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2018 Update on Pediatric Medical Overuse
A Review

Eric R. Coon, MD, MS; Ricardo A. Quinonez, MD; Daniel J. Morgan, MD, MS; Sanket S. Dhruva, MD, MHS; Timmy Ho, MD, MPH; Nathan Money, DO; Alan R. Schroeder, MD

IMPORTANCE Efforts to combat medical overuse have gained traction in recent years, but success has been intermittent and shortcomings have been recognized. A commitment to a strong evidence base is needed to more broadly engage clinicians and reduce overuse.

OBSERVATIONS A structured MEDLINE search and a manual review of tables of contents from selected high-impact journals was performed to identify original research published in 2017 relevant to pediatric overuse. Articles were scored from low to high for 3 categories: quality of methods, magnitude of potential harm, and number of patients potentially harmed. The top-scoring articles presented in this review highlight examples of safe reductions in treatment intensity, including in the setting of cancer, appendicitis, acute respiratory tract infection, and elective anesthesia. This year's articles also provide cautionary examples of rational interventions adopted without a full understanding of potential harms, including pharmacologic migraine therapies, docosahexaenoic acid supplementation for preterm neonates, tight glycemic control for individuals with critically illness, and prophylactic antibiotics for children with vesicoureteral reflux.

CONCLUSIONS AND RELEVANCE The articles represent high-quality, original research from 2017 that may help mitigate overuse. These works should be fundamental to the maturation of the pediatric overuse field.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Eric R. Coon, MD, MS, Division of Inpatient Medicine, Department of Pediatrics, University of Utah School of Medicine, Primary Children's Hospital, 100 North Mario Capecchi Dr, Salt Lake City, UT 84113 (eric.coon@hsc.utah.edu).

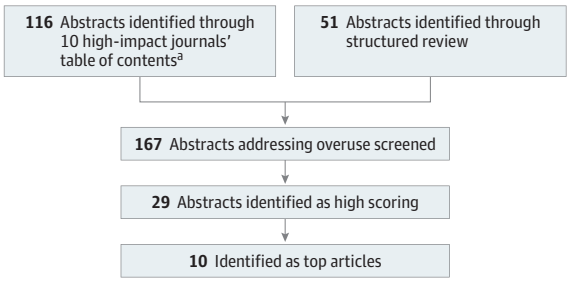
Despite increasing recognition and action to address medical overuse, it remains prevalent. In a recent survey, US physicians estimated that 20% of medical care is unnecessary.[1] An analysis of commercial claims data found that 10% to 14% of children are exposed to 1 of 20 services that typically do not improve child health.[2] Gaps in the medical overuse movement have been illuminated, including suggestions that the overuse message is sometimes oversimplified and undersupported by evidence.[3] Furthermore, initiatives to reduce overuse on a large scale have achieved inconsistent success.[4,5]

Successful diffusion and increased acceptance of medical overuse themes will depend on careful messaging and grounding in strong evidence. Clinicians will be more likely to reconsider potentially overused interventions if they perceive the message as uncomplicated, compatible with their values and beliefs, and beneficial to patients.[6] Our annual reviews of the pediatric overuse literature[7,8] align with these recommendations, providing concise summaries of 8 to 10 articles of the highest methodologic quality and the greatest potential to protect children from unnecessary medical harm. Our objective remains to update pediatricians on the latest original research demonstrating medical overuse and to provide an evidence-based foundation for pediatric overuse messaging, education, and practice change.

Methods

The process by which we identified articles for inclusion was modeled after prior annual reviews of the medical overuse literature.[7-11] Screening for potential articles was performed via a structured MEDLINE search strategy and a manual review of tables of contents from selected high-impact journals. The structured MEDLINE review identified articles in PubMed published in 2017 indexed with the Medical Subject Headings term *health services misuse* or with any of the following words in the title: *overuse*, *overtreatment*, *overdiagnosis*, *inappropriate*, or *unnecessary*. The same search was performed in Embase, with the addition of the Emtree term *unnecessary procedure*. Articles with the terms *overuse injury* or *overuse injuries* in the title, articles not written in English, and articles that did not present original research were excluded. The title and abstract of each study identified by the structured MEDLINE search was reviewed by 1 author (E.R.C., D.J.M., or S.S.D.) to determine whether the study addressed pediatric overuse. Screening was augmented by a manual review of all studies published in 2017 within 10 selected high-impact journals: *Archives of Disease in Childhood*, *Archives of Disease in Childhood: Fetal & Neonatal*, *BMJ*, *Journal of Pediatrics*, *Journal of Perinatology*, *JAMA*, *JAMA Pediatrics*,

