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Research Matters

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Le Bonheur Children's Hospital

Multiple MIS-C Mystery

Le Bonheur physicians highlight case of patient with two distinct illnesses consistent with multisystem inflammatory syndrome in children

Some children may be at risk for multiple episodes of multisystem inflammatory syndrome in children (MIS-C), according to a new *Pediatrics* article from physicians at Le Bonheur Children's Hospital and the University of Tennessee Health Science Center (UTHSC). The article describes the case of one child with two distinct illnesses seven months apart that were both consistent with MIS-C. The report highlights the need for more guidance and better understanding of the syndrome in order to improve diagnosis and treatment of these patients.

Caleb Hancock, MD, former Pediatric Hospital Medicine Fellow (left) and Infectious Disease Specialist Bindiya Bagga, MD

The article was published by a group of Le Bonheur and UTHSC physicians — former Pediatric Hospital Medicine Fellow W. Caleb Hancock, MD, Infectious Disease Fellow Amanda M. Green, MD, Child Neurology Resident Sariha Moyen, MD, Pediatrics Resident Caitlin Creel, MD, Rheumatologist Kathleen P. Collins, MD, Vice Chair of Clinical Affairs and Rheumatologist Terri Finkel, MD, PhD, Hospitalist Stephen D. Pishko, MD, and Infectious Disease Specialist and UTHSC Pediatrics Residency Program Director Bindiya Bagga, MD.

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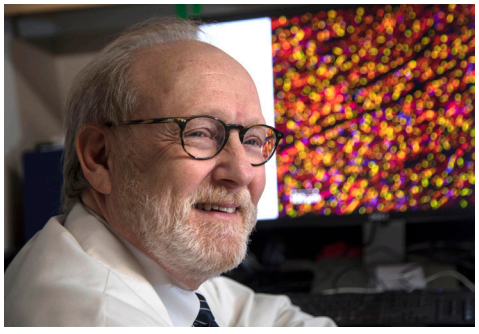
A Consensus Care Model for HCM

Le Bonheur Heart Institute Co-Executive Director publishes new guidelines for diagnosis, evaluation and management of hypertrophic cardiomyopathy



Co-Executive Director of Le Bonheur's Heart Institute Jeffrey A. Towbin, MD

Co-Executive Director of Le Bonheur Children's Heart Institute Jeffrey A. Towbin, MD, recently published the state-of-the-art reviews "Diagnosis and Evaluation of Hypertrophic Cardiomyopathy" and "Management of Hypertrophic Cardiomyopathy" with an expert panel for the *Journal of the American College of Cardiology* (*JACC*).

These consensus documents create a comprehensive best care model for hypertrophic cardiomyopathy (HCM) based on clinical practice experience, personal research and peer-reviewed literature. Towbin is also chief of Cardiology and medical director of the Cardiomyopathy, Heart Failure and Heart Transplant Program at Le Bonheur Children's, medical director of Cardio-Oncology and Cardio-Hematology at St. Jude Children's Research Hospital and professor of Pediatric Cardiology at the University of Tennessee Health Science Center.

According to the reviews, HCM is an under-recognized disease that occurs in one in 200 to one in 500 individuals worldwide. Because HCM is highly treatable, has seen advances in care and provides family screening opportunities, a timely diagnosis is crucial. In the first article, the *JACC* expert panel systematically reviewed a range of issues related to HCM, from best practices for initial evaluation to genetic testing to exercise and physical activity in an effort

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"Our patient exhibited two distinct illnesses, both of which met the clinical and laboratory case definitions of MIS-C and could not be unambiguously explained by another etiology," said Bagga. "Our case introduces the possibility that a subset of children may be more likely to have repeat MIS-C."

In June 2020, a child presented to Le Bonheur Children's with primarily neurological and gastrointestinal symptoms as well as elevated inflammatory markers. A COVID-19 PCR test was negative, but the child had suspected exposure to COVID-19. When an extensive workup for alternative diagnoses was negative, a SARS-CoV-2 antibody test was positive and the viral respiratory panel was negative, physicians gave the diagnosis of MIS-C. The child improved after intravenous immune globulin (IVIG) treatment and spent 14 days inpatient. Three weeks after discharge in outpatient follow up, the child had fully recovered from all symptoms.

