ACCP Adult Medicine PRN Fall 2021 Newsletter

Edited by Rachel W. Flurie, PharmD, BCPS and Leslie Wooten, PharmD, BCPS

Message from the Chair

Every morning at 8am, the pharmacy team at my hospital gathers for a quick huddle. During those huddles, we often share quotes of motivation. While searching for quotes, I came across this one:

"Sometimes you forget you're awesome so this is your reminder"

This quote stood out to me as being very fitting for the times. As the struggle with COVID-19 battles on, it can be easy to lose hope, become frustrated and burnt out. So when you find yourself feeling that way, take a moment to remember that you are awesome!



Carmen B. Smith, PharmD, BCPS

Throughout this past year members of AMED have demonstrated resilience and dedication to the profession and to the PRN in many ways. Our External Affairs Committee has done an excellent job connecting with our members, new and old, maintaining the mentor-mentee program, and keeping us all up to date with the latest ACCP announcements, guideline releases, member literature publications, and member highlights on Twitter. The Internal Affairs and Trainee Engagement Committees continue to provide us with high quality programming via newsletters, journal clubs, and student case presentations while the Programming Committee has developed what is sure to be an interesting and informative PRN Focus Session on "Persistence in the Face of Resistance: Antibiotic Treatment Updates for the Adult Medicine Practitioner."

The Walk-Rounds and Research Committees continue to highlight and promote research, thinking of new creative ways to engage our members such as the first annual trainee poster review service put on by the Walk-Rounds Committee in collaboration with the Trainee



Engagement Committee. Finally, the Nominations and Training and Travel Committees have diligently promoted our PRN awards and identified eight deserving award winners for 2021 (see page 9).

It has truly been an honor to have served on the AMED leadership team over the last three years and as your Chair this past year. Though the Annual Meeting will not be in person, I look forward to celebrating our many PRN achievements and interacting with you all at the AMED business meeting and virtual poster sessions!



@ACCPAMEDPRN #AMEDPRN



ACCP Adult Medicine PRN



Inside this Issue

Message from the Chair		1
2021 ACCP Annual Meeting	Clickable	4
ACCP Adult Medicine PRN Announcements Nominations Committee External Affairs Committee	tuble of contents:	6 6 6
AMED PRN Seed Grant Award Winners 2019		7
AMED PRN Award Winners 2021		
AMED PRN Training & Travel Award Winners 2021		
Adult Medicine PRN Officers		
Member Accomplishments Promotions Awards Grants Publications Other Notable Achievements		10 10 10 11 11 16
Update on Asthma Management With a Focus on Inhaled Corticosteroids		
Update on Direct Oral Anticoagulants in Obesity		
Vancomycin Therapeutic Drug Monitoring		



ACCP Annual Meeting is Virtual

The 2021 ACCP Annual Meeting is completely virtual with some notable differences from last year's meeting. Visit <u>ACCP's website</u> for more information.



AMED PRN Focus Session

Persistence in the Face of Resistance: Antibiotic Treatment Updates for the Adult Medicine Practitioner

Moderator: Jon P. Wietholter, Pharm.D, BCPS, FCCP

Topic 1: Kevin W. Garey, Pharm.D., M.S., FASHP, Resistance Stinks: Changes to *Clostridioides difficile* resistance patterns and treatment options

Topic 2: Ryan Moenster, PharmD, FIDSA, BCIDP, Resistance Burns: Emerging gram-negative bacterial resistance and its impact on treatment of urinary tract infections Topic 3: Vanthida Huang, Pharm.D., BSPHM, FCCP, Resistance Suffocates: Emerging

gram-positive bacterial resistance and its impact on treatment of gram-positive pneumonias

A recording of the focus session will be released on **November 10th** for viewing by registered members

AMED PRN Business Meeting and Networking Forum

Monday October 25th from 5:00PM to 7:00PM CST (6:00-8:00 EST; 3:00-5:00 PST) via Zoom

Business meeting highlights include:

- Updates from ACCP Board of Regents
- PRN committee announcements
- Presentations from our student and resident award winners

Look out for an email with the Zoom link. Attendance is free and open to all members!

Annual Meeting Scientific Poster Session



Scientific Poster Sessions

Posters Displayed October 16-24, 2021

Interactive Session, I October 19, 2021

Interactive Session, II October 20, 2021

Sessions run from 6:00 to 8:00 PM CDT. Virtual viewing of posters is free and open to all members.



ACCP Adult Medicine PRN Announcements

Nominations Committee

AMED Name Dropper

Visit the AMED PRN Name Dropper via the link below to nominate colleagues for PRN officer positions or awards. The committee will review these submissions when the call for nominations comes out next year. Please consider adding your email address so the committee can contact you with any questions. Thanks for helping to recognize our colleagues! https://forms.gle/pzZyzSeqFT4W89oS9

ACCP Nominations

Nominations for the ACCP Awards and elected positions listed below are due by November 30th. More information on these awards & positions can be found at: https://www.accp.com/membership/nominations.aspx

Please contact the Nominations Committee chair at r.owens@wingate.edu for any help with navigating the nominations process. Our committee can review any nomination packet to provide feedback prior to submission to help strengthen the nomination. We would love to support an AMED PRN member's application in one of these awards or positions!

<u>ACCP Awards</u>: Robert M. Elenbaas Service, C. Edwin Webb Professional Advocacy, Russell R. Miller, Clinical Practice, and Education Award; Therapeutic Frontiers Lecture <u>Elected Positions</u>: President-Elect, Secretary, Regents, ACCP Foundation Trustees

External Affairs Committee

AMED PRN Member Spotlight

Consider nominating yourself or other ACCP AMED PRN members, residents, or student chapter representatives to be features on AMED PRN social media pages: <u>https://forms.gle/2qLdYRUaaf3hAJTL8</u>



AMED PRN Seed Grant Award Winners 2019



Jennie Jarrett, PharmD, BCPS, MMeddEd, FCCP

Do you mind? A mindfulness practice curriculum for the pharmacy workforce

Presented at 2020 ACCP Annual Meeting

Abstract citation: McQuade BM and Jarrett JB. Do you mind? A mindfulness practice curriculum for the pharmacy workforce. *J Am Coll Clin Pharm*. 2020;3:1616.

Sarah E. Petite, PharmD, BCPS

Evaluation of dipeptidyl peptidase-IV (DPP-IV) inhibitor use in hospitalized patients with diabetes

Published 2021

Full article citation: Petite SE and Hill MC. Evaluation of dipeptidyl peptidase-IV inhibitor use in hospitalized patients with diabetes. *Ann Pharmacother*. 2021. Epub ahead of print.





