

You will greatly enjoy reading the wonderful articles in this edition of Leading the Way and a big thank you to all of the authors. A special thank you to Stu Wilson and Steve Kappes for the article in tribute to Dr. John Just, who left us at the end of March after a difficult battle with idiopathic pulmonary fibrosis. As you will appreciate from the Wilson/Kappes article, John Just

# Venous Thromboembolism in High-Risk Pediatric

Venous thromboembolism (VTE) includes the diagnoses of deep vein thrombosis (DVT), pulmonary embolism, and embolism. It is overall a rare event following pediatric trauma. While the rate of VTE in pediatric patients appears much lower than in adults, the setting of high-risk factors, the rate of VTE in injured children approaches 10%. High-risk factors include severity of injury, prolonged ICU stay, central venous lines, transfusion, traumatic brain injury, and non-weight-bearing fractures. When VTE occurs, it necessitates treatment and puts the patient at risk of recurrence or post-thrombotic syndrome. VTE also contributes to increased healthcare costs and hospitalization. However, perceived low rates of VTE in pediatric patients and concern for risk of bleeding from chemical prophylaxis results in many children not receiving prophylaxis following trauma. Additionally, current pediatric prophylaxis guidelines are based on low quality evidence and single institution studies.

The Midwest Pediatric Surgery Consortium (MWPSC) is a collaboration of eleven academic children's hospitals within the Midwest, representing some of the largest and highest volume pediatric surgical practices within the country, including Children's Wisconsin. The mission of the MWPSC is to advance the field of pediatric surgery through multi-institutional clinical studies examining high-impact pediatric surgical diseases. Due to the rarity of many pediatric surgical diseases, this collaboration allows accrual of large study populations. We harnessed the power of the Consortium to prospectively study the impact of pediatric VTE.

The NO CLOT study aimed to examine existing high-risk criteria, identify VTE events in a high-risk pediatric population, and demonstrate safety and effectiveness of chemical VTE prophylaxis. We conducted a prospective, multi-institutional study at eight sites within the MWPSC between 2019 and 2022. All pediatric patients were screened on admission and included if 8 years or older with 2 VTE high-risk factors, or older than 8 years with physician discretion. No bleeding complications were

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identified in the 251 patients who received prophylaxis. We identified 28 VTE events in 25 patients, for a VTE rate of 5.4% in this high-risk population. Two patients developed pulmonary embolism, and the remainder of the VTE events were DVTs. There was no significant difference in the rate of VTE based solely on receipt of prophylaxis, but patients who received prophylaxis earlier had significantly lower rates of VTE.

**Central Lines** – There is significant variability in management of central line-associated thrombosis between institutions and pediatric providers. Our study found 60% of the DVTs were central line-associated, defined as a DVT at the site of a central line. Contrary to common belief that central line-associated thrombosis is largely asymptomatic and inconsequential, we found that a third of the line-associated thromboses presented symptomatically and one asymptomatic patient subsequently developed a pulmonary embolism. Placement and duration of central lines represent a modifiable risk factor and an area for quality improvement in preventing pediatric post-traumatic VTE.

In conclusion, we completed the largest, prospective, multi-institutional study demonstrating that high-risk guidelines allow for safe and appropriate administration of chemical VTE prophylaxis following

Our results highlight 3 general takeaways that counter common myths in post-traumatic pediatric VTE:

1. **Safety** – Concerns about bleeding risk is a commonly cited reason for withholding prophylaxis from pediatric trauma patients. Our study identified no complications from prophylactically dosed anticoagulation. This finding emphasizes the importance of early prophylaxis to prevent VTE that necessitates therapeutic anticoagulation, which carries a more significant bleeding risk. A limitation of our study was that nearly half of the patients never received prophylaxis as recommended despite their high risk and a significant percentage (41%) received prophylaxis more than 24 hours after injury. Future studies may be beneficial to determine if earlier prophylaxis within 24 hours can reduce VTE rates without increasing bleeding complications. Our study's demonstration of safety of prophylaxis in a large cohort provides evidence to diminish barriers and sets a path for further implementation studies.
2. **Age** – Historically, the youngest pediatric patients have been omitted from post-traumatic prophylaxis guidelines due to a perceived low VTE risk prior to puberty. However, previous pediatric critical care literature has reported significant rates of DVT in the very young children and infants, owing to small vessel size. Our study uniquely included children of all ages and found a substantial VTE rate of 8% in high-risk children 8 years or younger. This demonstrates that in the presence of high-risk factors, younger injured children develop a rate of VTE comparable to older children. As such, post-traumatic pediatric prophylaxis guidelines should address children of all ages.



a detour to the Octopus Car Wash before heading out on their appointed rounds.