In January 2021 after seven months of good health, the child presented again — this time with fever, rash, gastrointestinal symptoms, elevated inflammatory markers and dilation of the left anterior descending coronary artery. The child had no known direct exposure to COVID-19. Symptoms, findings on electrocardiogram (EKG) and transthoracic echocardiogram (TTE) and abnormal laboratory results again led to a diagnosis of MIS-C. Treatment with high-dose aspirin, IVIG and methylprednisolone was initiated and by day five, all lab results except D-dimer were normal. At a follow up with cardiology two weeks after discharge, the coronary dilation had resolved.

"In the interim between illnesses, the patient returned to a usual state of good health and demonstrated resolution of laboratory abnormalities," said Bagga. "This case is not consistent with prior reports that have described rebound MIS-C symptoms after completion of therapy — it is possible the separate illnesses were triggered by different variants of SARS-CoV-2."

Le Bonheur physicians posit that some high-risk variants of SARS-CoV-2 may be more likely to trigger MIS-C and that individuals with defects in inflammatory pathways may also be at increased risk.

"Further immunologic and virologic characterization of cases of MIS-C is warranted to improve our understanding of this entity, and we hope our case report increases awareness of the possibility that repeat MIS-C illness can occur in their patients," said Bagga.

Good Stewards

National diagnostic stewardship initiative reduces blood culture, antibiotics overuse

Diagnostic stewardship can reduce blood culture overuse in the Pediatric Intensive Care Unit (PICU) and thereby reduce the use of broad-spectrum antibiotics, according to research published in *JAMA Pediatrics*. The research was published by the Bright STAR Authorship Group, which included Le Bonheur Children's Medical Director of Infection Prevention Nick Hysmith, MD, MS, and shared the results of a clinical decision support tool developed by critical care intensivists in Le Bonheur's PICU led by Sachin Tadphale, MBBS, MPH. Results showed that implementation of a decision support tool for blood culture guidance reduced blood culture rates by 33% and the rate of broad-spectrum antibiotic use by 8%.

Sachin Tadphale, MBBS, MPH, (above center) led the development of a decision support tool to reduce blood culture overuse.

Bright STAR is a national quality improvement collaborative that aims to reduce overtesting and bacterial culture overuse, also known as diagnostic stewardship, thereby decreasing antibiotic use and potential for antibiotic resistance in critically-ill children.

"Blood cultures are the gold standard to identify sepsis but can be taken excessively, typically leading to antibiotic use for non-specific symptoms," said Hysmith. "By reducing unnecessary blood cultures, we hoped to reduce the use of broad-spectrum antibiotics and the possibility of critically-ill children developing antibiotic resistance."

Each site developed a clinical decision support tool to reduce blood cultures, targeting relatively stable patients with a fever but no additional sepsis signs. The purpose of the tool was to determine which patients could be monitored without blood culture after thoughtful evaluation. To measure the impact of this tool, analyses of specific outcomes were conducted from 24 months before to 18 months after the new tool was implemented. A project team was formed at each site to conduct a pre-implementation assessment and then develop a clinical decision support tool and implementation plan. The major goals were standardizing the decision to order blood culture and highlighting any patient safety concerns. Le Bonheur implemented the decision tool in the PICU as well as the Intermediate Care Unit (IMCU) and Neuro Intensive Care Unit (Neuro ICU).

Results from the 14-site study included:

- Reduction in total blood cultures from 37,527 to 20,340.
- Reduction in blood culture rates at 13 of 14 sites.
- 33% relative reduction rate in mean number of blood cultures per 1,000 patient days per month.
- 13% relative reduction of total days of broad-spectrum antibiotic use per 1,000 patient days per month.
- 35% reduction in central line blood stream infection (CLABSI) rates.
- Similar rates of PICU mortality, length of stay and readmission after implementation.
- Only one episode out of 793 positive blood cultures where the new clinical diagnostic tool may have delayed a blood culture.

