VOLUME 1, ISSUE 2
SUMMER 2023

The EchOH

The Official Biannual Report from the Ohio Chapter of SCCM

The Ohio Chapter of the Society of Critical Care Medicine

INSIDE THIS ISSUE

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Message from the President

It is my personal mission to provide high-quality care that aligns with patient and patient family values, and I am honored to be part of the Ohio Chapter. I fully support the endeavor of elevating the quality of critical care in Ohio through inclusivity and diversity of critical care practitioners at a statewide level.

I first became involved with the Ohio Chapter in 2019 at a business meeting in San Diego, California at the suggestion of a colleague. Because of this I must highlight the importance of networking. I then became a member of the Membership Committee and then ventured into the leadership realm as Chair-elect and then Chair of the Membership Committee. I then served as President-elect and now President. I have learned so much along the way and met so many critical care providers across the state through being involved with the Ohio Chapter. My favorite part has been networking and working together for a common cause, and I look forward to seeing how the Ohio Chapter will continue to grow.

Message from the President

I have the privilege of working with a great team who is committed to the success of the Ohio Chapter. I am looking forward to what our Membership, Communication and Education Committees have in store for members this year. The Ohio Chapter provides a platform to highlight contributions of members from the Ohio Chapter and provides speaking, writing and networking opportunities. The Ohio Chapter is a space where every discipline can grow and advance together with the goal of improving lives in Ohio. The Ohio Chapter is for all of us!

Markisha R. Wilder, MS, APRN- CNP
President, Ohio Chapter
Acute Care Nurse Practitioner
Wexner Medical Center Division of Critical Care, Trauma, & Burn

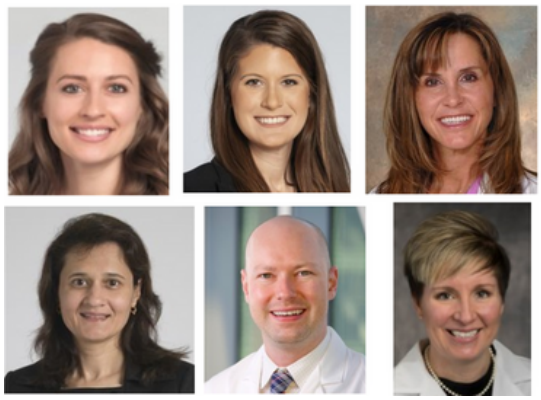
Meet the Rest of Our Team

Claire Murphy, Pharm.D.
Immediate Past-President

Keaton Smetana, Pharm.D.
President-Elect

Reddy Singasani, MBBS, MD
Secretary

Michael Rudoni, Pharm.D.
Treasurer



MEMBERS-AT-LARGE

Kathryn Bash, MHSc, MSN, ACNPC - AG (2021 -2024)

Gretchen Sacha, PharmD (2021 -2024)

Suzanne Bennett, MD (2022 -2025)

Kshama Daphtary, MD, MBI (2022-2025)

Joshua Trester, MD (2023 -2026)

Angela Johnson, MD (2023 -2026)

Committee Updates

Education Committee

The Education Committee is now under the leadership of its new chair, Mary Curran, and chair-elect, Layla Sankari. The committee and its members held their last meeting at the end of June as they began planning the program for this academic year.

As we've done in recent years, we will continue to hear from content experts during our quarterly webinars. Trainees in critical care programs will also be invited to present during our virtual journal clubs. We'll finish out 2023 with our Annual Symposium and welcome the warm weather when we host our Research Day in Spring of 2024.

Our next event is the Virtual Journal Club which will be on Thursday, August 17th at 13:00. Be on the lookout for how to register!

If interested in contributing to any of these great educational activities—as a planner, moderator, or speaker—reach to our chair (curranm2@ccf.org) and chair-elect (Layla.Sankari2@UHhospitals.org).

Communication Committee

The Communication Committee supports the Chapter by managing the website, social media, and SCCM connect. We are pleased to announce our new Chair Dalton Kuebel, Pharm.D. and Chair-Elect Casey May, Pharm.D. who will begin July 2023. We are a group of creative individuals working to create content that is engaging and informative for members. We are always looking for members to join and welcome suggestions on how to better serve the Chapter.

Membership Committee

Greetings from the Membership Committee! We've already had an exciting start to the year, with the opportunity to interact with members through a few networking events!

In January, many members who attended the SCCM Annual Congress joined us for the Ohio Chapter Reception. It was wonderful to be able to meet in person again and connect with many of you! Additionally, in June, we hosted three **Networking Events** in Cincinnati, Columbus, and Cleveland following the Chapter's Research Day.

The Chapter also participated in SCCM's "Turn Your ICU Blue Day" by designing and distributing Chapter t-shirts to members and providing small social gatherings at hospitals throughout the state.

We continue to recognize **Outstanding Critical Care Teams** every other month with a recognition party and social media posting. Recent winners include the ICU Pharmacy Team at Ohio Health Riverside Methodist Hospital and the Cardiac Intensive Care Unit Team at University Hospitals Cleveland Medical Center. If you work with an incredible critical care team, we'd love to recognize them! **Submit a nomination using this link**: https://www.surveymonkey.com/r/OutstandingCCTeam.

I'd like to thank Keaton Smetana for his leadership of the membership committee this past year and I look forward to serving as the chair this coming year. I would also like to welcome Alyssa Meester, who will be assuming the role of chair-elect for the committee. We look forward to coordinating more Chapter events to engage our members as well as finding new ways to highlighting the work of members in the coming year.

Please contact us if you are interested in becoming a member of the membership committee (Jessica.Elefritz@osumc.edu or Alyssa.Meester@ohiohealth.com).

2023 NETWROKING EVENT

Congratulations!...

...to our Ohio Chapter members for being recognized for their achievements and contributions to critical care excellence with the prestigious credentials of...

FELLOW OF CRITICAL CARE MEDICINE

Michael W. Dingeldein, MD, FCCM
Pediatric Surgery, Pediatric Trauma Director, Surgical Director PICU
Rainbow Babies & Children's Hospital

Eduardo Mireles-Cabodevila MD, FCCM
MICU Director, Vice Chair Critical Care Medicine
Cleveland Clinic

The Ohio Chapter of the Society of Critical Care Medicine

SEEKING NOMINATIONS FOR THE OUTSTANDING CRITICAL CARE TEAM RECOGNITION

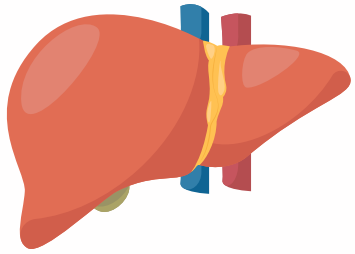
WINNER SELECTED EVERY OTHER MONTH

- **SCCM OHIO CHAPTER WOULD LIKE TO RECOGNIZE THE ACCOMPLISHMENTS OF AN EXCEPTIONAL TEAM!**

Selected teams will receive reimbursement towards a recognition party of their choosing and be highlighted on SCCM Ohio Chapter's social media accounts!

SCAN HERE TO SUBMIT NOMINATIONS:

Guideline Updates



Gastroenterology/Hepatology

Summarized by: Dalton Kuebel, Pharm.D., BCCCP

Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Neurology, Peri-Transplant Medicine, Infectious Disease, and Gastroenterology Considerations

Nanchal R, Subramanian R, Alhazzani W, et al. Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Neurology, Peri-Transplant Medicine, Infectious Disease, and Gastroenterology Considerations. Crit Care Med. 2023;51(5):657-676. doi:10.1097/CCM.0000000000005824

- Patient population for recommendations: include critically ill patients with acute liver failure (ALF), acute on chronic liver failure (ACLF), liver transplant recipient (LT).
- Best practice statements made for early EGD (within 12 hours of presentation) and for LVP for tense ascites and intra-abdominal hypertension or hemodynamic, renal, or respiratory compromise.
- Strong recommendations made for using antibiotic prophylaxis for upper GI bleeding, albumin for SBP, PPI pantoprazole and octreotide use in portal hypertensive bleeding, and broad-spectrum antibiotics for initial SBP management.
- Favorable conditional recommendations made for the following interventions: lactulose, polyethylene glycol, rifaximin, and plasma exchange for hepatic encephalopathy; hypertonic saline sodium chloride for intracranial hypertension; TIPS over continued endoscopic therapy for variceal bleeding, antibiotics within 1 hour of septic shock and SBP recognition, peri-transplant management utilizing balanced crystalloids, corticosteroids, fluid management for deceased liver donors, and antifungal prophylaxis in high risk patients; either extracorporeal liver support or standard medical therapy.
- Conditional recommendations made against use of the following interventions: invasive intracranial monitoring or induced hypothermia in advanced-grade encephalopathy or those at-risk of developing intracranial hypertension; certain hepatic encephalopathy therapies (flumazenil, zinc supplementation, glycerol phenylbutyrate, probiotics, acarbose); in LT recipients selective bowel decontamination or antifungal prophylaxis for those at low risk; LVP, terlipressin, or midodrine in setting of SBP; in LT recipients selective bowel decontamination or antifungal prophylaxis for low risk patients.