One day, Dr. Just got a flat tire on his car. When AAA was slow to respond, Basil Salaymeh jumped into action and quickly changed the tire. Dr. Just was in disbelief. Basil's clothes became soiled, and Dr. Just insisted that he pay for dry cleaning himself.

A couple of the philosophies he expounded upon were regarding hard work and family. Several residents commented on his work ethic. His descriptions of his early years of practice re-emphasized what the residents could see daily. Dr. Just prided himself on being available any day, any night whether it was an emergency thoracotomy or a chest tube that needed to be placed. It was also noted that he was very proud of his children and their accomplishments. As John Densmore describes it, "I knew that they were emulating his work ethic. There was pride and love, which impressed me beyond the material gains. A gentleman to the end, driven to honor family and patients alike." Basil Salaymeh acknowledged that Dr. Just tried speaking to his five children every day. As Basil put it, "What a great lesson on parenting."

His caring style extended to the residents as well. Bobby Wu was on service towards the later years of the rotation. After residency, at the age of thirty-eight, Dr. Wu required a cardiac catheterization. Dr. Just came to visit him in the hospital, which left a lasting impression on Bobby. Years later, Bobby arranged a dinner for "Double J" and several former residents attended. This speaks to the on-going admiration the residents have for this man. In 2008, Todd Neideen would be the last resident to have this wonderful experience. Todd described the sense of getting e t (oucls [(wha)1.1her it w)9 (a)1 s alikg e tre-

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The annual incidence of venous thromboembolic (VTE) disease, which consists of deep venous thrombosis (DVT) and pulmonary embolism (PE), is estimated to be ~100 per 100,000 per son-years.

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subjected to the polytrauma model and 48 hours later subjected to IVC ligation and sacrificed 48 hours later (Fig. 2A-B). We found that fibrinogen concentration was significantly lower in the mice treated with siFibrinogen following combined polytrauma and thrombosis (Fig. 2C). Finally, we determined that for each dose of siFibrinogen, there was a significant reduction in thrombus burden as assessed by clot weight. There was no difference in survival episodes of bleeding in mice treated with siFibrinogen (data not shown). These findings suggest that siFibrinogen can effectively reduce the risk of post-traumatic DVT in mouse models.

As mentioned, the conversion of soluble circulating fibrinogen to fibrin results in the formation of a matrix that serves as a platform for thrombus formation and is critical in the coagulation pathway for hemostasis. Therefore, there is a theoretical risk of bleeding with siFibrinogen. We have advanced our siFibrinogen technology and have begun studies in pigs. We have

## Second Primary Breast Cancer

Breast cancer survival has dramatically improved over the last few decades, with a stunning 40% overall reduction in breast cancer-related deaths since 1990. This is largely due to increased mammography screening and increased awareness, resulting in earlier stage diagnosis, and improvements in treatment. In many ways breast cancer remains the quintessential example of how aggressive screening and targeted therapy can make long-term survival attainable for patients.

However, as patient outcomes improve, second primary breast cancers (SPBCs) are emerging as a major hurdle in maintaining long-term disease-free survival. SPBCs are defined as a distinct new tumor that emerges in the breast of breast cancer survivors. Between 1994 and 2010, the rate of SPBC among patients with

a prior history of breast cancer increased by more than 5-fold. This trend coincides with longer survival times for patients with breast cancer; at 20 years after an initial diagnosis, survivors have a cumulative incidence of SPBC of approximately 20%. However, survival is significantly worse following a second primary tumor as compared to a primary tumor, and to date there are no known biomarkers that identify patients who may be at higher risk of a SPBC.

The molecular mechanisms driving SPBC onset remain undefined. Germline mutations, such as Li-Fraumeni syndrome or BRCA1/2, are known contributing factors, although non-germline (somatic) mutations are also at increased risk. SPBCs are also at increased risk of acquired somatic mutations in response to cytotoxic therapies. In many cases, second primary cancer risk in children treated with radiation or chemotherapy is also increased.

In both of these contexts, it is important to consider that acquisition of mutations alone is insufficient to drive tumorigenesis<sup>5</sup>. This is strongly supported by observations in patients and mouse models demonstrating that only a few cells will give rise to cancers even in germline carriers.

