Adult Medicine PRN Fall Newsletter

Edited by Jon P. Wietholter, Pharm.D, BCPS and Kathleen K. Adams, Pharm.D, BCPS

VOLUME 15, ISSUE 2 FALL 2020

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Message from the Chair

Ryan E. Owens, Pharm.D, BCPS

Submitted: August 28, 2020

"Sometimes the bravest and most important thing you can do is just show up."
- Brené Brown

The past six months have been anything but ordinary in our personal and professional lives. Our daily work responsibilities, significantly altered. Our gatherings with friends and family, socially distanced. Our travel plans, cancelled. Despite all of these changes, we have continued to show up - for our patients, for our PRN, and for ourselves.

Pharmacists are essential workers and a variety of practice settings have been showcased through ACCP's Clinical Pharmacy in Action column and externally to the general public through media outlets. Our members have continued providing direct patient care (for both patients with and without COVID-19), conducting research, and educating pharmacy students/residents to enter the workforce as essential workers themselves in the near future. By exercising adaptability and creativity, we have managed to continue advancing patient care in the midst of a pandemic. Our collective efforts over the past several months have further highlighted that pharmacy services are not only essential, but valuable as well.

Our committees have also continued their work throughout the year to help advance our PRN initiatives. I especially appreciate the work of the Chairs and Vice-Chairs of all the committees as they managed to continue leading charges to push our PRN forward. A few of the new initiatives this year included:

- Student-led PRN Medicine Grand Rounds (led by Emmeline Tran and Tressa McMorris on the new Trainee Engagement Committee)
- Poster review service for PRN students (led by Ryan D'Angelo and Josh Gaborcik on the Walk Rounds Committee)
- Educational webinars for PRN members (led by Jamie Sebaaly and Sarah

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"ACCP ADULT MEDICINE PRN"

Congratulations to our 2020 ACCP AMED PRN Fellows!

Holly E. Gurgle, Pharm.D, University of Utah College of Pharmacy

Jon P. Wietholter, Pharm.D, BCPS, West Virginia University School of Pharmacy

Kessler on the External Affairs Committee)

·Emerging PRN member award for new practitioners < 5 years from terminal training or degree (led by Andrew Miesner and Nancy Yunker on the Nominations committee)

Carmen Smith & Jon Wietholter have been great resources in their officer positions while navigating PRN changes as well. The leadership of the PRN this year has been a collective effort and I am excited to see the PRN continue to grow under their leadership in subsequent years. I appreciate the opportunity to work with the various AMED PRN leadership teams over the past 3 years and look forward to continued involvement with the PRN in the future. When the call for committee volunteers occurs this fall, I encourage everyone to consider volunteering. While the work of our PRN may sometimes seem small, the work of our committee volunteers can have a large impact.

Most of all, I want to encourage everyone to continue to show up for themselves. Take the time to check in with yourself to assess how you are doing, both physically and emotionally. We cannot adequately take care of our patients' needs if we cannot take care of our own needs first. While the pandemic may have placed an increased demand on our professional lives, I believe it has also caused us to slow down in our personal lives, to reset our priorities and outlook. We may have spent more time outdoors, connecting with family or friends via technology, or taken up new hobbies. Regardless of how long this pandemic lasts, I hope we all continue to take the time to prioritize our personal wellbeing well beyond its end.

Thank you all for continuing to show up.

2020 ACCP Annual Meeting:

Adult Medicine PRN Save-the-Dates

Monday, October 26th, 2020

- Adult Medicine PRN Focus Session – Direct Oral Anticoagulant Use in Special Populations

  Streams Live 12:15 PM – 1:45 PM CDT

- Adult Medicine PRN Business Meeting and Networking Forum

  Streams Live 5:30 PM – 7:00 PM CDT

*****Please check the ACCP website for further details as they are released**

ADULT MEDICINE PRN ANNOUNCEMENTS

Nominations Committee

- While deadlines have come and gone for this year's PRN awards, did you know you can still place another PRN member's name into consideration for the 2021 PRN awards and PRN officer nominations? All you have to do is drop their name!

  Visit the AMED Name Dropper at tinyurl.com/AMEDnamedropper. It only takes a few seconds and lets us know who we should contact for self-nominations next year!

- Nominations for ACCP Awards are due November 30th. This includes prestigious awards such as the Parker Medal, Elenbaas Service Award, and C. Edwin Webb Advocacy Award. Contact andrewmiesner@gmail.com to get the Nominations Committee's assistance or find out more by going to https://www.accp.com/membership/nominations.aspx

- Nominations for ACCP Officers are also due November 30th. This includes President-Elect, Board of Regents, and ACCP Foundation Trustees. We want to see the AMED PRN represented! Contact andrewmiesner@gmail.com to get the Nominations Committee's assistance with your nomination!

Trainee Engagement Committee

- Join us for the 2020-2021 eJournal Club series! eJournal Clubs will start on September 16th and continue every third Wednesday of the month at 3 pm Eastern/2 pm Central/1 pm Mountain/ 12pm Pacific.

- Join us for the 2020-2021 Medicine Grand Rounds series! Students present interesting patient cases on a variety of medicine topics. Medicine Grand Rounds are held on the fourth Wednesday of most months at 3 pm Eastern/2 pm Central/1 pm Mountain/12 pm Pacific.

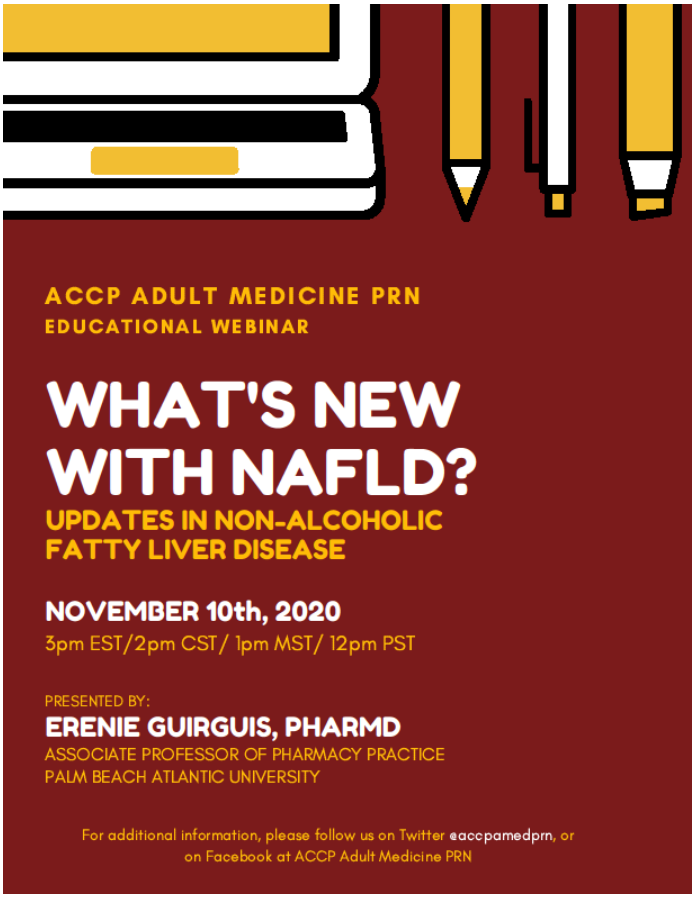
- Save the date for the 1st AMED PRN Virtual Scavenger Hunt held October 1st through October 26th. Winners will be entered into a drawing for gift cards to the ACCP Bookstore.

