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: THE ELUSIVE CORONAVIRUS DENOMINATOR: Today is Sunday, April 5, 2020. By the time this piece appears, it will be summer, and hopefully, the world will have found itself on the right side of the death-rate incidence curve. Our planet is under siege by a 100nm enemy. A sizable part of the globe is in some sort of "lockdown." The world economy is faltering. As of today, 1.2 million people world-wide have tested positive for the novel coronavirus 2019 (COVID-19) and 65 600 people have succumbed to COVID-19, mathematically corresponding to a 5.4% case-fatality rate. However, this rate may be misleading. While healthcare practitioners and administrators and government officials are putting forth an awesome effort, we are still in the dark as to what is the true case-fatality rate. The reason we do not know the true rate is that the majority of those tested were probably symptomatic, likely very symptomatic—this inflates the rate. The vast majority of those who contracted COVID-19 probably were not tested, did not and do not have severe disease, or even realize that they were infected. The result of all this uncertainly is that we really do not have a satisfactory measure as to how populous is the case-fatality rate's denominator. The larger the denominator, the lower the case-fatality rate. Is the denominator twice as large, 5 times, 10 times? We do not know, but we should. If the rate is actually 0.54%, our approach to the situation would likely look differently than it does today. Extraordinary measures are in place around the world—limiting movement of people, closing down businesses and industries, causing major and not easily-reversable damage to local and international economies. Are those measures warranted? Again, we do not know. Early-acquired, accurate rate statistics, generated by frequent, wide-spread, random testing would provide a reliable rate estimate, perhaps providing sufficient information to implement, safely, targeted case/contact identification and isolation, and to target, early on, movement of life-saving equipment and healthcare-professional-protection materials where it will most likely be needed. This will allow everyone else—those less likely to be infected—to go to work. Large-scale social isolation for weeks and months, coupled with a disintegrating economy, may lead, eventually, to severe, unintended consequences, such as social unrest and disregard of authority—consequences that could be far worse than the direct effects of COVID-19 itself. Let us find the denominator for the current pandemic and prepare for the next, as it certainly will arrive.

—Jordan Hupert, MD

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Considering an otitis media antibiotic change

Wald ER, DeMuri GP. Antibiotic Recommendations for Acute Otitis Media and Acute Bacterial Sinusitis: Conundrum No More. *Pediatr Infect Dis J* 2018;37:1255-17.

Question In the era of the pneumococcal vaccine, what is the evidence for adjusting high-dose beta-lactam antibiotic recommendations for acute otitis media (AOM)?

Design Review and recommendations.

Setting Laboratory and clinical evidence.

Participants Children with AOM.

Intervention Nasopharyngeal swab specimen culture.

Outcomes Relative presence of nasopharyngeal-cultured respiratory bacterial organisms.

Main Results There has been an increase in recovery of Haemophilus influenzae and a decrease in recovery of penicillin-resistant Streptococcus pneumoniae from nasopharyngeal specimens.

Conclusions Recent microbiologic data suggest a treatment recommendation of regular dose amoxicillin-clavulanate.

Commentary Pneumococcal conjugate vaccination has impacted the proportion of AOM infections, and presumably acute bacterial sinusitis infections caused by pneumococci. Based on our publication in 2017[1] and other sources, I agree that use of amoxicillin-clavulantate in preference to amoxicillin would be appropriate because about 50% of Haemophilus influenzae and all Moraxella catarrhalis isolated from middle ear fluid are resistant to amoxicillin.[1] However, as the paper by Wald and DeMuri point out the situation is