AMED PRN Award Winners 2021

Mentoring Award



Nicole L. Metzger, PharmD, BCPS

To honor an Adult Medicine PRN member whose outstanding teaching and guidance inspires students, residents, fellows, and others in the profession of pharmacy in a way that significantly impacts the careers of their mentees

Outstanding Paper of the Year Award 2021

Jamie Sebaaly, PharmD, BCPS

Direct Oral Anticoagulants in Obesity: An Updated Literature Review

In recognition of an outstanding contribution to the biomedical literature relevant to pharmacy practice in the area of adult medicine

Clinical Practice Award 2021

Anastasia L. Armbruster, Pharm.D., FACC, BCCP

In recognition of excellence in adult medicine pharmacy clinical practice



AMED PRN Training & Travel Award Winners 2021

Resident Research Award

"Teaching psychiatric disorders to pharmacy learners in South Africa via distance-based technology: development of an educational framework by a PGY-2 internal medicine pharmacy resident"

Erin McMahan, PharmD, PGY2 Internal Medicine, West Virginia University

"Medication access services provided by pharmacists decrease 30-day hospital readmissions" Heidi King, PharmD, PGY2 Internal Medicine, Emory University

Student Research Award

"Assessment of midodrine prescribing in the acute care setting" Amy Chan, PharmD Candidate 2022, Virginia Commonwealth University School of Pharmacy

"Characterization of sleep aid medication prescribing during transitions of care for hospitalized medical patients"

Sona Ghorashi, PharmD Candidate 2023, University of Maryland School of Pharmacy

Practitioner Award

Sarah Kessler, PharmD, BCPS, BCGP, Denver Health Medical Center

2021-2022 AMED PRN Officers

Jon P. Wietholter - Chair, West Virginia University School of Pharmacy Rachel W. Flurie - Chair-Elect, Virginia Commonwealth University School of Pharmacy Nicole L. Metzger - Secretary/Treasurer, Mercer University College of Pharmacy Carmen B. Smith - Immediate Past Chair, St. Louis College of Pharmacy

Member Accomplishments

Promotions

Ryan D'Angelo: Clinical Coordinator, Thomas Jefferson University Hospital.

Julie A. Murphy: Director of the Office of Undergraduate Research and the Office of Competitive Fellowships, University of Toledo.

Sarah Petite: Associate Professor of Pharmacy Practice (with tenure), University of Toledo College of Pharmacy and Pharmaceutical Sciences.

Susan M. Smith: Associate Professor of Pharmacy, Wingate University.

Taylor Steuber: Associate Clinical Professor, Auburn University Harrison School of Pharmacy.

Awards

Paul Dobesh: Outstanding Teaching Award, University of Nebraska Medical Center.

Eliza Dy-Boarman: Experiential Education Section Award for Excellence in Experiential Education, American Association of Colleges of Pharmacy.

Eliza Dy-Boarman: Rho Chi Faculty Award, Drake University Rho Chi Chapter.

Meredith Howard: 2021 HSC Faculty Achievement Award, University of North Texas Health Science Center, College of Pharmacy Finalist.

Melanie M. Manis: Faculty Preceptor of the Year, Samford University McWhorter School of Pharmacy.

Manis MM, Cimino L, Dugan BD, Brown SA, **Kyle JA**, et al. Best Poster, Assessing pharmacists' need for insulin pump and continuous glucose monitoring (CGM) education in Alabama. Presented at: Alabama Society for Health System Pharmacists (ALSHP); 2021 Summer Meeting; Pensacola, FL.

Andrew Miesner: C. Boyd Grandberg Professional Leadership Award, Drake University College of Pharmacy & Health Sciences.

Ashley Otto: Assistant Residency Program Director, PGY2 Internal Medicine, Mayo Clinic-Rochester.

Taylor Steuber: Auburn University Research Excellence Award.

Alexandra W. Tatara: Stanley Wyman Award, Massachusetts General Hospital Department of Medicine Internal Medicine Residency Program.



Grants

Wes Lindsey, **Taylor D. Steuber**, Shahariar Mohamed Fahim, Adelia Grabowsky. Drug Effectiveness Review Project: Pharmaceutical Treatments for Transfusion Dependent Beta Thalassemia Systematic Review. Center for Evidence-based Policy, Oregon Health and Science University. Contract Amount: \$50,000. Funded March 2021.

Wendy St. Peter:

Co-investigator, 1R01DK124333-01A1 Immobilized phosphate affinity material for the treatment of hyperphosphatemia. NIDDK. Contract Amount: \$343,902. Funded September 2020-August 2025. Principal investigator, Reduce Medication-Related Disparities in African American Patients with Chronic Kidney Disease. Office of Development and Technology, University of MN. Contract Amount: \$37,500. Funded August 2021-July 2022.

Publications

Adams KK, McManus D, Topal J, et al. Re-evaluating aztreonam and ceftazidime hypersensitivity: fraternal not identical twins. J Antimicrob Chemother 2021 Jun 30. [Epub ahead of print]

Adams KK, Machnicz M, Sobieraj DM. Initiating buprenorphine to treat opioid use disorder without prerequisite withdrawal: a systematic review. Addict Sci Clin Pract 2021;16:36.

Shah S, **Adams K**, Merwede J, et al. Three is a crowd: clinical outcomes of a twice daily versus a thrice daily metronidazole dosing strategy from a multicenter study. Anaerobe 2021 May 6. [Epub ahead of print]

Nardolillo JA, **Marrs JC**, **Anderson SL**, et al. Retrospective cohort study of statin prescribing for primary prevention among people living with HIV. JRSM Cardiovasc Dis 2021;10:20480040211031068.

Cornelison P, **Marrs JC**, **Anderson SL**. Clinical pharmacist outreach to increase statin use for patients with cardiovascular disease in a safety-net healthcare system. Am Health Drug Benefits 2021;14:63-9.

White BM, **Anderson SL**, **Marrs JC**. Antihypertensive prescribing patterns and hypertension control in females of childbearing age. Am J Health Syst Pharm 2021;78:1317-22.

O'Brien K, Badowski M, Bartoo AS, Peppard W, Schwarz K, Sharpe A, **Austin Szwak J.** Determining support for and barriers to pharmacist-driven research: results of a national survey. J Am Coll Clin Pharm. [In press]

Boylan PM, Santibañez M, Lounsbury N, et al. A nonthrombotic pulmonary embolus caused by polyalkylimide dermal filler: a case report and literature review of medication management. J Am Pharm Assoc 2021;61:324-31.

Cutshall BT, **Tatara AW**, Upadhyay N, Adeola M, Putney D, **Ruegger M**. Evaluating time to in-hospital venous thromboembolism in obese patients. J Pharm Pract 2021;34:190-8.



Dobesh, PP. Anticoagulation. In: 2021 Updates in Therapeutics[®]: Pharmacotherapy Preparatory Review and Recertification Course. Lenexa, KS: American College of Clinical Pharmacy, 2021.

Dobesh, PP. Anticoagulation. In: 2021 Cardiology Pharmacy Preparatory Review and Recertification Course. Lenexa, KS: American College of Clinical Pharmacy, 2021.

Beavers CJ, Effoe SA, **Dobesh PP**. Selatogrel: a novel subcutaneous P2Y12 inhibitor. J Cardiovasc Pharmacol 2021.

Dering-Anderson AM, Mone MA, **Dobesh PP**. When the simulation becomes real. Am J Pharm Educ 2021 Jul 22. [Epub ahead of print]

The INSPIRATION Investigators. Intermediate-dose versus standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to the intensive care unit: 90-day results from the INSPIRATION randomized trial. Thromb Haemost 2021.

The INSPIRATION Investigators. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: The INSPIRATION randomized clinical trial. JAMA 2021;325:1620-1630.

Dobesh PP, Kernan MM, Lueschen JJ. Direct oral anticoagulants in the treatment of venous thromboembolism: use in patients with advanced renal impairment, obesity, or other weight-related special populations. Semin Respir Crit Care Med 2021;42:233-49.