Figure. Selection of Articles for Inclusion



[a] *Lancet*, *BMJ*, *JAMA*, *New England Journal of Medicine*, *Pediatrics*, *JAMA Pediatrics*, *Journal of Pediatrics*, *Journal of Perinatology*, *Archives of Disease in Childhood*, and *Archives of Disease in Childhood: Fetal & Neonatal*.

Lancet, *New England Journal of Medicine*, and *Pediatrics*. Each of the 10 journal tables of contents were independently reviewed by 2 of the 5 pediatric authors (E.R.C., R.A.Q., N.M., T.H., or A.R.S.) to identify articles relevant to pediatric overuse.

All abstracts found to address pediatric overuse by the structured PubMed review or manual table of contents review were then independently evaluated by 3 of the 5 pediatric authors, scoring articles from low to high for 3 categories: quality of methods, magnitude of potential harm, and number of patients potentially harmed. Methodologic quality was assessed using the Oxford Centre for Evidence-based Medicine's levels of evidence,[12] which considers study design and the individual quality of the study (for example, randomized clinical trials [RCTs] score highly but can be moved up or down in score according to risk of bias). The magnitude of potential harm score was patterned after the Joint Commission on Accreditation of Healthcare Organizations patient safety event taxonomy, which emphasizes injury severity and permanence.[13] Number of patients potentially harmed was judged according to the frequency of the clinical scenario and the resulting harm. Because the precise prevalence of various clinical scenarios and their associated harms are generally not well described, authors were asked to broadly approximate them in a dichotomous manner as either common or uncommon, with common clinical scenarios involving common harms scoring the highest. The 20 articles with the top mean scores and any article for which 1 author scored it highly in at least 2 of the 3 categories were summarized and discussed by the authors via a series of conference calls, with group consensus determining which 10 articles merited highlighting in this review.

In an effort to maximize scoring consistency across raters, 2 practice scoring sessions were conducted prior to releasing the full set of abstracts to authors. For each practice session, the pediatric authors scored the same 5 overuse-related abstracts and then participated in an hour-long facilitated discussion addressing the extent to which their scores aligned with the provided scoring rubric, within each category, for all 5 articles. Given that each abstract was scored by 3 different authors, we evaluated the interrater reliability of our scoring rubric at the conclusion of the study by calculating an average intraclass correlation coefficient with corresponding 95% CI. We used an average intraclass correlation coefficient because our unit of analysis was a mean rating over several raters,[14] and we excluded abstracts used for the practice sessions from these calculations.

Results

The structured PubMed review identified 1446 articles published in 2017 that met our search criteria (**Figure**). Manual review of these abstracts determined that 51 (3.5%) specifically addressed pediatric overuse. The table of contents review included 4216 research articles, 116 (2.8%) of which addressed pediatric overuse. Four articles were identified by both the structured review and the table of contents review. The average intraclass correlation coefficient for our scoring rubric was 0.66 (95% CI, 0.54-0.76), representing good interrater agreement.[15] Of the 167 original research articles addressing pediatric overuse in 2017 identified by our review (eTable in the Supplement), the top 10 are highlighted here.