- Be on the lookout for opportunities to participate in educational programming for our trainees during the AMED PRN Business Meeting at the 2020 ACCP Annual Meeting.

ADULT MEDICINE PRN ANNOUNCEMENTS

External Affairs Committee

- Consider nominating yourself or other ACCP AMED PRN members, residents, or student chapter representatives to be featured on AMED PRN social media pages: https://forms.gle/yFmgHo36fziESWPw9



- On November 10th at 3 pm EST, please join us for a webinar by dialing into the conference line. When prompted, enter the Access Code followed by the pound key. To join the online meeting, click on the meeting link and follow the prompts to join the meeting. For 24/7 customer service please call 844-844-1322

  1. Dial into the conference:
  Dial-in Number for the US: (605) 472-5234 Access Code: 942723
  International Dial-in Numbers: https://www.freeconferencecall.com/wall/accpamedprn/#international

  ****Please make sure to mute yourself when joining to avoid background noise****

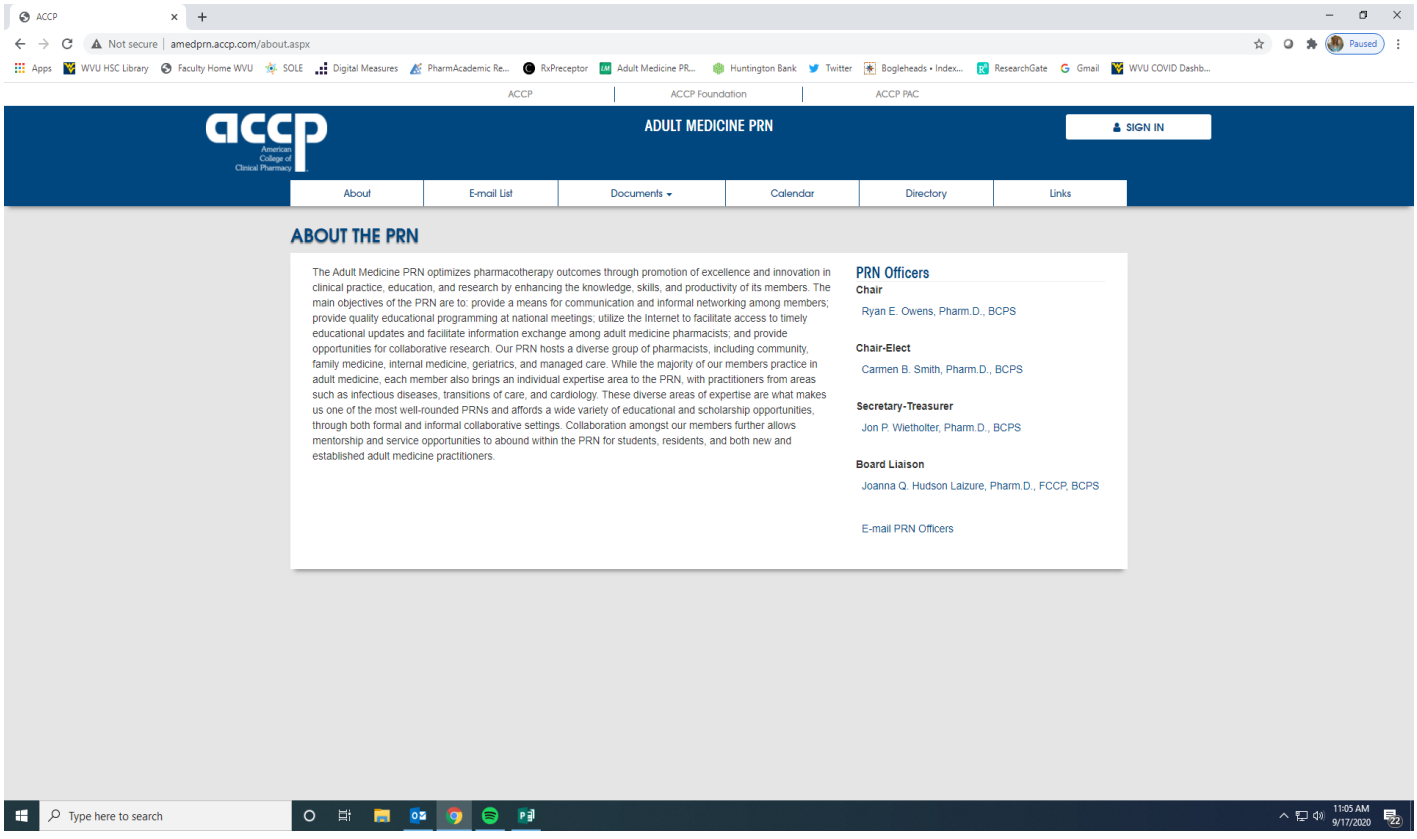
  2. Join the online meeting:
  Online Meeting Link: https://join.freeconferencecall.com/accpamedprn
  Online Meeting ID: accpamedprn

DID YOU KNOW???

- The ACCP AMED PRN page provides access to:
  - Past PRN newsletters, annual meeting minutes, grant applications, and PRN awards criteria
  - Guidelines, P&T documents, polices & procedures, presentations, and protocols submitted by AMED PRN members
  - A directory of all AMED PRN members

To access the PRN page:

1. Go to www.accp.com
2. Select “PRNs” and then “PRN Members”
3. Select the “Adult Medicine” PRN



***Additionally, all emails sent via listserv to the entire AMED PRN are archived at http://lyris.accp.com/read/login/. To login, simply use your ACCP login information.

Member Accomplishments 02/2020-08/2020

Promotions:

Meredith Howard, Pharm.D, BCPS, Promoted to Associate Professor, University of North Texas System College of Pharmacy

Julie A. Murphy, Pharm.D, FASHP, FCCP, BCPS, Promoted to Associate Professor with Tenure, University of Toledo College of Pharmacy and Pharmaceutical Sciences

Carmen Smith, Pharm.D, BCPS, Promoted to Associate Professor, Clinical Pharmacy, St. Louis College of Pharmacy

Awards:

Sarah Eudaley, Pharm.D, BCPS, *2020 Pharmacy Recent Alumnus Award Winner*, University of Tennessee

Andrew Miesner, Pharm.D, BCPS, *Health-System Pharmacist of the Year*, Iowa Pharmacy Association

Mate M. Soric, Pharm.D, BCPS, FCCP, *Top Downloaded Paper 2018-2019,* Journal of the American College of Clinical Pharmacy

Jon P. Wietholter, Pharm.D, BCPS, *2020 Excellence in Health Systems Pharmacy Award*, West Virginia Society of Health-System Pharmacists

Grants:

Kathleen Adams, Pharm.D, BCPS, University of Connecticut, Creating an inclusive climate within pharmacy practice, American Association of Colleges of Pharmacy Scholarship of Teaching and Learning, $4,000

Jennifer Austin Szwak, Pharm.D, BCPS, University of Chicago, COPD Virtual Medication Reconciliation and Education Pilot: COPD V-M(ED) Pilot, Bucksbaum Institute National Pilot Grant, $15,000

Jennie B. Jarrett, Pharm.D, BCPS, MMedEd, FCCP, University of Illinois at Chicago, Primary Care Training Enhancement: Residency Training in Primary Care (Substance use disorder and severe mental illness in rural and urban underserved communities), Health Resources and Services Administration, $2,500,000

Andrew Miesner, Pharm.D, BCPS, Drake University College of Pharmacy & Health Sciences, A Community Antibiogram and Prescriber-Focused Educational Intervention in Des Moines, Iowa, Society of Infectious Disease Pharmacists, $2057.90

Julie A. Murphy, Pharm.D, FASHP, FCCP, BCPS, University of Toledo College of Pharmacy and Pharmaceutical Sciences, Evaluation of Burnout among Pharmacy Residents in the United States, 2020-2021 ASHP Foundation New Practitioner Leadership Research Development Grant, $5,000

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Jarrett JB, Lounsbery JL. Trends in Clinical Pharmacist Integration in Family Medicine Residency Programs in North America. *Pharmacy (Basel)* 2020;8(3):E126.

