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Prenatal Versus Postnatal Tobacco Smoke Exposure and Intensive Care Use in Children Hospitalized With Bronchiolitis

Michelle D. Stevenson, MD, MS; Jonathan M. Mansbach, MD, MPH; Eugene Mowad, MD; Michelle Dunn, MD; Sunday Clark, ScD, MPH; Pedro A. Piedra, MD; Ashley F. Sullivan, MS, MPH; Carlos A. Camargo, Jr., MD, DrPH

From the Department of Pediatrics, University of Louisville, Louisville, Ky (Dr Stevenson); Department of Medicine, Boston Children's Hospital (Dr Mansbach), Department of Emergency Medicine, Massachusetts General Hospital (Ms Sullivan and Dr Camargo), Harvard Medical School, Boston, Mass; Department of Pediatrics, Akron Children's Hospital, Akron, Ohio (Dr Mowad); Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Children's Hospital of Philadelphia, Philadelphia, Pa (Dr Dunn); Department of Emergency Medicine, Weill Cornell Medical College, New York, NY (Dr Clark); and Departments of Molecular Virology and Microbiology, and Pediatrics, Baylor College of Medicine, Houston, Tex (Dr Piedra)

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Address correspondence to Michelle D. Stevenson, MD, MS, 571 S. Floyd St. Suite 300, Louisville, KY 40202 (e-mail: michelle.stevenson@louisville.edu).

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Abstract

Objective: Among children hospitalized with bronchiolitis, we examined the associations between in utero exposure to maternal cigarette smoking, postnatal tobacco smoke exposure, and risk of admission to the intensive care unit (ICU).

Methods: We performed a 16-center, prospective cohort study of hospitalized children aged <2 years with a physician admitting diagnosis of bronchiolitis. For 3 consecutive years, from November 1, 2007 until March 31, 2010, site teams collected data from participating families, including information about prenatal maternal smoking and postnatal tobacco exposure. Analyses used chi-square, Fisher's exact, and Kruskal-Wallis tests and multivariable logistic regression.

Results: Among 2207 enrolled children, 216 (10%) had isolated in utero exposure to maternal smoking, 168 (8%) had isolated postnatal tobacco exposure, and 115 (5%) experienced both. Adjusting for age, sex, race, birth weight, viral etiology, apnea, initial severity of retractions, initial oxygen saturation, oral intake, and postnatal tobacco exposure, children with in utero exposure to maternal smoking had greater odds of being admitted to the ICU (adjusted odds ratio [aOR] 1.51, 95% confidence interval [CI] 1.14–2.00). Among children with in utero exposure to maternal smoking, those with additional postnatal tobacco exposure had a greater likelihood of ICU admission (aOR 1.95, 95% CI 1.13–3.37) compared to children without postnatal tobacco smoke exposure (aOR 1.47, 95% CI 1.05–2.04).

Conclusions: Maternal cigarette smoking during pregnancy puts children hospitalized with bronchiolitis at significantly higher risk of intensive care use. Postnatal tobacco smoke exposure may exacerbate this risk. Health care providers should incorporate this information into counseling messages.

Keywords: bronchiolitis; cigarette smoking; intensive care unit; respiratory syncytial virus; tobacco

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What's New

Maternal cigarette smoking during pregnancy puts children hospitalized with bronchiolitis at significantly higher risk of requiring intensive care. Postnatal tobacco smoke exposure may exacerbate this risk. Health care providers should incorporate this information into counseling messages.

In the United States, bronchiolitis causes approximately 290,000 emergency department (ED) visits each year. Approximately 26% of these children are admitted to the hospital, with a median hospital length of stay of 2 to 3 days. Although the overall mortality rate is low, 3% to 5% of infants with bronchiolitis who visit the ED require mechanical ventilation and admission to the intensive care unit (ICU).[1]

Annually, 22,000 hospitalizations related to respiratory syncytial virus (RSV) bronchiolitis are attributable to parental cigarette smoking, a costly and preventable cause of morbidity and mortality.[2] In 2006, the United States Surgeon General summarized the evidence surrounding involuntary tobacco smoke exposure (TSE) and lower respiratory infections such as bronchiolitis in young children. Across studies from diverse settings, infants exposed to parental cigarette smoking after birth are at increased risk of lower respiratory infection,[3] possibly due to inhibition of the interferon β and γ–mediated response to viral infection in airway epithelium.[4,5] In addition, in utero TSE adversely affects developing lungs, causing structural changes and

limitations in air flow.[3,6–9] The surgeon general's report noted a paucity of data examining the effects of in utero and postnatal smoke exposure separately.[3]