Bryant GA, **Dy-Boarman EA**, Herring MS, et al. Use of a script concordance test to evaluate the impact of a targeted educational strategy on clinical reasoning in advanced pharmacy practice experiential students. Curr Pharm Teach Learn 2021;13:1024-31.

Dy-Boarman EA, Bryant GA, Herring MS. Faculty preceptors' strategies for teaching clinical reasoning skills in the advanced pharmacy practice experience (APPE) setting. Curr Pharm Teach Learn 2021;13:623-7.

Skrupky LP, **Dy-Boarman EA**, Gurgle HE, Isaacs AI, McCreary EK, **Nisly SA**, Paloucek F, Peterson DM, Smith A, Schramm GE. Letters of reference for PGY1 pharmacy residency candidates: a survey of residency program directors and opinion statement. J Am Coll Clin Pharm 2021;4:379-89.

Froomkin J, Knoebel RW, Dickerson D, Soni H, **Szwak J.** Impact of ketamine in the management of painful sickle cell disease vaso-occlusive crisis. Hosp Pharm 2021 Mar 6. [Epub ahead of print]

Gibson CM. Chronic Care in Cardiology. In: 2021 Updates in Therapeutics[®]: Pharmacotherapy Preparatory Review and Recertification Course. Lenexa, KS: American College of Clinical Pharmacy, 2021.

Garcia B, **Gonzalez J**, Chaudhry S. Clinical outcomes for telavancin for salvage therapy in methicillin-resistant Staphylococcus aureus bacteremia: a case series. Infect Dis Clin Pract. [In press]



Deville R, Fellers CM, **Howard ML**. Lessons learned pivoting to a virtual OSCE: Pharmacy faculty and student perspectives. Curr Pharm Teach Learn 2021 Jun 20. [Epub ahead of print]

Howard ML, Atanda A, Gaviola ML. A multi-pronged approach to teaching end-of-life care to student pharmacists. J Am Coll Clin Pharm 2021;4:498-506.

Manis MM, Cummins L, **Kyle JA**, et al. Successful use of apixaban in Paget-Schroetter syndrome in a pediatric patient. J Pediatr Pharmacol Ther 2021;26:508-11.

Butler JA, Kassel L, **Miesner AR**, Grady SE, **Wall GC**. Incidence of a negative hidden curriculum, cynicism, and burnout within pharmacy resident education: a nationwide survey. Curr Pharm Teach Learn 2021;13:922-7.

Mihm AE, **Eudaley ST**, **Szwak J**, et al. Preparing for post-graduate year one pharmacy residency interviews: a focus on clinical knowledge and problem-solving assessments. Am J Health Syst Pharm 2021 May 29. [Epub ahead of print]

Moore DC, Thompson D. A review of the Bruton Tyrosine Kinase inhibitors in B-cell malignancies. J Adv Pract Oncol 2021;21:439-47.

Vadehra D, Pallas CR, **Moore D**, et al. Observed survival benefit with limited exposure of durvalumab in unresectable stage III non-small cell lung cancer at a large community-based institution. J Clin Oncol 2021;39(suppl 15):e20539.

Wooten KM, Arnall JR, Bowser KM, Pennell LJ, Wade-Davis JN, Olin JL, Taylor M, **Moore DC.** Publication rates of hematology/oncology abstracts presented at major pharmacy association meetings. J Oncol Pharm Pract 2021 Mar 27. [Epub ahead of print]

Hamadeh IS, **Moore DC**, Martin A, et al. Transition from intravenous to subcutaneous daratumumab formulation in clinical practice. Clin Lymphoma Myeloma Leuk 2021;21:470-5.

Arnall JR, Tran T, Elmes J, Downing L, DiSogra K, **Moore DC.** Comparative utilization and efficacy of thrombopoietin receptor agonists in relapsed/refractory immune thrombocytopenia. Am J Ther 2020 Jan 8. [Epub ahead of print]

Murphy JA, Curran BM, Gibbons WA 3rd, et al. Adjunctive phenobarbital for alcohol withdrawal syndrome: a focused literature review. Ann Pharmacother 2021 Mar 7. [Epub ahead of print]

Kinney EM, Vijapurapu S, Covvey JR, **Nemecek BD**. Clinical outcomes of concomitant rifamycin and opioid therapy: a systematic review. Pharmacotherapy 2021;41:479-89.

Cawoski JR, DeBiasio KA, Donnachie SW, Timanus EA, Zimmerman DE, Guarascio AJ, Montepara CA, Covvey JR, **Nemecek BD**. Safety and efficacy of intravenous hydralazine and labetalol for the treatment of asymptomatic hypertension in hospitalised patients: A systematic review. Int J Clin Pract 2021;75:e13991.



Buck MM, Haddon AM, Paneccasio A, Skoloda DJ, Zimmerman DE, Guarascio AJ, **Nemecek BD**, et al. Safety and efficacy of rivaroxaban and apixaban in patients with increased body mass: a systematic review. Clin Drug Investig 2021;41:353-69.

Nisly SA, Guzik B, Cunha A, Sturdivant B, Brennan L, **Sebaaly J**, **Smith S.** Concentrated learning experiences across two different health-systems. Innov Pharm 2021;12:10.24926/iip.v12i1.3374.

Mihm AE, Hicklin HE, Cunha AL, **Nisly SA**, et al. Direct oral anticoagulants versus warfarin for the treatment of left ventricular thrombosis. Intern Emerg Med 2021 Jun 24. [Epub ahead of print]

Nisly SA, Mihm A, Gillette C, et al. Safety of direct oral anticoagulants in patients with mild to moderate cirrhosis: a systematic review and meta-analysis. J Thromb Thrombolysis 2021 Mar 16. [Epub ahead of print]

Smith S, **Sebaaly J**, Brennan L, Haltom W, Meade L, **Nisly SA**. Accomplishing CAPE domain 3 during APPE rotations: student perceptions J Pharm Pract 2021. [Epub ahead of print]

Otto A, **Pecora Fulco P**. A retrospective evaluation of highly active antiretroviral therapy simplification in patients with end-stage renal disease receiving hemodialysis. Int J STD AIDS 2021;32:963-7.

Otto AO, Rivera CV, Zeuli JD, et al. Hepatotoxicity of contemporary antiretroviral drugs: a review and evaluation of published clinical data. Cells 2021;10:1263.

Smith SM. Yarn and thread, blessings ahead. Christianity and Pharmacy 2021;24:5-8.

Smith SM, **Sebaaly J**, Brennan L, Haltom W, Meade L, **Nisly SA**. Accomplishing CAPE Domain 3 During APPE Rotations: Student Perceptions. J Pharm Pract 2021 Mar 19. [Epub ahead of print]

Walkerly A, Neugebauer RE, Misko B, Shively D, Singh S, Chahda B, Dhanireddy S, King K, Lloyd M, Fosnight S, Costello M, Palladino C, **Soric MM**. Prevalence, predictors, and trends of opioid prescribing for lower back pain in United States emergency departments. J Clin Pharm Ther 2021;46:698-704.

Soric MM. Lost in translation: What residency program directors really want from references. J Am Coll Clin Pharm 2021;4:270.

Zhao JZ, Weinhandl ED, Carlson AM, **St. Peter WL.** Glucose-lowering medication use in CKD: Analysis of US Medicare Beneficiaries between 2007 and 2016. Kidney Med 2020;3:173-82.e1.