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Kanmaz TJ, Culhane NS, Berenbrok LA, **Jarrett JB**, et al. Curriculum Crosswalk of the Core Entrustable Professional Activities for New Pharmacy Graduates. *Am J Pharm Educ* 2020 [Epub ahead of print].

Psenka TM, Freedy JR, Mims LD, DeCastro AO, Berini CR, Diaz VA, **Jarrett JB**, Steyer TE. A cross-sectional study of United States family medicine residency programme director burnout: implications for mitigation efforts and future research. *Fam Prac* 2020 Jul 23 [Epub ahead of print].

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Wietholter JP. Chapter 114: Vitamin B_{12} Deficiency. In: Pharmacotherapy Casebook: A Patient-Focused Approach. 11th ed. New York: McGraw-Hill, 2020: 305-307.

Fellowship:

Sarah L. Anderson, Pharm.D, FCCP, FASHP, BCPS, BCACP, University of Colorado, American Society of Health-System Pharmacists (ASHP)

Other Notable Achievements:

Lindsay M. Arnold, Pharm.D, BCPS, Awarded a faculty appointment as an Assistant Professor of Medicine at Tufts University School of Medicine

Sharon See, Pharm.D, BCPS, BCGP, FCCP, Elected Regent for ACCP

Sharon See, Pharm.D, BCPS, BCGP, FCCP, Board Certified in Geriatrics (BCGP)

Grant Sklar, Pharm.D, BCPS, Agency for Care Effectiveness, Ministry of Health (Singapore), Retiring after 21 years of working in Singapore and almost 30 years in multiple countries

Autumn Walkerly, Pharm.D, Member-at-Large for ACCP National Resident Advisory Committee for 2020-2021

Autumn Walkerly, Pharm.D, Featured in the Member Spotlight of the August ACCP Report Presentation: "How to prepare for the next step: overcoming impostor syndrome" at the Ohio Pharmacists Association Virtual 2020 Annual Conference

Brittany White, Pharm.D, BCPS, CACP, Certified Anticoagulation Care Provider through the Board of Anticoagulation Care Providers

Congratulations to our 2020-2021 ACCP Adult Medicine PRN Officers

- **Carmen B. Smith** — Chair
  St. Louis College of Pharmacy
- **Jon P. Wietholter** — Chair-Elect
  West Virginia University School of Pharmacy
- **Rachel Flurie** — Secretary/Treasurer
  Virginia Commonwealth University School of Pharmacy

Congratulations to our 2020-2021 ACCP Adult Medicine Award Winners

2020 Mentoring Award

- **Sarah L. Anderson**, Pharm.D, FCCP, FASHP, BCPS, BCACP — University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

2020 Outstanding Paper of the Year Award

- **Jacqueline L. Olin,** M.S., Pharm.D, BCPS, CDCES, FASHP, FCCP — Wingate University School of Pharmacy

The Value of Hindsight

Elizabeth Price, Pharm.D, MSCR, BCPS and Emmeline Tran, Pharm.D, BCPS

"Experience is the teacher of all things." – Julius Caesar

It can be extremely frustrating as you start out in your pharmacy career to hear the above quote, as experience is generally intimately connected to time. That being said, utilizing individuals who have built experience can provide insight. Below is a compilation of questions often asked by students and residents, and the responses from ACCP AMED PRN members regarding what they wish they would have known as a student and/or resident.

What can I do as a mentee to make the relationship with my mentor as beneficial as possible?
Any relationship takes work and the common phrase "what you put in is what you get out" also holds true. The dynamics of each mentor-mentee pairing will be unique, but in general, it is important to discuss, understand, and agree to the expectations and roles of each party. As a mentee, being receptive to feedback and assuming responsibility for your own growth and development are two qualities that have been identified in successful mentor-mentee relationships. It can oftentimes be perceived by mentees that they may be "bothering" their mentors; however, mentees should not be afraid to initiate the process and communicate specific needs to their mentors. Mentors are generally willing to help, but may not know when their mentees need it if it is not communicated. Moreover, self-reflection or self-assessment can help mentees be prepared to discuss their progress, obstacles, and action items with their mentors to make for more fruitful meetings.

What are some non-clinical resources I can utilize to enhance my personal and professional growth?
Podcasts are a great way to start the workday. When I want to feel motivated by success stories, I love turning on "Skimm'd from the Couch." There are some amazing interviews showcased on this podcast that leave me feeling motivated to tackle the day. I also turn on "Safe for Work" when I want to hear some sage advice on how to approach problems that one could encounter in any work environment, not just pharmacy. In addition to finding podcasts that motivate and educate you, I would also recommend reading books devoted to personal growth and development. Though there are many options available on the market today, my top three recommendations include: 1. Atomic Habits by James Clear, 2. The Obstacle is the Way by Ryan Holiday, and 3. Big Magic, by Elizabeth Gilbert. These happened to be books that resonated with me and I encourage you to find your own "Top 3" that help guide you, both personally and professionally.

How do I select my residency program rankings in preparation for "The Match?"
Even prior to the interview process, develop a spreadsheet that details each residency program to allow you to easily compare and contrast. Add columns for basic information, like type of institution, number of co-residents, and location. But also add columns for specific criteria you are looking for in a program like opportunities for publishing, distance from home, etc. You can also add columns for additional notes as you start to interview. Be extensive in your data collection and use this to guide your decision-making. Don't overthink and try to "outsmart" the matching system. Select your rankings based on where you feel will be the best fit.

How do I begin the process of finding my clinical research "niche?"
Having a specific interest area oftentimes helps provide the best avenue to finding your research niche—you definitely want the niche to be an area that you are passionate about, especially if you are going to be intimately involved with studying it! Like with most discoveries, your research niche may end up finding you rather than you finding it. You may have been exposed to a topic by a mentor or through a previous project (e.g. student or residency research projects). These exposures and experiences already give you a leg up in being the expert on the topic and having knowledge about remaining questions, feasibility, standards in definitions and outcomes, and clinical relevance. Moreover, things may align from a resource or collaboration standpoint that may make it more advantageous for you to pursue a specific research area. Overall, find something that piques your interest and be open to opportunities that can further enhance your ability to study it.

What are things that I should do in my first 3-5 years of practice in order to set myself up for success in the future?
I can wholeheartedly say I wouldn't be where I am today without my mentors and collaborators. Find individuals that inspire you. Seek out mentorship. Create close connections with individuals you can find yourself working closely with. These are the individuals that will be "your people" to advocate for you, support you, and help you achieve your goals.

Overview of 2019 ATS/IDSA CAP Guidelines

Madeline Belk, Pharm.D, Taylor Epperson, Pharm.D, BCPS, Sarah Niemi, Pharm.D, BCPS

"This update addressed several areas of antimicrobial stewardship in which pharmacists can directly impact practice, such as decreasing unnecessary antibiotic usage and appropriate antibiotic de-escalation in the era of rising antimicrobial resistance."