Nonoperative, Antibiotic Treatment of Uncomplicated Appendicitis

Background

Between 1% and 8% of children who present with acute abdominal pain to the emergency department are diagnosed as having acute appendicitis. These children usually undergo appendectomy, with the attendant risks of an invasive procedure and general anesthesia. Several well-conducted studies involving adult patients suggest that nonoperative, antibiotic treatment of uncomplicated appendicitis may be safe and effective.[16]

Findings

A meta-analysis of 4 single-center prospective non-RCTs and 1 single-center RCT totaling 404 pediatric patients found that nonoperative, antibiotic treatment was successful in 152 of 168 patients (91%).[17] Forty-five patients (27%) received interval appendectomy within 1 year, 37 (22%) of which were due to treatment failure or recurrence. A separate meta-analysis of 7 prospective and 3 retrospective studies (including 4 of the studies reported in the other meta-analysis) found that nonoperative, antibiotic treatment was successful as the initial treatment in 97% of children.[18] While follow-up durations varied, 82% of patients were determined to have long-term efficacy of nonoperative treatment. Total duration of hospitalization and complications were similar between children who received nonoperative, antibiotic treatment vs appendectomy. Only 1 RCT was included in the 2 meta-analyses. The evidence quality is 2a (systematic review of cohort studies).

Implications

For children with uncomplicated appendicitis, nonoperative treatment with antibiotics could be considered as the initial treatment strategy. Such an approach would reduce risks associated with surgery and general anesthesia.

Amitriptyline and Topiramate for Treatment of Pediatric Migraine

Background

Amitriptyline and topiramate are frequently used for migraine prevention in the pediatric population.[19] Evidence supporting their efficacy for this indication is lacking.

Findings

A double-blind, placebo-controlled RCT compared the impact of amitriptyline, topiramate, and placebo on migraine reduction in 361 pediatric patients aged 8 to 17 years over a 24-week period.[20]

Amitriptyline, topiramate, and placebo were equally efficacious in reducing migraine frequency to more than 50% below baseline, with success rates of 52%, 55%, and 61%, respectively. There was also no benefit of the medications over placebo in terms of total number of headache days and headache-related disability. The trial was stopped early for futility. Adverse events were higher in the amitriptyline and topiramate groups when compared with placebo (most commonly: paresthesia, fatigue, dry mouth, and weight loss). Five serious treatment-related adverse events occurred in the medication groups, including altered mood (n = 3), syncope (n = 1), and suicide attempt (n = 1). Sixty-four of 361 patients (18%) who underwent randomization did not have measured end point data. The evidence quality is 1b (individual RCT).

Implications

The 2 most commonly used preventive medications for pediatric migraine are no more effective than placebo. Greater reliance on nonpharmacologic treatment strategies for children experiencing migraines would limit the harm of serious medication adverse effects.

Prophylactic Antibiotics for Urinary Tract Infection and Risk of Renal Scarring

Background

Because childhood urinary tract infection (UTI) is associated with renal scarring, prophylactic antibiotics have been advocated to decrease risk of recurrent UTI, with the hope of preventing long-term kidney damage. Individual RCTs have not been powered to detect differences in renal scarring.

Findings

A meta-analysis of 7 RCTs of prophylactic antibiotics vs placebo involving 1427 patients demonstrated no significant impact on the development of renal scarring by dimercaptosuccinic acid scan (pooled risk ratio, 0.83; 95% CI, 0.55-1.26).[21] A subgroup analysis involving only patients with vesicoureteral reflux yielded similar findings (pooled risk ratio, 0.79; 95% CI, 0.51-1.24). Approximately half of patients included in this meta-analysis had no or low grade (<grade III) vesicoureteral reflux at the time of study enrollment, and renal scarring was a secondary outcome in all of the included trials. The evidence quality is 1a (systematic review of RCTs).

Implications

Although prophylactic antibiotics are modestly effective in preventing recurrent UTIs, the goal of preventing renal scarring is not supported by the summary data from this meta-analysis. Given the high number needed to treat to prevent 1 infection (daily antibiotics for 8 patients for 2 years, or 5840 total doses of antibiotics per the most recent RCT),[22] and the concerns about promotion of antimicrobial resistance and other drug-related adverse effects, routine prophylactic antibiotics following UTI should be discouraged. Additionally, the findings bring into question whether the link between UTI and renal scarring is causal.[23]

Broad-Spectrum Antibiotics for Pediatric Acute Bacterial Respiratory Tract Infections

Background

Antibiotics are the most frequently prescribed medications in children, most commonly for otitis media, sinusitis, or pharyngitis.[24] Broad-spectrum antibiotics such as amoxicillin/clavulanate, cephalosporins, and macrolides are increasingly used based on theoretical benefits against emerging resistant pathogens.