dynamic. Since publication of our paper, we have observed a dramatic increase in pneumococcal AOM,[2] returning to an incidence similar to pre-pneumococcal vaccine (PCV)13 (Kaur et al, manuscript submitted) and rising. In particular, we found that serotypes 35B and 35F are increasing in frequency and these strains are penicillin and multi-antibiotic resistant.[2] Neither serotype will be included in forthcoming PCVs from Merck (PCV15) or Pfizer (PCV20). Also, we and others have found that H. influenzae is the most important pathogen causing recurrent AOM, chronic AOM, otitis media with effusion, and otitis media-associated hearing loss. The bacteria often form biofilms in the nasopharynx and middle ear, leading to the false impression of a "spontaneous cure" rate, often quoted to be 50%. Thirdly, disturbance of the resident, commensal microbiome in the nasopharynx and gut by antibiotic use can be harmful, with adverse effects on innate and adaptive immunity, autoimmunity, etc. Broader spectrum antibiotics, especially those that have activity against anaerobes such as amoxicillin-clavulanate, disturb the microbiome more than narrow spectrum antibiotics such as amoxicillin. Therefore, antibiotic treatment decisions are complicated by the need to weigh benefits and risks. My treatment of choice in today's practices would be high-dose amoxicillin-clavulanate for a shortened 5-days treatment to optimize cure and reduce microbiome-disturbing adverse effects.

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Asymptomatic bacteriuria prevalence

Shaikh N, Osio VA, Wessel CB, Jeong JH. Prevalence of Asymptomatic Bacteriuria in Children: A Meta-Analysis. *J Pediatr* 2020;217:110-7.e4.

Question Among well children, what is the prevalence of asymptomatic bacteriuria (AB)?

Design Systematic review and meta-analysis of studies measuring prevalence of AB.

Setting International.

Participants Asymptomatic children, 0-19 years of age.

Intervention Bladder catheterization, suprapubic aspiration, or 3 consecutive clean catch urine samples.

Outcomes ≥1 organism with 100 000 colony forming units per milliliter (CFU/mL) for samples obtained by catheterization and 10 000 CFU/mL for samples obtained using suprapubic aspiration, with and without pyuria.

Main Results 14 studies (49 806 children) demonstrated an overall AB prevalence of 0.37% (95% CI, 0.09-0.82) and 0.47% (95% CI, 0.36-0.59), and an AB prevalence without pyuria of 0.18% (95% CI, 0.02-0.51) and 0.38% (95% CI, 0.22-0.58), in boys and girls, respectively. Median AB duration from one study was 1.5 – 2 months.

Conclusions AB prevalence is notably lower than that of urinary tract infection (UTI) in most subgroups, and therefore, a negative urinalysis (UA) with growth on urine culture should not be assumed to exclude a UTI.

Commentary Historically, many clinicians have treated a positive urine culture with a negative UA as a true UTI, though these findings could also represent a false positive urine culture from either contamination or AB. Shaikh et al conclude that the prevalence of AB is too low to use it as an explanation for positive urine cultures without pyuria. However, although the absolute prevalence of AB may be low, the proportion of positive urine cultures caused by AB is still relatively high. For example, if 3.1% of patients with bronchiolitis have positive urine cultures,[1] and the prevalence of AB is 0.4-0.5%, then AB would account for over 10% of these cultures: [(0.4-0.5%)/3.1% >10%]. Additionally, in 13/14 studies in the meta-analysis by Shaikh et al, the method of collection was either suprapubic aspirate or "'clean catch" (with 3 successive positive cultures required to be considered AB). As such, the pooled prevalence in their study does not factor in contamination, an important cause of false positive urine cultures in the real world. Shaikh et al suggest reconsidering the AAP guideline[2] recommendation to incorporate pyuria in the definition of UTI. We worry that treating all positive urine cultures without pyuria as true UTI will drive excessive antibiotic use, hospitalization, and imaging.

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Ingestion of infant formula constituted from fluoridated water associated with IQ deficit

Till C, Green R, Flora D, Hornung R, Martinez-Mier EA, Blazer M, et al. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. *Environ Int* 2020;134:105315.

Question Among otherwise normal preschool children, what is the association between fluoridated water used to constitute formula as infants/toddlers and IQ?