Johansen KL, Chertow GM, Foley RN, Gilbertson DT, Herzog CA, Ishani A, Israni AK, Ku E, Tamura MK, Li S, Li S, Liu J, Obrador GT, O'Hare AM, Peng Y, Powe NR, Roetker NS, **St. Peter WL**, et al. US Renal Data System 2020 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2021;77(4 suppl 1):A7-A8.

Delgado C, Baweja M, Ríos Burrows N, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey-Mims MM, Roberts GV, **St. Peter WL**, et al. Reassessing the inclusion of race in diagnosing kidney diseases: an interim report from the NKF-ASN Task Force. J Am Soc Nephrol 2021;32:1305-17.



Delgado C, Baweja M, Ríos Burrows N, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey-Mims MM, Roberts GV, **St. Peter WL**, et al. Reassessing the inclusion of race in diagnosing kidney diseases: an interim report from the NKF-ASN Task Force. Am J Kidney Dis 2021;78:103-15.

St. Peter WL, Aungst TD. Twenty-first century solutions to increase medication optimization and safety in kidney transplant patients (invited editorial). Clin J Am Soc Nephrol 2021;16:679-81.

Hall RK, Morton S, Wilson J, Ephraim P, Boulware L, **St. Peter W**, et al. Risks associated with continuation of potentially inappropriate antihypertensive medications in older adults receiving hemodialysis. BMC Nephrol 2021;22:232.

Williams B, Muklewicz J, **Steuber TD**, et al. Comparison of inpatient standard-of-care to outpatient oritavancin therapy for patients with acute uncomplicated cellulitis. J Pharm Pract 2021 Jun 3. [Epub ahead of print]

Nixon CG, **Steuber TD.** You cannot always warfarwin: a case of significant INR fluctuation with brand to generic conversion of warfarin. Eur J Med Case Rep 2021;5:106-8.

Steuber TD, Andrus MR, Wright BM, et al. Effect of interprofessional clinical debates on attitudes of interprofessional teams. PRIMER 2021;5:14.

Thiriveedi M, **Steuber TD**, Hasan M, et al. Infliximab-induced lupus causing pericarditis: a case report and review of the literature. J Gen Intern Med 2021;36:2134-8.

Cabri A, Barsegyan N, Postelnick M, Nguyen V, **Szwak J**, et al. Pharmacist intervention on prescribing errors: development of a standardized approach in the inpatient setting. Am J Health Syst Pharm 2021 Jul 20.

Yun S, Sevinsky R, Spracklin T, **Tatara A**, et al. Characterization of apixaban bleeding rates correlated with dosing in patients with chronic kidney disease. Proc (Bayl Univ Med Cent) 2021 Jun 4. [Epub ahead of print]

Nguyen SN, **Ruegger MC**, Salazar E, Dreucean D, **Tatara AW**, et al. Evaluation of anti-Xa apixaban and rivaroxaban levels with respect to known doses in relation to major bleeding events. J Pharm Pract 2021 Apr 12. [Epub ahead of print]

Cheung F, Doherty S, **Tatara A**. Ketamine in refractory cyclic vomiting syndrome: a case report and review of the literature. J Pharm Pract 2021 Apr 5. [Epub ahead of print]

Van Prooyen AM, Hicks JL, Lin E, et al. Evaluation of an inpatient pharmacy consult on discharge medications in bariatric surgery patients. J Pharm Pract 2021 Jul 6. [Epub ahead of print]

White B, Snyder H, Van Berkel Patel, M. Evaluation of medications used for hospitalized patients with sleep disturbances: a frequency analysis and literature review. J Pharm Pract 2021 Jun 7. [Epub ahead of print]



Wietholter JP, Sizemore J, Piechowski K. Crushing of deutetrabenazine tablets limited to individual case. Am J Health Syst Pharm 2021 Mar 25. [Epub ahead of print]

Other Notable Achievements

Sarah Nisly: Earned M.Ed. with a focus in Measurement, Evaluation, Statistics, & Assessment, University of Illinois Chicago.

Sarah L. Anderson: Started a new job as a Scientific Director, Clinical Care Options.

Caitlin Gibson: Started a new job as Associate Professor, Virginia Commonwealth University School of Pharmacy



Update on Asthma Management With a Focus on Inhaled Corticosteroids

Ellen Berkley, PharmD, PGY1 Ambulatory Care Resident, UC Davis Health Kathie Le, PharmD, BCPS, Senior Clinical Pharmacist UC Davis Health, Associate Professor, UCSF School of Pharmacy

Asthma is a chronic disease characterized by airway inflammation and symptoms such as coughing, wheezing, shortness of breath, and chest tightness. It affects nearly 25 million individuals across the United States and around 300 million people worldwide.¹ Although asthma currently does not have a cure, it is highly manageable with treatment, allowing individuals living with asthma to lead a completely functional life.² Inhaled corticosteroids (ICS) have been the cornerstone of asthma treatment regimens since they were first introduced in the 1970s.³

This review article focuses on the recent treatment updates of asthma in individuals ages 12 years and older. Guidance for asthma treatment has largely come from the Global Initiative for Asthma (GINA) report,⁴ and the National Asthma Education and Prevention Program (NAEPP) guidelines.⁵ The GINA has been making regular updates and the NAEPP recently published a 2020 update to the 2007 guidelines.⁶ Based on several research studies that have come out in the last decade, there are some key differences between NAEPP and GINA treatment recommendations that warrant attention.

Studies have elucidated the benefits of ICS on asthma morbidity and mortality, primarily due to the anti-inflammatory effects in the airways, leading to their strongly recommended use in persistent asthma.⁷ In fact, the START study found that early intervention with ICS-based treatment lowered the risk of exacerbations even in mild asthma and those with low baseline symptom burden.⁸ The effect of ICS on lung function seems to be related to reducing asthma exacerbations, which can lead to structural lung function decline and airway remodeling. It is well known in the literature that consistent use of low-dose ICS reduces risk of death from asthma and that discontinuation of ICS can be dangerous.^{9,10} Despite the availability of efficacious treatment, achieving optimal asthma control remains challenging for many patients. Optimal asthma control consists of not only addressing symptom burden and perceived functional limitation, but also minimizing the risk of asthma exacerbations and subsequent lung function deterioration.¹¹ Poor adherence is frequently the most common reason for uncontrolled asthma across all asthma severities.¹² Since patients with mild asthma can have a low symptom burden, many resort to only using a reliever inhaler as needed (PRN), in most cases, a short acting beta agonist (SABA). Therefore, oftentimes patients receive no anti-inflammatory medication to reduce their risk of exacerbation and help with the underlying disease control.

Four studies evaluated the use of an ICS-containing reliever, budesonide-formoterol, in reducing asthma exacerbation risk.^{12–15} The first two randomized, controlled studies were SYmbicort Given as needed in

Mild Asthma (SYGMA) 1 and (SYGMA) 2, while the other two studies were open label design, PRACTICAL and Novel START, to simulate real-world practice.