Abbreviations: EGD – esophagogastroduodenoscopy; GI – gastrointestinal; LVP – large volume paracentesis; SBP – spontaneous bacterial peritonitis; TIPS – transjugular intrahepatic portosystemic shunt

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Neurocritical Care

Summarized by: Grace Conroy, Pharm.D., BCCCP

2023 Guideline for the Management of Patients with Aneurysmal Subarachnoid Hemorrhage: A Guideline from the American Heart Association/American Stroke Association

Hoh BL, Ko NU, Amin-Hanjani S, et al. 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2023;54(7):e314-e370. doi:10.1161/STR.0000000000000436

General aSAH Management

- It is reasonable to treat severe hypertension (> 180-200 mm Hg) on presentation, but there is insufficient evidence to recommend a particular BP target. Profound reduction of BP should be avoided (avoid MAP < 65 mm Hg). Increased BP variability has been associated with worse outcomes in aSAH.
- Use of antifibrinolytics is not recommended as it does not improve functional outcomes.
- For patients who present with seizures, treatment with ASM for < 7 days is reasonable to reduce seizure-related complications in the perioperative period.
- Patients without epilepsy who present with seizures, treatment with ASM beyond 7 days is not effective to reducing future SAH-associated seizure risk.

aSAH related Vasospasm/ DCI

- Maintaining euvolemia can be beneficial in preventing DCI and improving functional outcomes and reduces cardiac and pulmonary complications.
- Avoid prophylactic hemodynamic augmentation.
- For patients with symptomatic vasospasm, elevating systolic BP may be reasonable to reduce the progression and severity of DCI.
- Available evidence suggests that milrinone is well tolerated as an intravenous infusion through the period of peak DCI risk and may have a beneficial effect in preventing symptomatic vasospasm or DCI. The role of milrinone, although promising, requires further investigation.

Abbreviations: aSAH – aneurysmal subarachnoid hemorrhage; ASM – anti-seizure medication; BP – blood pressure; DCI – delayed cerebral ischemia; MAP – mean arterial pressure; SAH – subarachnoid hemorrhage

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Respiratory & Infectious Diseases

Summarized by: Hannah Hixenbaugh, Pharm.D., BCPS

Global Strategy for Asthma Management and Prevention: 2023 GINA Main Report

What's new in the 2023 GINA Report?

- ICS-formoterol is the preferred as-needed therapy for asthma in adults and adolescents. ICS-formoterol reliever reduces the risk of severe exacerbations and is simpler for patients since it uses the same medication for reliever and maintenance treatment, compared with using a SABA reliever.
- New guide to the management of asthma exacerbations for patients ≥ 6 years of age has been provided. Start treatment with repeated administration of SABA, early introduction of oral corticosteroids, and controlled flow oxygen if available. Give ipratropium bromide only for severe exacerbations and consider IV magnesium sulfate for severe exacerbations not responding to initial treatment. It is recommended to not routinely obtain a CXR or prescribe antibiotics for asthma exacerbations. Sedative agents should be avoided.
- Notable safety issues: 1) Under conditions of hypoxemia, oxygen saturation may be over-estimated by pulse oximeters in people with dark skin color; 2) Potential drug interactions with COVID-19 therapy nirmatrelvir-ritonavir due to the potent CYP3A4 inhibitor of ritonavir. Be cautious if considering use in patients taking ICS-salmeterol or ICS-vilanterol, as the interaction may increase cardiac toxicity of the LABA. If prescribed, consider prescribing ICS alone or ICS-formoterol during therapy and for a further 5 days.

Global Strategy for Prevention, Diagnosis, and Management of COPD: 2023 GOLD Report

What's new in the 2023 GOLD Report?

- Expansion of COPD taxonomy to include non-smoking related COPD types.
- Evolution of the ABCD assessment tool to the ABE assessment tool to recognize the importance of exacerbations. The previous A and B groups remain unchanged, but C and D groups are now merged into a single E group.
- Consider chest CT imaging in stable COPD patients with persistent exacerbations, symptoms out of proportion to disease severity on lung function testing, FEV ≤ 45% predicted with significant hyperinflation and gas trapping, or for those who meet criteria for lung cancer screening.
- Proposed surgical and bronchoscopic interventions in stable COPD have been expanded.
- When initiating long-acting treatment, the preferred choice is combination LAMA+LABA.
- The only pharmacologic therapy shown to reduce mortality in COPD is triple therapy with LAMA+LABA+ICS.
- Can consider adding PDE4 inhibitor (roflumilast) for patients with severe airflow limitation, chronic bronchitis, and exacerbations.
- New definition of COPD exacerbation (ECOPD) has been included with a new set of parameters to assess exacerbation severity as mild, moderate, or severe at the point of care, rather than post-exacerbation. A table of confounders or contributors to be considered in patients presenting with exacerbation with worsening respiratory symptoms, particularly dyspnea, without the classic characteristics of ECOPD has been provided.

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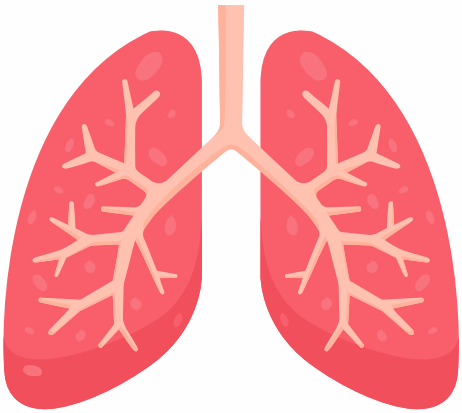
ERS/ESICM/ESCMID/ALAT Guidelines for the Management of Severe Community-Acquired Pneumonia

Martin-Loeches I, Torres A, Nagavci B, et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia [published correction appears in Intensive Care Med. 2023 May 17;:]. Intensive Care Med. 2023;49(6):615-632. doi:10.1007/s00134-023-07033-8

- All recommendations for sCAP refer to CAP requiring ICU admission and all are considered to be conditional with only very low to moderate quality evidence.
- Suggest using HFNO instead of standard oxygen in acute hypoxemic respiratory failure not needing immediate intubation. NIV might be an option in certain patients with persistent hypoxemic respiratory failure due to hypoventilation or with increased work of breathing
- Suggest the use of corticosteroids if shock is present.
- For antibiotic therapy: the addition of a macrolide, not fluoroquinolone, to beta-lactams as empiric antibiotic therapy in hospitalized patients; integration of specific risk factors based on local epidemiology and previous colonization to guide decisions for antibiotic selection for patients at risk for drug-resistant pathogens; no specific therapy targeting anaerobic bacteria.
- Suggest sending lower respiratory tract sample for multiplex PCR testing whenever non-standard sCAP antibiotics are prescribed or considered.
- Suggest the use of oseltamivir for patients with sCAP due to influenza confirmed by PCR or empiric use during influenza season when PCR is not available.
- Suggest the use of PCT to reduce the duration of antibiotic treatment; however, when clinical stability is achieved and duration of antibiotic therapy is between 5 and 7 days, biomarkers do not add much clinical benefit.

Abbreviations: CYP – cytochrome P450; CXR – chest x-ray; ICS – inhaled corticosteroid; IV – intravenous; LABA – long-acting beta-agonists; SABA – short-acting beta-agonists; COPD – chronic obstructive pulmonary disease; CT – computed tomography; FEV – forced expiratory volume; ICS – inhaled corticosteroid; LABA – long-acting beta-agonists; LAMA – long-acting muscarinic antagonists; PDE4 – phosphodiesterase-4; ALAT – Latin American Thoracic Association; CAP – community-acquired pneumonia; ERS – European Respiratory Society; ESCMID – European Society of Clinical Microbiology and Infectious Disease; ESICM – European Society of Intensive Care Medicine; HFNO – high-flow nasal oxygen; NIV – non-invasive mechanical ventilation; PCR – polymerase chain reaction; PCT – procalcitonin; sCAP – severe community-acquired pneumonia



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CHEST Guidelines

Summarized by: Elisha Fleig, PA-C

Operational Definitions Related to Pediatric Ventilator Liberation

Abu-Sultaneh S, Iyer NP, Fernández A, et al. Operational Definitions Related to Pediatric Ventilator Liberation. Chest. 2023;163(5):1130-1143. doi:10.1016/j.chest.

- Eight topic areas were reviewed by the panel, establishing sixteen operational definitions which can be reviewed in Table 2.
- Respiratory support defined as invasive mechanical ventilation (MV) or noninvasive respiratory support (NRS), the latter of which differentiates noninvasive ventilation, CPAP, negative pressure ventilation, high-flow nasal cannula, and conventional oxygen therapy.
- Liberation from invasive MV occurs when ETT or positive pressure via tracheostomy removed and not re-initiated within 48h. Similarly, respiratory support liberation defined as patient no longer receiving invasive MV or NRS, and no re-initiation within 48h.
- Total duration of invasive MV is time from MV initiation until successful liberation, where if MV resumed >48h after initial liberation, it is considered a new ventilation course.
- Spontaneous breathing trial differentiated from extubation readiness test, where the former systematically reduces MV support and the latter adds elements to assess factors such as sedation, airway control, hemodynamics, and secretions.
- Twenty-eight ventilator-free days (VFDs-28) defined based on survivorship. For survivors, this equals 28 minus the sum of MV days during first 28d after MV initiation. For non-survivors, will be zero if death within 28h of MV initiation. If death after 28d, calculation same as for survivors.

Consensus Statements on Deployment-Related Respiratory Disease, Inclusive of Constrictive Bronchiolitis

Falvo MJ, Sotolongo AM, Osterholzer JJ, et al. Consensus Statements on Deployment-Related Respiratory Disease, Inclusive of Constrictive Bronchiolitis: A Modified Delphi Study. Chest. 2023 Mar;163(3):599-609. doi: 10.1016/j.chest.2022.10.031.

- With a modified Delphi technique, an expert panel defined constrictive bronchiolitis (CB) and both its clinical presentation and evaluation.
- CB defined as a histological pattern of lung injury characterized by subepithelial fibrosis of the small airways that narrows and sometimes obliterates bronchiolar lumens. It is recommended to use deployment-related respiratory disease (DRRD) when referring to broad respiratory conditions post-deployment and before confirmed specific diagnosis.
- Panel agreed that a range of respiratory symptoms can exist, and evaluation can be performed in a tiered fashion based upon complexity level. Basic screenings (e.g., H&P, CXR, CT chest, TTE) can occur in standard hospital setting. If further evaluation required, patients can be referred to specialty centers for procedures such as laryngoscopy or methacholine challenge tests. In cases where advanced evaluations such as surgical lung biopsies are required, patients should still be referred to specialty centers.
- Designation between facility types is noteworthy, as these tiered facility recommendations are based on presumed resource and personnel availability, as well as accounting for complexity of interpreting and performing advanced evaluations.
- Consistent terminology plus systematic evaluation can advance both the care and health of previously deployed individuals.