Design Multicenter, prospective study drawn from participants in the Maternal-Infant Research on Environmental Chemicals (MIREC) program.

Setting 6 cities across Canada.

Participants 398 mother-child dyads, the children of which were 3-4 years old.

Intervention Wechsler Primary and Preschool Scale of Intelligence-III.

Outcomes IQ score.

Main Results 38% of the dyads lived in cities with fluoridated water. An increase of 0.5 mg/L in water fluoride concentration corresponded to a 9.3- and 6.2-point decrement in Performance IQ among both formula-fed (95% CI: −13.77 to −4.76) and breast-fed children (95% CI: −10.45 to −1.94), respectively.

Conclusions Ingestion of formula constituted from fluoridated water is associated with Performance IQ deficits.

Commentary This study by Till et al used data from the MIREC Study to demonstrate that fluoride intake from infant formula constituted from tap water is associated with lower performance IQ at age 3-4 years. Despite some limitations, eg, the use of estimated vs directly measured exposures to fluoride, the possibility of bias or confounding appears low. The results are consistent with increasing evidence suggesting that early life exposure to fluoride (prenatal and infancy) is associated with adverse neurobehavioral impacts. Evidence includes experimental studies in rodents as well as 3 recent longitudinal birth cohort studies (1 involving MIREC and 2 involving ourselves and colleagues) demonstrating significant associations between individual measures of prenatal fluoride exposure and lower performance on offspring measures of intelligence and behavior.[1-3] Overall, these studies inform the ongoing debate over the benefits vs risks associated with the fluoridation of water. Clearly, more research is needed. Meanwhile, since the beneficial effects of fluoride predominantly occur at the tooth surface after teeth have erupted, whereas fluoride is not essential for growth and development, a cautious step could be avoidance of fluoridated products and water by women during pregnancy and by infants during the first 6 months of life.

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Mandatory vaccine policies associated with increased vaccination rates and decreased measles incidence

Vaz OM, Ellingson MK, Weiss P, Jenness SM, Bardají A, Bednarczyk RA, et al. Mandatory Vaccination in Europe. *Pediatrics* 2020;145: pii e20190620.

Question Among children living in Europe, what is the association between mandatory vaccination and vaccine-preventable disease reduction?

Design Data analysis from the data banks of the European Centre for Disease Prevention and Control and the World Health Organization.

Setting 29 European countries.

Participants Children vaccinated.

Intervention Vaccination rates from 2006 to 2015 for measles, 2006 to 2016 for pertussis, and mandatory vaccination policies.

Outcomes Measles and pertussis vaccine coverage and the annual incidence of these diseases.

Main Results Mandatory vaccine policies were associated with higher vaccination prevalence, 3.71% (95% CI, 1.68 - 5.74) and 2.14% (95% CI, 0.13 to 4.15) for measles and pertussis, respectively. Some countries imposed a monetary penalty for non-compliance. Every €500 increase in the maximum penalty demonstrated an increase of 0.8% and 1.1% for measles pertussis vaccination prevalence, respectively ($P < .0001$ for both). Only countries without non-medical exemptions demonstrated an association with a lower measles rate compared with countries without a mandatory vaccine policy, adjusted incidence rate ratio, 0.14 (95% CI, 0.05 to 0.36). Pertussis rates were not statistically different.

Conclusions Mandatory vaccination policies were associated with higher vaccination rates and a decreased measles incidence.

