Translating Best Evidence into Best Care

EDITOR'S NOTE: Studies for this column are identified using the Clinical Queries feature of PubMed, "hand" searching *JAMA*, *JAMA Pediatrics*, *Pediatrics*, *The Journal of Pediatrics*, and *The New England Journal of Medicine*, and from customized EvidenceAlerts.

EBM PEARL: QUALITATIVE RESEARCH (QLR): Clinical research may be divided into quantitative and qualitative types. Quantitative research addresses hypotheses and clinical questions with numerical answers, and the quantitative researcher works to be "blinded" from the data collection and analysis processes. QLR addresses the contextual human clinical experience with thematic descriptions and hypothesis/theory generation, and the researcher is essential to theme and hypothesis/theory development. QLR questions not how many, but how was it perceived, not what is the mean, but what is the theme, not what is the *P* value, but what is the context. Interviews and focus groups generate the raw data of QLR. These data typically include comments, but photographs and videos may be part of the data set. Data are organized by coding – words or phrases assigned to participant comments or other data. Codes are organized into potential themes, which may be further categorized and defined. A common, final QLR product in medicine is a description of, and more profound insight into, patients' clinical experiences. The article by Freeman et al, below, is an example of QLR within the context of adolescent online health-information searching behavior.

Distrust, but use it anyway – adolescent online health-information searching behavior

Freeman JL, Caldwell PHY, Scott KM. The Role of Trust When Adolescents Search for and Appraise Online Health Information. *J Pediatr* 2020;221:215-23.e5.

Question What thematic issues emerge from adolescent online-health-information searching behavior studies?

Design Systematic review of qualitative studies.

Setting International.

Participants Adolescents, 13-18 years old.

Intervention Online health-information searching.

Outcomes Theme development related to trusting online health information.

Main Results There were 4 themes identified: information use despite distrust, heuristic reliance, websites more trustworthy compared with social media, action based on level of trust.

Conclusions Adolescents are likely to benefit from health-literacy-evaluation tools.

Commentary As one of the most active groups of internet users, adolescents frequently turn to online sources for health information and guidance to support their health and well-being.[1] Health information technology offers many positives including empowerment, privacy, anonymity, a stigma-free environment, and removal of barriers to accessing health services.[1,2] Numerous studies have demonstrated that adolescents' skills are highly variable with regard to their ability to find, assess, and appraise relevant health information online.[3] Normal adolescent development requires youth to develop independence and the ability to formulate abstract thought. Consistent with this, it is important that young people develop the ability to discern the relevance and quality of the information they encounter. In their article, Freeman et al explore one component of this process—trust, a complex construct, incorporating beliefs, intentions, motivations, emotions, and expectations. They use thematic synthesis methodology to extract and combine similar concepts among 22 quantitative and qualitative studies about adolescent internet use for health information to produce four key analytical themes. These themes include: adolescents generally distrust the internet but use it anyway, adolescents use heuristics to appraise the trustworthiness of online health information, adolescents trust websites more than social media, and adolescents' level of trust in online information guides their actions and responses. Their review of the qualitative literature uses strong methodology, including a broad literature search, appraisal for transparency employing a commonly used framework (COREQ), and using reporting methods recommended for synthesis of qualitative research (ENTREQ). The findings are therefore likely credible, dependable, and confirmable. Limitations of this study, as with other systematic reviews of qualitative research, include the potential minimization of cultural and contextual differences within individual studies, and potential barriers in incorporating diverse study designs. The authors' conclusions are potentially helpful in creating eHealth literacy interventions to assist adolescents in their evaluation of online health information. In addition to assisting adolescents with functional eHealth literacy (eg, using correct terms in searching) it is important to equip them with critical eHealth literacy (eg, differentiating accurate vs inaccurate information). Understanding the role of trust may be helpful in achieving this goal.

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Early-childhood prescribed antibiotics associated with type 1 Diabetes

Wernroth ML, Fall K, Svennblad B, Ludvigsson JF, Sjölander A, Almqvist C, et al. Early Childhood Antibiotic Treatment for Otitis Media and Other Respiratory Tract Infections Is Associated With Risk of Type 1 Diabetes: A Nationwide Register-Based Study With Sibling Analysis. *Diabetes Care* 2020;43:991-9.

Question Among young children, what is the association of antibiotic prescriptions for otitis media and respiratory tract infections, compared with no prescriptions, in developing type 1 diabetes mellitus (DM1)?

Design Retrospective, cohort, secondary analysis of the Swedish Prescribed Drug Register and the National Patient Register.

Setting Sweden.

Participants All singleton children born in Sweden between 1 July 2005 and 30 September 2013.

Intervention Antibiotics prescriptions for otitis media and respiratory infections vs none.

Outcomes DM1.

Main Results 1,297 children (0.2%) developed DM1 (median age 4.0 years, range 0–8.3). Antibiotics prescribed in the 1st year of life were associated with an increased risk of DM1, adjusted hazard ratio, 1.19 (95% CI, 1.05–1.36) with a higher risk among children born by cesarean delivery.