Intravenous Hydrocortisone

By: Kari Gorder, MD

If you work in healthcare, you have likely perceived a post-pandemic increase in the occurrence of drug shortages. Everything from injectable lidocaine to epinephrine in the crash cart to even normal saline seems to be on backorder or out of stock, and the "supply chain" has never been more frequently discussed! And while we have often been able to circumvent these issues with alternative dosing regimens, second-line agents or other creative solutions, it seems as if it may be only a matter of time before a critical life-saving medication is truly unavailable.

Long before the COVID-19 pandemic, drug shortages have caused challenges for clinicians and patients alike. In fact, despite advances in pharmaceutical technology and increasing globalization of health care, the frequency of drug shortages increased throughout the early 2000s.[i] Challenges with manufacturing abilities, unbalanced supply and demand cycles, complex regulatory requirements, and inconsistent access to raw materials led to increased disruptions of "just-in-time" supply chains. Injectable drugs were the most commonly affected category of medications, as the necessary sterility of these agents required more complex manufacturing processes with increased vulnerability to disruption or delay. Additionally, drugs with low profit margins – including many generic drugs – were particularly at-risk, as there is often only one manufacturer of these products. Despite several United States agencies dedicating significant resources to monitoring, responding to, and preventing drug shortages – such as the FDA and the American Society of Health-System Pharmacists (ASHP) – many of the root causes of shortages remain a challenge.

The pandemic brought these issues into sharp relief. Not only were certain medications being used more frequently than usual, such as albuterol or antibiotics, but the entire global manufacturing pipeline was temporarily halted. China and India — two of the largest suppliers of generic drugs in the world – were hit very hard by the pandemic, with the latter country curtailing pharmaceutical exports to other parts of the world to provide for its own citizens.[ii] The worldwide drug shortages during the pandemic saw clinicians and health care facilities forced to consider medication rationing and the use of alternate therapies. Despite the end of the pandemic, our drug shortage crisis shows no sign of ending: at the end of 2022, the United States experienced a record five-year high of 295 active drug shortages, according to a recent Senate report.[iii] As of the time of publication of this article, the FDA lists 208 active or recently resolved drug shortages on its website.[iv]

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One drug currently in shortage is hydrocortisone sodium succinate, known in the US by its trade name Solu-Cortef®. Manufactured by the pharmaceutical company Pfizer, Solu-Cortef® is an injectable systemic corticosteroid with both glucocorticoid and mineralocorticoid activity. It is used for a wide variety of conditions, including the treatment of adrenal crisis and septic shock. The shortage started in March 2023 and is ongoing. The FDA currently lists shortages for seven different "presentations" of hydrocortisone sodium succinate (e.g., 100 mg vials, 250 mg single dose ACT-O Vials) on its drug shortage website, all with various dates of anticipated recovery of stock through December of 2023. Citing "manufacturing delays," Pfizer is allocating its distribution of these products to certain healthcare institutions and only via direct order.[i] However, it is not just Pfizer or the United States that is affected: other countries such as Canada, Australia and the United Kingdom are also experiencing shortages of both oral and intravenous steroids with other hydrocortisone manufacturing companies.[ii]

Given hydrocortisone's integral role in treating several different critical illnesses, this shortage poses a serious challenge to both clinicians and patients. Patients who are steroid-dependent, such as those with Addison's Disease, are particularly vulnerable to interruptions in the corticosteroid supply chain. For clinicians working in the critical care space, it is integral to know your institution's access to this important medication and potential limitations, as this will likely vary from hospital to hospital. Physicians, pharmacists, and hospital administration must work closely to understand their unique resources with regards to hydrocortisone and be proactive in anticipation of shortages. Resource allocation and implementation of use criteria may be required.

In the rare but possible scenario of complete lack of this medication, understanding alternate steroid regimens is key. Dexamethasone sodium phosphate (Decadron®) or methylprednisolone sodium succinate (Solu-Medrol®) are parenteral alternatives to Solu-Cortef®. However, they have different potencies and duration of action. Most notably, the mineralocorticoid activity is significantly lower (methylprednisolone) or absent (dexamethasone) in these agents compared to hydrocortisone. As such, patients who require mineralocorticoid activity in addition to glucocorticoid effect, such as those with adrenal insufficiency, will need supplementation with fludrocortisone. Steroid conversion charts, such as the one below, are helpful for understanding alternative regimens.

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In sum, drug shortages are not a new phenomenon in the healthcare landscape but have certainly gotten worse in the post-pandemic world. Due to the complex nature of the pharmaceutical supply chain in the United States, this issue is not going away any time soon. Critical care providers must be aware of drug shortages that affect our practice, and work together to ensure that our most critically ill patients receive the medications they require.

Corticosteroid Conversion Chart				
Glucocorticoid	**Approximate Equivalent Dose (mg)**	**Relative Anti-Inflammatory (Glucocorticoid) Potency**	**Relative Mineralocorticoid (Salt-Retaining) Potency**	**Biological Half-Life (Hours)**
Short-Acting				
Cortisone	25	0.8	0.8	8 – 12
Hydrocortisone	20	1	1	8 – 12
Intermediate-Acting				
Methylprednisolone	4	5	0.5	18 – 36
Prednisolone	5	4	0.8	18 – 36
Prednisone	5	4	0.8	18 – 36
Long-Acting				
Dexamethasone	0.75	25	0	36 – 54
Meikle AW et al. Potency and Duration of Action of Glucocorticoids. AM J of Med. 1977. 63 (2);200-207. PMID: 888843				

[i] Ventola CL. The drug shortage crisis in the United States: causes, impact, and management strategies. PT. 2011;36(11):740-757.

[ii] Bookwalter, C. Drug Shortages Amid the COVID-19 Pandemic. US Pharm. 2021;46(2):25-28

[iii] United States Senate Committee on Homeland Security and Governmental Affairs. Short Supply: The Health and National Security Risks of Drug Shortages. HSGAC Majority Staff report March 2023. https://www.hsgac.senate.gov/wp-content/uploads/2023-06-06-HSGAC-Majority-Draft-Drug-Shortages-Report.-FINAL-CORRECTED.pdf

[iv] https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm

[v] Pfizer. Notice Regarding Solu-Cortef Availability. March 22, 2023. https://www.fda.gov/media/166443/download

Growing Concerns of *Candida auris*

Is there a Fungus Amungus?

By: Darrick Emery, Pharm.D.

A New or Existing Threat

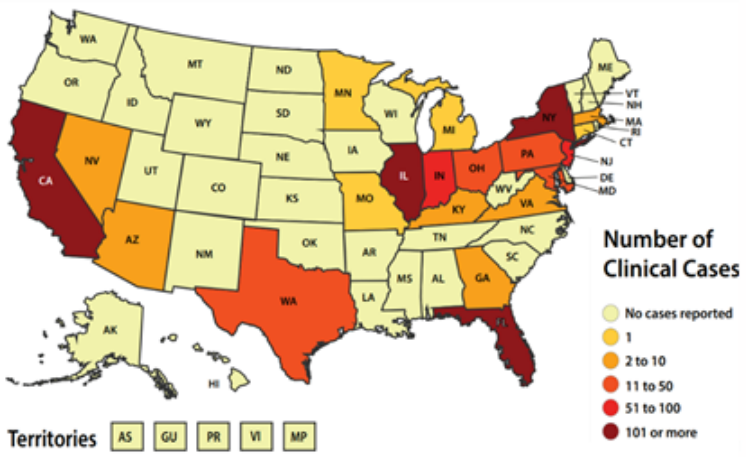

Figure 1. Reported clinical cases in the United States in 2021[7]

In March 2023, the Centers for Disease Control and Prevention (CDC) issued a press release detailing an evolving antimicrobial resistance threat to healthcare facilities worldwide.(1) The first report of novel *Candida auris* was isolated in 2009 in Japan, however samples as far back as 1996 have now been re-identified as *C. auris*.(2) Microbiologists suspect biochemical phenotyping misidentified *C. auris* as other Candida species including *C. haemulonii, C. famata, C. lusitaniae, C. guilliermondii*, and *Saccharomyces cerevisiae*.(3) The CDC previously issued a warning and classified the pathogen as an "urgent threat" in 2019 given its potential to cause severe, invasive infections associated with high mortality rates.(4) Currently, MALDI-TOF mass spectrometry and other methods of DNA sequencing detect *C. auris* more rapidly and reliably than previous techniques to help combat this new threat.(5)

Five phylogenetically distinct clades of *C. auris* have since been recognized in separate geographical regions, each with unique considerations or antiungal resistance. Since *C. auris* was first reported in the US in 2016 each clade has spread to various regions across the nation with growing prevalence of the South Asian (I) and South American (IV) clades. National surveillance from 2019 to 2021 demonstrate an increasing percentage of clinical cases each year from 44 up to 95%. In two years alone, 17 states identified their first case of *C. auris*. Perhaps more unsettling was the 3-fold increase in cases resistant to echinocandin antifungal agents over the course of the survey. In the same surveillance data of more than 10,000 isolates of *C. auris* (3270 clinical cases including invasive infections and 7413 screening cases), high levels of azole resistance was found across most regions (Table 1).(6) Unlike other Candida species, resistance is often anticipated with *C. auris*, which guides first-line treatment options employed in suspected and confirmed invasive disease.