Findings

An investigation examined 1 retrospective (n = 30 159) and 1 prospective (n = 2472) cohort, both of which comprised patients aged 6 months to 12 years with an acute respiratory infection (acute otitis media, acute sinusitis, or group A streptococcal pharyngitis) and antibiotic prescription within an outpatient network of 31 pediatric primary care practices in Pennsylvania and New Jersey.[25] In the retrospective cohort, 14% were prescribed broad-spectrum antibiotics. A propensity-matched analysis found no difference in the primary outcome of treatment failure at 14 days for broad- vs narrow-spectrum antibiotics (3.4% vs 3.1%; risk difference, 0.3%; 95% CI, −0.4% to 0.9%). The prospective cohort found that patient-centered outcomes were not improved for those receiving broad-spectrum antibiotics (no difference in missed school or daycare; slightly worse quality of life) and that adverse events were higher, whether reported by clinicians (3.7% broad- vs 2.7% narrow-spectrum) or patients (35.6% broad- vs 25.1% narrow-spectrum). Although the study used propensity score and sensitivity analyses to address bias, some degree of residual confounding may exist (ie, sicker or more complicated patients being more likely to receive broad spectrum antibiotics). The evidence quality is 2b (individual cohort study).

Implications

Narrow-spectrum antibiotics (eg, penicillin, amoxicillin) should be the mainstays for antibiotic treatment of acute otitis media, acute sinusitis, and group A streptococcal pharyngitis. Broad-spectrum antibiotics do not confer additional treatment benefit and may be associated with more adverse events.

Decreased Reliance on Radiation Therapy and Subsequent Risk of Malignancy Among Childhood Cancer Survivors

Background

Pediatric cancer therapies have resulted in significant gains in cure rates but have also been associated with increases in subsequent malignancy secondary to the original treatment.[26] As a result, modifications have been made to therapeutic regimens over the years to mitigate the late effect harms while still providing curative treatment.[27]

Findings

Among a multicenter retrospective cohort of 23 603 patients diagnosed as having childhood cancer between 1970 to 1999 who survived at least 5 years from diagnosis, declines in the proportion of patients exposed to radiation therapy (78% in the 1970s vs 37% in the 1990s) and the maximum radiation dose received (30 Gy in the 1970s vs 26 Gy in the 1990s) were observed.[28] The risk of subsequent neoplasm decreased for every 5-year increase in diagnosis year (relative rate, 0.91; 95% CI, 0.84-0.98), including risk for subsequent malignant neoplasm (relative rate, 0.93; 95% CI, 0.86-1.00). Mediation analyses demonstrated that changes in radiation exposure were the primary influence on the decreased rate of subsequent neoplasms over time. One-third of eligible childhood cancer survivors chose not to participate or could not be included in the

analysis because of incomplete data. The evidence quality is 2b (individual cohort study).

Implications

Efforts to safely reduce exposure to curative but toxic agents in the treatment of childhood cancer have been associated with a decrease in long-term harms from treatment, including risk of future malignancy. This is a generalizable lesson for all pediatricians: efforts should be made to limit medical harms, even among effective, life-saving interventions.

Laryngeal Mask Airways and Risk of Adverse Events for Infants Undergoing General Anesthesia

Background

Perioperative respiratory adverse events (PRAE) are common for children undergoing anesthesia, and infants are at the greatest risk by age group.[29] Use of a laryngeal mask airway has been shown to decrease the incidence of PRAE compared with use of an endotracheal tube, but previous trials either excluded or did not report the number of infants included.[30]

Findings

This RCT of 181 infants undergoing general anesthesia for minor elective surgery and deemed suitable for either a laryngeal mask airway or an endotracheal tube by their anesthesiologist found that infants who received an endotracheal tube experienced a higher incidence of any PRAE (53% vs 18%; risk ratio, 2.94; 95% CI, 1.79-4.83) and major PRAE (19% vs 4%; risk ratio, 5.30; 95% CI, 1.62-17.35) compared with infants who received a laryngeal mask airway.[31] Major PRAE was defined as laryngospasm or bronchospasm, with any PRAE also including desaturation, airway obstruction, severe coughing, or postoperative stridor. Individuals responsible for measurement of the study outcomes were not blinded to participant treatment assignment. The evidence quality is 1b (individual RCT).