## Injury, Resolution, and the Emergence of Unstable Cells

A growing body of evidence suggests that tumor-initiating mutations cause cancer only if they occur in a cell of a certain epigenetic state or microenvironmental context

permissive of cancer initiation. To this end, recent studies from the laboratory of Dr. Robert Weinberg demonstrated that the state of mammary epithelial cells prior to tumor-initiation can significantly impact the risk of tumor initiation and tumor phenotype. Introduction of the same tumor-initiating mutation into the same epithelial cell type led to significantly different tumor progression when the tumor-initiating cell population was isolated from age-matched pre- or post-menopausal



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Our collaborator, Dr. Ian Macara, recently published findings demonstrating that the DNA-damaging agent cisplatin causes normal mammary basal cells to transdifferentiate (switch cell fates) to mammary luminal cells (Figure 1, left). Further, recent studies from the Lytle lab demonstrated that mammary luminal progenitor cells that arise from fate-switched basal cells do not fully resolve into a homeostatic luminal progenitor state (data unpublished). Rather, fate-switched luminal progenitors retain a hybrid epigenetic state with “footprints” of the basal cell epigenome. As cell-state instability and fate-switching have been shown to be an early step in tumor initiation, we hypothesize that unstable, highly plastic cells resulting from therapy-induced cell fate switching may contribute to SPBC initiation.

#### Future Studies to Test Cell-Fate Switching in SPBC initiation

The Lytle lab, in collaboration with Dr. Tina Yen, was selected as a recipient for the Medical College of Wisconsin Cancer Center – American Cancer Society Institutional Research Grant (ACS-IRG) to determine if therapies commonly used to treat breast cancer are responsible for basal cell–fate-switching to unstable luminal cells,

Muslim physicians make up over 4.5% of the physician workforce in the United States. Muslim trainees, especially those who wear the hijab (head scarf), continue to face discrimination in medicine. In 2016, MCW professor Aasim Padela MD conducted research on Muslim American physicians and religious discrimination; he found that 19% of Muslim physicians reported “sometimes” experiencing discrimination in the workplace while 5% reported “often or always” during their training. This study was replicated in 2021 and the results showed an increase in the percentages regarding discrimination with 41% of Muslim physicians reported “sometimes” experiencing religious discrimination while 12% reported “often or always.”

Medical trainees who wear the hijab are often in limbo when navigating the operating room due to strict policies implemented by hospitals. Much of the concern regarding the permissibility of wearing hijab in the OR has been around sterility. While there is limited data regarding whether wearing outside hijabs increases risk of contamination, two studies conducted in the United Kingdom concluded that there is no evidence of a difference in efficacy of decontamination of uniforms/clothing between industrial and domestic laundry processes, or that the home laundering of uniforms provides inadequate decontamination. Another study conducted in the United Kingdom looked at the Department of Health’s “bare below the elbows guidelines” where they compared the density of bacterial colonies between doctors who wore nothing below elbow versus those who did not (ex. long sleeves) before and after hand washing and concluded that there was no difference in density or type of baseline bacterial flora on hands operating in the OR.

### FH IPAC Surgical Attire Policy #766

“For religious preferences, those needing to perform hand antisepsis may wear a low-linting (e.g., polyester fabric, athletic material) long sleeve shirt under their surgical attire. Refer to FH IPAC Hand Hygiene Policy for surgical antisepsis in this situation.”

“All head hair, including sideburns and neckline hair, must be covered by a clean, procedural area dedicated, lint-free head covering or surgical hood while in the Restricted and Semi-Restricted Area. Personal head covers (e.g., – hijab, yarmulke, head scarf) may be worn if it meets the requirements listed above and must be changed daily.”

### FH IPAC Hand Hygiene Policy #771

“For religious preferences, persons may wear a low-linting (i.e. polyester based fabric, athletic material) long-sleeve shirt under their surgical attire as long as the sleeves are raised to the level of the elbow to allow for proper Surgical Hand Antisepsis.”

“Persons not wanting to perform the first scrub of the day in a public area may do this scrub in a gender-specific locker room.”

For further details, you can find the updated policies on the [Froedtert intranet page](#)

Acknowledgments: We would like to thank Lisa Buttweiler and Lisa Spencer for their help and dedication to this project.