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Year	Azoles	Polyenes	Echinocandins
2018 (n=463)	80.3 %	32.6 %	0.4 %
2019 (n=1006)	78.2 %	24.1 %	1.4 %
2020 (n=1294)	85.7 %	25.6 %	1.2 %

Table 1. Resistance rates of *C. auris* by year[6]

Why So Problematic?

Candida species are widely-accepted as a colonizer of the human body, with large amounts of these organisms found in the gastrointestinal tract. *C. auris* is distinct in that colonization also occurs on the skin, leading to increased risk of exposure through normal contact with colonized patients or adjacent surfaces. In patients with frequent or extended hospitalizations, the likelihood of transmission to those at higher risk of invasive infection is greater if proper prevention and control measures are not followed. Coupled with the increase in screening by over 200% from 2020 to 2021 in patients at high risk of colonization with *C. auris*, this has led to increased awareness of the presence of *C. auris* in various healthcare settings.(60 Currently, the CDC recommends against treatment for colonized patients given limited evidence to suggest a clinical benefit from eradicating colonization.(8)

Candida species commonly employ three types of resistance mechanisms: mutations in the drug target, overexpression of the drug target, and overexpression of efflux pumps which actively remove the antifungal agent from the cell. Further complicating management, each C. auris clade possesses different acquired mechanisms of resistance. ERG11 gene mutations leads to changes in the azole target enzyme and prevents inhibition of ergosterol biosynthesis required for cell wall integrity. MDR1-mediated efflux pump overexpression results in decreased concentrations of available antifungal agents within cells. Echinocandin resistance occurs primarily through hotspot mutations in the FKS genes involved in encoding β-D glucan synthase, decreasing enzyme sensitivity to the antifungal agent.(4,9)

The lack of *C. auris*-specific breakpoints traditionally reported by both the Clinical Laboratory Standards Institute (CLSI) and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) further complicates selecting an antifungal agent based on resistance patterns. The CLSI only reports a single MIC susceptibility breakpoint ≤ 0.5 for the recently approved, long-acting echinocandin, Rezafungin.(11) No EUCAST MIC breakpoints are available for C. auris. Tentative MIC breakpoints are proposed by the CDC (Table 2) to help guide treatment selection.(10)

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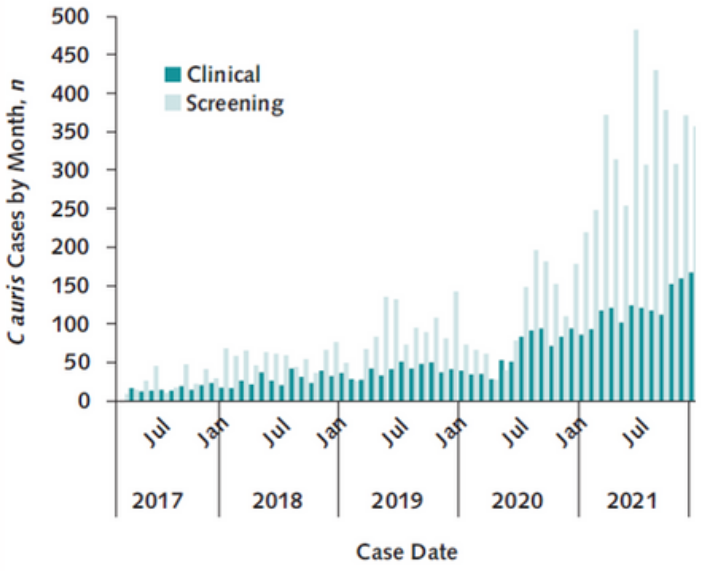

Figure 2. Clinical and screening cases 2017 to 2021[6]

Triazole Class	Tentative MIC Breakpoints (µg/mL)
Fluconazole	≥ 32
Voriconazole	Consider fluconazole susceptibility as a surrogate for second generation azole antifungals
Posaconazole	
Itraconazole	
Isavuconazole	
Polyene Class	**Tentative MIC Breakpoints (µg/mL)**
Amphotericin B	≥ 2
Echinocandin Class	**Tentative MIC Breakpoints (µg/mL)**
Anidulafungin	≥ 4
Caspofungin	≥ 2
Micafungin	≥ 4
Rezafungin	≥ 1

Table 2. CDC tentative MIC breakpoints for *C. auris*[10,11]

Study	Antifungal Treatment	Infection Characteristics	Outcomes Reported	Antifungal Resistance
Simon et al, 2022[12] United States N=83	Echinocandin - Micafungin: 89% - Caspofungin: 11%	Candidemia source - CVC present: :51.8% - Unknown: 22.9% - GI tract: 9.6% - Urinary tract: 7.2% - Wound 3.6%	30-day mortality: 30%	Fluconazole: 100% AMB: 67-86% Caspofungin: 3.2% Micafungin: 0% Anidulafungin: 0%
Pandya et al, 2021[13] 5 countries N=41	Echinocandin: 83% Fluconazole: 11% Voriconazole: 2% AMB: 2% AMB + Caspofungin: 2%	Positive culture site - Blood: 76% - Skin and soft tissue: 11% - Respiratory: 9% - Urinary: 4%	30-day mortality: 37% Microbiological clearance: 60% Lower mortality associated with: - treatment (OR 0.27) - Source removal (OR 0.74)	Fluconazole: 78% AMB: 57% Caspofungin: 16% Anidulafungin: 5% Micafungin: 0%
Mulet Bayona et al, 2020[14] Spain N=47	Echinocandin: 47% Echinocandin + AMB: 26% Echinocandin + ISA: 21%	Candidemia - CVC present: 83% - Urinary catheter present: 81%	30-day mortality: 23% Candidemia recurrence: 15% Candidemia persistence: 12.8%	Fluconazole: 100% AMB: 0% Echinocandin: 0%
Barantsevich et al, 2020[15] Russia N=38	Echinocandin - Caspofungin: 13% - Micafungin: 8% Fluconazole: 66% Voriconazole: 3% AMB: 3%	Candidemia - CVC present: 100% - Urinary catheter present: 100%	Mortality: 55%	Fluconazole: 97% AMB: 76% Echinocandin: 0%
Armstrong et al, 2019[16] Colombia N=40	Fluconazole: 40% Caspofungin: 33% AMB: 20% Voriconazole: 3% Combo therapy: 48% No treatment: 5%	Candidemia - CVC present: 100% - Surgical procedure: 70%	30-day mortality: 43%	AMB: 29% Fluconazole: 18% Echinocandin: 0%
Ruiz-Gaitan et al, 2018[17] Spain N=41	Echinocandin: 60% Echinocandin + AMB: 40%	Candidemia - CVC: 100% - Urinary catheter: 95% - Intra-abdominal surgery: 9.8%	30-day mortality: 41%	Fluconazole: 100% AMB: 0% Echinocandin: 0%

Table 3. Outcomes and resistance patterns of *C. auris* infections
AMB= Amphotericin B; CVC = central venous catheter; ISA = Isavuconazole

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Treatment Approach

Fluconazole use in *C. auris* is discouraged due to high levels of baseline resistance observed across multiple studies.(12-17) The majority of *C. auris* isolates in the US have retained susceptibility to echinocandins and this class remains first-line therapy for invasive infections per CDC recommendations (Table 4). Since *C. auris* develops resistance quickly, close monitoring for clinical improvement is crucial. In patients without clinical improvement or persistent fungemia for greater than 5 days, the CDC recommends switching to liposomal amphotericin B.(8)

Antifungal Agent	Recommended Dosing
Anidulafungin	200 mg IV loading dose, then 100 mg IV daily
Caspofungin	70 mg IV loading dose, then 50 mg IV daily
Micafungin	100 mg IV daily
Amphotericin B liposomal	5 mg/kg IV daily

Table 4. CDC recommended echinocandin dosing for *C. auris* infections[8]

The potential synergistic activity of combination antifungal therapy may increase the likelihood of therapeutic success and prevent the emergence of resistance during treatment.(18) In studies investigating flucytosine plus amphotericin B, micafungin, anidulafungin, and voriconazole, synergistic activity was seen in-vitro with decreased MICs in resistant strains.(19) Flucytosine is not utilized as monotherapy due to rapid selection of resistant mutants during treatment, but may prove useful as part of a combination regimen. Other studies show limited synergistic activity with combination therapy involving flucytosine, though no antagonistic activity was noted to suggest harm with this therapeutic approach.(20) The conflicting results may be due to different *C. auris* clade presence, combinations of antifungals used, or methods used to assess synergistic activity.

Multiple studies suggest synergism between echinocandins and azole antifungal agents. Synergistic, but non-fungicidal activity, was detected with combinations of isavuconazole plus anidulafungin, micafungin, and to a lesser extent caspofungin in a study utilizing checkboard results and time-kill assays.(21) Anidulafungin plus voriconazole or isavuconazole showed partial synergy or synergy in 36 isolates with varying degrees of resistance.(18) The combination of voriconazole and micafungin was observed to have synergistic activity in 10 strains, while fluconazole in combination with echinocandins possessed no synergy.(22)

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When No Available Treatment Option Remains

The use of combination therapy targeted at treating invasive *C. auris* infections has shown positive results in laboratory testing and has been employed as a management strategy in patients with limited therapeutic options. However, an approach using newer agents should also be considered. Rezafungin, the newest echinocandin to receive FDA-approval following the ReSTORE trial, possesses a long half-life and appealing once weekly dosing.(23) No patients in this trial had invasive candidiasis secondary to *C. auris* infection. However, in-vitro data of 100 *C. auris* isolates from four unique clades found an achievable MIC90 of 0.5 µg/mL for rezafungin. Four of the eight isolates with an elevated MIC to historical echinocandins also exhibited an elevated MIC for rezafungin due to FKS1 hotspot gene mutations. With multiple mechanisms of *C. auris* resistance to all echinocandins the role of rezafungin may still be limited.(24) In a murine model of disseminated candidiasis, treatment with rezafungin resulted in significantly lower log10 cfu/g of tissue compared to both amphotericin B-treated (P<0.0001) and micafungin-treated (P=0.0128) mice on day 10 of therapy.(25) Human studies are needed to compare the efficacy of rezafungin versus other echinocandins for the treatment of invasive infection due to *C. auris*, especially in the setting of existing echinocandin resistance.

