CJC Pediatric and Congenital Heart Disease 3 (2024) 229–236

Society News

Fourteenth International Kawasaki Disease Symposium: Learning From the Past, Looking to the Future

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The 14th International Kawasaki Disease Symposium (IKDS) was held in Montreal, Canada, on August 26-29, 2024, led by IKDS presidents Drs Nagib Dahdah and Adriana Tremoulet. There were 269 attendees spanning 23 nations and 6 continents, and topics ranged from basic science of Kawasaki disease (KD) to etiology and management. The programme for the 14th IKDS is available at www.ikds.org (Fig. 1). Although there have been tremendous advances in our collective understanding of KD since Dr Tomisaku Kawasaki reported the first 50 patients in 1967,[1] there is much more work to do. What is the true etiology for KD? How can we accurately identify patients who are at high risk for tailoring their therapies accordingly? How do we optimize long-term management of coronary artery aneurysms (CAAs) to avoid adverse outcomes? As we heard from international experts, our Science Digest team was assembled to provide daily "take-home" messages for the audience each morning (Fig. 2). We asked each Science Digest team member from these sessions about the highlights from the conference.

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https://doi.org/10.1016/j.cjcpc.2024.10.002
2772-8129

Figure 1. Visit www.ikds.org for more information.

Figure 2. Seven members of the Science Digest team (second and third rows), along with IKDS co-presidents (first row). Top row: Nagib Dahdah and Adriana H. Tremoulet. Middle row: Audrey Dionne, Matthew D. Elias, and Luisa B. Gámez-González. Bottom row: Fujito Numano, Federica Anselmi, Rakesh Kumar Pilania, and Alan P. Wang.