See page 13 for references

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durable LVAD, they had worse 1-year and 5-year survival rates and were more likely to require post-HT dialysis compared to isolated HT in the same patient population. MCS-induced systemic inflammation and machine-induced stress, along with an increase in organ ischemic time with the new allocation system's broader geographic sharing, may have contributed to worse CHKT outcomes.

On September 28, 2023, UNOS implemented new criteria for CHKT to achieve the best use of scarce donor organs and improve equity in transplant opportunities for multiple and single organ candidates. Under the new policy, CHKT is offered to candidates who meet specific criteria of sustained acute kidney injury and chronic kidney dysfunction (Table 1).-Most importantly, there is a safety net policy which offers priority in allocation for patients who become dialysis-dependent or have an eGFR < 20 mL/min/1.73 m<sup>2</sup> at any point between 60 and 365 days after isolated HT. Experience with safety net policies in liver-kidney transplantation since 2017 has demonstrated use of donor organs with a 16% decrease in the need for combined liver-kidney transplants. This policy also allows for use of living kidney donation with superior outcomes and an increase in the overall kidney donor pool.

The new policy will be reviewed periodically to report waitlist registrations, heart-kidney transplant volumes, kidney after heart transplant volumes, and associated outcomes including mortality. This will allow close monitoring of the metrics and possible revisions to the policy as needed. It will be interesting to watch the evolution of this change and observe the impact this new policy brings to the CHKT field and specifically our heart transplant program here at MCW which has limited experience with CHKT. With a defined set of criteria for dual organ listing and the availability of a safety net, we should be able to broaden our program experience and take calculated risks knowing that there is an exit strategy for these complex patients.

For additional information on this topic, visit [mchw.edu/surgery](https://mchw.edu/surgery) or contact Dr. Ali atakali@mcw.edu.

See page 19 for references

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# Putting the patient and family voice first



**Katy Flynn-O'Brien, MD, MPH**

Assistant Professor of Surgery, Division of Trauma and Acute Care Surgery; Assistant Professor, Department of Epidemiology

**Emmanuel AH**

On average, 2,300 assault-injured children and youth are treated in an Emergency Department in Southeastern Wisconsin every year.

In fact, firearm injury is now the leading cause of death in children, surpassing motor vehicle collisions and falls. Likewise, the magnitude of firearm injuries in children and youth treated at CW has increased exponentially (Figure 1). The impact of these injuries extends well beyond the hospital encounter.

## Optimizing the care we provide

Firearm-injured children have both physical and mental health-care needs after injury. They are at increased risk of post-traumatic stress and recurrent injury, and are almost twice as likely to have a subsequent violence-related arrest. However, there has been little effort to address the long-term post-trauma quality of life (TQOL) outcomes of chronic pain, depression, post-traumatic stress disorder (PTSD), and functional disability in this population. Despite notable and often multidisciplinary healthcare needs after injury, including injury-specific follow-up and mental health services, the CW care model after injury has traditionally been fragmented. The surgical subspecialties work in silos, and clinics require patients and their families to travel to various sites, which are often far from home. There is an estimated 50% missed appointment rate in the CW General Surgery clinic alone following firearm and/or trauma injury (internal data), highlighting the need for an alternative standard of care that better serve this vulnerable population. Furthermore, little is known about who needs and obtains mental health care services following violent injury.

Finally, it is unknown how many children in the community are potentially injured but do not get seen at CW and would potentially benefit from a trauma-informed pediatric-focused care model. With these issues in mind, we partnered with Froedtert TQOL experts and have been using a mixed-method approach to better understand the barriers to receipt of medical care after pediatric violence, and to explore the role for a multidisciplinary clinic focused on the complex needs of these children.

In the summer of 2023, with the support of the 2023 CTSI Patient-Centered Award, we recruited and started meeting with a Community Advisory Board (Figure 2). This group included patients and their families, in addition to community leaders who work with vulnerable youth in Milwaukee County. We met once a month and discussed gaps in the current care model, and the ideal infrastructure for a Pediatric TQOL Clinic (Figure 3). This included how a clinic would integrate into the community, improve communication, and optimize the utilization of community services. We recorded, transcribed, and synthesized the content of these meetings using qualitative methods. Additionally, from a quantitative perspective, we are actively analyzing a combination of trauma registry and electronic health record data to explore unmet need for services as defined by “No Show” visits and late cancellations. These

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is unique, with short- and long-term impacts on physical, me

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Mary F. Otterson, MD, MS  
Professor  
Division of Colorectal Surgery

As of July 1, 2024, the Division of Colorectal Surgery, the Department of Surgery, the Medical College of Wisconsin, and the Department of Veteran's Affairs Hospital in Milwaukee, will have changed. Dr. Mary Otterson, MD, Professor of Surgery, is retiring. Forty-four years at the Medical College is a long time. Let me detail what those years looked like, followed by some thoughts on what those years have meant.

