collection, storage, and distribution of feces from screened undirected healthy donors. Using banked stool also reduces the likelihood of confidentiality concerns for the donor because they are not directly known to the recipient. Typically healthy, younger individuals (<40 years) with normal BMI are preferred as potential donors, and it is not uncommon for the vast majority of potential donors to be excluded from stool donation after screening medical evaluation.[35]

If FMT is being performed with an identified donor known to the recipient, the processing of the fresh fecal material, such as homogenizing with saline and filtration, is often performed immediately before administration. If donor feces are to be banked, after processing, it is divided into aliquots, preferably with a cryoprotectant, and stored at −80°C. Fecal material for FMT can be delivered via oral capsules; nasogastric, nasoduodenal, gastrostomy, or jejunostomy tube; enema; or colonoscopy. For children and adults, most FMTs in the United States are performed by gastroenterologists who acquire material from donor stool banks and administer the transplant via colonoscopy, but in some institutions, infectious disease specialists also perform FMT.[26] Safety of intragastric administration has been reported in children.[36]

SAFETY AND POTENTIAL ADVERSE EVENTS

FMT is vulnerable to a misperception that it can be performed safely as a "do-it-yourself" at-home procedure.[37] Lack of access to a provider who performs FMT, perceived delay in being able to obtain an FMT, associated cost, or a growing preference to managing conditions with little medical evidence have led to individuals

performing FMTs at home either on themselves or their children using information from the internet or social media. In these do-it-yourself cases, recipients typically receive stool from a donor who is known to them. A clear risk in performing FMT in this manner is that the donor is not rigorously screened for chronic conditions and communicable diseases as is currently performed in clinical settings. There is also potential risk of damaging the colon or rectum while administering the enema. FMT also presents particular ethical issues that impact children, who are a vulnerable group because parents or guardians give consent on behalf of the child.[37] It is not uncommon for parents to believe that FMT is "safe" because they view it as more "natural" than medications.[38]

Safety remains one of the greatest concerns with this procedure. Patients receiving FMT need to be monitored for procedure-related adverse reactions, including transmission of significant infections (eg, viral hepatitis or resistant organisms), hospitalizations, life-threatening events, and death. It is important to highlight that the FDA policy of enforcement discretion and the wide adoption of FMT in clinical practice has occurred without standard investigatory pathways being undertaken, such as larger randomized controlled trials that provide safety data before a product comes to market. Encouragingly, infectious short-term adverse reactions have been quite rare—in the range of 1% to 2%—even for immunocompromised adults.[25,39,40] However, serious infections have been highlighted by an FDA report in 2020 of 2 adult cases, including 1 fatality, of extended-spectrum β-lactamase-producing *Escherichia coli* infections that were suspected of being transmitted via donor stool that had not been screened for the organism.[41] The need for appropriate donor screening was further highlighted after the announcement in March 2020 by the World Health Organization designating coronavirus disease 2019 as a pandemic.[42] In the same month, the FDA provided an alert that informed of the potential risk of FMT transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and recommended that any FMT products manufactured from stool donated on or after December 1, 2019 should not be used clinically until additional tests and criteria were met, including donor screening for SARS-CoV-2 diagnosis and testing to detect the presence of SARS-CoV-2 virus or RNA in the donor stool.[43] This led to Openbiome (Cambridge, MA), a nonprofit stool bank, discontinuing the provision of FMT material except in emergency cases from July 2020 until May 2021 while the company worked to develop and validate a test for SARS-CoV-2 in stool. However, providers were still able to obtain fecal material for emergency cases from a stock the company had collected before December 1, 2019.

Other short-term adverse events have been reported and may vary by route of FMT delivery. These include aspiration pneumonia when FMT is delivered via nasogastric or nasoduodenal and perforation when administered via colonoscopy.[27,39] The potential for other long-term consequences of FMT remains unknown. Although new conditions have been reported after FMT, no cause and effect has been proven.[44] The intestinal microbial community's impact on human health and disease is significant, and although at this time we do not have clear knowledge as to whether transferring the microbiome from one individual to another will lead to long-term adverse effects, this concern may be more than theoretical, because transferring the microbiome in laboratory animals can increase the risk for certain chronic and/or autoimmune diseases associated with a particular microbiome.[45] The FDA requires that before FMT, informed consent be obtained and include a statement highlighting that the procedure remains investigational and that there are unknown future risks associated with FMT, including increased risk of developing a disease phenotype (eg, obesity) or a chronic disorder (eg, an autoimmune condition) that may be associated with intestinal microbiome changes.