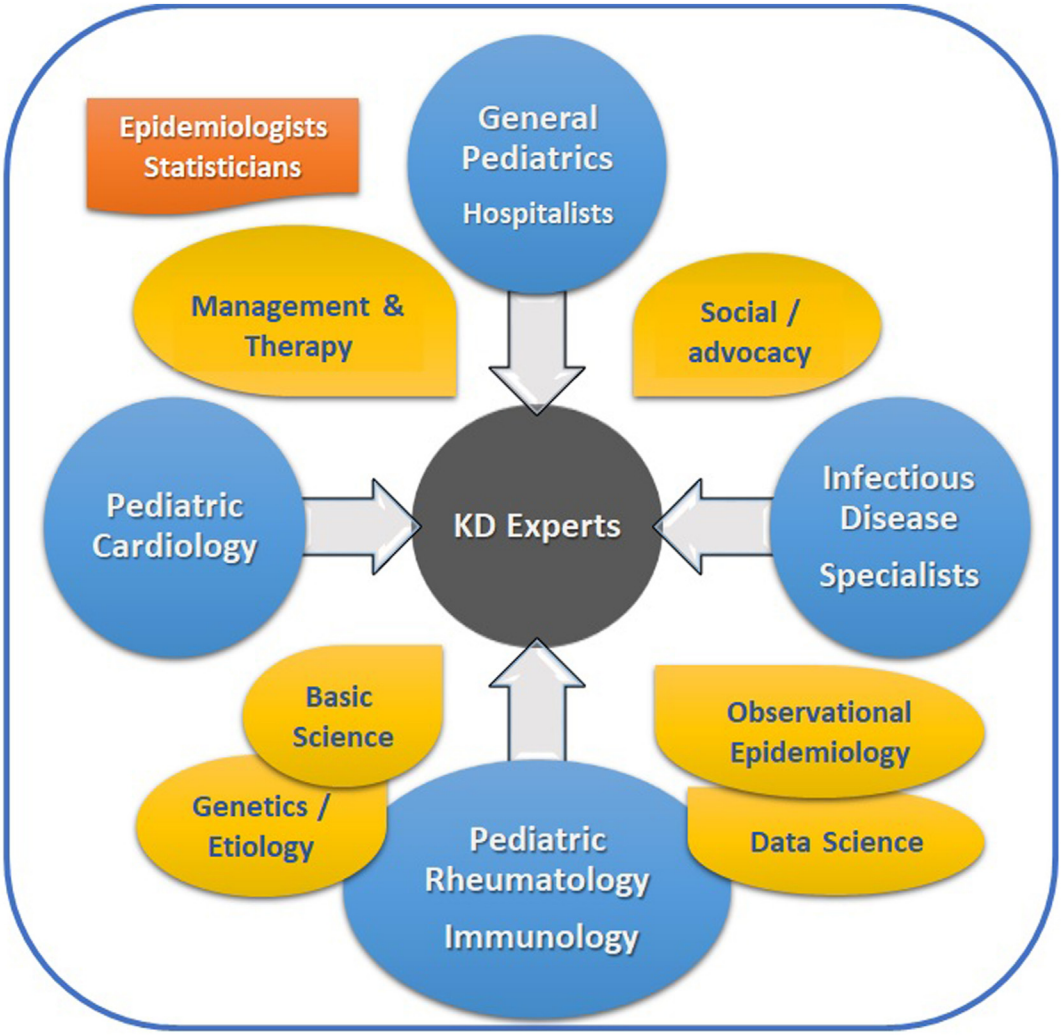

Figure 3. Multidisciplinary collaboration in Kawasaki disease (KD).

What Did You Learn About the Importance of Collaboration to Improve the Care of Patients With Kawasaki Disease?

Before the conference, the IKDS presidents circulated a survey to various KD organizations across the globe to understand more about these groups. The majority of organizations have an organized governance and steering committee, yet most have no formal funding. The common overarching goal is to learn more about KD and to improve the lives of children who encounter this disease. For these organizations and for everyone caring for patients with KD, collaboration is paramount (Fig. 3), as emphasized by Dr Brian McCrindle in the Tomisaku Kawasaki Memorial Lecture. The management of KD commonly includes general paediatricians or hospitalists and paediatric cardiologists, as well as subspecialists with expertise in paediatric rheumatology, infectious disease, and/or immunology. The science of KD spans basic science evaluating mouse models of KD, observational and epidemiologic studies of populations, climatologists and virologists evaluating potential etiologies of KD, and many more. We need to collaborate not only within the paediatric community but also with the adult community, both in the transition of patients to adult cardiology care and to learn from our adult cardiology colleagues and their wealth of experience in coronary artery (CA) disease.

The necessity for collaboration increases as the prevalence of KD itself continues to increase in many regions of the world. In Australia, there has been a 3.5% annual increase in KD hospitalization rates over 25 years,[2] and we heard about the increase in KD cases in Chandigarh, India, from 1.4 per 100,000 children <5 years old in 1994 to 9.72 per 100,000 as of 2019. As the prevalence increases, access to care remains an issue. The KD Arab Initiative (Kawarabi) surveyed 13 Arab countries and noted significant disparity in health care quality and availability of KD treatment, particularly between larger cities and remote regions.[3] Similarly, in a survey across 15 countries in the Latin American Kawasaki Disease Network (REKAMLATINA), less than 50% reported a timely diagnosis and treatment for KD. A survey from the Asian Pacific Collaboration identified a wide range in the timing of KD diagnosis across various regions in Asia. By learning from each other and sharing our experiences, we can bridge these gaps. Furthermore, there is a current effort engaging the World Health Organization to place KD in the world map of its

priorities, as explained by Dr Surjit Singh during his address in the Yuki Lynn Memorial Lecture.

Collaboration takes many forms. During the IKDS, we discussed the variability among even the most standard elements of KD—the echocardiographic measurement of CAs with *z*-scores, where the internal diameter is normalized for body surface areas and represents standard deviations from the mean. The *z*-score provides a standardized approach to assess the severity of CAAs, which impacts management decisions, yet there are different methods of calculating *z*-scores, reflecting different normative values in diverse patient populations and various methodologies. While one *z*-score calculator may measure the left anterior descending CA *z*-score as 2.47 (in the "mild dilation" range), another calculator using the same internal diameter may measure the same left anterior descending to have a *z*-score of 4 (in the "small aneurysm" range). Calculations of *z*-score should not be used interchangeably, and consistency is important. Perhaps a collaborative effort for a more universal *z*-score calculation and correlation with outcomes will be beneficial and necessary in the future.