SYGMA 1 randomized patients to one of three treatment groups: twice daily placebo plus PRN terbutaline (SABA), twice daily placebo plus PRN budesonide-formoterol (ICS-LABA), and twice daily budesonide (ICS) maintenance plus PRN terbutaline (SABA).¹² For the primary outcome, symptom burden, measured in mean percentage of weeks with well-controlled asthma, SYGMA 1 found that while PRN ICS-LABA was superior to PRN SABA, it was inferior to ICS maintenance therapy.¹² Although PRN ICS-LABA was inferior to ICS maintenance (but superior to PRN SABA) in terms of symptom control, adherence to ICS was 78.9%, which is not reflective of clinical practice where adherence can be below 35%.¹⁶ The study also looked at annual rate of severe exacerbations and found that PRN ICS-LABA was superior to PRN SABA and no different than ICS maintenance therapy.¹²

SYGMA 2, parallel to SYGMA 1, was initiated based on patients' poor adherence to ICS and subsequent reliance on SABAs in mild asthma. SYGMA 2 trial had a more pragmatic study design, in that investigators did not include daily reminders to use maintenance medication. As a result, adherence was lower than in SYGMA 1 at around 63%, yet still higher than in the real-world.¹³ SYGMA 2 randomized patients to one of two treatment groups: twice daily placebo plus PRN budesonide-formoterol (ICS-LABA), or twice daily budesonide (ICS) maintenance plus PRN terbutaline (SABA).¹³ For the primary outcome, annual rate of severe exacerbations, with a prespecified noninferiority limit of 1.2, SYGMA 2 found that PRN ICS-LABA was noninferior to ICS maintenance therapy.¹³ This was consistent with the results of SYGMA 1. Additionally, PRN ICS-LABA was inferior to ICS maintenance therapy with respect to secondary outcomes that measured symptom control.¹³ For example, one test used to assess symptom burden was the Asthma Control Questionnaire–5 (ACQ-5) that uses a scale from 0 (no impairment) to 6 (maximum impairment). The ACQ-5 score decreased (indicating less impairment) more in the ICS maintenance group than the PRN ICS-LABA group.¹³ However, these differences were smaller than the accepted minimal clinically important differences.

The Novel START extends the findings of the SYGMA trials with an open-label design that reflects real-world practice.¹⁴ Novel START randomized patients to one of three treatment groups: PRN albuterol (SABA), twice daily budesonide (ICS) maintenance plus PRN albuterol (SABA), or PRN budesonide-formoterol (ICS-LABA).¹⁴ No strategies were offered to improve adherence, unlike in many clinical trials, including SYGMA 1. For the primary outcome, annual rate of asthma exacerbations, Novel START found that PRN ICS-LABA was lower than PRN SABA and no different than ICS maintenance therapy. The number of severe exacerbations was lower with PRN ICS-LABA than with both PRN SABA and ICS maintenance therapy. For other secondary outcomes that measured symptom control, the ACQ-5 was lower in the PRN ICS-LABA group than PRN SABA, but higher than in the ICS maintenance group.¹⁴

Overall, neither SYGMA studies found a significant difference in severe exacerbations between PRN ICS-LABA and ICS maintenance therapy plus PRN SABA, whereas the Novel START study found fewer

severe exacerbations with PRN ICS-LABA compared to ICS maintenance therapy plus PRN SABA, perhaps related to capturing the suboptimal real-world adherence with an open-label design.¹⁴

The PRACTICAL study built on the findings from both SYGMA trial and Novel START trial.¹⁵ PRACTICAL randomized patients to one of two treatment groups: PRN budesonide-formoterol (ICS-LABA) or twice daily budesonide (ICS) maintenance plus PRN terbutaline (SABA).¹⁵ For the primary outcome, rate of severe exacerbations, PRN ICS-LABA was superior to ICS maintenance therapy. PRN ICS-LABA also found a longer time to first severe exacerbation than ICS maintenance therapy.¹⁵ For measures of symptom control such as ACQ, there was no statistically significant difference in asthma control with PRN ICS-LABA compared to ICS maintenance therapy.¹⁵ This is slightly different from the previous three studies, which reported mildly higher measures of symptom burden with PRN ICS-LABA compared with maintenance ICS therapy.

The open-label designs of both the PRACTICAL and Novel START studies complemented the SYGMA studies, providing better evidence of real-world effectiveness.¹⁷ Although the results in terms of ongoing asthma symptom control were slightly better for the ICS maintenance regimen compared with PRN ICS-LABA, ICS adherence is a major barrier, especially in patients with mild asthma who have overall lower symptom burden, which would classify patients as Step 1 or 2 in the treatment algorithms (Table 1).

In the SYGMA trials, the relative rate of severe exacerbations with PRN ICS-LABA therapy compared to ICS maintenance therapy was noninferior, while in both the PRACTICAL study and the Novel START study, the relative rate of severe exacerbations was lower with PRN ICS-LABA compared with ICS maintenance therapy (31 vs 56%, respectively).^{14,15} These findings suggest that the use of a PRN reliever that contains ICS (via the co-formulation with faster acting formoterol) for patients that experience any symptoms, reduces the risk of severe exacerbation.

Overall, the findings from these four studies have led to the significant change in recent GINA reports, suggesting PRN budesonide-formoterol as the preferred reliever treatment, rather than PRN SABA in adults with mild asthma.^{4,12–15} PRN budesonide-formoterol reduces the risk of most serious outcomes such as exacerbations and subsequent lung function decline in comparison to both PRN SABA alone and ICS maintenance plus PRN SABA at 17% to 25% of the daily ICS dose of ICS maintenance therapy, leading to less side effects and cost burden.⁷ This is especially relevant in the United States, where the average cost of an ICS inhaler is approximately \$218 per month, and widespread insurance coverage of these preferred treatments is lacking.

NAEPP does not distinguish preferred reliever treatment, while GINA lists daily maintenance ICS monotherapy with PRN SABA as an alternative to preferred therapy with PRN ICS-formoterol, largely on the basis of the real-world evidence of non-adherence rates. Rather than publish guidelines, GINA provides recommendations for clinicians to consider in order to individualize disease management. The NAEPP guidelines 2020 update focused on several key issues, one of which was the appropriate level of treatment for mild persistent asthma.^{6,18} The recommendation was "conditional", to either use daily ICS plus PRN SABA or to use both ICS and PRN SABA when symptoms occur. NAEPP based the

recommendation on the findings from two open-label trials, PRACTICAL and Novel START. These studies support the use of PRN ICS in mild asthma, with a preference for PRN ICS-formoterol. This more closely aligns with the GINA 2020 report than the NAEPP guidance for patients with intermittent and mild persistent asthma. GINA combines "intermittent" and "mild persistent asthma," citing an outdated classification and false assumption that low symptom burden would not yield benefits from ICS treatment. In fact, patients with mild asthma had similar exacerbation rates and risks of airway remodeling compared to patients with moderate, persistent asthma. The finding helped justify the key distinction in GINA to no longer suggest PRN SABA monotherapy to manage mild asthma. The PRACTICAL and Novel START trials demonstrated that for patients with mild to moderate asthma, PRN ICS-formoterol for symptom relief was more effective at preventing severe exacerbations than low-dose ICS maintenance plus PRN SABA.^{14,15} Overall, this supports the recommendation for patients with mild asthma to use PRN ICS-formoterol as the preferred regimen to daily low-dose ICS.¹⁵

While GINA updates focus largely on mild asthma, there is strong evidence in moderate persistent asthma for the use of ICS-formoterol as a single maintenance and reliever therapy (MART).¹⁹ MART is an approach where patients use ICS-formoterol in a single inhaler for both daily maintenance and a reliever for symptoms. Formoterol is the only Long-Acting Beta Agonist (LABA) that can be used in combination with an ICS in MART due to its fast onset and sustained duration of action to help with symptom relief, while the ICS helps treat the underlying inflammation. It is well known that treatment with LABAs (formoterol or salmeterol) yields better symptom control and lung function than SABAs.²⁰ In addition, formoterol, unlike other LABAs, has a fast onset of action, which makes it suitable as a reliever. This is an important concept that pharmacists are well positioned to educate the patient care team when making treatment recommendations. MART has been shown to reduce severe exacerbations and provide similar if not better asthma control than higher fixed doses of ICS-formoterol or ICS plus as needed SABA, with an overall lower daily ICS dose. The NAEPP update also discussed the use of MART, ICS-formoterol as both controller and reliever, consistent with GINA 2020 guidance. While NAEPP guidance highlights the MART approach with ICS-formoterol for moderate persistent asthma, it also acknowledges concerns with the United States payer coverage of using more than one of the same inhaler per month.