To address this information gap, we investigated the association between prenatal smoke exposure and bronchiolitis, stratified by postnatal smoke exposure, in a large multicenter prospective cohort of hospitalized children with bronchiolitis. Recently, our group found that prenatal smoke exposure was an independent predictor of severe bronchiolitis, as defined by mechanical ventilation.[10] Given this important finding and the lack of data about the health effects of prenatal in relation to postnatal smoke exposure, in this analysis, we examined the relationship between smoke exposure and bronchiolitis severity in more detail by exploring both pre- and postnatal smoke exposure and by broadening the outcome to include all ICU admissions. We specifically focused on the risk of admission to an ICU among children with in utero exposure to maternal smoking, stratified by postnatal TSE.

METHODS

STUDY DESIGN

We performed a planned secondary analysis of data collected during a prospective, multicenter cohort study. The original study was conducted during the 2007 to 2010 winter seasons (November through March) at 16 large urban pediatric teaching hospitals as part of the Multicenter Airway Research Collaboration (MARC), a program of the Emergency Medicine Network (EMNet) (www.emnet-usa.org/). MARC members are listed in the Appendix. The enrollment period was limited to months in which the diagnosis of bronchiolitis is most common in order to best characterize its epidemiology. As previously described, site investigators used a standardized protocol to enroll a target number of consecutive children with bronchiolitis age <2 years from the inpatient ward and ICU, with purposeful oversampling of ICU patients.[11] All patients were treated at the discretion of the treating physician. Inclusion criteria were an attending physician's diagnosis of bronchiolitis, age <2 years, and the ability of the parent/guardian to provide informed consent. Patients were enrolled within 18 hours of admission. The exclusion criteria were previous enrollment or transfer to a participating hospital >48 hours after the original admission time. The consent and data collection forms were translated into Spanish. The institutional review boards at all participating hospitals approved the study.

DATA COLLECTION

During the prospective cohort study, investigators conducted a structured interview during the index hospitalization that assessed patients' demographic characteristics, medical and environmental history, duration of symptoms, and details of the acute illness. Interviews were conducted by site primary investigators, research nurses, and/or study coordinators using standardized case report forms. All study personnel had standardized training before local data collection. Medical records were reviewed to obtain clinical data from the preadmission evaluation (clinic or ED) and the child's inpatient course, including respiratory status, initial oxygen saturation at triage, medical management, and disposition. Data were submitted electronically to the EMNet Coordinating Center, where manual review for quality assurance was performed. On the basis of these checks, sites submitted any missing data and/or corrected discrepant data.

Prenatal TSE was determined using the following question: "Did the mother of [*child*] smoke cigarettes during the pregnancy?" Postnatal TSE was determined using the following question: "Does anyone who lives with [*child*], or who sees [*child*] on a regular basis, or who takes care of [*child*] in your house or somewhere else, *ever* smoke while in the same room as [*child*]?"

NASOPHARYNGEAL ASPIRATE COLLECTION AND VIROLOGY TESTING

Nasopharyngeal aspirates were performed within 24 hours of a child's arrival on the ward or medical ICU using a standardized protocol and shipped on dry ice to Baylor College of Medicine.[11] Polymerase chain reaction (PCR) assays were conducted as singleplex or duplex 2-step real-time PCR (rtPCR). Real-time reverse transcriptase PCR was used for the detection of RNA respiratory viruses, which included RSV types A and B, human rhinovirus (HRV), parainfluenza virus types 1, 2, and 3, influenza virus types A and B, 2009 novel H1N1, human metapneumovirus, coronaviruses NL-63, HKU1, OC43, and 229E, and enterovirus. rtPCR was used for the detection of DNA pathogens that included adenovirus, *Mycoplasma pneumoniae,* and *Bordetella pertussis*.[12–14]

STATISTICAL ANALYSES

All analyses were performed by Stata 12.0 (Stata Corp, College Station, Tex). Data are presented as proportions with 95% confidence intervals (CIs) and medians with interquartile ranges. We performed unadjusted analyses using chi-square, Fisher's exact, and Kruskal-Wallis tests, as appropriate. All P values are 2-tailed, with $P < .05$ considered statistically significant.