Collaboration may involve institutions pooling their patients in a larger cohort for analysis, on a local, regional, national, or international stage. That may include formal multicentre studies or discussing shared experiences at venues such as the IKDS. Whether it is the initial diagnosis or the experience in the treatment of KD and the cardiac sequelae, global collaboration with our KD colleagues will allow us to expand our understanding of KD even further.

What Are the Most Recent Updates and Theories About the Etiology and Potential New Therapeutic Strategies of Kawasaki Disease?

Recent research has provided significant insights into the etiopathogenesis and predisposing factors of KD, focusing particularly on vascular inflammation and arterial remodelling, including the following topics discussed at the IKDS.

Central role of interleukin-1 in KD vasculitis

Experimental murine models of KD vasculitis have significantly improved our understanding of the disease's pathophysiology, particularly highlighting the roles of the NLRP3 inflammasome and the interleukin-1 (IL-1) signalling pathway.[4] KD is an inflammatory disease, and Drs Moshe Arditi and Asli Atici emphasized the abundant evidence for the role of IL-1 in its pathogenesis. IL-1, a master proinflammatory cytokine, has been shown to have a dysregulated and uncontrolled production of IL-1β, which is linked to the development of KD. Moreover, blood samples from patients with acute KD have higher levels of circulating IL-1β in their serum, along with higher expression of IL-1-related genes in the peripheral blood than healthy control subjects.[5] This increase is normalized in the convalescent phase of the disease after intravenous immunoglobulin (IVIG) treatment. IL-1 signalling has also emerged as a key mechanism in the pathogenesis of coronary vasculitis in KD. Recent studies have highlighted that inhibiting this pathway could prevent inflammation and vascular damage. These findings support the potential use of anti-IL-1 therapies, such as anakinra, to reduce the risk of severe complications including CAAs.

Modulation of coronary stenosis through retinoic acid

A recent study by Suganuma et al.[6] evaluated the effects of all-trans retinoic acid in a murine model of KD, demonstrating its capacity to alleviate coronary stenosis by regulating the function of vascular smooth muscle cells. These findings highlight all-trans retinoic acid's therapeutic potential in preventing vascular dysfunction associated with KD, suggesting a new approach to managing cardiovascular complications in patients with KD.

mTOR inhibition in arterial remodelling

The inhibition of the mechanistic target of rapamycin (mTOR) pathway has been shown to effectively prevent CA remodelling in murine models of KD. A recent study by Stock et al.[7] using murine models of KD demonstrated the *in vivo* efficacy of mTOR inhibition with therapeutic rapamycin to decrease vascular fibrosis and intimal hyperplasia of CAs. This study provides compelling evidence that mTOR activation plays a critical role in the cardiovascular pathology of KD, positioning mTOR inhibitors as promising candidates for the preventive treatment of arterial remodelling in the disease.

Convergent antibody response in plasmablasts

The analysis of plasmablasts from children with KD revealed a convergent immune response towards a specific protein epitope. Rowley et al.[8] hypothesize that a shared antigen, potentially of infectious origin, may trigger the disease, offering new insights into the underlying immunological mechanisms. This finding may also have diagnostic implications, aiding in the identification of specific biomarkers for KD.

Intestinal microbiota and cardiovascular inflammation

The intestinal microbiota has been shown to significantly contribute to immune-mediated cardiovascular inflammation and vasculitis in murine models of KD, as discussed by Dr Magali Noval Rivas.[9] Targeting the microbiota may represent a novel therapeutic approach for managing KD. The development of murine model KD vasculitis was associated with alterations in the intestinal microbiota composition and, notably, a decreased abundance of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii.* Oral supplementation with either of these live or pasteurized individual bacteria, or with short-chain fatty acids produced by them, attenuated cardiovascular inflammation. Treatment with Amuc_1100, the TLR-2 signalling outer membrane protein from *A. muciniphila*, also decreased the severity of vascular inflammation.