Studies have shown that the addition of formoterol to ICS treatment reduced the risk of both mild and severe asthma exacerbations regardless of budesonide dose, consistent with the preference of adding a LABA to ICS in patients with persistent symptoms, before increasing the ICS dose.²¹ Further studies have confirmed the finding that combining ICS with LABA yields better asthma control than doubling the ICS dose.^{22,23} Literature has shown that when stepping up ICS monotherapy, there is a dose-response relationship increasing from low to medium doses, but diminishing marginal benefit when increasing to higher doses. Safety concerns with high-dose ICSs potentially outweigh the clinical benefit. Therefore, when managing asthma, a step-up ICS approach is best when the ICS is already combined with LABA and used daily for maintenance and as needed for symptom relief in a single inhaler, re-emphasizing the utility of MART and using a lower ICS dose to maximize the risk versus benefit ratio while still decreasing risk of exacerbations.

In moderate to severe persistent asthma, ICSs are still first line, though many need additional maintenance treatments. Some patients may still have persistent symptoms and exacerbations even while on optimized treatment with ICS and LABA. When adding alternative treatments, factors such as cost, side effects, and marginal efficacy should be considered. The Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) study shows that use of tiotropium, a long-acting muscarinic antagonist (LAMA), was superior to doubling the ICS dose on symptom control and lung function for patients with uncontrolled asthma, also demonstrating similar effects to salmeterol, a LABA.²⁴ Both GINA and NAEPP updates suggest maximizing low to medium dose ICS therapy with combination LABA.²⁵ From there, GINA suggests a LAMA for patients with uncontrolled asthma who either cannot use a LABA or have been maximized on ICS-LABA treatment. Two clinical trials, PrimoTinA-asthma 1 and PrimoTinA-asthma 2, showed that the addition of tiotropium led to a reduction in severe exacerbations and asthma symptom worsening in patients with uncontrolled asthma despite maximized ICS-LABA, and in some patients, other maintenance therapies.²⁶ NAEPP's focused update also recommends the addition of a LAMA in uncontrolled asthma for patients who are optimized on ICS-LABA, unless the patient has a risk of glaucoma or urinary retention, the most common side effects of the medication. GINA's 2021 update also expands on the suggestion of adding tiotropium to include ICS-LABA-LAMA triple therapy for patients greater than or equal to 18 years in step 5 of their treatment algorithm. See Table 1 for preferred asthma treatment algorithms by NAEPP and GINA and for more information on treatment steps.

The use of LABAs has been controversial in asthma treatment history due to two large clinical trials, Serevent Nationwide Surveillance (SNS) trial and Salmeterol Multicenter Asthma Research Trial (SMART), that found an increased risk of asthma related deaths in patients on LABA maintenance therapy during a time when ICSs were not routine in maintenance therapy. Therefore in 2008, the FDA requested manufacturers of LABA containing medications to inquire further into the data. In 2010 per FDA request, large clinical trials found that ICS-LABA was noninferior to ICS alone with regards to asthma-related death.^{27,28} While safety was the primary outcome, a secondary outcome was looking at the efficacy of ICS-LABA in comparison to ICS monotherapy. Studies found that ICS-LABA was not associated with increased risk of death and also lowered the risk of severe exacerbation by 21% compared to ICS monotherapy, suggesting additional benefit from LABAs without increased risk of death.²⁹

Asthma treatment suggestions prefer ICS as the first line maintenance therapy for asthma, therefore the role of alternative medications such as Leukotriene Antagonists (LTRA)s montelukast and zafirlukast is less well defined. While studies suggest minimal real-world effectiveness between LTRA and ICS as a first line controller, and LABAs for add-on therapy to an ICS, there is caution when integrating LTRA into treatment regimens as they are not preferred in either NAEPP or GINA updates.³⁰ Additionally, GINA no longer suggests many of the historically used, now less desirable and available asthma medications such as cromolyn, nedocromil, and theophylline, but has included more literature on cutting-edge treatments such as biologics. Biologics are small molecules and antibodies that are immunomodulatory, targeting inflammatory pathways present in persistent asthma.¹⁹ For example, GINA suggests add-on therapy with omalizumab (anti-immunoglobulin E (IgE) antibody) in patients greater than or equal to 12 years old with

severe eosinophilic asthma. Promising data has been released on additional biologics such as anti-IL5 receptor antibody benralizumab, decreasing exacerbations and improving asthma symptoms in clinical trials, ZONDA, SIROCCO, and CALIMA. The addition of anti-IL4 receptor antibody, dupilumab has also demonstrated efficacy in pivotal trials. As more targeted therapies are coming out, further studies are necessary to demonstrate efficacy and safety and explain their role in asthma maintenance treatment.³¹

In summary, ICSs are the backbone therapy for asthma. GINA lays out the asthma treatment algorithms through two different tracks based on the choice of reliever. Track 1 is preferred, with low dose PRN ICS-formoterol as the reliever, while Track 2 is an alternative track with PRN SABA. From there, GINA refers to the preferred track 1 using MART with ICS-formoterol for both maintenance and reliever. Treatment can then be stepped up or down within a track using the same reliever at each step, or switched between tracks, according to patient-specific circumstances. NAEPP also highlights preferred and alternative recommendations, although does not specify different tracks based on the choice of reliever. The most important takeaways from both GINA and NAEPP updates are the utility of ICS regardless of asthma severity, the use of formoterol as the unique LABA in combination with ICS as the preferred reliever, and the use of LAMAs as add-on therapy in uncontrolled asthma despite optimized ICS-LABA therapy. While treatment algorithms differ in the details, the role of ICSs as anti-inflammatory powerhouses, even at low doses, is more well defined in decreasing exacerbations and subsequent lung function decline. It is important to utilize the literature to counsel patients on the benefits of these medications as well as continue aiding with adherence, inhaler technique, and environmental exposures