Commentary High rates of vaccination coverage are important in preventing infectious diseases. Strategies adopted by European Union countries to achieve and maintain high immunization rates in target populations include compulsory and recommended vaccinations, free of charge and co-payment.[1] In Europe, mandatory vaccination policies vary not only in the presence or absence of a mandate but also in the implementation and enforcement of the mandates as well as in the consequences faced by individuals who fail to comply with their country's policy. This study found that mandatory vaccination against both measles and pertussis was associated with a higher prevalence of vaccination when compared with countries that did not have mandatory vaccination. Moreover, the magnitude of fines (in those European countries which imposed them) was associated with higher vaccination coverage. Currently, within the scientific community, there is an ongoing debate concerning compulsory vaccination.[2] The findings from Vaz et al suggest mandatory immunization programs increase measles and pertussis coverage. Health care policy makers may find these results useful in identifying effective immunization rate-enhancing strategies.

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Antibiotic-treated otitis media and adverse events

Hum SW, Shaikh KJ, Musa SS, Shaikh N. Adverse Events of Antibiotics Used to Treat Acute Otitis Media in Children: A Systematic Meta-Analysis. *J Pediatr* 2019;215:139-43.e7

Question Among children treated with antibiotics for acute otitis media (AOM), what is the incidence of common antibiotic-attributable adverse events (AEs)?

Design Systematic review, meta-analysis.

Setting Presumably outpatient and presumably in developed countries.

Participants Children, 0-19 years old, treated with antibiotics for otitis media.

Intervention Antibiotic (amoxicillin, amoxicillin/clavulanate, azithromycin, and cefdinir) treatment of AOM.

Outcomes Incidences of diarrhea, generalized rash, diaper rash, and candidal diaper dermatitis.

Main Results The meta-analysis included 82 articles. The incidences were of diarrhea: azithromycin (2.2%), placebo (6.9%), low-dose amoxicillin (8.7%), cefdinir (13.0%), high-dose amoxicillin (13.8%), and high-dose amoxicillin/clavulanate (18.9%); of generalized rash: azithromycin (1.4%), placebo (2.3%), low-dose amoxicillin (2.9%), high-dose amoxicillin/clavulanate (4.9%), and high-dose amoxicillin (6.5%); of diaper rash: placebo (4.6%), low-dose amoxicillin (6.4%), cefdinir (10.1%), and high-dose amoxicillin/clavulanate (14.8%); of candidal diaper rash: high-dose amoxicillin/clavulanate (3.3%), low-dose amoxicillin (5.8%).

Conclusions The incidence of common AEs varied widely among commonly employed antibiotics.

Commentary Antibiotics are the most commonly prescribed drug class for children,[1] as well as the leading cause of emergency department visits for adverse drug events in children.[2] Knowledge of antibiotic AEs is therefore important for pediatric providers. The results of this meta-analysis should be interpreted with some caution, due to significant heterogeneity of included studies and a high risk of bias related to AE reporting. Still, the pooled AE rates provide useful insight into the frequency of common AEs observed with antibiotic therapy for AOM. The authors suggest that these AE rates may be helpful to clinicians when selecting antibiotics for AOM. Indeed, the highest rate of diarrhea (18.9%) occurred with high-dose amoxicillin/clavulanate, the recommended second-line agent for AOM.[3] This underscores limiting its use to children who recently received amoxicillin, have otitis-conjunctivitis syndrome, or are failing high-dose amoxicillin. However, high-dose amoxicillin, the recommended first-line agent, had the second-highest rate of diarrhea (13.8%) and the highest rate of generalized rash (6.5%). Does this mean we should abandon high-dose amoxicillin in favor of other agents? High-dose amoxicillin has the highest activity of the commonly prescribed oral agents against the most common bacterial AOM pathogen, Streptococcus pneumoniae, and it retains activity against more than half of Haemophilus influenzae strains. It is also the most narrow-spectrum drug of these agents and is well tolerated. Thus, for children who truly need antibiotics, high-dose amoxicillin is still the best choice. A better question, then, may be whether antibiotics are warranted at all. Observation is a guideline-recommended option for select groups of children with AOM, and it is also the best way to avoid antibiotic AEs. This study is an important reminder that even the "best" antibiotics carry risk, and the need for judicious antibiotic prescribing is paramount.

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