Temporal clustering of Kawasaki disease cases globally

As reviewed by Dr Jennifer Burney, recent epidemiological studies have identified temporal clustering of KD cases worldwide, suggesting the influence of environmental or infectious factors in disease onset.[10] The identification of these temporal patterns supports the hypothesis that KD may be triggered by seasonal or environmental agents, offering new directions for investigating predisposing factors.

Dynamic changes in ventricular wall involving fibroblasts and adipocytes

Dr Adrián Villalba presented his team's findings of myocardial changes that occur after KD. An analysis of

autopsies and transplanted hearts after KD identified a chronic, remodelling process of the myocardium, with various distributions and extent of fibrosis among patients, distinct from the remodelling processes seen in other acute or chronic ischemic events such as ventricular hypertrophy or myocardial infarctions. This research should open more avenues for the identification of pertinent mechanisms in KD pathology.

How Are Bioinformatics and Artificial Intelligence Applied to Kawasaki Disease?

Artificial intelligence (AI) and bioinformatics are revolutionizing the understanding, diagnosis, and management of medical issues. Currently, AI and bioinformatics applications in KD are focused on 3 primary areas: identifying patient subgroups/clusters, developing diagnostic and management algorithms, and predicting cardiovascular risk.

Identification of patient subgroups/clusters

AI has proven effective in identifying distinct patient subgroups of KD and related conditions such as multisystem inflammatory syndrome in children (MIS-C). By using data-driven, multiomics approaches, researchers have been able to integrate various data types—including genomic, transcriptomic, proteomic, and clinical data—to better characterize these conditions.

Studies presented by Drs Sophie Sun and Pedrom Farid involved patients with MIS-C and patients with prepandemic KD using advanced techniques such as probabilistic principal component analysis, Gaussian mixture models, and uniform manifold approximation and projection to reveal 4 distinct and homogeneous patient subgroups with unique clinical and biological signatures. These results suggest a shared disease spectrum between KD and MIS-C and determined that a proportion of patients with prepandemic KD had a clinical and biological profile consistent with pandemic-era MIS-C subgroups. These findings highlight that cluster classification supplements traditional clinical diagnoses in identifying homogeneous patient groups. Likewise, bioinformatics techniques on cell-free RNA signatures, presented by Dr Conor Loy, identified different molecular profiles of 4 distinct KD subgroups, indicating different cell types of origin and biological pathways. These findings highlight the critical role of AI and bioinformatics in distinguishing subgroups of KD, which may enable the development of targeted therapies and predictive tools to enhance patient outcomes.

Development of diagnostic and management algorithms

AI is also impacting the development of diagnostic and management algorithms for KD. One notable example is MISKD, a clinical decision support system designed by Dr Cedric Manlhiot to assist in diagnosing and managing patients across the KD-MIS-C spectrum. MISKD uses AI-powered predictive algorithms to address the diagnostic challenges posed by the overlapping clinical features of KD and MIS-C. MISKD is not only able to differentiate between KD and MIS-C by providing a probability score but also to predict patient responses to various treatments and risk of complications. MISKD could therefore become a useful tool to monitor disease progression, provide short- and long-term prognostic insights, and optimize personalized therapeutic strategies, thus improving outcomes and reducing unnecessary treatments. In addition to MISKD, Kawasaki MATCH is another AI-based tool, presented by Dr Jonathan Lam, that aids clinicians in diagnosing KD by calculating a risk score based on clinical signs and laboratory data.[11] Validated in multiple clinical settings, Kawasaki MATCH has demonstrated high accuracy in predicting KD, supporting timely and accurate diagnosis, and will possibly be integrated into digital health platforms for wider use. These AI-driven tools represent a significant advancement in the clinical management of KD, enabling more accurate diagnoses, personalized treatment strategies, and efficient use of health care resources.