References available here

	NAEPP 2020 ⁶ preferred therapy	GINA 2021 ⁴ preferred therapy
Step 1 intermittent asthma	SABA as needed	 Low dose ICS-formoterol as needed (preferred Steps 1 and 2 combined)
Step 2 mild persistent asthma	 Daily low-dose ICS plus SABA as needed ICS and SABA as needed Alternative: Daily LTRA and SABA as needed Cromolyn, or nedocromil, or zileuton, or theophylline and SABA as needed 	 ICS and SABA as needed (Step 1) Daily low dose maintenance ICS plus SABA as needed (Step 2)
Step 3 moderate persistent asthma	 Low dose ICS-formoterol in single inhaler (MART) daily and as needed Alternative: Daily medium dose ICS and SABA as needed Daily low dose ICS-LABA or daily low-dose ICS plus LAMA or daily low-dose ICS plus LTRA and SABA as needed Daily low dose ICS plus theophylline or zileuton and SABA as needed 	 Low dose ICS-formoterol in single inhaler (MART) daily and as needed (preferred) Low dose ICS-LABA plus SABA as needed
Step 4	 Medium dose ICS-formoterol in single inhaler (SMART) daily and as needed Consult with asthma specialist if step 4 or higher Alternative Daily medium-dose ICS-LABA or daily medium-dose ICS plus LAMA and SABA as needed Daily medium-dose ICS plus LTRA or daily medium-dose ICS plus theophylline or daily medium-dose ICS plus zileuton and SABA as needed 	 Medium-dose ICS-formoterol in single inhaler (SMART) daily and as needed (preferred) Medium to high dose ICS-LABA plus SABA as needed
Step 5 moderate-severe persistent asthma	 Daily medium-high dose ICS-LABA plus LAMA and SABA as needed Alternative: Daily medium-high dose ICS-LABA or daily high-dose ICS plus LTRA and SABA as needed 	 Add on LAMA Refer for phenotypic assessment plus anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol/LABA
Step 6 Severe persistent asthma	 Daily high-dose ICS-LABA plus oral systemic corticosteroids plus SABA as needed Consider adding Asthma Biologics (eg. anti-IgE, anti-IL5, aunty-IL5R, anti-IL4/IL13) 	No Step 6

Article peer-reviewed and edited by Sarah E. Petite, PharmD, BCPS Associate Professor of Pharmacy Practice, The University of Toledo



Update on Direct Oral Anticoagulants in Obesity

Zachary Powers, PharmD Candidate 2022, Virginia Commonwealth University School of Pharmacy

For treatment of venous thromboembolism (VTE) the 2016 International Society on Thrombosis and Haemostasis (ISTH) guidelines raised some concerns for the use of direct oral anticoagulants (DOACs) in the morbidly obese. This population was historically underrepresented in clinical trials, which led to uncertainty in the guideline recommendations. The guidance suggested that DOACs should not be used in patients with a BMI > 40 kg/m² and a weight > 120 kg, because of this lack of clinical evidence and concerns for underdosing, and if they were to be used, that clinical decision making should be guided by measured peak and trough levels.¹

Since 2016, more data has been published, prompting the ISTH to publish an updated guidance. Recommendations by the ISTH are now DOAC-specific. For prevention and treatment of VTE, the ISTH suggests that standard doses of apixaban and rivaroxaban are appropriate options regardless of BMI and weight.² This comes from phase 3 and 4 clinical data, systematic review/meta-analyses, and pharmacokinetic/pharmacodynamic (PK/PD) studies. The evidence from phase 3 and 4 trials for the use in treatment of VTE with rivaroxaban and apixaban is summarized in table 1. Overall, the data from observational studies concluded at least similar efficacy and safety with rivaroxaban and apixaban, each compared to warfarin. Dabigatran, edoxaban, and betrixaban are still not suggested for VTE treatment and prevention in patients with BMI > 40 kg/m² or weight > 120 kg, as there is a general lack of clinical evidence or PK/PD data to support their use. Additionally, regularly following peak or trough drug-specific DOAC levels is not suggested because the research thus far has not shown a clinically significant relationship between laboratory values and disease outcomes.²

With the recent publication of clinical and PK/PD studies for the use of DOACs in obesity, the ISTH has updated some of its recommendations, broadening the choice of anticoagulants in this population. Pharmacists working on the front lines of healthcare can make interventions using the latest guidelines that may make the treatment and prevention of VTE in obese patients much more manageable.

Rivaroxaban			
Study	Efficacy	Safety	
Di Nisio M, et al. (2016) ³	No significant difference in recurrent VTE, for rivaroxaban vs. warfarin, in BMI \geq 35 at both 21 days (9/427	No difference in major bleeding for rivaroxaban vs. warfarin (5/426 [1.2%] vs. 7/432 [1.6%]; HR 0.71;	
Phase 3 EINSTEIN post-hoc analysis	[2.1%] vs. 4/434 [0.9%]; HR 2.22; 0.68–7.26) and 12 months (13/427 [3%] vs. 9/434 [2.1%]; HR 1.45;	0.22–2.24)	
<u>Population</u> BMI <u>≥</u> 35 kg/m²	0.62–3.39)		
N = 861	No difference in recurrent VTE for		

Table 1. Summary of clinical data for the efficacy and safety of rivaroxaban and apixaban for treatment of venous thromboembolism in obese patients

Wt: 120-140 kg N = 222 Wt ≥ 140 kg N = 81	rivaroxaban vs warfarin, in patients ≥120 to 140 kg (2/119 [1.7%] vs. 3/103 [2.9%]) and ≥140 kg (1/40 [2.5%] vs. 1/41 [2.4%])	
Costa OS, et al. $(2021)^4$ Observational study using electronic health records <u>Population</u> BMI $\ge 30 \text{ kg/m}^2$ N = 13510 BMI $\ge 35 \text{ kg/m}^2$ N = 7106	Rivaroxaban reduced recurrent VTE compared with warfarin at 3, 6, and 12 months (HR: 0.61 [0.51–0.72]; HR: 0.65 [0.55–0.77]; HR: 0.63 [0.54–0.74]) respectively Reduced risk of recurrent VTE BMI \geq 35 for rivaroxaban vs. warfarin at 3, 6, and 12 months (HR 0.60 [0.48–0.76]; HR 0.64 [0.51–0.81]; HR 0.63 [0.51–0.78]) respectively	No difference in major bleeding BMI \geq 30 at 3 months for rivaroxaban vs. warfarin (HR: 0.99 [0.68–1.44]) and at 12 months (HR: 1.00 [0.73–1.36]) Reduced risk of major bleeding in BMI \geq 35 for rivaroxaban vs. warfarin (HR at 3, 6, and 12 months of 0.99 [0.61–1.63], 0.85 [0.54–1.36], and 0.95 [0.64–1.43]) respectively
Perales IJ, et al. $(2020)^5$ Single-center retrospective study <u>Population</u> BMI $\ge 40 \text{ kg/m}^2 \text{ or}$ Wt $\ge 120 \text{ kg}$ N = 109	Similar 12-month rates of recurrent VTE for rivaroxaban vs. warfarin (2/47 vs. 4/62; p=0.61)	Similar outcomes in the 12-month composite of major and clinically relevant non-major bleeding for rivaroxaban vs. warfarin (3/47 vs. 2/62; p=0.26)
Kushnir M, et al. $(2019)^6$ Single-center retrospective study <u>Population for</u> <u>rivaroxaban</u> BMI $\ge 40 \text{ kg/m}^2$ N = 319 BMI $\ge 50 \text{ kg/m}^2$ N = 82	Similar rates of recurrent VTE for rivaroxaban vs. warfarin for BMI \ge 40 (3/152 [2.0%, 0.0–4.2] and 2/167 [1.2%, 0.0–2.9]) In patients with BMI \ge 50 there were no events of recurrent VTE (0/30) in those on rivaroxaban and two events (2/52) in those on warfarin (p=0.50)	Similar rates of major bleeding for rivaroxaban vs. warfarin in BMI ≥ 40 (2/152 [1.3%, 0.0–3.1] and 4/167 [2.4%, 0.1–4.7])
Spyropoulos AC, et al. (2019) ⁷	Similar risks of recurrent VTE (OR 0.99; 0.85–1.14) for patients with obesity treated with rivaroxaban	Similar risks of major bleeding (OR 0.75; 0.47–1.19) for patients with obesity treated with rivaroxaban