Introduction

Community acquired pneumonia (CAP) is an acute infection of the pulmonary parenchyma acquired outside of the hospital. CAP is one of the most common and morbid conditions causing 1.7 million emergency visits in 2016 and 50,000 deaths in 2017.[1] The Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) updated their CAP guidelines in October 2019.[2]

Diagnosis

Pneumonia is diagnosed by clinical assessment and confirmed by identification of a lung infiltrate on chest radiograph. The only way to determine the causative organism of pneumonia is to obtain cultures, which help with appropriate antibiotic selection. Unfortunately, these cultures generally have poor yield with sputum cultures returning positive only 9-44% of the time and blood cultures only 2-9%.[3-6] Due to poor yield and lack of high quality evidence that cultures improve patient outcomes, the ATS/IDSA 2019 CAP Guidelines only recommended obtaining cultures for patients with severe CAP or patients treated with broad spectrum antibiotics.[2] The definition of severe CAP has not changed from previous guidelines and is shown in **Table 1**. Of note, no recommendation is provided regarding whether sputum cultures should be obtained for all hospitalized patients and this decision should be left to clinical judgement and possible benefit for antimicrobial stewardship at each institution.

Table 1: ATS/IDSA Criteria Defining Severe CAP

Severe CAP:
Either one major or 3+ minor criteria
Major Criteria:
Septic shock with need for vasopressors
Respiratory failure requiring mechanical ventilation
Minor Criteria:
Respiratory rate $\geq$ 30 breaths/min
$PaO_2/FiO_2 \leq 250$
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN $\geq$ 20 mg/dl)
Leukopenia (WBC < 4,000 cells/mm^3)
Thrombocytopenia (platelets < 100,000 cells/mm^3)
Hypothermia (< 36°C)
Hypotension requiring aggressive fluid resuscitation

Urine antigen testing for *Streptococcus pneumoniae* and *Legionella* species has the potential to aid in rapid diagnosis and tailoring of antibiotics, but their clinical impact is unclear. Two observational studies showed a mortality benefit. The first found that urine antigen testing for both *Streptococcus pneumoniae* and *Legionella* significantly reduced 30-day mortality with a stronger association as disease severity increased.[7] The other study showed an in-hospital mortality benefit with use of only *Legionella* urine antigen studies.[8] On the other hand, two randomized controlled trials failed to show any benefit of pathogen directed therapy with antigen testing compared to guideline-directed therapy in antibiotic failure, mortality, duration of antibiotic use, hospital length of stay or ICU admission.[9-10] Another

observational study evaluated pneumococcal antigen testing and found that it had no impact on antibiotic de-escalation and was not cost effective.[11] Due to conflicting data, the ATS/IDSA guidelines recommend limiting the use of urine antigen testing to patients with severe CAP.[2]

The guidelines also reflected on the place in therapy of serum procalcitonin as a guide to initiate antibiotics. There are several meta-analyses showing both a mortality benefit and reduction in antibiotic use by using procalcitonin in acute respiratory infections.[12-13] Unfortunately, these reviews included a wide variety of indications including chronic obstructive pulmonary disease (COPD), asthma, acute bronchitis, and pneumonia. Kamat et al. reviewed studies that solely evaluated the utility of procalcitonin in CAP.[14] They concluded the sensitivity for predicting bacterial infection with procalcitonin ranged from 38-91% and found varying procalcitonin cutoff values used ranging from 0.15 to 1.5 ng/mL. Although the use of procalcitonin to determine bacterial infection shows promise for some infections, the ATS/IDSA guidelines recommend against use of procalcitonin to guide initiation of antibiotics for cases of clinically confirmed CAP at this time.[2]

One rapid diagnostic test recommended for use is the methicillin-resistant *Staphylococcus aureus* (MRSA) nasal swab, also referred to as a nasal polymerase chain reaction (PCR) assay.[2] A negative nasal swab is accurately able to rule out MRSA pneumonia due to the high negative predictive value ranging from 96-99%.[15-16] Due to the poor positive predictive value, a positive nasal swab does not accurately identify MRSA pneumonia and adjustments in antibiotics should be based on other factors such as cultures and clinical assessment. A MRSA nasal swab should be ordered for all patients receiving treatment covering for MRSA and patients who may have risk factors that are not receiving coverage.[2]

Due to known viral co-infection and the ease of rapid influenza testing, the ATS/IDSA guidelines recommend concurrent influenza testing for all CAP patients when influenza is circulating. This is in concordance with the Centers for Disease Control and Prevention recommendation.[17] Empiric antiviral treatment, such as oseltamivir, should be started regardless of the duration of symptoms for patients who have suspected influenza and are admitted to the hospital, are at high risk of influenza complications, or have progressive disease.

Outpatient Therapy

The ATS/IDSA guidelines updated the recommendations for empiric outpatient therapy which is summarized in **Table 2**. The first major update is a conditional recommendation for macrolide monotherapy. Macrolides historically have been a popular option due to the ease of daily administration of azithromycin for five days. Due to emerging resistance of *Streptococcus pneumoniae* with rates greater than 30% in some areas of the United States, local resistance patterns should be assessed prior to continued use of macrolide monotherapy.[18]

Another change is the addition of high dose amoxicillin monotherapy as an option for patients without comorbidities or risk factors for multi-drug resistant organisms.[2] Several studies showed no difference in the efficacy of amoxicillin compared to moxifloxacin, sparfloxacin, or telithromycin in CAP despite its lack of atypical coverage.[19-21] While there is emerging resistance of *Streptococcus pneumoniae* to macrolides, there seems to be minimal resistance to penicillins with rates of less than 3% in some parts of the United States.[18]

Empiric antibiotic recommendations for outpatient management in patients with comorbidities remain the same. These patients require broader spectrum antibiotics because they are more vulnerable if not adequately treated and many have an increased risk of antibiotic resistance due to previous healthcare system or antibiotic exposure.

Inpatient Therapy

The most significant change to the ATS/IDSA 2019 CAP guidelines is the abandonment of HCAP. This classification, which associated patients with drug-resistant organisms like MRSA and *Pseudomonas aeruginosa* (PsA), resulted in excess use of broad-spectrum antibiotics without an improvement in patient outcomes.[22] The guidelines strongly recommend abandoning the classification, but they provide little guidance on who to treat with anti-MRSA and/or anti-PsA therapy with a recommendation to cover if locally validated risk factors are present.[2] For individual institutions, resources including time, personnel, and funds will be needed to determine which risk factors are present and significantly associated with drug-resistant pathogens within their community. As a result, many institutions are relying on risk scoring systems that have

Table 2: 2019 ATS/IDSA Outpatient CAP Treatment	
No Comorbidities or Risk Factors for MRSA or *Pseudomonas aeruginosa*[1]	Amoxicillin[2] Doxycycline[3] Macrolide (if local pneumococcal resistance is < 25%)[4]
Comorbidities (Chronic heart, lung, liver or renal disease; diabetes mellitus; malignancy; asplenia; alcoholism)	Amoxicillin/clavulanate[5] or cephalosporin[6] AND Macrolide[4] or doxycycline[3] OR Respiratory fluoroquinolone monotherapy[7]

PO: by mouth; TID: three times daily; BID: twice daily

[1] Risk factors include prior respiratory isolation of MRSA or P. aeruginosa or recent hospitalization AND receipt of parenteral antibiotics in the last 90 d

[2] Amoxicillin 1 g three times daily

[3] Doxycycline 100 mg twice daily

[4] Azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, or clarithromycin ER 1,000 mg daily

[5] Amoxicillin/clavulanate 500 mg/125 mg three times daily, 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily

[6] Cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily

[7] Levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily

previously been identified and validated. The guidelines do highlight that the strongest risk factor to take into consideration is prior infection with either MRSA or PsA.