Additionally, investigational agents with novel antifungal mechanisms are being actively evaluated to combat the resistance threat posed by *C. auris*. Two unique agents with promising in-vitro efficacy undergoing Phase II and III clinical trials include ibrexafungerp and fosmanogepix.(8)

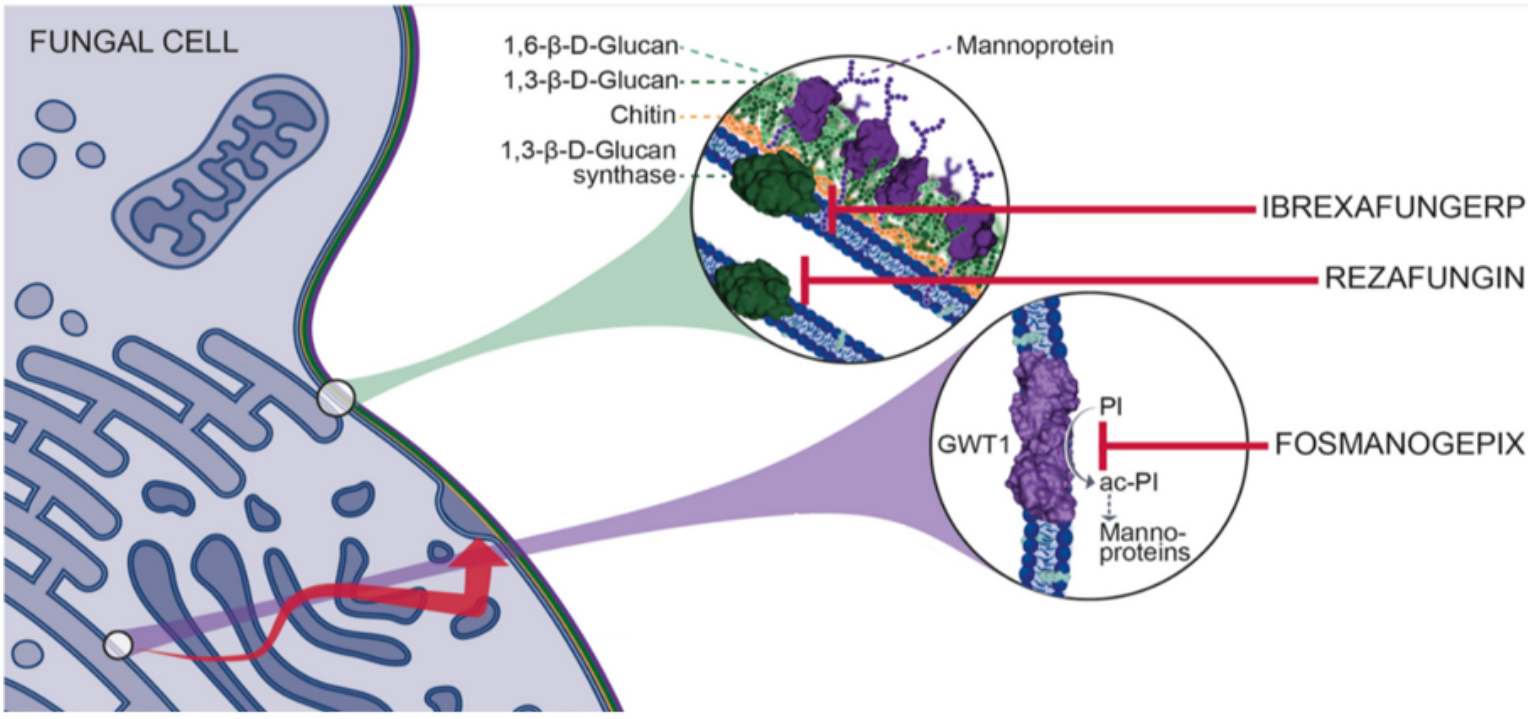

Figure 3. Recently approved antifungals and mechanisms of action[30]

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Ibrexafungerp is the first agent from the novel class of triterpenoid antifungal agents. The mechanism of action involves inhibition of glucan synthase, preventing the formation of 1,3-β-D glucan required for fungal cell wall integrity. Ibrexafungerp possesses concentration-dependent fungicidal activity and has shown activity against a variety of Candida species including *C. auris*. Given high bioavailability, it is administered orally with a half-life of approximately 20 hours. It is a CYP3A4 inhibitor and undergoes CYP3A4-mediated hydroxylation to an inactive form with over 50% excreted unchanged in the feces with <1% urinary recovery.(26) An open-label single-arm (CARES) trial evaluating oral ibrexafungerp in patients with systemic *C. auris* infections is ongoing. Preliminary data of 18 patients is encouraging (77.8% complete or partial response, 11.1% stable disease, 5.6% no response, and 5.6% indeterminate). Sources of infection included bloodstream (66.7%), lower urinary tract (27.8%), and intra-abdominal (5.6%). Eligible patients received a loading dose of 750 mg ibrexafungerp twice daily for two days, followed by 750 mg daily for up to 90 days.(27) Ibrexafungerp is currently FDA approved for vulvovaginal candidiasis, but expanded access through the drug manufacturer, Scynexis, is available for invasive *C. auris* infections.

Fosmanogepix is another promising agent for *C. auris* infections based on in-vivo and murine in-vitro data.(28,29) This agent acts by targeting the Gwt1 enzyme required to localize anchored proteins to fungal cell walls. Fosmanogepix is not an FDA-approved agent, but Amplyx Pharmaceutics, Inc. has an expanded access program.

Sound the Alarm – but Don't Panic Just Yet

Candida auris poses a serious concern to healthcare facilities worldwide as a commensal organism that can spread via contaminated surfaces and transmission between patients. With improvements in detection and surveillance since the pathogens discovery in 2019, it is likely that clinical and screening cases will continue increasing as awareness of the fungus grows. Fortunately, first-line echinocandins retain high degrees of susceptibility to the majority of isolates and should be employed in suspected invasive infection. Further in-vivo evidence is needed to better reveal benefits of combination antifungal therapy to combat resistant infection. For the first time in over 20 years, multiple antifungal agents with novel mechanisms of action are in development with promising initial data to combat resistant infections due to C. auris and other invasive fungal pathogens.

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Diagnosing Heparin-Induced Thrombocytopenia in Extracorporeal Membrane Oxygenation

By: Megan Shulkosky, Pharm.D.

What is Heparin-Induced Thrombocytopenia?

Heparin has been a mainstay anticoagulant therapy for hospitalized patients due to its rapid onset, ease of monitoring, short half-life, ability to use in renal dysfunction, and reversibility.(1) However, one of the drawbacks of heparin is the rare but serious risk of heparin-induced thrombocytopenia (HIT), a complex immune-mediated condition that occurs in 0.5-1% of patients exposed to unfractionated heparin.(2)

HIT develops when platelet factor 4 (PF4) binds to exogenous heparin and forms heparin-PF4 complexes.(1) IgG recognizes the complex and forms autoantibodies against the heparin-PF4 complex. This antibody-heparin-PF4 complex binds to Fc receptors on platelets causing platelet activation, releasing thrombin and more PF4. Therefore, the cycle continues and a hypercoagulable state develops. Macrophages engulf the antibody-heparin-PF4 complex bound to platelets to remove them, but this then decreases circulating platelets leading to thrombocytopenia.

Clinical Scoring Tools

The 4T score is a validated clinical scoring tool used to assess the clinical pre-test probability that a patient has HIT (Table 1).(3) A score of 0-3 indicates a low probability of HIT, 4-5 indicates an intermediate probability and 6-8 indicates a high probability of HIT. Other tools include the HIT expert probability score or the Lillo Le Louet Score, which was developed for post cardiopulmonary bypass (CBP) patients.(4)

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Table 1- Elements of the 4T Score

Category	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20	Platelet count fall 30-50% or platelet nadir 10-19	Platelet count fall <30% or platelet nadir <10
Timing of Platelet Count Fall	Clear onset between days 5-10 or platelet fall ≤1 day (prior heparin exposure within 30 days)	Consistent with days 5-10 fall, but not clear; onset after day 10; or fall ≤1 day (prior heparin exposure 30-100 days ago)	Platelet count fall <4 days without recent exposure
Thrombosis or Other Sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction post intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other Causes of Thrombocytopenia	None apparent	Possible	Definite

Laboratory Diagnosis of HIT

Laboratory testing is required to diagnose HIT.(5) Immunological assays, including PF4 enzyme linked immunosorbent assay (ELISA), test for the presence of HIT-related antibodies. It has excellent negative predictive value, helpful for ruling out HIT, but lacks specificity because of the occurrence of asymptomatic seroconversion. The standard cut off optical density (OD) value for a positive ELISA is ≥ 0.4. Any positive immunological assay result should be confirmed with a functional assay such as the serotonin release assay (SRA) or heparin induced platelet activation (HIPA), which test for platelet activation.(6) These are more complex assays and takes days to result.

What is ECMO and why do we use heparin?

Extracorporeal membrane oxygenation (ECMO) provides support for patients with refractory cardiopulmonary failure.(7) Venovenous (VV) ECMO is indicated for patients with impaired gas exchange but adequate cardiac function. Venoarterial (VA) ECMO provides gas exchange and circulatory support for patients with severe cardiac failure with or without impaired gas exchange.