Retrospective study of administrative claims data	compared with VKA.	compared with VKA		
Population Morbid obesity per ICD codes N = 5780				
Apixaban				
Study	Efficacy	Safety		
Cohen A, et al. $(2021)^8$ Observational study of insurance claims <u>Population</u> BMI $\ge 40 \text{ kg/m}^2$ N = 19,751	Lower risk of recurrent VTE for apixaban vs. warfarin (5.3 vs. 8.1 per 100 person-years [HR 0.63; 0.52–0.78])	Lower risk of major bleeding for apixaban vs. warfarin (4.5 vs. 6.2 per 100 person-years [HR 0.70; 0.56–0.89])		
Kushnir M, et al. $(2019)^6$ Single-center retrospective study <u>Population for</u> <u>apixaban</u> BMI $\ge 40 \text{ kg/m}^2$ N = 214 BMI $\ge 50 \text{ kg/m}^2$ N = 62	Similar incidences of recurrent VTE for apixaban vs. warfarin (1/47 [2.1%; 0.0-6.3] vs. 2/167 [1.2%; $0.0-2.9$]. Patients with a BMI \ge 50 had similar rates of recurrent VTE (0/10 on apixaban and 2/52 on warfarin (p=0.53))	Similar incidences of major bleeding for apixaban vs. warfarin, in patients with a BMI \ge 40 (1/47 [2.1%, 0–6.3] vs. 4/167 [2.4%, 0–4.7] and a BMI \ge 50 (0/10 on apixaban and 2/52 on warfarin)		

References available here

Article reviewed and edited by Rachel W. Flurie, PharmD, BCPS Assistant Professor, Virginia Commonwealth University School of Pharmacy



Vancomycin Therapeutic Drug Monitoring

Amy R. Chan, PharmD Candidate 2022, Virginia Commonwealth University School of Pharmacy

The 2020 vancomycin dosing guidelines published in AJHP contain some notable differences from the previous iteration. One change in particular is that they no longer recommend trough-based management of vancomycin for serious methicillin-resistant staphylococcus aureus (MRSA) infections. The definition of serious MRSA infection includes bacteremia, infective endocarditis, meningitis, osteomyelitis, pneumonia, and sepsis. Previously, the 2009 guidelines recommended that serum trough concentrations of 15 to 20 mg/L be used as a surrogate marker for monitoring the ratio of area under the curve (AUC) to minimum inhibitory concentration (MIC).¹ Trough levels only ensure a minimum cumulative exposure at a single exposure point, whereas AUC is the integrated quantity of cumulative drug exposure over a defined interval and is known to be the primary PK/PD predictor of vancomycin efficacy.² With the revised guidelines, an individualized target AUC/MIC_{BMD} ratio of 400 to 600 (assuming a vancomycin MIC_{BMD} of 1 mg/L) should be achieved early within 24 to 48 hours to achieve clinical efficacy while improving patient safety.² Up to this point there has not been well described evidence that attainment of therapeutic trough values is linked with clinical success, although the practice of monitoring troughs has been widely implemented since its recommendation in 2009.³

The range of 15 to 20 mg/L was recommended because trough values over 15 mg/L will always achieve a 24-hour AUC value (AUC₂₄) \geq 400 mg·h/L, the threshold where vancomycin is considered to exhibit near maximal bactericidal activity against MRSA that has a MIC of 1 mg/L or less.^{3,4} Trough-based monitoring is problematic because trough values between 15 to 20 mg/L have considerable inter-patient variability in the upper bound of the AUC, reaching levels upwards of 1200 mg·h/L.⁴ This upper bound of AUC falls well into the range of 650-1300 mg·h/L where there is known to be increased risk of nephrotoxicity.² Trough levels are not entirely indicative of the relationship between vancomycin AUC and exposure-related nephrotoxicity, which makes it a poor clinical surrogate marker for monitoring therapy.

There have been studies validating the necessity for AUC-guided dosing in minimizing nephrotoxicity. Finch et al. found AUC monitoring had an approximately 50% decrease in rates of acute kidney injury (AKI) compared to trough monitoring (95% CI, 0.34-0.80; p=0.003).⁵ The trough-guided group had a mean trough of 14.2 mg/L and mean AUC₀₋₂₄ of 705 mg·h/L⁵. Notably, the mean trough was not in the target range of 15-20 mg/L, yet the mean AUC₀₋₂₄ was in the AUC range associated with nephrotoxicity. They also demonstrated that therapeutic AUC values can still be achieved at trough concentrations lower than those recommended in the 2009 guidelines, since the AUC-guided dosing group had a mean trough of 12.5 mg/L yet a therapeutic mean AUC₀₋₂₄ at 474 mg·h/L.⁵ Neely et al. in a 3-year prospective study showed that transitioning from targeting trough concentrations of 10 to 20 mg/L in year 1 to targeting AUC/MIC ratios ≥400 using Bayesian software in years 2 and 3 led to marked benefit with reduced nephrotoxicity, fewer patient drug sampling, and decreased overall length of therapy, while maintaining efficacy in eradicating infection. Their institution went from 19% therapeutic trough concentrations to 70% therapeutic AUCs (p<0.0001) during the conversion and also reduced nephrotoxicity rates from 8% with trough-based to 0% and 2% with AUC-guided dosing in years 2 and 3.6 These two pivotal studies informed us that shifting to AUC-guided dosing results in less vancomycin-associated AKI while maintaining efficacy, which led to the revised recommendation in the 2020 consensus statement.

A key factor that contributed to the previous recommendation to use a surrogate marker was the impracticality of AUC monitoring. AUC monitoring used to require the collection of multiple levels during a single dosing interval, which was simply too difficult to do in clinical practice. There are now two methods to estimate AUC that require limited PK sampling and are more clinically feasible than ever before. The

first is using Bayesian software programs to estimate vancomycin AUC using one or two vancomycin concentrations. This method, shown to be effective in the Neely et al. study, allows for rapid, real time monitoring within the first 24 to 48 hours of beginning treatment, since it does not require steady state serum vancomycin concentrations for assessment of AUC.² The second approach involves collecting two concentrations (usually a peak and a trough) and using first-order analytic PK equations to estimate AUC values. Regardless of which method is used, transitioning from trough-based to AUC-guided dosing and monitoring will require institutions to overcome many logistical barriers. Multidisciplinary education involving pharmacists, prescribers, nurses, phlebotomy, and laboratory staff on the rationale and required procedural changes for AUC/MIC based monitoring is critical for therapeutic drug monitoring to continue to improve and follow updated guidelines.⁷ As AUC-guided dosing and monitoring become more common, pharmacists may present continuing education, support implementation efforts, and conduct quality improvement projects to support their institution and ultimately benefit their patients.

References available here

Article reviewed and edited by Rachel W. Flurie, PharmD, BCPS Assistant Professor, Virginia Commonwealth University School of Pharmacy