The Bright STAR Collaborative hopes to take these findings and implement them on a wider scale while monitoring for effectiveness and patient safety.

Trauma-Informed Care

First year of results from Le Bonheur's Family Resilience Initiative shows high prevalence of adverse childhood events, social determinants of health

In its first year of operation, Le Bonheur's Family Resilience Initiative (FRI) showed that of the 246 families enrolled in the program, more than half of caregivers reported one or more adverse childhood events (ACEs) for their child and a social determinants of health (SDOH) need according to research published in *Clinical Pediatrics*. The FRI program is a multidisciplinary collaborative that screens for ACEs and SDOH in Le Bonheur's ULPS General Pediatrics Clinic and connects families with needed services to mitigate and prevent future ACEs.

Adverse childhood experiences are potentially traumatic events in childhood that can be emotionally painful or distressing and have effects that persist for years. Social determinants of health are defined by the World Health Organization as the non-medical factors that influence health outcomes. These include conditions in which people are born, work and live and economic, social and political forces and systems.

"Adverse childhood experiences have been described as the public health emergency of our time," said Jason Yaun, MD, division chief of Outpatient Pediatrics and medical director for FRI. "The primary care setting is an ideal place for screening for ACEs and SDOH and providing evidence-based interventions."

FRI is embedded in the primary care setting and funded through a grant from the Urban Child Institute. Outreach coordinators screen patients ages 9 months to 5 years as a part of their well-child visit using the Accountable Health Communities (AHC) Health-Related Social Needs (HRSN) screening tool for SDOH and a modified version of the Pediatric ACEs and Related Life Events Screener (PEARLS) tool for identifying ACEs. Families that have a SDOH need or an ACE are enrolled in the FRI program. If SDOH are identified, the outreach coordinator connects the family with resources to help meet their needs, and if any ACEs are identified free counseling is offered through a child psychologist embedded in the clinic. All families receive education and prevention strategies for ACEs. The outreach coordinators communicate findings to the medical team documenting ACEs and SDOH in the medical record. They follow up with families based on intensity of needs. The screening process is repeated on an annual basis.

During the first year of intake, FRI had 246 participants. Primary results showed 39.4% of families in the program reported both ACEs and SDOH with 56.9% reporting at least one ACE. At least one SDOH-related need was reported by 63% of families.

The Family Resilience Initiative is embedded in Le Bonheur's ULPS General Pediatric Clinic. Above, Jason Yaun, MD, (left) and Outreach Coordinator Christen Henderson (far right) meet with a patient and parent during clinic.

Additional results included:

- The most common ACE reported was separation or divorce of parents/guardians (40.7%) followed by child living or having lived with a household member who was depressed, mentally ill or attempted suicide (13.4%).
- The average number of ACEs per patient was .94.
- 40 families (33.1%) received a referral for psychology services.
- The most common SDOH issues were around food insecurity (36.1%) followed by utility needs (19.6%) and transportation (18.4%).
- Outreach coordinators conducted 2,240 follow-up activities.

"The successful design, implementation and experience of the FRI model in our first year shows that this model is a feasible approach to implement trauma-informed care," said Yaun.

Yaun says that provider awareness of the ACEs and SDOH needs of patients practically impacts patient care. Approaching care with a trauma-informed lens allows the clinic to view patients and families with greater empathy and probe into the root of the issue for anything from behavioral problems to appointment no-shows. Providers also can connect how trauma and ACEs play into health-related problems like feeding, development and sleep.

FRI research supports the evidence that ACEs are common from a young age which further emphasizes the need to mitigate effects of previous ACEs, while providing resiliency building and empowerment to prevent future ACEs. Next, the FRI program hopes to evaluate FRI interventions and impact on child development, health outcomes, health care utilization and more, potentially expanding enrollment to adolescents.

Le Bonheur researchers publish more than 100 articles in 2022

CFRI researchers continue to publish cutting-edge studies that help children with serious diseases who depend on Le Bonheur. Since Jan. 1 of this year, 118 articles have been published by Le Bonheur-affiliated authors and researchers and can be found on PubMed.gov. This volume of peer-reviewed research builds upon the astounding publishing output of 317 articles seen in 2021.

