Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Evidence-Based Medicine in the Time of COVID: We Have a Problem

A baby with D-transposition of the great arteries, intact ventricular septum, and restrictive atrial septal communication was born to a coronavirus disease 2019 (COVID-19)–positive mother. Urgent intervention was warranted, but balancing quality care with testing constraints and local logistical factors created a safety quagmire. Perinatal transmission of COVID-19 virus is unlikely, and if it occurs likely is due to close contact between the infected mother and baby; vertical transmission is unlikely and has not yet been reported.[1] This baby had no contact with his mother after birth and the chance of a positive test was not high; early repair would improve the baby's postoperative course and outcomes. At the same time, a complex congenital cardiac surgery on a neonate with COVID-19 infection is potentially dangerous for the baby, as well as the staff who risk exposure.

This scenario has played out for many of us over the last months in trying to balance the risk of infection with the urgency of a given child's surgical condition. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has highlighted innovation and resilience, but also has called attention to many deficiencies and inconsistencies in the healthcare system, both in the United States and worldwide. The need for information about this new virus has outstripped the ability to conduct evidence-based research. Case series and even case reports are taking on elevated importance as practitioners share data and make medical decisions.

Evidence-based medicine (EBM) is purportedly the gold standard but in reality is not widely practiced. EBM is defined as the "use of best evidence with current expertise and patient values to guide healthcare decisions."[2] Systematic reviews and randomized controlled trials form the apex of the EBM pyramid, but these types of studies are also subject to corruption. To be useful, randomized trials must ask the correct question, be designed to answer that question, and have adequate sample size, methodology, and follow-up. To be useful in the situation of a particular patient, that patient must be similar to study patients. Inappropriately applied evidence may cause harm. Given all of these caveats to the gold standard of applied research, it is not surprising that there is no proof that EBM improves outcomes.

Large randomized trials are particularly lacking in pediatric populations, in which target groups are smaller and research dollars harder to obtain. Attempting to apply EBM in pediatric congenital cardiac surgery and anesthesia further underscores the problems with holding EBM as the gold standard. Systematic reviews and metanalyses in the adult cardiac population are often considered a homogeneous population, with a higher ratio of randomized trial to observational or retrospective studies. In contrast, pediatric congenital cardiac patients are a heterogeneous population with high complexity, and it is difficult to prove outcomes benefits for a given strategy for a particular subpopulation.

Database research has helped answer many clinical questions in congenital cardiac anesthesia and surgery. Database research is resource heavy, but not as resource heavy as randomized trials. The Society for Thoracic Surgeons Congenital Heart Database (STS CHDB) is a repository for perioperative information on children and adults with congenital heart disease; in 2010 the Congenital Cardiac Anesthesia Society began adding anesthetic data to the database. Currently, the STS CHDB collects information worldwide, capturing data on nearly all congenital cardiac surgery programs; anesthetic contribution is present in about 50% of programs.[3] Database research is hindered, however, by the quality of the data. The STS CHDB is only one of more than 40 registries addressing congenital heart disease; all of these registries must contend with issues of data integrity, including missing values, risk adjustments, varied validation, oversight and data usage, and privacy concerns.[4] A secondary problem with using data obtained in registries is the time necessary to examine and report trends. For example, an analysis of the STS CHD from 2010 to 2014 was published in 2018[5]; with the rapid pace of changes in clinical medicine, this time lag means that some data will be too old to be useful by the time it is published.

The global pandemic due to SARS-CoV-2 infection requires rapid information sharing to learn how to deal with all aspects of the disease. In a one-year period from October 2019 through October 2020, more than 48,000 articles on coronavirus/COVID-19 were introduced on the National Institutes of Health, National Library of Medicine's PubMed; about 7,000

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were review articles, and fewer than 300 were randomized or therapeutic trials. Only about 3,200 articles pertained to pediatric patients. Most articles were observational studies, guideline papers, or expert opinion pieces.

These observational studies are crucial to understanding of the COVID-19 virus. In particular, the hyperinflammatory condition that some children develop after SARS-CoV-2 infection, termed "multiorgan inflammatory syndrome in children" (MIS-C) in the United States, has been characterized by anecdotal evidence only—a mixture of case reports, case series, and expert opinions. Anecdotal data sharing taught us that children are far less affected than adults in the COVID-19 global pandemic, but a subset of children may be susceptible to severe disease from the virus. In April 2020, the UK National Health Service issued an alert regarding a hyperinflammatory syndrome in children with recent SARS-CoV-2 infection or exposure; they termed it "pediatric inflammatory multisystem syndrome"—temporarily associated with SARS-CoV-2.

Since that alert from the United Kingdom, this constellation of signs and symptoms has been identified in children worldwide. Three definitions—one each from the World Health Organization, the United States Centers for Disease Control and Prevention (CDC), and the United Kingdom Royal College of Pediatrics—describe the syndrome.[6-8] Common to all three definitions are presence of fever, multiorgan involvement, laboratory evidence of elevated inflammatory markers (eg, erythrocyte sedimentation rate, c-reactive protein, fibrinogen), lack of evidence of other infections that would explain symptoms, and either recent SARS-CoV-2 infection or significant exposure.[9] Many children present in vasoplegic shock that is responsive to vasopressor and inotropic support; few have respiratory failure requiring ventilatory support.[10]

The World Health Organization, CDC, and UK Royal College of Pediatrics did not develop these guidelines and recommendations based on randomized trials or meta-analyses. Rather, a look at the references for each publication shows that small case series, retrospective studies, and even case reports were used to gather the data to paint a picture of this syndrome. Moreover, the definitions of this hyperinflammatory condition rapidly are evolving as understanding of the disease advances, and more studies describing symptomology, treatment, and outcomes are published. The first report summarizing the experience of children in the United States with MIS-C examined characteristics of 186 children across 20 states who met CDC definitions of MIS-C. This report, published in the *New England Journal of Medicine* in June 2020, described the epidemiology, presenting signs and symptoms, and outcomes of these initial infections.[11]

Such anecdotal evidence and retrospective research on pediatric hyperinflammatory reaction after SARS-CoV-2 infection have been critical to understanding of this disease complex, but lives at the bottom of the EBM pyramid. Its importance in clinical decision-making and offering support to patients and their families does not jibe with this position.

There are many scenarios in medicine when clinical disease processes evolve at a pace faster than can be scrutinized and determined scientifically. Databases and registries processes move too slowly to inform bedside decisions for an individual patient who needs urgent surgery. EBM fails us in the current global pandemic, and in many cases of unique diseases. Continuous quality improvement initiatives provide valuable opportunities to rapidly assess new interventions and strategies in patient care. Case reports and retrospective reviews should not be eschewed as poor evidence. Practitioners should encourage informal communication and facilitate real-time discussion of patient problems and creative solutions. While there should be caution over fake news, practitioners must remain open-minded as to the challenges of abrupt changes in clinical disease. Anecdotal and retrospective evidence is having a well-deserved moment in the spotlight. This should be remembered when the pandemic is over and there is a temptation to fall back into old patterns of evidence judging.

Conflict of Interest

None.

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