Dr. Otterson came to MCW to start medical school in 1980. Before that, she spent a year at Marquette University, and then she went to New York city to train in ballet. She came back to Milwaukee and did her undergraduate work in Clinical Dietetics and Chemistry at Mount Mary College. After graduating medical school, she started her General Surgery Residency here at MCW, under former Chairman, Robert E. Condon. A year of her residency was spent in the then flourishing GI motility lab working with Dr. Condon, Gordon Telford, Sushil Sarna, and Vern Cowles. In that year in the lab, she earned a Master of Science in Physiology. She had an obvious talent for research and science. Six months of her training was spent as a General Surgery Registrar in Oxford, England, and she completed her training as Administrative Chief Resident in 1990. Dr.





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When patients are grateful for the extraordinary care we provide, we are inviting faculty and staff to be our partners. They often want to express their gratitude by giving back.

Giving doesn't just create happiness – it also leads to better health. Positive feelings, like those generated when engaged in or recalling a philanthropic event, have far-reaching benefits, including a stronger immune system and a cardiovascular system that is less reactive to stress (Konrath, 2013).

Additionally, people who have suffered significant losses are particularly motivated to help others not only despite their difficult experiences, but precisely because of them. A key task in effective healing is to restore their shattered assumptions of the world (Jano-Bulman, 1992). Giving is a way people can find meaning and value following a heartbreaking loss.

One year ago, the Office of Institutional Advancement at MCW and the Froedtert Hospital Foundation launched a new grateful patient program, called "Healthcare Philanthropy." Through this exciting initiative, we unlock the healing power of philanthropy that allows our patients to give back to causes near and dear to their hearts and families. This program leads with gratitude and inspires patients to be a part of something bigger than themselves and create a legacy of impact – all while raising essential funds for the Department of Surgery and other areas across our institutions.

It's important to note three key elements of Healthcare Philanthropy:

1. Healthcare Philanthropy is not about a financial transaction, but a natural extension of the clinical experience you and your team are providing to patients. Our philanthropy team is looking to build meaningful relationships with patients who express their gratitude at an extraordinary level.
2. We understand that you may have concerns about the complexities of sharing patient information. We want to assure you that our philanthropy team takes this responsibility very seriously. The Healthcare Philanthropy program has been thoroughly reviewed and approved by our privacy office and legal team and is completely HIPAA compliant. If you have specific concerns, we encourage you to contact Liz Montgomery, who serves as the Department of Surgery's philanthropic liaison.
3. We are not asking you to request gifts from your patients. In-

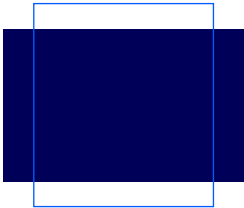
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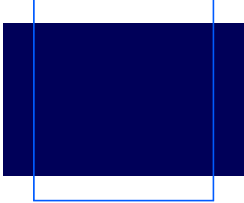
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# Leading The Way

## Division of Trauma and Acute Care Surgery



Allyson Hynes, MD joined the Department of Surgery faculty as Assistant Professor of Surgery in September 2019. She received her medical degree from the University of Nebraska Medical Center before completing her Emergency Medicine residency from St. Vincent Mercy Medical Center. She then completed a two-year Trauma and Surgical Critical Care fellowship at the University of Pennsylvania, where during her second year she served as the Chief Administrative Surgical Fellow. Dr. Hynes then served as an Assistant Professor at the University of New Mexico for three years before moving to the Midwest. Dr. Hynes is currently finishing her Master of Science in Clinical Epidemiology through the University of Michigan Perelman School of Medicine.



Allegra Saving, MD joined the Department of Surgery faculty as Assistant Professor of Surgery in September 2019. She received her medical degree from Wayne State University. She completed her Emergency Medicine residency at the University of Michigan and her Trauma and Surgical Critical Care fellowship at the University of Michigan. Dr. Saving is currently finishing her Master of Science in Clinical Epidemiology through the University of Michigan Perelman School of Medicine.

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