Multivariable logistic regression was conducted to evaluate independent predictors of a hospitalization requiring an ICU stay at any time during the admission, with prenatal and postnatal tobacco exposure the key exposures of interest. Other factors were tested for inclusion in the model if they were found to be associated with the outcome in unadjusted analyses ($P < .20$, eg, birth weight[15]) or were considered to be of potential clinical significance (eg, infant age). Variables were evaluated in the multivariable models in the same form as analyzed in the unadjusted analysis (ie, continuous vs categorical). The final multivariable model accounts for potential clustering by site, with results reported as odds ratios with 95% CIs.

RESULTS

Among 2207 enrolled children, 14 were missing data for one (n = 12) or both (n = 2) of the smoke exposure

variables (prenatal or postnatal). Table 1 depicts the proportion of enrolled infants with smoke exposure (prenatal and/or postnatal). There were 216 children (10%) with in utero exposure to maternal smoking who did not have postnatal TSE. Another 168 children (8%) were not exposed to maternal smoking in utero but had postnatal TSE. One hundred fifteen children (5%) had both in utero exposure to maternal smoking and postnatal TSE.

Child exposure to maternal smoking during pregnancy varied by site of enrollment ($P < .001$, data not shown) and was more common in the South and Midwest regions of the United States and less common in the West (Table 2). In utero exposure to maternal smoking was reported less often for white children and more often for black children. Children of Hispanic ethnicity were less likely to have in utero exposure to maternal smoking. Children with no parental history of asthma were less likely to be exposed in utero to maternal smoking, while those with a mother or father with a history of asthma were more likely to have mothers who smoked during pregnancy.

Children with in utero exposure to maternal smoking were less likely to weigh ≥7 pounds (Table 2). Children with in utero exposure to maternal smoking also were less likely to be breast-fed. In contrast, the infant's medical history, including history of wheezing, eczema, intubation, and comorbid medical disorders, did not differ across groups.

Some markers of bronchiolitis severity differed between the 2 groups in unadjusted analyses (Table 3). Presence of apnea was slightly higher in those with in utero exposure to maternal smoking, although this difference was not statistically significant. Respiratory rate was similar for the 2 groups, but children exposed to smoke in utero were more likely to have an oxygen saturation value of ≥94%. Children with in utero exposure to maternal smoking were more likely to undergo endotracheal intubation during the index hospitalization and more likely to have an ICU stay. These children also were less likely to have only RSV as the cause of their symptoms. Among the relatively small number of children with postnatal smoke exposure without in utero exposure to maternal smoking (n = 168), 17% had an ICU stay and 6% required continuous positive airway pressure/intubation. These findings did not differ significantly for children with only in utero exposure to maternal smoking or for those exposed to both.

On multivariable analysis adjusting for 10 factors (age, sex, race, birth weight, RSV/HRV status, apnea, retractions, oxygen saturation, oral intake, and postnatal smoke exposure), children with in utero exposure to maternal smoking were more likely to require an ICU stay (adjusted odds ratio 1.51, 95% CI 1.14–2.00, $P < .004$).

We also found that children exposed in utero to maternal smoking were more likely to require an ICU stay whether or not there was subsequent postnatal TSE (Table 4). Additionally adjusting for history of being breast-fed and family history of asthma did not materially change the study results (data not shown).

Table 1. Frequency of Prenatal and Postnatal TSE Among Enrolled Infants

Exposure Type	n (%)*
Any TSE	334/2197 (15.2)
Any postnatal TSE	284/2201 (12.9)
Both postnatal and in utero TSE	115/2193 (5.2)
Postnatal TSE without in utero TSE	168/2193 (7.7)
In utero TSE without postnatal TSE	216/2193 (9.8)

TSE indicates tobacco smoke exposure.
*Denominators differ slightly as a result of missing data.