Conclusions Early-life prescribed antibiotics for otitis media and respiratory infections, are associated with DM1 development, with a higher risk in cesarean delivery birth.

Commentary Antibiotics are widely used in children worldwide based on the clinical premise of important benefit and minimal risk, but antibiotic overuse is well-documented.[1] Wernroth et al examined whether use of antibiotics in pregnancy or infancy could increase risk of developing DM1. The authors conducted a large and well-executed cohort study with careful adjustment for measured confounders and a sibling-comparison design to reduce unmeasured genetic and environmental confounding. They showed a small but relatively consistent association between early antibiotic exposures and DM1 diagnosis before age 10, with larger effects in children delivered by cesarean section. One hypothesis is that this association was explained by residual confounding from the infections (often viral) that were treated with antibiotics; the authors did not directly adjust for infections. An alternative hypothesis is that early-in-life antibiotic exposure, whether prenatally, perinatally, or during infancy, disrupts the development of infants' intestinal microbiome, disturbing immunologic development and ultimately promoting auto-immunity.[2] Nonetheless, as assessments of causal relationships are rarely conclusive in observational studies, experimental models in predisposed animals are crucial for dissecting causation and mechanism.[3] Clinicians should be aware of growing evidence suggesting that antibiotic-associated perturbation of early-life microbiota may be contributing to rising rates of DM1 across the globe.

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Kawasaki-like disease among Italian children in the COVID-19 era

Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An Outbreak of Severe Kawasaki-like Disease at the Italian Epicentre of the SARS-CoV-2 Epidemic: An Observational Cohort Study. *Lancet* 2020;395:1771-8.

Question Among children with Kawasaki-like disease, what is the demographic and disease-related parameters in the COVID-19 era, compared with children diagnosed with Kawasaki disease in the pre-COVID-19 era?

Design Retrospective, cohort study.

Setting Bergamo, Italy.

Participants Children with Kawasaki disease, diagnosed between January 1, 2015, and April 20, 2020.

Intervention With and without COVID-19 infection.

Outcomes Incidence. Kawasaki disease shock syndrome was defined by presence of circulatory dysfunction, and macrophage activation syndrome (MAS).

Main Results The 19 pre-COVID-19 era patients, mean age 3.0 (SD 2.5) years, January 1, 2015 – February 17, 2020, were compared with 10 COVID-19 era patients (80% antibody positive), mean age 7.5 (SD 3.5) years, February 19 – April 20, 2020. Those diagnosed in the COVID-19 era demonstrated a higher incidence: 10 vs 0.3 per month, mean age: 7.5 vs 3.0 years, Kawasaki disease shock syndrome: 50% vs 0%, MAS: 50% vs 0%, and steroid requirement: 80% vs 15%, all $P < .01$.

Conclusions Children with Kawasaki disease in the COVID-19 era, 80% of whom were antibody positive, were older and demonstrated more severe disease compared with those with Kawasaki disease prior to the COVID-19 era.

Commentary A thirty-fold increased incidence of so-called Kawasaki-like disease was reported from Italy during the SARS-CoV-2 epidemic in 2020. Eight of the 10 patients with Kawasaki disease tested positive for COVID-19 with a high incidence (6/10) of cardiac involvement. News from New York, France, and England also showed an increased incidence and severity of Kawasaki disease. Prior to COVID-19, coronavirus had been previously isolated in 7.1% of patients with Kawasaki disease.[1] The incidence of Kawasaki disease is not increasing in Japan, Taiwan, Korea, Hong-Kong, or China, suggesting the importance of genetic issues in the relationship between Kawasaki disease and COVID-19. In this study, the Kobayashi score, which identifies patients at high risk of IVIG resistance,[2] revealed that of the 10 patients with Kawasaki disease, none were younger than 12 months and all had platelet counts less than 300×10^9/L. Results from this study suggest that COVID-19 may be one of the triggers of Kawasaki disease. Kawasaki disease in older patients with COVID-19 is associated with an increased incidence of cardiac involvement, lower platelet counts, MAS, and Kawasaki disease shock syndrome. Early adjunctive steroid treatment to prevent coronary artery lesions should be considered in these patients with COVID-19 Kawasaki disease.[3]

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Social/digital media exposure early in life associated with autistic symptoms

Heffler KF, Sienko DM, Subedi K, McCann KA, Bennett DS. Association of Early-Life Social and Digital Media Experiences With Development of Autism Spectrum Disorder-Like Symptoms. *JAMA Pediatr* 2020:e200230.

Question What is the association of social/digital media viewing in the first 18 months of life and autism spectrum disorder (ASD)?

Design Cohort study based on data from the National Children's Study archive.

Setting US.

Participants 2152 children enrolled at birth, 2010-2012, analyzed at 26.6 (2.1), mean (SD), months of age.