Prediction of cardiovascular risk

The prediction of cardiovascular risk, particularly the risk of CAA, represents another critical application of AI in KD. Traditional methods for assessing CAAs currently rely on geometric metrics like aneurysm diameter, which may not adequately predict thrombus formation. Dr Jongmin Seo discussed the analysis of computational fluid dynamics and of haemodynamic factors, such as time-averaged wall shear stress and residence time, which have shown superior predictive performance for thrombus formation compared with traditional geometric metrics. The integration of computational fluid dynamics–derived parameters into clinical practice could significantly improve decision-making and treatment guidelines for patients with KD. Moreover, AI facilitates real-time prediction of thrombosis risk in patients with KD by combining machine learning with haemodynamic simulations. Techniques like convolutional neural networks enable faster, more accurate, and less expensive predictions. As presented by Dr Elie Hachem, by training these networks with simulation data, this approach could provide clinicians real-time decision support, allowing faster and more informed decision-making.

What Are the Latest Advances in the Long-term Follow-up and Monitoring of Patients With Coronary Artery Aneurysms?

Long-term follow-up of CAA in KD requires detailed analysis of the CAA, beyond the routine surveillance of echocardiography. Although invasive angiography has been the traditional imaging modality to evaluate CAs, cross-sectional imaging such as computed tomography angiography (CTA) has become increasingly prevalent in recent years, providing similar coronary angiography without the need for invasive procedures. Compared with echocardiography, CTA provides improved specificity and sensitivity for detecting localized CA stenosis. Radiation remains a concern and varies according to body size, although recent techniques use lower radiation doses. Newer imaging procedures such as calcium score and fractional flow reserve derived from CTA, plaque analysis and AI-guided plaque staging, computational flow dynamics for complex lesions, and positron emission tomography/computed tomography are now being implemented to assess further advances over morphology, such as vascular reserve function and the properties of the vascular wall.

There are various options to evaluate for inducible ischemia, including stress echocardiography, nuclear medicine myocardial perfusion, and cardiac magnetic resonance

imaging (MRI). Drs Nobutaka Noto and Michelle Grenier discussed stress echocardiography, which can be performed either with routine exercise stress tests or via pharmacologic therapy, such as dobutamine, without the risk of radiation exposure. By increasing myocardial oxygen demand, stress echocardiography can assess for wall motion abnormalities, via visual observation and strain analysis. Nuclear medicine perfusion imaging, discussed by Dr Kenji Suda, provides detailed analysis of perfusion defects with physiologic or pharmacologic exercise, although with the risk of radiation exposure. Drs Supriya Jain and Tam Doan discussed the potential and limitations of stress cardiac MRI among patients with KD. Stress MRI provides superior spatial resolution and radiation-free imaging compared with nuclear stress perfusion imaging. Cardiac MRI has the advantages of assessing CA anatomy, ventricular function, late gadolinium enhancement (myocardial scar), and myocardial perfusion. Given the complexities involved though, stress MRI in KD is generally only performed in specialized centres with extensive experience in both paediatric cardiology and advanced cardiac imaging. Nevertheless, the potential for stress perfusion MRI is considered to be quite significant in KD. With any of these options, it is useful, and necessary in many centres, to rely on adult cardiology colleagues with expertise in stress testing due to the low volume in paediatrics, especially the low number of patients with ischemia and positive test results.

Long-term management of KD requires careful monitoring for CA thrombus formation, particularly among patients with large/giant CAAs. For those highest risk patients, the traditional anticoagulation agents have included warfarin and low-molecular-weight heparin. Warfarin has many drug and food interactions, requires frequent monitoring, and tends to have poor compliance. Low-molecular-weight heparin has more predictable pharmacokinetics and requires less frequent monitoring, but subcutaneous administration is often difficult for children and families. More recently, many KD centres have transitioned from more traditional anticoagulation to direct oral anticoagulants (DOACs), as discussed by Drs Christina VanderPluym and Leonardo Brandão. DOACs have an oral formulation with wide therapeutic and safety margins, decreasing the need for routine monitoring, along with fixed dosing and fewer drug-drug interactions. However, there are still limited paediatric DOAC data in KD. DOACs may still require laboratory monitoring, often depending on availability, and the therapeutic range for DOACs requires further clarification. Despite these limitations, there is a role for DOACs in the management of KD and increasing experience with its use.