Table 2. Characteristics of Children Hospitalized for Bronchiolitis According to In Utero Exposure to Maternal Smoking*

Characteristic	No (n = 1863)	Yes (n = 334)	P
Region, %			<.001
Northeast	19	14	
Midwest	18	28	
South	32	45	
West	30	14	
Age, mo, median (IQR)	4.1 (1.7–8.7)	3.7 (1.8–7.4)	.11
Sex, %			.69
Male	59	60	
Female	41	40	
Race, %			.007
White	68	63	
Black	26	33	
Other	6	4	
Ethnicity, %			<.001
Non-Hispanic	60	86	
Hispanic	40	14	
Has private insurance, %	34	19	<.001
Family history of asthma, %			<.001
Neither parent	70	54	
Either mother or father	25	36	
Both parents	4	5	
Don't know/missing	1	5	
Gestational age, %			.42
<32 wk	6	7	
32–36 wk	17	20	
≥37 wk (full term)	76	73	
Birth weight, %			<.001
<3 pounds	5	5	
3–4.9 pounds	7	11	
5–6.9 pounds	34	43	
≥7 pounds	54	41	
Kept in ICU/special care facility when born, %	25	27	.51
Is or was breast-fed, %	64	45	<.001
History of wheezing, %	22	27	.06
Received palivizumab	10	9	.88
History of eczema, %	15	16	.64
History of intubation, %	10	10	.98
History of chronic lung disease, %	2	2	.95
Major, relevant, comorbid medical disorder, %	21	22	.64

IQR indicates interquartile range; ICU, intensive care unit.
*Slight discrepancies in row totals are the result of missing data.

DISCUSSION

In this large multicenter, multiyear study of children hospitalized with bronchiolitis, we found that the children

Table 3. Association between In Utero Exposure to Maternal Smoking and Bronchiolitis Course*

Characteristic	No (n = 1863)	Yes (n = 334)	*P*
History and findings of physical examination			
Presence of apnea (chart)	7	9	.07
Respiratory rate, breaths per min, median (IQR)	48 (40–60)	48 (38–60)	.78
Retractions, %			.01
None	22	22	
Mild	43	38	
Moderate	25	23	
Severe	4	5	
Missing	6	11	
Air entry, %			.86
Normal	35	36	
Mild	34	31	
Moderate	13	14	
Severe	2	2	
Missing	15	16	
RDSS, median (IQR)	4 (3–6)	4 (3–6)	.72
Oxygen saturation by pulse oximeter or ABG, %			.03
<90	12	12	
90–93.9	18	12	
≥94	71	77	
Infectious etiology			
RSV/HRV status, %			.003
RSV alone	50	42	
HRV alone	7	11	
RSV + HRV	12	16	
RSV + any other non-HRV pathogen	10	13	
HRV + any other non-RSV pathogen	5	3	
Neither RSV nor HRV	16	15	
Resource utilization			
High flow oxygen, %	8	11	.16
CPAP, %	5	3	.30
Intubation, %	4	8	.006
ICU stay, %	17	23	.008
Hospital length of stay, %			.10
<3 days	56	52	
≥3 days	44	49	

IQR indicates interquartile range; ABG, arterial blood gas; RDSS, respiratory distress severity score; CPAP, continuous positive airway pressure; ICU, intensive care unit; RSV, respiratory syncytial virus; and HRV, human rhinovirus.

*Slight discrepancies in row totals are the result of missing data.

of mothers who smoked cigarettes during pregnancy had 51% greater odds of being admitted to the ICU and were more likely to require endotracheal intubation.

Table 4. Association Between In Utero Exposure to Maternal Smoking and Admission to Intensive Care Unit Among Children Hospitalized for Bronchiolitis, Stratified by Postnatal Tobacco Smoke Exposure*

Smoke Exposure in Home	Odds Ratio	95% Confidence Interval	*P*
No	1.47	1.05–2.04	.02
Yes	1.95	1.13–3.37	.02

*Multivariable model adjusted for age, sex, race, birth weight, respiratory syncytial virus/human rhinovirus status, apnea, retractions, oxygen saturation, and oral intake.