Several scoring systems have been validated for the assessment of PsA and MRSA risk. These include the Shorr Score, Aliberti Score, Shindo Score, DRIP Score, and Frei Score for PsA, as well as another scoring tool by Shorr et al. for MRSA.[23-30] The most common risk factors between the scoring systems for PsA are recent hospitalization within 90 days and nursing home residence. For MRSA, the most common risk factors in the scoring systems are hospitalization within 90 days and intensive care unit admission. The biggest takeaway is that cumulative risk (i.e. more than one risk factor) is a better indicator of drug-resistant organisms than a single risk factor alone.

In the absence of previously isolated MRSA or PsA and/or risk factors for these organisms, empiric treatment for inpatient non-severe CAP remains similar to outpatient regimens (see **Table 3**). Suggested regimens consist of a β-lactam plus atypical coverage or a respiratory fluoroquinolone. The guidelines recommend the use of doxycycline for atypical coverage only in the setting of non-severe CAP if a patient has a contraindication to both macrolides and fluoroquinolones. However, doxycycline is likely an appropriate alternative to macrolides as Teh et al. found no difference in efficacy and identified shorter lengths of stay with the use of doxcycyline.[31] Although fluoroquinolones are recommended as potential first-line agents for CAP treatment, the risks of these agents often outweigh the benefits; thus, this class of antibiotics should be utilized only if necessary. In the setting of severe CAP, a fluoroquinolone must be used in combination with β-lactam therapy, but stronger evidence supports use of a β-lactam/macrolide combination due to a possible mortality benefit.[32-33]

Regarding empiric treatment of CAP, providers must remain vigilant in choosing the most narrow-spectrum agents available. Although the guidelines include carbapenems as appropriate agents for empiric coverage against PsA (see **Table 4**), agents with a narrower spectrum should be utilized if possible. Similarly, although ceftaroline is included as an appropriate empiric β-lactam, narrower spectrum agents should be considered initially. Given the lack of sufficient data at this time, newer antimicrobial agents such as omadacycline and lefamulin were not included in this guideline update. In alignment with the previous guidelines, the authors recommend a minimum duration of treatment of 5 days, with discontinuation only after clinical stability has been achieved (e.g. normalization of vital signs, diet, mental status, etc.). Regarding atypical coverage, however, Schonwald et al. reported that 3 days of azithromycin is sufficient in the setting of CAP, as long as a total of 1.5g was administered (i.e. 500mg daily x 3 days).[34] Longer courses of treatment are required for patients with MRSA or PsA or in those with deep seated infection (i.e. empyema, abscess, endocarditis).

Table 3: 2019 ATS/IDSA Inpatient CAP Treatment		
	Non-Severe	**Severe**
Empiric	β-lactam + macrolide OR Respiratory fluoroquinolone	β-lactam + macrolide OR β-lactam + respiratory fluoroquinolone
Prior respiratory isolation of PsA	Add PsA coverage + obtain cultures	
Recent hospitalization and parenteral antibiotics or locally validated risk factors for PsA	Obtain cultures but withhold empiric PsA coverage	Add PsA coverage + obtain cultures
Prior respiratory isolation of MRSA	Add MRSA coverage + obtain cultures/nasal PCR	
Recent hospitalization and parenteral antibiotics or locally validated risk factors for MRSA	Obtain cultures but withhold empiric MRSA coverage Until culture results are available, ONLY initiate MRSA coverage if the nasal PCR assay is positive	Add MRSA coverage + obtain cultures/nasal PCR
PsA: *Pseudomonas aeruginosa*; MRSA: methicillin-resistant *Staphylococcus aureus*; PCR: polymerase chain reaction		

To give or not to give: steroids and anaerobic coverage

A strong recommendation is made against the use of steroids in patients with CAP. Various studies demonstrated improvement in clinical stability, but with more hyperglycemia and without a difference in mortality or other more meaningful, clinically relevant endpoints.[35-36] It is important to recognize the cohorts of patients in which this recommendation should not be applied to, including those with comorbid diseases that warrant steroid usage in the acute setting (i.e. COPD, asthma, and certain autoimmune conditions). The ATS/IDSA guidelines do endorse the Surviving Sepsis Campaign; thus, steroids should be considered in patients with septic shock refractory to fluid resuscitation and vasopressors.

Although not mentioned in the previous update, the 2019 guidelines briefly address the subject of aspiration pneumonia. The authors note that aspiration pneumonia is difficult to define and contrary to older evidence, anaerobic bacteria do not predominate in the setting of aspiration. The addition of anaerobic coverage is only recommended in two specific patient populations: 1) those with suspected or confirmed lung abscess or 2) empyema. Additionally, standard empiric regimens for CAP adequately cover upper airway and oral anaerobes.

Conclusion

The ATS/IDSA 2019 CAP guidelines addressed several controversial topics, including appropriate empiric coverage and terminology. With the formal removal of "HCAP" and guidance regarding broad-spectrum coverage, the authors hope to decrease inappropriate antibiotic usage in the setting of CAP. However, they provide little guidance with respect to coverage of resistant pathogens. These guidelines place a large emphasis on institutions and healthcare providers to be cognizant of local pathogens and rates of resistant pathogens to guide empiric therapy by conducting their own research to determine locally validated risk factors or adopting previously published risk scoring tools. This update addressed several areas of antimicrobial stewardship in which pharmacists can directly impact practice, such as decreasing unnecessary antibiotic usage and appropriate antibiotic de-escalation in the era of rising antimicrobial resistance.

Table 4: Recommended Intravenous Antimicrobials for Inpatient CAP	
β-lactams	Ampicillin-sulbactam 1.5-3g q6h Cefotaxime 1-2g q8h Ceftriaxone 1-2 g q24h Ceftaroline 600mg q12h
Macrolides	Azithromycin 500mg q24h Clarithromycin 500mg q12h
Fluoroquinolones	Levofloxacin 750mg q24h Moxifloxacin 400mg q24h
Anti-MRSA	Vancomycin 15 mg/kg q12h[1] Linezolid 600mg q12h
Anti-PsA	Piperacillin-tazobactam 4.5g q6h Cefepime 2g q8h Ceftazidime 2g q8h Imipenem 500mg q6h Meropenem 1g q8h Aztreonam 2g q8h
PsA: *Pseudomonas aeruginosa*; MRSA: methicillin-resistant *Staphylococcus aureus* [1] Adjust based on levels	

Tables adapted with permission of the American Thoracic Society.

Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019;200(7):e45-e67.

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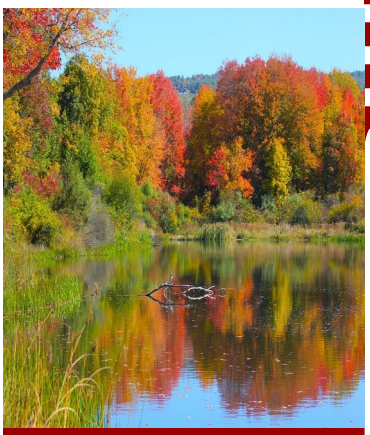

The use of DOACs in morbid obesity: what do we know?