ECMO requires continuous exposure of blood to foreign material within the extracorporeal circuit that creates an ongoing stimulus for the activation of platelets, clotting factors, and fibrinolysis.7 This creates prothrombotic and antithrombotic effects that can manifest as clotting, bleeding, or both. Due to increased risk of thrombosis, anticoagulation, such as heparin, is frequently used, as recommended by Extracorporeal Life Support Organization (ELSO).(8)

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Challenges of Diagnosing HIT in ECMO

Thrombocytopenia, a complications of ECMO, occurs in up to 50% of patients due to platelet activation, sequestration and consumption within the device circuit, and destruction of the platelets within the ECMO circuit and oxygenator.(9) The degree of critical illness necessitating ECMO may also worsen thrombocytopenia due to due sepsis, medications, recent surgery or the use of the cardiopulmonary bypass and other intravascular devices, among other causes.

Because of these factors, HIT diagnosis in ECMO patients is a challenge. Prevalence of HIT in ECMO ranges from 0.3% to 5.3% as described in the studies in Table 2.(10-15) Many of these studies are small, heterogeneous, and have different definitions of HIT. Despite the limitations, the studies highlight the difficulties of utilizing scoring tools such as the 4T score due to its lack of correlation in ECMO patients. This blurs the line of when to send a PF4 test or refrain.

Risks of sending PF4 ELISA tests unnecessarily include the cost of the lab and low specificity. If the results are positive there are implications on patient care, including the need to send further confirmatory assays that take days to process, and the need for alternative anticoagulation with medications such as bivalirudin which is more expensive and have no reversal agent. More precise clinical scoring tools or laboratory interpretations are needed to better rule out or diagnose HIT in the ECMO patient population to combat the dilemmas currently faced in clinical practice.

Modified 4T Score in VA ECMO

Understanding the current limitations with diagnosing HIT in ECMO patients, Renou and colleagues designed The Modified 4T Score for Patients on VA ECMO (Table 3).(16) A score of ≥ 42 points showed an increased risk of HIT. There were 117 patients (21 confirmed HIT vs. 96 non-HIT) included in the internal validation and found that compared to the 4T Score, the modified 4T Score had better performance with an AUROC of 0.89 (0.83–0.96) vs. 0.81 (0.74–0.89), p=0.01. The external validation confirmed the performance of the modified 4T Score with an AUROC of 0.94 (0.90–0.97). While this study offers valuable insight, this is only applicable for VA ECMO, not VV ECMO, and larger validation studies should be completed before routinely implementing this tool at the bedside.

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Table 2- Studies Evaluating the Risk of HIT and Utilization of the 4T Score in ECMO

Study	Patient Population	Comparison Groups	Definition of HIT	Confirmed HIT	4T Score Correlation Outcomes
Kimmoun et al.[10] 2018 (N=39)	VA ECMO and positive PF4 testing	positive functional test vs negative functional test	PAT or HIPA or SRA positive	0.36% (21/5797) -any positive functional test -denominator: number of patients on ECMO screened	4T score > 4 and positive PF4 did not correlate well with a positive functional test
Vayne et al.[11] 2019 (N=57)	VA ECMO with PF4 and SRA testing	No comparator groups	SRA positive	5.3% (3/57) -SRA positive	-Did not evaluate 4T score
Sullivan et al.[12] 2020 (N=39)	VV ECMO or VA ECMO with PF4 testing	Positive PF4 vs Negative PF4	PF4 Positive	5.1% (2/39) -SRA positive 15.4% (6/39) PF4 positive	-4T score, HIT expert probability and Lilo-Le Louet all had a low PPV
Lubnow et al.[13] 2022 (N=507)	VV ECMO and VA ECMO	Patients on ECMO without HIT vs Patients on ECMO with suspected HIT	HIT 4T Score ≥4 (then further divided based on testing)	3.2% (16/507) -HIPA positive	-Did not assess if 4T score and PF4 correlated
Zaaqoq et al.[14] 2022 (N=114)	VV ECMO and VA ECMO with paired PF4 and SRA tests	SRA positive vs SRA negative	SRA positive	3.6% (15/417) -SRA positive -denominator: number of patients on ECMO screened	-Did not evaluate 4T score
Lusebrink et al.[15] 2023 (N=373)	VA ECMO	Patients on ECMO (N=373) then broken down into patients with excluded HIT (n=40) vs confirmed HIT (n=13)	PAT or HIPA or SRA positive	3.5% (13/373) -any positive functional test	Median 4T score of 4 in patients with excluded HIT vs 5 in patients with confirmed HIT (p=0.054)

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Table 3- Modified 4T Score for Patients on VA ECMO

Characteristic	Modality	Points
History of chronic obliterative arteriopathy	Yes	0
	No	14
History of cancer	Yes	7
	No	0
Cardiogenic shock secondary to pulmonary embolism	Yes	7
	No	0
Cardiogenic shock secondary to cardiac surgery	Yes	12
	No	0
Multiple organ failure	Yes	8
	No	0
4T score item: Thrombosis associated with thrombocytopenia	None	0
	Progressive or recurrent thrombosis; non-necrotizing skin lesions, suspected thrombosis	26
	New thrombosis or skin necrosis; acute systemic reaction post-IV heparin bolus	25
4T score item: Timing of onset of thrombocytopenia	Platelet count fall <4 days without recent exposure	0
	Consistent with days 5-10 fall, but not clear or onset after day 10 or fall ≤1 day (prior heparin exposure within 30-100 days)	16
	Clear onset between days 5-10 or platelet fall ≤1 day (prior heparin exposure within 30 days)	27

Alternative PF4 OD Cut Off

Currently, a PF4 ELISA test is considered positive if the OD value is ≥ 0.4.(5) Studies evaluating traditional patients have shown correlations between higher OD values and clinical HIT.(17) Zaaqoq and colleagues designed a retrospective review to assess utilizing higher OD cut offs for diagnosis of HIT in ECMO patients.(14) They included VA and VV ECMO patients in whom HIT ELISA and SRA tests were ordered while on ECMO. Definite HIT was defined as a positive SRA. Of the 114 patients in the cohort, 42 had a positive OD ≥ 0.4, 15 had a positive SRA, and one patient had a positive SRA but a negative OD. Their overall confirmed HIT diagnosis was 3.6%.

The mean OD value in those without confirmed HIT was 0.41 ± 0.52 compared to an OD value of 2.10 ± 0.90 in patients with SRA confirmed HIT (p=0.001). Numerically more patients with SRA positive HIT had venous thromboembolisms (20.0% vs 11.0%, p=0.393). There was no difference in hospital mortality between SRA positive and SRA negative patients (53.3% vs 59.6%). By increasing the OD cut off to ≥ 1.2, they found that it would result in 2 additional cases of HIT being missed but the number of patients over diagnosed with HIT would fall by 67.9%. The results from analyzing different OD break points is shown in Table 4. This small, single center, retrospective study warrants further evaluation before implementing new OD breakpoints for ECMO patients.

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Table 4- Screening characteristics of various OD thresholds

Optical Density	Sensitivity (%)	Specificity (%)	Negative Predictive Value (%)	Positive Predictive Value (%)	Accuracy (%)
≥ 0.4	93.3	71.7	98.6	33.3	74.6
≥ 0.8	86.7	87.8	97.8	52.0	87.8
≥ 1.0	80.0	88.9	96.7	52.2	87.8
≥ 1.2	80.0	90.9	96.8	57.1	89.5

Conclusion and Application

There are many tools clinicians can utilize for the work up and diagnosis of HIT in a standard patient. As highlighted, diagnosis of HIT is much more challenging in patients on ECMO. The risk of missing HIT or risk of over diagnosis of HIT with PF4 ELISA testing are challenges clinicians face daily. Better diagnostic tools are needed to improve screening and testing for HIT in patients on ECMO. Utilizing what is available now, clinicians can consider the following when assessing a patient for diagnosis of HIT:

- Calculate a 4T Score
  - While it has not shown to correlate with patients on ECMO, a 4T Score may help a clinician think critically about the patient
  - Consider counting ECMO as a possible cause of thrombocytopenia
  - Consider clots in the ECMO oxygenator/need for oxygenator exchanges due to clotting as a point for thrombosis
  - Consider sending a PF4 even if the 4T is low but clinical suspicion for HIT is high
- Did the drop in platelets correlate with the timing of ECMO initiation or heparin initiation?
  - However, sometimes these may be initiated on the same day
- Was the patient on CBP? If so, how many days since CBP?
  - A platelet count that begins to recover after CPB but then begins to fall again > 4 days after CBP may be more suggestive of HIT
  - Consider evaluation using the Lillo Le Louet Score
- Other scores such as the Modified 4T Score for Patients on VA ECMO may be utilized in addition to clinical judgement but should not be the sole determinant
- Suggest against increasing the OD threshold at present. If an OD score results ≥ 0.4, would treat as HIT until ruled out with an SRA
  - Risks of missing HIT diagnosis is worse than the risks of stopping heparin, switching to a different anticoagulant and treating HIT

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Member Spotlight

Josh Trester, MD

Dr. Josh Trester is an Anesthesiologist and Intensivist at the University of Cincinnati Medical Center (UCMC). He is the Associate Program Director for the Critical Care Fellowship and Thoracic Anesthesiology team leader there. He works as a Critical Care Attending Physician in the Cardiovascular ICU, Burn, and ENT units at UCMC. He has traveled abroad five times on surgical mission trips in the past few years working as an Anesthesiologist. Most recently, in May 2023, he traveled with other UCMC Anesthesia team members and a local non-profit to Kampala, Uganda for the second time to provide anesthesia support for complex Head and Neck surgical procedures at the Uganda Cancer Institute. The non-profit mission is to provide health care in developing countries through sustainable education, research, and surgical programs.