Several studies have demonstrated an association between postnatal TSE (during infancy) and risk of bronchiolitis. In 2011, an updated meta-analysis confirmed the increased risk of acquiring bronchiolitis during the first 2 years of life among children exposed to smoking by any household member.[16] A large study of Tennessee Medicaid claims reported that maternal smoking is an independent risk factor for a health care evaluation for bronchiolitis, defined as a clinic encounter, ED visit, or hospitalization.[17] Moreover, a multicenter prospective birth cohort study in Spain revealed that the adverse effect of TSE on lower respiratory illness during infancy is strongest when the mother smokes prenatally.[18] Our study extends these findings through establishing the adverse impact of maternal smoking during pregnancy on ICU admission in a diverse cohort of US children hospitalized for bronchiolitis.

One other single-center study (n = 206) has evaluated the relationship between postnatal TSE and the risk of severe bronchiolitis, as defined by low oxygen saturation during hospitalization. In contrast to our findings, these investigators found that in utero smoke exposure did not affect oxygen saturation, but they did find that postnatal cigarette smoke exposure was an independent risk factor for severe bronchiolitis.[19] However, only 10 infants in this cohort had isolated prenatal smoke exposure without subsequent postnatal TSE. This small sample limited the investigators' ability to fully explore the complex relationship between prenatal and postnatal TSE.

In our study, there were 216 children with isolated prenatal smoke exposure, enabling us to explore how cigarette smoke exposure after birth affected the risk of ICU admission among children exposed to maternal smoking in utero. In our stratified regression models, children with in utero smoke exposure were more likely to be admitted to the ICU for bronchiolitis, independent of postnatal smoke exposure. Among children exposed to in utero maternal smoking, the adjusted odds for ICU admission increased from 1.47 to 1.95 for those children also exposed to smoke after birth. Although an interesting finding, the relatively small numbers (after stratification) and overlapping confidence intervals make this conclusion somewhat speculative. Others, however, have found similar relationships. Specifically, Li and colleagues[20] found that among children with asthma, in utero exposure to maternal smoking was independently associated with deficits in lung function. Subsequent postnatal TSE did not result in additional loss of lung function. Overall, our results support the concept that prenatal smoking is a significant determinant of bronchiolitis severity, as defined by admission to an ICU.

Our findings have potential implications for the counseling delivered by clinicians regarding the health risks of TSE. Ideally, counseling messages conveyed by physicians who care for children could be coupled with delivery of effective smoking cessation interventions. A recent systematic review published by the Cochrane Collaboration examined the body of literature regarding the efficacy of such interventions for parents who smoke. In a variety of clinical settings, the effectiveness of parental education

and counseling programs on reducing children's TSE was not clearly demonstrated.[21] However, among studies of parents of children with respiratory illnesses, 4 of 13 studies showed significant effects on child health outcomes[22,23] and/or smoking cessation.[24,25] Studies that showed efficacy primarily used intensive counseling or motivational interviewing methods, which may hold the greatest potential for reducing the morbidity associated with TSE in children.

Obstetricians and health care providers for pregnant women may have a greater ability to affect the future respiratory health of the infant. A similar meta-analysis published by the Cochrane Collaboration examined the effects of psychosocial interventions on smoking cessation by pregnant mothers. Overall, counseling interventions were significantly more likely to result in smoking abstinence in late pregnancy compared to usual care (average risk ratio 1.44, 95% CI 1.19–1.75), particularly when provided in conjunction with other smoking cessation strategies.[26]

Our results reinforce the need for smoking cessation intervention by obstetricians at the first prenatal visit.[27] Investment in resources to improve prenatal smoking cessation services could prove to be cost-effective, given that the cost of a hospitalization for bronchiolitis requiring an ICU admission is up to 4 times greater than hospitalizations that do not require intensive care.[28] Pediatricians should consider referral of mothers who smoked tobacco prenatally for targeted, intensive smoking cessation counseling, especially if their infant presents with a respiratory illness. Finally, families and providers should be aware that maternal history of smoking tobacco in the prenatal period may be a marker for a more severe course of bronchiolitis.