Why Is Early Diagnosis Important, and How Do We Avoid Missing the Diagnosis of Kawasaki Disease?

Early diagnosis of KD is critical to prevent severe complications, particularly CAAs, as presented by Dr Toni Hospach. Given its diverse clinical presentations, KD can be easily misdiagnosed, leading to delayed treatment and potentially life-threatening outcomes. If left untreated, up to 25% of patients can develop CAAs, but with timely treatment, this risk decreases to less than 5%. The risk of adverse cardiovascular events is substantially higher with *z*-scores $\geq$10. Among these giant CAAs, there are markedly increased risks for CA thrombosis, stenosis, and major adverse cardiovascular events, including myocardial ischemia and death. Acute CA thrombosis is most likely to occur within the initial 1-3 months after diagnosis,[12] but thrombosis and ischemia may develop years after KD, primarily due to the process of luminal myofibroblastic proliferation.[13] Luminal myofibroblastic proliferation is a smooth muscle cell−derived myofibroblastic process that results in progressive luminal narrowing over time, starting in the initial 2 weeks after KD onset and persisting for months or years. Patients who experience signs and symptoms of acute myocardial ischemia require rapid intervention to restore blood flow and prevent further ischemia damage.[14] A particularly concerning early adverse outcome is the risk of CAA rupture, which is quite rare but certainly catastrophic and nearly always fatal. As reviewed by Dr Mamoru Ayusawa in his Richard Rowe Memorial Lecture, these so-called supergiant CAAs often grow over 10 mm in diameter rapidly within 10-15 days. Long-term, a study from the International Kawasaki Disease Registry demonstrated that patients with large/giant CAAs had a significant 10-year risk of luminal narrowing, CA thrombosis, and major adverse cardiovascular complications (20% $\pm$ 3%, 18% $\pm$ 2%, and 14% $\pm$ 2%, respectively).[15]

The diagnosis of KD is challenging. Each clinical feature of KD can occur in other disease processes, and there is no single diagnostic test for KD. Approximately 33% of patients with KD have at least one other confirmed infection at the time of diagnosis.[16] In the diagnostic evaluation, the clinician should consider the local epidemiology and patient exposures. Fever is typically unresponsive to antipyretics, which can help differentiate KD from other febrile illnesses. Even a positive test for group A streptococcal pharyngitis can still be compatible with a KD diagnosis. However, a genuine pathogen isolated from a sterile site may suggest an alternate diagnosis. KD in young infants poses a significant diagnostic challenge, often presenting with incomplete features yet being higher risk for CAA development. Clinicians must remain vigilant and consider pre-emptive intensification of treatment in this subset of patients to prevent serious cardiovascular complications.

To aid in this diagnostic challenge, Wang et al.[17] recently identified 4 distinct subgroups of patients with KD with significant clinical heterogeneity. These subgroups also exhibited variations in treatment response, particularly in resistance to IVIG and differences in the development of CAAs. These findings highlight the complex pathophysiology and heterogeneity of KD, with implications for personalized management and research. These subgroups include the following:

- Liver subgroup is characterized by hepatobiliary involvement, with elevated alanine transaminase, γ-glutamyl transferase, and total bilirubin. This group has the highest rate of IVIG resistance but the lowest risk for CAAs and occurred in older patients.
- Band subgroup exhibits high neutrophil band counts and the highest rate of KD shock syndrome, with intermediate risk of CAA and IVIG resistance.
- Lymph node subgroup is marked by cervical lymphadenopathy, high inflammatory markers, and lower haemoglobin, with intermediate risk of CAA and IVIG resistance.

- Young subgroup is characterized by the youngest patients with high platelet counts, lower inflammatory markers, highest risk of CAAs, and lowest risk of IVIG resistance.