Implications

Among infants undergoing general anesthesia, use of laryngeal mask airway may reduce the risk of serious adverse events, including laryngospasm and bronchospasm, compared with use of an endotracheal tube. A large number of patients who undergo general anesthesia for minor surgery could be managed with a laryngeal mask airway instead of a more invasive endotracheal tube.

Less Invasive Surfactant Administration for Preterm Infants

Background

Surfactant administration improves outcomes for preterm infants with respiratory distress syndrome in the neonatal intensive care unit.[32] While surfactant is most commonly administered after endotracheal intubation, a growing body of evidence suggests that surfactant administration via a thin catheter without endotracheal intubation (less invasive surfactant administration) may be superior.

Findings

A systematic review and meta-analysis examined 6 RCTs comparing less invasive surfactant administration with surfactant administration after endotracheal intubation.[33] Among preterm infants younger than 34 weeks' gestational age requiring fractional inspired oxygen greater than 0.3, less invasive surfactant administration decreased bronchopulmonary dysplasia at 36 weeks (risk ratio, 0.72; 95% CI, 0.53-0.97) and decreased the need for mechanical ventilation during the neonatal intensive care unit stay (risk ratio, 0.66; 95% CI, 0.47-0.93). There was no difference in the risk of death. The included RCTs did not measure long-term neurodevelopmental outcomes. The evidence quality is 1a (systematic review of RCTs).

Implications

Less invasive surfactant administration should be the preferred technique for delivering surfactant to preterm infants who otherwise do not require intubation and mechanical ventilation. Longer follow-up duration is necessary to assess differences in neurodevelopmental outcomes.

Tight Glycemic Control in Critically Ill Children

Background

Although early trials of tight glycemic control in adult intensive care unit patients were promising,[34,35] subsequent trial data demonstrated an increased risk of mortality with intensive glucose control.[36] Previous multicenter trials in children, predominantly among those who had undergone cardiac surgery, did not demonstrate a benefit to tight glycemic control.[37,38] Studies involving tight glycemic control in pediatric patients with critical illness and other conditions are lacking.

Findings

A 35-center RCT evaluated tight glycemic control among 713 pediatric patients with respiratory or cardiovascular failure and confirmed hyperglycemia.[39] The primary outcome, number of intensive care unit–free days to day 28, did not differ between the lower glucose (80-110 mg/dL) and higher glucose (150-180 mg/dL) target groups, measuring 20.0 and 19.4 days, respectively (P = .58). Patients in the lower target group had greater incidence of severe hypoglycemia (<40 mg/dL) compared with the higher target group (5.2% vs 2.0%, P = .03). No significant difference was seen in 28- and 90-day mortality, ventilator-free days, severity of organ dysfunction, or hospital-free days between groups. A significant increase in health care–associated infections was seen in the lower glucose target group (3.4% vs 1.1%, P = .04). Medical teams were not blinded to study group assignment. The evidence quality is 1b (individual RCT).

Implications

Tight glycemic control was not shown to be beneficial when treating children with critical illness and hyperglycemia and led to increased risk of severe hypoglycemia and health care–associated infections. Clinicians may safely use higher glucose targets (150-180 mg/dL) for glucose control and thus avoid adverse effects from insulin overtreatment.