Our study has several limitations. Although a significant number of children required admission to the ICU, endotracheal intubation was a relatively rare event, precluding a detailed analysis of the effects of smoke exposure on this outcome. We may have been unable to detect differences in chronic lung disease or extreme prematurity as a result of the small number of children with this history in our cohort. We defined postnatal TSE as exposure to any individual (living with, regularly visiting, or caring for the child) who ever smoked tobacco in the same room as the child. We did not collect details about secondhand smoke exposure during the prenatal period. This may underestimate in utero TSE, particularly in the 168 children whose mothers did not report smoking while pregnant but had postnatal TSE. However, some of these children may have had postnatal TSE only in a child care setting without in utero exposure. Infants of mothers who smoke in the same room have a higher risk of hospitalization for respiratory infections than infants whose mothers smoke after birth, but not in the same room.[29] Among children with in utero exposure to maternal smoking, subsequent postnatal TSE ($n = 115$) was less common than no subsequent TSE ($n = 216$). Although some mothers may have quit smoking during pregnancy, underreporting of postnatal TSE may have occurred. Alternatively, some mothers who continued to smoke after birth may not have smoked in the same room as their infant, causing failure of some of these infants to meet our definition of postnatal TSE. Although infants of mothers who smoked elsewhere (eg, outside) may still have experienced significant smoke exposure,[30] this potential underestimation does not detract from the prenatal smoke exposure finding. We relied on caregiver report of maternal cigarette smoking during pregnancy and postnatal TSE. It was not feasible from a cost standpoint to obtain biochemical confirmation of TSE with cotinine levels given the specific aims of our original cohort study.

Although self-report is commonly utilized in the literature, our study may underestimate the impact of smoke exposure on the risk of severe bronchiolitis. One small study of hospitalized children and their families demonstrated that a structured caregiver interview for the presence of secondhand smoking in any location had 100% sensitivity for child cotinine levels of >1 mg/dL.[31] In contrast, a recent systematic review demonstrated the increased sensitivity of salivary cotinine compared to self-report, which tended to underestimate smoking prevalence.[32] Some have suggested that parent report of smoking status, the number of cigarettes smoked per day, and smoking restrictions in the home are reasonable estimates of children's urinary cotinine levels when taken together.[33] We did not collect all of these details about parental smoking habits. Using questions similar to ours, a provocative analysis of a prospective cohort of children admitted for asthma found that although serum and salivary cotinine levels were associated with readmission for asthma, caregiver report was not.[34] Their results may reflect a bias toward underreporting TSE in the inpatient setting. If the same potential for misclassification applies to smoking during pregnancy, our finding of a strong association between maternal smoking and risk of ICU admission is more noteworthy.

CONCLUSIONS

Using self-reported smoking data, we found that maternal cigarette smoking during pregnancy puts children hospitalized with bronchiolitis at a significantly higher risk of requiring an ICU admission. In addition to its other deleterious health effects, postnatal TSE may exacerbate this risk. Health care providers should incorporate this information into prenatal counseling messages as well as into the routine and acute care of all infants.

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APPENDIX

PRINCIPAL INVESTIGATORS AT THE 16 PARTICIPATING SITES IN MARC-30

Besh Barcega, MD, Loma Linda University Children's Hospital, Loma Linda, Calif; John Cheng, MD, and Carlos Delgado, MD, Children's Healthcare of Atlanta at Egleston, Atlanta, Ga; Dorothy Damore, MD, and Nikhil Shah, MD, New York Presbyterian Hospital, New York, NY; Haitham Haddad, MD, Rainbow Babies & Children's Hospital, Cleveland, Ohio; Paul Hain, MD, and Mark Riederer, MD, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tenn; Frank LoVecchio, DO, Maricopa Medical Center, Phoenix, Ariz; Charles Macias, MD, MPH, Texas Children's Hospital, Houston, Tex; Jonathan Mansbach, MD, MPH, Boston Children's Hospital, Boston, Mass; Eugene Mowad, MD, Akron Children's Hospital, Akron, Ohio; Brian Pate, MD, Children's Mercy Kansas City, Kansas City, Mo; M. Jason Sanders, MD, Children's Memorial Hermann Hospital, Houston, Tex; Alan Schroeder, MD, Santa Clara Valley Medical Center, San Jose, Calif; Michelle Stevenson, MD, MS, Kosair Children's Hospital, Louisville, KY; Erin Stucky Fisher, MD, Rady Children's Hospital, San Diego, Calif; Stephen Teach, MD, MPH, Children's National Medical Center, Washington, DC; Lisa Zaoutis, MD, Children's Hospital of Philadelphia, Philadelphia, Pa.