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"As we still do not have robust literature evaluating DOACs in the obese patient population, patients should be evaluated on a case-by-case basis for the risks versus benefits of DOAC prescribing. It appears that apixaban and particularly rivaroxaban may be the most appropriate DOACs to use in the morbidly obese patient population for both NVAF and VTE. "

Introduction

Direct oral anticoagulants (DOACs) are commonly used for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF), venous thromboembolism (VTE) treatment, and VTE prophylaxis. The DOAC class is composed of apixaban, dabigatran, edoxaban, and rivaroxaban which were brought to market as results of separate trials that have shown these medications to be non-inferior to warfarin. The 2016 Chest Guideline and Expert Panel Report on antithrombotic therapy for VTE recommends the use of DOACs over warfarin for patients without cancer.[1] The 2019 AHA/ACC/HRS focused update on the 2014 guideline for management of patients with atrial fibrillation recommend DOACs over warfarin for patients that do not have severe mitral stenosis or a mechanical heart valve. However, the trials showed evidence favoring DOAC use did not include a large proportion of patients at the extremes of body weights (including obesity), thus leaving use of DOACs in question for patients with extremes of weight.[2]

Body mass index (BMI) is often used to define the status of a person's weight. It is measured by dividing a person's weight in kilograms by square height in meters. Obesity in general is defined by a BMI > 30.0 kg/m^2. This can then be divided out into three sub-classes: obesity class I (BMI 30.0 – 34.9), obesity class II (BMI 35.0 – 39.9), and obesity class III (BMI ≥ 40.0). Obesity class III is also classified as extreme obesity.[3] Patients at extremes of weight were not included in the landmark trials that supported the use of DOACs. Due to this, the 2016 Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis (ISTH) recommended that a DOAC should not be used in patients with a BMI > 40 kg/m^2 or weight of > 120 kg due to the lack of clinical data on efficacy and safety available for patients at extremes of weight.[4]

Pharmacokinetics

Several studies have sought to evaluate the pharmacokinetic and pharmacodynamic components of DOACs in patients at extremes of weight to assist with the understanding of safety and efficacy. In a study by Upreti et al., the group looked at the safety and tolerability of apixaban in patients with extremes of weight. This group looked at 19 patients with weights over 120 kg and compared pharmacokinetics and pharmacodynamics to both low body weight (≤ 50 kg) and reference weight (65 – 85 kg) patients. Compared to the reference group, the high body weight group had 20% less exposure to apixaban after a single dose of apixaban 10 mg during collection up to 72 hours post dose.[5] A study by Kubitza et al. reviewed safety, tolerability, pharmacokinetics, and pharmacodynamics of rivaroxaban in healthy patients. Patients were divided out into three groups of weights ≤ 50 kg, 70 – 80 kg, or > 120 kg. Subjects then received a single dose of rivaroxaban 10 mg. They found the C_{max} to be similar in the 70 – 80 kg group and > 120 kg group and found that the anti-Xa activity had no significant difference between all groups. However, anti-Xa activity was found to be numerically lower in the > 120 kg group.[6] Both of these studies found a difference between different weight groups, but the clinical significance is still unknown. If DOACs must be used in patients with BMI > 40 kg/m^2 or > 120 kg, the ISTH guidelines recommend monitoring of peak and trough anti-Xa levels. If anti-Xa levels fall below the expected range, then it is recommended to change to a vitamin K antagonist (VKA).[4]

Non-Valvular Atrial Fibrillation

According to the Centers for Disease Control and Prevention (CDC), obesity was prevalent in about 40% of Americans in 2017 – 2018.[7] A risk factor for the development of atrial fibrillation is obesity.[8] Some available literature suggests there is a paradoxical effect in obese patients with atrial fibrillation, which is a possible decrease in adverse outcomes such as mortality and

stroke.[8,9] This concept is important to understand when reviewing the limited literature covering use of DOACs in obese patients with atrial fibrillation.

All landmark studies for the DOACs in NVAF had post-hoc analyses that grouped patients by BMI or weight (Table 1). Balla et al. used data from ROCKET-AF (rivaroxaban) to evaluate a composite of stroke and systemic embolism in three BMI groups. In the BMI > 30 kg/m^2 group, the HR was 1.02 (CI 0.76 – 1.36; *p = 0.40*) with no significant difference among the three BMI groups. However, there was a significant difference when comparing the three BMI groups and non-major clinically relevant (NMCR) bleeding.[9] ARISTOTLE (apixaban) was evaluated by weight groups (low ≤ 60 kg, mid-range 60 – 120 kg, high > 120 kg) using multiple efficacy endpoints such as stroke, systemic embolism, and all-cause mortality. There were no significant differences for all of the efficacy endpoints in the high weight treatment group.[10] In a post-hoc analysis of RE-LY (dabigatran), the patients were grouped by BMI with the upper 10% weight group having BMIs > 36 kg/m^2. Major bleeding rates along with one year stroke and systemic embolism rates were comparable across all subgroups in the upper weight group. [11] In the post-hoc analysis of ENGAGE AF TIMI-48, the 60 mg dose of edoxaban was compared to warfarin across BMIs with no significant differences noted in the efficacy and safety outcomes.[12]

Perales et al. compared patients at extremes of weight (BMI > 40 kg/m^2 or weight > 120 kg) on rivaroxaban for NVAF or VTE. The primary endpoint was a composite of VTE recurrence, stroke incidence, or mortality within the first 12 months of initiation. In the patients with an indication for NVAF, there were no incidences of clinical failure in the rivaroxaban group (n = 37).[13]

Several studies retrospectively reviewed multiple DOACs (Table 2). Kushnir et al. evaluated 429 patients on apixaban, rivaroxaban, and warfarin for NVAF that had a BMI ≥ 40 kg/m^2. Incidence of stroke was low among the three treatment groups with apixaban 1/103, rivaroxaban 4/174, and warfarin 2/152; *p = 0.71*. Major bleeding was also not significantly different (*p = 0.063*) among the treatment groups: apixaban 3/103, rivaroxaban 5/174, and warfarin 12/152.[14] Kido and colleagues included apixaban, dabigatran, and rivaroxaban in a retrospective cohort study versus warfarin in patients with a BMI > 40 kg/m^2 or weight > 120 kg. The primary efficacy outcome was incidence of ischemic stroke or transient ischemic attack. Incidence was 1.75% per year in the DOAC treatment group vs. 2.07% per year in the warfarin group (incidence rate ratio = 0.84, [95% CI 0.23 – 3.14]; *p = 0.8*). Major bleeding rates between groups were also not statistically significant (2.18% in DOAC group vs. 4.97% in warfarin group; *p = 0.11*). Interestingly, dabigatran had a higher event rate (4.03%) than the other DOACs (1.07% rivaroxaban, 0% apixaban). However, the study was not powered to evaluate the DOACs individually.[15] Another retrospective cohort study looked at apixaban (n = 126), dabigatran (n = 36), and rivaroxaban (n = 137) for NVAF or VTE with patients grouped by BMI where efficacy was a secondary outcome.[16] The largest BMI group included was for BMI ≥ 30 kg/m^2. There was no significant difference found in efficacy (stroke or TIA) across the BMI groups for apixaban or rivaroxaban.[16] A prospective registry based in Germany, the Dresden new oral anticoagulant (NOAC) Registry, enrolls patients voluntarily that will be on NOACs for at least 3 months. Using the World Health Organization (WHO) BMI classifications, a total of 3,432 patients enrolled, including 98 with a BMI > 40 kg/m^2. Even though there was a small proportion of patients considered morbidly obese, elevated BMI was not found to decrease NOAC effectiveness or safety.[17]