FMT AS POTENTIAL THERAPY FOR OTHER DISEASES

The increasingly rapid acquisition of information about the human gut microbiome, the clinical success of FMT for CDI, and the explosion of interest on these topics in the media have led many patients to seek FMT for a variety of indications other than treatment of CDI, despite limited data to suggest efficacy in other conditions. As such, it is important for the pediatric medical community to understand the current state of research in FMT. Similar to the intestinal dysbiosis associated with CDI, there is mounting evidence that alterations in microbial composition may result in disturbances in metabolic processing or localized inflammation and may also play a significant role in multiple disease conditions, such as Crohn disease, ulcerative colitis, obesity, metabolic syndrome, autism spectrum disorder, and reduction of intestinal multidrug-resistant bacteria.[46–52] However, most of these conditions are more complicated than CDI, and the high efficacy of FMT for CDI has not been replicated in other chronic conditions for which results have been modest at best, even with repeated FMTs and variable across patients. Therefore, at this time, there are insufficient data to recommend FMT as treatment of any of these indications in clinical practice, and currently FMT use for conditions other than CDI should be limited to the research setting.

EMERGENCE OF MICROBIOTA-BASED THERAPIES BEYOND FMT

With the significant rise of FMT for CDI since 2013, came the emergence of nonprofit stool banks such Openbiome, which started in 2012 and subsequently became the principal supplier within the United States for most institutions and practices offering FMT, including those that had initially offered FMT by screening donors and processing the stools themselves. Obtaining material from a

stool bank was advantageous to FMT providers, because as time went on, the expected screening process became more rigorous and laborious for individual clinical providers. The safety concerns involved with FMT, the realization that the demand for fecal material could outstrip supply, the decreased accessibility of FMT to many patients because of geographic location and the coronavirus disease 2019 pandemic, and the inherent variability of human feces led to pursuit of other options.[53] Inspired by the success of FMT for CDI, the race to find pharmacologic alternatives to FMT have led to the development of well-defined mixtures of selected microorganisms designed according to their proposed roles in the microbiota against CDI. Currently, several microbial therapeutics are in various stages of clinical trials in adults for CDI. The hope for the products, once approved, is that they will work similarly or better than FMT and will be simple to administer, reproducible, and cost-effective. Additionally, the development of standardized, laboratory-derived microbiota therapeutics has enabled research in a variety of conditions other than CDI.[54,55]

Although the anticipated benefit of these commercial microbiota therapeutics is appealing, they will likely come with their own set of challenges for children. Initial approval of any of these is likely to be for use in adults only, because these agents have not yet been studied in pediatric populations and there are no safety or efficacy data to inform therapy decisions in children. Although they could be prescribed for children for off-label use, accessibility will be difficult for pediatric patients because of lack of insurance coverage and lack of clear guidance on dosing. Inappropriate prescribing may also occur as patients may demand, and providers may prescribe, such products for conditions for which patients are unlikely to benefit. As with FMT, ensuring that these therapies are of reasonable cost and are covered by both public and commercial insurance will be key to increase availability to patients and reduce disparities in access to care. It is also important to advocate that clinical trials for microbial therapeutic products include pediatric populations.

SUMMARY

1. There are no prospective pediatric clinical trials using FMT to treat CDI.
2. Studies support the use of FMT in pediatric patients with moderate to severe or recurrent CDI.
3. FMT is not recommended for the clinical treatment of any other medical conditions at this time.
4. Do-it-yourself, at-home FMT should not be performed in children for safety reasons.
5. It is recommended that FMT be performed in a center with experience in the procedure.
6. There is a lack of regulatory standards for fecal preparations for FMT.
7. The long-term effects of FMT are unknown.
8. The field of microbial therapies is anticipated to quickly advance and potentially bring commercial products for the treatment of CDI.

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ABBREVIATIONS

CDI: *Clostridioides difficile* infection
FDA: US Food and Drug Administration
FMT: fecal microbiota transplantation

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