Intervention Modified Checklist for Autism in Toddlers (M-CHAT) and parent-child play.

Primary Outcomes M-CHAT and M-CHAT-R score associated with ASD symptoms and risk.

Main Results Television and/or video viewing at 12 months were statistically associated with ASD-like symptoms at 2 years of age, but not ASD risk. Parent-child play (daily vs not daily) was statistically associated with fewer ASD-like symptoms at 2 years of age, but not ASD risk.

Conclusions More early-age screen viewing and less parent-child play were associated with more ASD-like symptoms at 2 years of age.

Commentary Evidence is scarce linking early screen-media exposure and the emergence of ASD. Children with ASD were reported to have been exposed to TV at a younger age and spent more time watching TV than their counterparts.[1] Conversely, minimizing inappropriate screen-media exposure, in addition to behavioral and early intervention for young individuals with ASD or ASD-like behaviors, may improve developmental and behavioral outcomes, as often observed clinically. Although TV viewing and caregiver-child play were obtained by self-report of single questions by Heffler et al, their main findings are still intriguing for pediatric providers, as these experiential factors could be modifiable through high-quality parent-child interaction during early childhood development. These findings support another prospective study where children increasingly exposed to TV, including adult programs, from age 6 to 18 months, were more likely to have ASD-like symptoms at age 18 months.[2] Enriched parent-child interaction positively affects brain networks essential for cognitive, language, social, and emotional development during early childhood. Children, especially those at risk for ASD, should not be immersed in an environment with inappropriate and excessive screen media at a very young age. Emphasizing, at health supervision visits, the American Academy of Pediatrics recommendations regarding appropriate media use with children,[3] parents should also be apprised of the association between earlier screen exposure and the risk of developing ASD-like

symptoms, although currently, a causal relationship cannot be inferred.

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Report on birth settings in the US: maternal and neonatal outcomes

National Academies of Sciences, Engineering, and Medicine (NASEM) 2020. Birth Settings in America: Outcomes, Quality, Access, and Choice. Washington, DC: *The National Academies Press*. https://doi.org/10.17226/25636.

Question What are the maternal and neonatal outcomes in planned home birth compared with hospital birth?

Design Consensus report.

Setting US.

Participants Birthing women and neonates.

Intervention Home birth vs hospital birth.

Outcomes Rate of maternal medical intervention, intervention-associated maternal morbidity, and neonatal mortality risk.

Main Results The maternal rate of medical intervention and intervention-associated morbidity is lower in non-hospital birth settings. Neonatal mortality is 2-3-fold higher for non-hospital births. The neonatal mortality rate may be confounded by a lack of an integrated home-hospital system as exists in other countries, fetal/maternal risk stratification, birth-attendant-qualification regulation, and other factors.

Conclusions Increased non-hospital-birth neonatal mortality rates may be elevated due to modifiable systems-related factors.

Commentary The recent NASEM report is the most comprehensive examination to date of the state of US maternity care across birth settings (home, birth center, hospital). Following an extensive review of the literature, it found that, compared with hospital birth, low-risk US women choosing home birth have lower rates of intervention, including cesarean birth, operative vaginal delivery, induction of labor, augmentation of labor, and episiotomy, as well as lower rates of intervention-related maternal morbidity, such as infection, postpartum hemorrhage, and genital tract tearing.[1] US studies based on vital statistics data, found a higher risk of neonatal death in home compared with hospital births.[1] The committee included a review of the international data to better understand which systems-level factors influence maternal and neonatal outcomes. International studies suggest that home births may be as safe as hospital births for low-risk women and infants when: (1) they are part of an integrated, regulated system; (2) multiple provider options across the continuum of care are covered; (3) providers are well qualified and have the knowledge and training to manage first-line complications; (4) transfer is seamless across settings; and (5) appropriate risk assessment and risk selection occur across settings and throughout pregnancy.[1] However, the report found that such systems are currently rare in the United States,[1] which presents both a challenge and a road map for future improvement. Instead of discouraging home birth, physicians and midwives could work together to make birth in all settings safer. For example, guidelines for transfers of care between home and hospital are available,[2] and physicians and midwives could work to build relationships for seamless transfer of care when warranted. Although there are examples in the United States of such seamless transfers,[3] these are exceptions and not the norm.[4] Greater opportunities for interprofessional education, collaboration, and research across all birth settings are also critical to improving understanding between providers, as well as for improving the quality of care. Licensure and regulation for all US midwives that meet the International Confederation of Midwives (ICM) standards for midwifery education and practice will help to bring all midwives in line with established protocols for selection of low-risk women for home birth. Currently, midwives in a number of states educated to ICM standards are not able to access licensure. Ironically, expanding in-hospital access to services such as vaginal birth after cesarean, external cephalic version, vaginal breech birth (if version fails), and vaginal twin birth would in some cases prevent women from seeking these higher risk services elsewhere.

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