Venous Thromboembolism

Even fewer studies exist regarding DOAC use in the obese population for treatment of VTE. This may be due to a smaller patient population as compared to NVAF, or a hesitancy to utilize a less studied agent in morbid obesity for a treatment indication other than for stroke prevention in NVAF. Regardless, use in this patient population and for VTE treatment has increased. Table 2 highlights the overweight/obese patients enrolled in the DOAC landmark trials for VTE treatment and outcomes when compared to warfarin.[18-22] The percentage of overweight/obese patients was low in each of the studies, ranging from 15% of patients weighing > 100 kg in the Hokusai-VTE (edoxaban) study, to 28% of patients weighing > 90 kg in the EINSTEIN (rivaroxaban) studies.[19,20,22] To complicate analysis, each trial used a different weight or BMI cutoff to describe their patients. Many of these cutoffs to identify high weight or obese patients were quite low, such as > 90 kg or BMI ≥ 30. Despite the low patient numbers and variable cutoffs, each of the DOACs fared similarly to warfarin in terms of efficacy (VTE recurrence) and safety (bleeding) in obese patients. It is worth noting that the degree of obesity of patients at the upper end of the weight extremes in these trials are likely not as high as those seen in clinical practice, so caution should be used when applying this data to a 100 kg patient as compared to a patient with a higher degree of obesity.

Since the DOACs were initially approved for the treatment of DVTs and PEs, a variety of retrospective studies have emerged describing obese patients who have been treated with these agents (Table 3). Some of these studies compared outcomes of obese patients treated with DOACs vs. obese patients treated with warfarin, while others assessed outcomes of obese vs.

normal weight patients treated with DOACs. Limitations related to the retrospective nature of these studies limits the overall strength of the evidence, but none of the studies indicated any significant safety or efficacy concerns when using DOACs in this population. Rivaroxaban appears to be the most commonly used and studied agent in the obese patient population. A smaller number of patients were receiving apixaban or dabigatran, while no patients in these retrospective studies were using edoxaban for VTE treatment. [13,15,16, 23-25]

Table 1. Post-Hoc Analyses of NVAF studies

Design	Patients	Relevant Endpoints
Balla 2017 [9] ROCKET AF rivaroxaban vs warfarin	Normal weight: 3,289 Overweight: 5,535 Obese (BMI > 30 kg/m^2): 5,206 N = 14,030	HR (95% CI) of rivaroxaban vs warfarin for stroke and/or non-CNS embolism: normal weight 0.76 (0.56 – 1.03), overweight 0.89 (0.68 – 1.16), obese 1.02 (0.76 – 1.36); *p = 0.4* HR (95% CI) of rivaroxaban vs warfarin for major or NMCR bleeding: Normal weight 0.97 (0.84 – 1.13), overweight 1.18 (1.05 – 1.33), obese 0.93 (0.82 – 1.04)*; p = 0.01*
Hohnloser 2019 [10] ARISTOTLE apixaban vs warfarin	Low weight (≤ 60 kg): 1,985 Midrange weight (60 – 120 kg): 15,172 High weight (> 120 kg): 982 N = 18,139	HR (95% CI) of apixaban vs warfarin for stroke or systemic embolism: low weight 0.63 (0.41 – 0.96), midrange weight 0.85 (0.7 – 1.05), high weight 0.39 (0.12 – 1.22)*; p = 0.64* HR (95% CI) of apixaban vs warfarin for any bleeding: low weight 0.2 (0.53 – 0.73), midrange weight 0.73 (0.69 – 0.78), high weight 0.67 (0.53 – 0.85)*; p = 0.11*
Ezekowitz 2014 [11] RE-LY (abstract only) dabigatran vs warfarin	Bottom 10% (BMI ≤ 22.5 kg/m^2): 1,865 Middle 80% (BMI 22.5 - ≤ 36 kg/m^2): 14,435 Upper 10% (BMI > 36 kg/m^2): 1,787 N = 18,113	One year major bleeding rates (95% CI) in BMI > 36 kg/m^2: dabigatran 110 mg: 3% (1.6 – 4.4), dabigatran 150 mg: 4.4% (2.7 – 6.1), warfarin: 3.7% (2.2 – 5.2)*; p = 0.55* One year stroke or systemic embolism rates (95% CI) in BMI > 36 kg/m^2: dabigatran 110 mg: 1.2% (0.3 – 2.0), dabigatran 150 mg: 0.9% (0.1 – 1.6), warfarin: 1.3% (0.4 – 2.3)*; p = 0.6*
Boriani 2018 [12] ENGAGE AF- TIMI 48 edoxaban vs warfarin	Underweight:177 Normal weight: 4,491 Overweight: 7,903 Moderate Obesity: 5,209 Severe obesity: 2,099 Very severe obesity: 1,149 N = 21,028	HR (95% CI) of stroke or systemic embolism in 60 mg edoxaban vs warfarin: normal weight 1.03 (0.76 – 1.40*; p = 0.86*), very severely obese 1.37 (0.37 – 5.05)*; p = 0.63* HR (95% CI) of major or NMCR bleeding in 60 mg edoxaban vs warfarin: normal weight 0.8 (0.7 – 0.93; *p < 0.005)*, very severely obese 0.94 (0.71 – 1.25); *p = 0.68*