As reviewed by Drs David Burgner and Samuel Dominguez, to avoid missing the diagnosis of KD, clinicians must maintain a high index of suspicion, particularly in children with prolonged fever and atypical features. Examples include acute febrile illness with arthritis, unexplained aseptic meningitis, culture-negative urinary tract infections, culture-negative shock, age <6 months with prolonged fever and irritability, prolonged fever and cervical adenitis, inflamed Bacillus Calmette–Guérin vaccination site in a febrile child, and acute febrile illness associated with eosinophilia. Early diagnosis and timely treatment with IVIG can significantly reduce the risk of CA complications, ensuring better outcomes for patients.

Almost all morbidity and mortality associated with KD occurs in patients with giant CAAs. Therefore, the primary strategy to prevent adverse outcomes in KD is early diagnosis and timely treatment. Current guidelines recommend a combination of antiplatelet and anticoagulation therapies for patient with giant CAAs, and close follow-up is essential to monitor CA status and guide therapy adjustments.

What Are the Next Directions in the Care of KD?

Although the IKDS highlighted our current understanding of KD, the symposium also highlighted how much we still must learn about this disease. One of the biggest take-home messages from this meeting is the need for collaboration. As detailed above, this collaboration needs to be multidisciplinary. It needs to include different medical specialties from paediatrics to cardiology, rheumatology, immunology, infectious disease, pathology, genetics, and adult cardiology. This collaboration also needs to extend beyond physicians and include nurses, advance practice practitioners, psychologists, pharmacists, epidemiologists, climate scientists, sociologists, basic science researchers, data scientists, and engineers. This collaboration should be international. The epidemiology and incidence vary from country to country; however, it is present worldwide. There is significant variation in practice around the globe, which provides unique opportunities to learn from each other to improve patient care globally. Although KD may occur less frequently in certain regions, it still remains the most common cause of acquired heart disease in children. Thus, if we all come together, we can learn from each other and the hundreds of thousands of patients diagnosed and treated for KD worldwide.

We have learned about this disease from observational studies, ranging from case reports of rare outcomes to large registries with thousands of patients. However, there are inherent limitations of observational studies, including bias, confounding variables, and challenges to establish causation. We need these studies. We learn from these studies and will continue to learn, but we can do more. As Admiral Grace Hopper once explained, the most dangerous phrase in language is that "we've always done it this way." As we are thinking about the next steps in KD and collaboration, we have to rethink our research methods. Randomized clinical trials are very rare in paediatrics and KD, mostly because of the hurdles they pose with small patient populations, costs, and timelines to obtain necessary answers. However, that should not stop us. There are alternative designs that may help us obtain the same level of evidence without all their limitations. Possibilities include synthetic control arms, umbrella studies, basket trials, platform studies, and master observational trials. A large collaborating international network with thousands of patients may be the best setting to nest those trials. There are also some newer techniques that we can leverage to fill the gaps in knowledge. Bioinformatics and AI are very promising and can allow identification of subtle patterns and associations and personalize treatment. The discussion of AI in this symposium is really just the beginning, and there are many more ways to use AI in KD to personalize care and optimize outcomes.

But one thing we should keep in mind as we continue to study the many different facets of KD is to correlate our findings with outcomes, in order to have the most impact on our patients' quality of life and survival. That is especially critical for all our surveillance modalities and interventions.

Last but not least, and as a patient beautifully shared during this symposium, we have to be better at taking care of our patients throughout their lifespan. It is one thing to diagnose and treat them as young children, but we have to be able to educate and guide them through adolescence and into adulthood, from pregnancy to older adulthood with other comorbidities.

Our Science Digest team would like to thank the IKDS 2024 co-presidents Drs Dahdah and Tremoulet for this wonderful conference, along with all the past IKDS presidents whose contributions to the field established our current understanding of KD, and who have been exceptional mentors to the younger generations. We are confident that the best is yet to come.

Funding Sources

No funding.

Disclosures

Dr Tremoulet is a consultant for Janssen Pharmaceuticals. No other authors have any potential conflicts of interest to disclose.

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