Docosahexaenoic Acid and Risk of Bronchopulmonary Dysplasia in Infants Younger Than 29 Weeks' Gestation

Background

Docosahexaenoic acid (DHA) is an essential component for normal growth and neurodevelopment and is a common additive to commercial infant formulas.[40] Because preterm infants have lower levels of DHA and observational data has suggested that supplementation may be associated with improved neurodevelopment and

reduced bronchopulmonary dysplasia, experts recommend higher doses of DHA be provided to preterm infants.[41]

Findings

A multicenter, blinded RCT compared the effects of 60 mg/kg per day of enteral DHA to a control (soy) emulsion without DHA in 1273 preterm infants born at less than 29 weeks' gestational age.[42] Risk of physiologic bronchopulmonary dysplasia, the primary outcome, was increased for those infants who received DHA compared with controls (relative risk, 1.13; 95% CI, 1.02-1.25). Clinical bronchopulmonary dysplasia and a composite of physiologic bronchopulmonary dysplasia or death before 36 weeks of postmenstrual age were also slightly increased among infants who received DHA. Bronchopulmonary dysplasia is an imperfect outcome, as infants with a history of extreme prematurity who do not meet diagnostic criteria for bronchopulmonary dysplasia have been shown to have compromised lung function.[43] The evidence quality is 1b (individual RCT).

Implications

Enteral DHA supplementation for preterm infants born at less than 29 weeks' gestation does not reduce bronchopulmonary dysplasia risk and may increase it. Recommendations to provide high levels of DHA supplementation for very preterm infants should be reevaluated.

Discussion

Two generalizable lessons emerge from this year's review of articles addressing medical overuse in pediatrics. First, all medical interventions, even those that are evidence based and lifesaving, have associated risks. While the benefits of an intervention may very clearly outweigh potential harms, pediatricians should always be striving to limit those harms. Reducing the intensity of an intervention, while managing to maintain its effectiveness, can increase the benefit-to-harm ratio. The most striking example from this year's review came from pediatric oncology, where we have learned that efforts to safely reduce the intensity of radiation therapy for children with cancer have been associated with a decrease in secondary malignancies among survivors, without worsening cure rates. Other examples from our review that demonstrate the benefits of reducing treatment intensity while still effectively healing patients include less invasive surfactant administration for preterm infants, laryngeal mask instead of endotracheal tube intubation for infants undergoing general anesthesia, narrow- instead of broad-spectrum antibiotics for acute respiratory tract infections, and nonoperative treatment of uncomplicated appendicitis.

The second lesson from this year's top pediatric overuse articles is that we should be cautious in adopting rational, seemingly common sense therapies that are unproven. Our review highlighted studies testing the following logical assumptions: keeping a critically ill child's blood glucoses within a normal range will decrease their length of stay, the antiinflammatory effects of DHA will reduce the risk of bronchopulmonary dysplasia in preterm infants, prophylactic antibiotics will reduce renal scarring among children with vesicoureteral reflux, and migraine therapies that are effective in adults will be effective for children. In each case, the intervention was not only found to be ineffective but potentially harmful.

Our review is limited by a focus on articles from higher-impact journals, which received closer scrutiny for inclusion (structured keyword search and manual review of all tables of contents) compared with articles from other journals (structured keyword search only). While the authors completed an iterative scoring practice using a defined rubric and demonstrated good interrater reliability, a degree of subjectivity in article scoring likely remains. This review did not comprehensively enumerate all existing research addressing pediatric overuse. Rather, in line with prior overuse review methodologies,[7-11] we sought to highlight the most important original research addressing pediatric overuse published in the last year.

Conclusions

The studies highlighted in our review represent prominent contributions to the growing body of evidence that children are frequently affected—and often harmed—by medical overuse. Pragmatic dissemination of this evidence will strengthen the movement to reduce pediatric overuse.

ARTICLE INFORMATION

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Author Affiliations: Department of Pediatrics, University of Utah School of Medicine, Primary Children's Hospital, Salt Lake City (Coon); Section of Pediatric Hospital Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, Texas (Quinonez, Money); University of Maryland School of Medicine, Baltimore (Morgan); Veterans Affairs Maryland Healthcare System, Baltimore (Morgan); University of California, San Francisco, School of Medicine and San Francisco VA Healthcare System, San Francisco (Dhruva); Department of Neonatology, Beth Israel Deaconess Medical Center, Boston, Massachusetts (Ho); Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California (Schroeder).

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