Table 2. Other available literature in NVAF and VTE

	Patients	Relevant Endpoints	Discussion/Conclusions
Perales 2020 [13] Rivaroxaban vs Warfarin	*NVAF and VTE* Adults with BMI > 40 kg/m^2 or weight > 120 kg N = 176	• Clinical failure (VTE recurrence, stroke incidence, or mortality): rivaroxaban 5% vs warfarin 13%; *p = 0.06* • Major or NMCR bleed: rivaroxaban 8% vs warfarin 2%; *p = 0.06*	• Rivaroxaban did not have an increase in VTE recurrence, stroke, mortality, or bleeding complications in patients at extremes of weight. • Patients receiving rivaroxaban had a significantly shorter length of hospital stay compared to those treated with warfarin.
Kushnir 2019 [14] Apixaban, Rivaroxaban and Warfarin	*NVAF and VTE* Adults with BMI > 40 kg/m^2 N = 795	• Incidence of recurrent VTE: apixaban 2.1%, [95% CI 0.0 – 6.3], rivaroxaban 2%,[0.0 – 4.2], warfarin (1.2%,[0.0 – 2.9]; *p = 0.74* • Incidence of stroke: apixaban 1% [0.0 – 2.9], rivaroxaban 2.3%, [0.1 – 4.5%], warfarin 1.3%, [0.0 – 3.1]; *p = 0.71*	• There was similar efficacy and safety between treatment groups in the morbidly obese. • A subgroup analysis of patients with a BMI > 50 kg/m^2 found no statistically significant differences in VTE recurrence or stroke among the treatment groups.
Doucette 2020 [16] Apixaban and Rivaroxaban	*NVAF and VTE* Adults on a DOAC across all BMI weight groups N=398	• NVAF cohort incidence of combined bleeding (major + NMCR): apixaban BMI < 30 kg/m^2, 22.1% vs BMI $\geq$ 30 kg/m^2, 22%; *p = 0.997;* rivaroxaban BMI < 30 kg/m^2, 18.3% vs BMI $\geq$ 30 kg/m^2, 10.9%; *p = 0.25* • VTE cohort incidence of combined bleeding: BMI < 30 kg/m^2, 18.4% vs BMI $\geq$ 30 kg/m^2, 16.7%; *p = 0.866*	• Efficacy was similar across BMI categories for both treatments. • A total of 49 patients included in the analysis were BMI $\geq$ 40 kg/m^2
Kido 2019 [15] Apixaban, Dabigatran, Rivaroxaban and Warfarin	*NVAF* Adults with BMI > 40 kg/m^2 or weight > 120 kg N = 64	• Incidence of ischemic stroke or TIA in DOAC group vs warfarin: DOAC 1.75% per year vs warfarin 2.07% per year (incidence rate ratio= 0.84 [95% CI 0.23 – 3.14]); *p = 0.8*	• There was no significant difference in rate of ischemic stroke or TIA when comparing treatment groups. • Study was not powered to compare the DOACs individually.
Aloi 2019 [23] Apixaban, Dabigatran and Rivaroxaban	*VTE* Adults ≥ 120 kg N = 1196	• Overall VTE recurrence: 0.8% in ≥ 120 kg group vs 1.1% in < 120 kg group; *p = 0.69*	• Patients ≥ 120 kg made up only 11% of the total population, with a mean weight of 139.6 kg. • The sole VTE recurrence in the ≥ 120 kg group occurred in a patient on dabigatran.
Spyropoulos 2019 [24] Rivaroxaban vs Warfarin	*VTE* Matched pairs of morbidly obese adults N = 5,780	• Risk of recurrent VTE (hospitalization or ER visit): rivaroxaban 16.8% vs warfarin 15.9%, OR 0.99 (95% CI 0.85-1.14); *p = 0.844* • Major bleeding event via a validated claims algorithm: rivaroxaban 1.8% vs warfarin 2.5%, OR 0.66 (0.45-0.98); *p = 0.0937*	• Recurrence rates were similar between rivaroxaban and warfarin groups, with significantly less bleeding in the rivaroxaban group. • Also evaluated total healthcare costs which were similar between groups.
Coons 2020 [25] Apixaban, Dabigatran, Rivaroxaban and Warfarin	*VTE* Adults between 100 – 300 kg N = 1,840	• Recurrence of VTE within 12 months of the admission date: DOACs 6.5% vs warfarin 6.4%; *p = 0.93* • Bleeding within 12 months of admission date: DOACs 1.7% vs warfarin 1.2%; *p = 0.31*	• Based on large-scale retrospective data, there appears to be similar efficacy and safety between DOACs and warfarin for VTE treatment in patients between 100-300 kg.

Discussion

At this time, the available literature for morbidly obese patients on DOACs in NVAF is primarily limited to retrospective analyses. When discussing efficacy endpoints, it is important to note that in many of the studies reviewed in this article the time to therapeutic range was longer in higher weight patients on warfarin.[9,12] Time to therapeutic range with warfarin could

Table 3. DOAC VTE Landmark Studies

Design	Patients	Relevant Endpoints and Discussion
RE-COVER 2009 [18] Dabigatran vs Warfarin	*VTE* ≥ 100 kg: 502 BMI ≥ 35 kg/m^2: 306 N = 2,539	• Patients with recurrent VTE: - Weight ≥ 100 kg: 4.4% dabigatran vs 3.0% warfarin; p=0.76 - BMI ≥ 35 kg/m^2: 3.5% rivaroxaban vs 2.3% warfarin; p=0.89 • Only 20% of all patients had weight ≥ 100 kg and only 12% had a BMI ≥ 35
EINSTEIN-DVT 2010 [19] Rivaroxaban vs Warfarin	*DVT* > 90 kg: 977 N = 3,449	• Symptomatic, recurrent VTE: - Weight > 90 kg: 2.2% rivaroxaban vs 2.3% enoxaparin/warfarin (NS) • Major or clinically-relevant nonmajor bleeding: - Weight > 90 kg: 6.4% rivaroxaban vs 8.1% enoxaparin/warfarin (NS) • 28% of patients had weight > 90 kg, but no further description is provided regarding higher weights or BMI
EINSTEIN-PE 2012 [20] Rivaroxaban vs Warfarin	*PE* > 90 kg: 1,355 BMI > 30 kg/m^2: 1,496 N = 4,832	• Symptomatic, recurrent VTE: - Weight > 90 kg: 1.9% rivaroxaban vs 1.5% warfarin (NS) - BMI > 30 kg/m^2: 1.5% rivaroxaban vs 1.5% warfarin (NS) • Major or clinically relevant nonmajor bleeding: - Weight > 90 kg: 10.0% rivaroxaban vs 9.1% warfarin (NS) • 28% of patients had weight > 90 kg and 31% had BMI > 30 • No data was provided specifically on morbidly obese patients
AMPLIFY 2013 [21] Apixaban vs Warfarin	*VTE* ≥ 100 kg: 1,017 BMI ≥ 35 kg/m^2: 684 N = 5,395	• Symptomatic, recurrent VTE or death: - Weight ≥ 100 kg: 1.9% apixaban vs 1.5% warfarin (NS) - BMI > 35 kg/m^2: 2.01% apixaban vs 3.58% warfarin (NS) • ISTH major bleeding: - Weight ≥ 100 kg: 0.19% apixaban vs 1.93% warfarin (significant difference in favor of apixaban) - BMI > 30 kg/m^2: 0.55% apixaban vs 3.50% warfarin significant difference in favor of apixaban) • 19% of patients had weight ≥ 100 kg and 13% had BMI > 30
Hokusai-VTE 2014 [22] Edoxaban vs Warfarin	*VTE* > 100 kg: 1,265 N = 8,240	• Symptomatic, recurrent VTE: - Weight > 100 kg: 3.6% edoxaban vs 3.5% warfarin; p=0.6335 • Major or clinically-relevant nonmajor bleeding: - Weight > 100 kg: 8.8% edoxaban vs 8.3% warfarin; p=0.1470 • 15% of patients were > 100kg, but no further description on degree of obesity was provided

have impacted efficacy outcomes. Selection bias may play a role as it was noted that patients on warfarin tended to have more comorbidities or were higher risk patients.[13,14]

Similar to NVAF, data for DOAC use in the morbidly obese population for VTE is limited to subgroup analyses and retrospective studies. Rivaroxaban was the most common DOAC studied in obesity.[13,24] Other studies compared pooled DOAC users (rivaroxaban, apixaban, and dabigatran) compared to warfarin or pooled DOAC users in normal weight vs obese patients.[16,23,25] To date, no retrospective studies have assessed edoxaban use in morbid obesity for VTE treatment.

Conclusions

As we still do not have robust literature evaluating DOACs in the obese patient population, patients should be evaluated on a case-by-case basis for the risks versus benefits of DOAC prescribing. It appears that apixaban and particularly rivaroxaban may be the most appropriate DOACs to use in the morbidly obese patient population for both NVAF and VTE. Additionally, the obesity paradox that has been described in atrial fibrillation may give prescribers more confidence to prescribe DOACs in morbidly obese NVAF patients.[8,9,17]

Additional literature is on the horizon that may strengthen the evidence for or against DOAC use in obese patients. With time, the prospective registry out of Germany will hopefully gather more data in NVAF. The included study from the registry that was published in 2018 had less than 3% of patients with a BMI > 40 kg/m^2.[17] Upon review of clinicaltrials.gov, there are several future studies involving obese or bariatric surgery patients and the use of DOACs (NCT03893591, NCT02406885, NCT04180436, and NCT03448783). Hopefully as we gain more experience using DOACs in practice and with more studies being completed, we can come to a better conclusion about using DOACs with extremes of weight.

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