Please remember to include Le Bonheur in your authorship affiliation. CFRI's goal is to publish more than 200 manuscripts per year for a sixth year in a row, and affiliation is one way we track our progress.

Current clinical trial totals at Le Bonheur

Sponsored trials:	Full board-reviewed studies:	PI-initiated studies:
162	**75**	**53**

Meet the CFRI Team: Regulatory Core

CFRI is dedicated to furthering the research that promotes Le Bonheur's mission in preventing, treating and eliminating childhood disease. Our team members are available to provide support for Le Bonheur researchers. Our staff can assist with grant preparation, navigating research regulations, setting up clinical trials, requesting chart reviews, biostatistics, biomedical informatics and medical editing and writing.

Who are you?
We are the Regulatory Core team. Our staff includes Research Regulatory Manager Dalia Aguilar-Canseco, Clinical Research Coordinator Rose Prince and Clinical Research Coordinator Jehad Webb.

What can you do for researchers?
We can provide support for researchers in many ways, including preparing research projects, assisting with reviewing IRB applications prior to submission, helping answer and/or address provisos, completing and submitting IRB forms (upon request), obtaining Methodist Le Bonheur Healthcare (MLH) institutional approval, providing guidance and tools to meet regulatory requirements, reviewing study records and providing recommendations prior to audits by the IRB and FDA and guiding researchers through the process of using external IRBs.

How can researchers contact your team?
Feel free to contact any member of our team:

- Rose Prince: Rose.Prince@lebonheur.org, 901-287-4645
- Jehad Webb: Jehad.Webb@lebonheur.org, 901-287-5329
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to provide a best care model for this patient group. The second article covered the management of HCM including sudden death prevention, surgical options for reversing heart failure and considerations for heart transplant.

"In recent years, effective management strategies for major HCM complications have emerged which improve clinical course, lower mortality and morbidity rates substantially and enhance the likelihood of normal longevity and good quality of life," said Towbin.

Recommendations and insights from the expert panel in the review "Diagnosis and Evaluation of Hypertrophic Cardiomyopathy" included the following:

- Initial HCM evaluation should prioritize diagnosis with assessment of left ventricular (LV) morphology and function, symptom severity, sudden death risk, family history, lifestyle modification and a surveillance plan.
- Routine re-evaluation after diagnosis should take place at 12-month intervals.
- Echocardiography and cardiac magnetic resonance (CMR) imaging are established strategies for HCM diagnosis. CMR should be obtained on initial evaluation and every three to five years.
- Genetic testing is important for family screening, but not reliable for prognosis or clinical course. At-risk and asymptomatic family members, as well as those who can transmit the disease to children, should have genetic testing.
- First-degree and other close family members should begin HCM screening with diagnostic imaging on a yearly basis beginning at 12 years old until 18 to 21 years old and then at five-year intervals.
- The panel does not recommend screening prior to age 12 as HCM characteristics and adverse events are rare before adolescence, and screening can cause unnecessary anxiety and false positives.
- Most athletes with HCM should be disqualified from intense competitive sports because of the risk of sudden death. The responsibility for this decision should rest with the physician who understands the risk for their patient.

"Through these guidelines, our panel aimed to express key principles for HCM in 'real-world' clinical language, largely focused on young adults," said Towbin. "While we support and promote the advantages of HCM Centers of Excellence like Le Bonheur's, an equally important objective was to more expansively inform cardiovascular practitioners caring for HCM patients in general cardiology environments."

Better understanding of the disease, improved diagnostic technologies and advances in therapeutics have consequently transformed the treatment and management of HCM. This has evolved from management primarily through medication to management with devices and interventional therapies. As a result, HCM mortality has been reduced tenfold.

"Evidence-based and guideline-directed personalized treatment strategies have transformed HCM into a starkly different disease entity," said Towbin. "More widespread implementation of these advances in regional and community-based populations and worldwide remains an important challenge for this disease that has now emerged from the darkness."

Contact us

If you have any research news or announcements you would like to include in an upcoming issue of *Research Matters*, please email Andrew Gienapp at Andrew.Gienapp@lebonheur.org.