Following his trip, Dr. Trester had this to say about his experience doing mission work:

"*Spending a week caring for Head and Neck surgery patients at the Uganda Cancer Institute-patients most of whom live with more challenge and heartbreak than many of us will ever know-helped me remember that life isn't just about working, or socializing, or exploring. Life is about doing things that matter. It's about giving back. It's about trying to make a small part of the world better so that the world gets better for everyone. It's so easy to forget that what we do as healthcare workers matters. It matters so, so much. We help save lives, families, and friendships. We help heal bodies, and in turn, we rekindle spirits. We spend years learning to spend a lifetime helping. Weeks like this help me realize who I am and who I want to be. They remind me that all the hard work was worth it. They show that the world needs healing and people who can do it.*"

Thank you, Dr. Trester for your selfless dedication to provide care to those who are less fortunate. Dr. Trester has been an active member of the Society of Critical Care Medicine since 2017 and was recently elected as new member-at-large for the Ohio Chapter!

Member Spotlight

Josh Trester, MD

Research Day Abstracts

1. **Use of heated high flow nasal cannula (HHFNC) in progressive care unit during COVID-19 pandemic.** Akshay Vijayaraman, MD; C Divens; N Worobetz; N Bougebrayel; N Baltich, MS, APRN-CNS; M Wert, MD; M Exline, MD. *The Ohio State University Wexner Medical Center*.

2. **Vasoactive Agent Dosing in Different Weight Classes**. Renee McTee, PharmD; R Barcelona, PharmD, BCPS; R Josephson, MD; A Popa, PharmD, BCPS, BCCCP. *University Hospitals Cleveland Medical Center*.

3. **The Management of Pain, Agitation and Delirium With and Without the Use of Dexmedetomidine.** Alina Galant, PharmD; M Rangel, PharmD, BCCCP; A Popa, PharmD, BCPS, BCCCP; R Hejal, MD. *University Hospitals Cleveland Medical Center*.

4. **A Case-Control Study of Critically Ill Incarcerated COVID-19 Patients**. Michelle Gillespie, MD; L Leuenberger, MD; A Monoson, MD; K Stinehart, MD; N Brummel, MD; M Exline, MD; J Horowitz, MD; S Pannu, MD. *The Ohio State University Wexner Medical Center*.

5. **Comparison of Fixed Dosing vs Train of Four Titration of Cisatracurium in COVID-19 ARDS Patients.** Oyshik Banerjee, PharmD, BCCCP; J Elefritz, PharmD, BCCCP; B Doepker, PharmD, BCPS; S Atyia, PharmD, BCCCP; N Brummel, MD, MSCI; R Smith, MPH; K Cape, PharmD, BCPS. *The Ohio State University Wexner Medical Center*.

6. **Management of Acute Pulmonary Emboli (PE) with Right Atrial (RA) Thrombus in Transit.** Tashia Bailey, DNP, ACNP; T Smith, MD; K Gorder, MD. *Christ Hospital*.

7. **An Uncommon Presentation of Isolated Rectal Variceal Bleeding due to Suspected Autoimmune Hepatitis**. Amina Kunnummal, MD; S Raju, MD. *University Hospitals Cleveland Medical Center*.

The Ohio Chapter of the Society of Critical Care Medicine

1

Use of heated high flow nasal cannula (HHFNC) in progressive care unit during COVID-19 pandemic

Akshay Vijayaraman, MD; C Divens; N Worobetz; N Bougebrayel; N Baltich, MS, APRN-CNS; M Wert, MD; M Exline, MD
The Ohio State University Wexner Medical Center

Introduction: Patients admitted for respiratory failure increased due to COVID-19. At OSU, HHFNC has historically been used in the ICUs and ED exclusively. During the pandemic HHFNC was utilized in the PCUs out of necessity due to ICU bed availability. Prior evidence of HHFNC in ARDS shows decreased intubation rates, ventilator days, and mortality favoring HHFNC over NIMV for ARDS.

Methods: MRNs were obtained through EMR query for HHFNC use between November 2020 and June 2022 and verified by individual chart review. The PCU group consisted of patients who were initiated on HHFNC for a minimum of 4 hours with the intention to maintain the patient on PCU level. The ICU group consisted of patients who were transferred to the ICU directly for initiation of HHFNC. Concomitant use of NIMV with HHFNC was also included.

Results: A total of 39 and 86 patients maintained HHFNC in the PCU and ICU respectively. Of the 39 PCU patients, 25 required ICU transfer. On average, PCU patients used 4 days of HHFNC, and 2.2 days prior to ICU transfer. The ICU group was more likely to be younger, to have ILD, to have a diagnosis other than COVID, and to have a lower ROX index. SOFA scores were similar between the two groups at the time of HHFNC initiation. Death, mechanical ventilation, and cardiac arrest were similar between the two groups. Patients in the PCU were more likely to transition to DNR-CC. Of the 14 PCU patients that required mechanical ventilation, only 3 intubations were performed in the PCU, while the remainder were performed after ICU transfer. There were 3 cardiac arrests in the PCU group, all which occurred after transfer to ICU. There were 9 deaths which occurred while the patient was admitted in the PCU, and all these patients had been transitioned to DNR-CC.

Conclusions: Patients between the two groups had similar baseline characteristics and severity of illness. Outcomes such as death, mechanical ventilation, and cardiac arrest were similar between the two groups. Many of the patients in the study did have COVID 19 which conferred a high morbidity and mortality. Utilizing HHFNC in the PCU can save ICU beds when resources are limited. This study demonstrates safety and efficacy of HHFNC in the PCU at our institution.

2

Vasoactive Agent Dosing in Different Weight Classes

Renee McTee, PharmD; R Barcelona, PharmD, BCPS; R Josephson, MD; A Popa, PharmD, BCPS, BCCCP
University Hospitals Cleveland Medical Center

Introduction: Individualization of drug dosing is a cornerstone of proper, patient-specific treatment. One variable that impacts some dosing regimens is patient weight. Weight-based dosing is utilized in many medications, including vasoactive agents. An important pharmacokinetic consideration in obesity would be the degree of intravascular volume of distribution. As weight increases due to increased adipose tissue, primary vasculature is largely unchanged. The site of action of vasoactive drugs is the vasculature, so we do not expect to see a large difference in dose needed between patients of various weights. With this, weight-based dosing with actual body weight may cause unnecessarily high doses in the obese population. By investigating incidence of adverse effects and time to hemodynamic stability, the hope is to find a trend that could maximize hemodynamic outcomes and limit adverse effects.

Methods: This study is a retrospective chart review of patients that received norepinephrine, epinephrine, milrinone, or dobutamine between 10/1/2020 and 3/1/2022 at University Hospitals Cleveland Medical Center. Adult patients were included if they received one of the four vasoactive drugs for at least 12 hours. Vulnerable patient populations and patients with BMIs under 18.5 kg/m2 were excluded. Patients were evaluated in two groups: lower BMI (18.6-29.9 kg/m2) and higher BMI (≥ 30 kg/m2). The primary outcome is the presence of arrhythmia or ischemia within 48 hours. Secondary outcomes include time to hemodynamic stability and 28-day mortality. Outcomes were analyzed using a two-factor ANOVA test for numeric data and chi-square or Fisher's exact tests for categorical data.

Results and Conclusions: 200 patients underwent evaluation with 50 patients evaluated for each study drug. Of the 50 patients in each group, 25 patients had a BMI of 18.5-29.9 kg/m2, whereas the other 25 patients had a BMI ≥ 30 kg/m2. The primary outcome of arrhythmias or ischemia occurred in 71 of the 200 patients. In all drug groups, the primary outcome occurred in more patients with a BMI of ≥ 30 kg/m2. This trend introduces an area for advanced study: would ideal or adjusted body weight be more appropriate for dosing vasoactive agents in obese patients. Statistical analysis is in process.

3

The Management of Pain, Agitation and Delirium With and Without the Use of Dexmedetomidine

Alina Galant, PharmD; M Rangel, PharmD, BCCCP; A Popa, PharmD, BCPS, BCCCP; R Hejal, MD
University Hospitals Cleveland Medical Center

Introduction: The 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption in Adult Patients in the ICU (PADIS) recommends adequate pain control and maintenance of light sedation. As for delirium, the avoidance of antipsychotics and limiting modifiable risk factors are crucial for prevention. For treatment, the use of dexmedetomidine in mechanically ventilated patients is recommended. Dexmedetomidine, a selective alpha2-adrenoceptor agonist, prevents the release of norepinephrine and has anesthetics and sedative properties. A prior study evaluated the use of dexmedetomidine for the treatment of hyperactive delirium refractory to haloperidol in nonintubated ICU patients. Patients spent more time in satisfactory sedation levels when receiving dexmedetomidine. Additionally, patients who received haloperidol were oversedated and had more QTc prolongation. As for cost, while dexmedetomidine's direct cost is more expensive, the overall cost savings was greater in this group due to reduced length of ICU stay. The aim of this study is to fulfill a gap in literature by providing evidence and support for the management of agitation and delirium in non-ventilated patients.

Methods: This IRB-approved, single-center, retrospective chart review included patients at least 18 years of age or older, admitted to University Hospitals Cleveland Medical Center's Medical Intensive Care Unit between January 1, 2018 and October 31, 2022. These patients were not mechanically ventilated and ordered at least one sedative agent. The primary outcome is total number of rescue agents used during ICU stay, while secondary outcomes will be assessing safety endpoints related to the different agents.

Results and Conclusions: Results will be finalized and presented at Ohio SCCM Research Day.

4

A Case-Control Study of Critically Ill Incarcerated COVID-19 Patients

Michelle Gillespie, MD; L Leuenberger, MD; A Monoson, MD; K Stinehart, MD; N Brummel, MD; M Exline, MD; J Horowitz, MD; S Pannu, MD
The Ohio State University Wexner Medical Center

Introduction: Incarcerated individuals were disproportionately affected with COVID-19 leading to increased mortality compared to community patients. There is paucity of data on meaningful outcomes of hospitalization in this population. We report outcomes for critically ill incarcerated individuals with COVID-19.

Methods: This is a nested case-control study of critically ill patients with COVID-19 at OSUWMC from March 2020 to April 2021. Propensity based matching was done between incarcerated and community patients based on age, BMI, Charlsons Comorbidity index (CCI), and admission PaO2/FiO2 ratio. All patients received treatment in the closed ICUs with the same providers and similar mechanical ventilation and ICU protocols. The primary outcome was all-cause hospital mortality. Mean PaO2/FiO2 ratio, ventilator free days, and length of hospital stay were secondary outcomes. Wilcoxon-Kruskal Wallis test was used for matched nonparametric analysis.

Results: Among 3674 consecutive COVID-19 patients, 1443 patients had critical illness per NIH COVID guidelines. Of those, 245 were incarcerated. After 1:2 or 1:3 matching based, 132 incarcerated individuals (cases) were matched to 330 community patients (controls). Age, BMI, CCI, and admission PaO2/FiO2 ratio were similar except cases were predominantly male (98% cases vs 58.8% controls, p=0.001) and disproportionately Black (44% cases vs 25% controls, p=0.001). There was no difference in antiviral, steroid, immunomodulator, or antibiotic use between groups. The mean PaO2/FiO2 ratio was similar (p=0.1) in cases (142 +/- 44.2) and controls (135 +/- 66.8). There were no differences in median ventilator free days, 21 (IQR, 15-25) in cases vs 22 (IQR, 17-25) in controls, [p=0.3], and median length of hospital stay, 19 (IQR, 13-27) in cases vs 19 (IQR, 12-27) in controls, [p=0.9]. 38.8% controls died in the hospital compared to 36.7% cases (p=0.6).

Conclusions: Despite higher associations of incarceration and COVID-19 infection, utilization of standardized ICU protocols and COVID-19 guidelines resulted in similar mortality outcomes in incarcerated individuals. Delivery of equitable healthcare services to incarcerated individuals is a requisite for reducing disparities in clinical outcomes in the general population.

5

Comparison of Fixed Dosing vs Train of Four Titration of Cisatracurium in COVID-19 ARDS Patients

Oyshik Banerjee, PharmD, BCCCP; J Elefritz, PharmD, BCCCP; B Doepker, PharmD, BCPS; S Atyia, PharmD, BCCCP; N Brummel, MD, MSCI; R Smith, MPH; K Cape, PharmD, BCPS
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Introduction/Hypothesis: Cisatracurium (CIS) has been associated with improved outcomes in patients with early moderate-severe acute respiratory distress syndrome (ARDS). Fixed dose (FD) CIS has been compared to train-of-four (TOF) titration, suggesting increased drug utilization without benefits in oxygenation. We sought to determine if a novel FD CIS protocol using a lower FD was non-inferior to TOF CIS titration in improving the PaO2:FiO2 ratio (P/F) in COVID-19-related, moderate-severe ARDS patients on continuous infusion CIS.

Methods: This was a single-center, retrospective, cohort study comparing a historic cohort who received TOF CIS titration to post-implementation of the novel FD CIS protocol. Patients were included if 18-89 years old, received CIS infusion for >/=12h in the management of COVID-19 ARDS, and had a baseline P/F=200. The primary outcome was change in P/F at 48h from baseline. Secondary outcomes included change in P/F at 24h and 7 days, median rate and cumulative dose of CIS, and need for mechanical ventilation at day 28. The primary outcome was analyzed with a linear regression model adjusting for age, BMI, SOFA, volume status, and use of inhaled epoprostenol and proning.

Results: Analysis included 125 total patients, 65 in the TOF and 60 in the FD cohort. Severe ARDS was common with a baseline median P/F ratio of 79.5 vs 73.7, p=0.13. Use of inhaled epoprostenol and tocilizumab was less frequent in the TOF cohort. The change in P/F ratio at 48h after adjustment was larger in the TOF cohort (70.8 vs 24.9, p<0.005). There were no differences in other clinical secondary endpoints . The rate of infusion and total cumulative dose of CIS were lower in the TOF cohort (3 vs 5 mcg/kg/min, p<0.001; 612 vs 1034 mg, p<0.001) even with similar durations of infusion (48.5h vs 44.1h).

Conclusions: Patients in the TOF CIS cohort had improved P/F at 48h vs those in the FD cohort, while also using 60% of the cumulative dose utilized in the FD cohort. The analysis is limited by its retrospective design with inability to control for all potential confounders . This study found TOF titration resulted in improved early oxygenation in patients with moderate-severe COVID-19 ARDS while also facilitating drug conservation compared to a novel FD CIS protocol.

6

Management of Acute Pulmonary Emboli (PE) with Right Atrial (RA) Thrombus in Transit

Tashia Bailey, DNP, ACNP; T Smith, MD; K Gorder, MD
Christ Hospital

Introduction: Nearly 900,000 people are affected by DVT/PE each year in the US, with an estimated 100,000 deaths. (1) Unfortunately, sudden death is the presenting symptom in 25% of those diagnosed with PE. (1) Despite advances in treatment of acute high-risk PE, outcomes remain suboptimal. (2) We present a case where PERT (pulmonary embolism response team) protocol was utilized to rapidly stratify a patient with intermediate to high PE risk, with decision to pursue emergent thrombectomy, inferior vena cava (IVC) filter placement, and catheter-based pulmonary thrombolysis with EKOS, all successfully performed without the use of mechanical circulatory support (MCS).

Case: A 76-year-old male with obstructive coronary artery disease, heart failure with intermediate reduced left ventricular (LV) EF 45-50%, DVT without active anticoagulation due to history of traumatic subdural hematoma, and history of asthma, presented with acute hypoxia, hypotension, and altered mentation. CTPA demonstrated bilateral PE extending from the segmental main arteries with large thrombus in transit in the RA. Right ventricular (RV) strain and markedly reduced LVEF 10% found on echocardiogram. Pulmonary Embolism Severity Index Score (PESI) score approximately 106. Discussion: Multi-disciplinary team decision deemed patient too high risk for routine mechanical thrombectomy given acute biventricular dysfunction and hemodynamic compromise, making the need for mechanical circulatory support during intervention likely. In the cardiac catheterization suite under visualization of intracardiac echocardiography (ICE), the patient underwent thrombectomy of large right atrial thrombus in transit with utilization the AngioDynamics AlphaVac system. This was followed by placement of IVC filter and then left and right pulmonary arterial thrombolysis catheters (e.g., EKOS) with tissue plasminogen activator (TPA) infusion for 12 hours duration (6 mg/lung total). These successful catheter-directed interventions were completed without the need for MCS.

Conclusion: Engagement of multiple specialty teams is pertinent in the management of hemodynamically compromised acute PE to acutely risk stratify the patient and develop and implement an immediate action plan for optimal outcomes.

7

An Uncommon Presentation of Isolated Rectal Variceal Bleeding due to Suspected Autoimmune Hepatitis

Amina Kunnummal, MD; S Raju, MD
University Hospitals Cleveland Medical Center

Introduction: Ectopic variceal hemorrhage is rare in patients with liver cirrhosis (1). Here, we report the case of a 63-year-old female with decompensated cirrhosis secondary to non-alcoholic fatty liver disease (NAFLD) and autoimmune hepatitis (AIH), who presented with life-threatening isolated rectal variceal bleeding.

Case: A 63-year-old female with a history of decompensated liver cirrhosis secondary to NAFLD and suspected AIH complicated by hepatic encephalopathy (HE), spontaneous bacterial peritonitis and ascites presented with rectal bleeding. Prior esophagoduodenoscopy showed grade 1 esophageal varices and portal hypertensive gastropathy. On presentation she had acute anemia (hemoglobin 9.4). Flexible sigmoidoscopy showed a bleeding rectal varix. Band ligation failed; octreotide was started. Sclerotherapy was unsuccessful. She was not a candidate for surgical management, and was a poor candidate for transjugular intrahepatic portosystemic shunt (TIPS) given her Model for End-Stage Liver Disease score of 28 and history of HE. She re-bled and successfully underwent rectal sclerotherapy via splenic approach. Discussion: Varices form in 5-15% of cirrhotic patients per year and are typically esophageal or gastric. A third develop variceal hemorrhage.Therapeutic mainstays include therapy with vasopressin or somatostatin analogs, endoscopic therapy, TIPS, and shunt surgery (1). Ectopic varices develop at other sites including the duodenum, rectum, and around stoma sites. Rectal varices are seen in 40-56% of cirrhotic patients. Significant hemorrhage occurs in 0.5-5% of cirrhotic patients, and is uncommon enough that therapeutic guidelines are limited (2). Case reports suggest they can be managed with ligation, glue injection, coil placement, TIPS, or BRTO (4,5). This case is remarkable as it is an unusual presentation of isolated, hemodynamically significant rectal variceal bleeding in a cirrhotic patient.

Conclusions: Isolated rectal variceal bleeding is a rare but life-threatening complication in patients with decompensated cirrhosis. This case highlights the importance of ectopic varices as a source of bleeding in cirrhotic patients. Timely diagnosis is crucial for the management of rectal variceal bleeding and for optimizing patient outcomes.

Thank You

Special thanks to those who contributed to the planning and content of this issue!

Nicole Allen-Payne
Kathryn Bash
Suzanne Bennett
Stephanie Ciapala
Grace Conroy
Jessica Elefritz
Darrick Emery
Elisha Fleig
Kari Gorder
Hannah Hixenbaugh
Dalton Kuebel
Chaitanya Mishra
Claire Murphy
Silvia Perez-Protto
Megan Phelps
Michael Rudoni
Gretchen Sacha
Megan Shulkosky
Donna Tanner
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