GULF COAST SOCIETY OF HEALTH-SYSTEM PHARMACISTS

VOLUME 25

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EDITOR-IN-CHIEF: IAN DUNNE, PHARMD, BCPS

OFFICER NOMINATIONS

Interested in getting more involved with a great organization and working with a dedicated group of pharmacy professionals? Become an officer!

We are accepting nominations for this upcoming year's officer positions. The following page includes the list of positions up for election this year and the associated description of the position's responsibilities. Following our bylaws, there is a nominating committee that will review nominations and submit the final ballot to the membership for voting. You can submit anonymous nominations via the survey link below. Thanks for your participation in this important process!

The deadline to submit nominations is February 19th, 2021.

Nominations Survey

OFFICER NOMINATIONS

President-Elect (3 year commitment)

The President-elect shall perform the duties of the office of the President whenever the President shall be unable to do so. He/She shall be a member of the Board of Directors and serve as its ViceChair. He/She shall be a member of TSHP and shall represent GCSHP through service as a member of the TSHP Board of Directors.

Director 1 (2 year commitment)

The two Directors shall represent the general membership on the Board of Directors. The second-year Director shall serve as the Society's major annual event planner and the first-year Director shall serve as vice-chair.

Recording Secretary (2 year commitment)

1. Record, prepare, and distribute agenda and minutes of all Society business meetings and all meetings of the Board of Directors;
2. Prepare and distribute with the Communications Secretary all official documents of the Society as required by the Board of Directors and the President

Communications Secretary (2 year commitment)

1. Maintain membership records;
2. Prepare and distribute ballots for all Society elections;
3. Prepare and distribute proposed changes to the Constitution and Bylaws to the membership for approval;
4. Distribute GCSHP newsletters and meeting notices to the membership

New Practitioner Ambassador (2 year commitment)

The New Practitioner Ambassador shall represent the Society within the TSHP New Practitioner Section, and serve as a liaison between the Society and TSHP. He/She shall foster the development of New Practitioner resources and retention within the Society. Additionally, he/she shall collaborate with the education chair to facilitate Grand Rounds.

GCSHP MONTHLY MEETINGS AND RESIDENT GRAND ROUNDS

Get Connected! Stay Involved!
Introducing GCSHP Monthly Meetings and Resident Grand Rounds Series

New year, new opportunities! GCSHP will now be holding monthly meetings for our general membership! These meetings will serve as a forum to stay in the know, to network, and to get involved in your local organization. We're also excited to announce the start of a new education series presented by our local pharmacy residents! The residents will have the opportunity to work with a member of the GCSHP Board of Directors and TSHP to obtain ACPE approval for a presentation over hot topics to our GCSHP membership. This means every month you can tune in for general membership updates as well as some great CE! We look forward to kicking this off in Spring of 2021.

Look for an email invitation for our first presentation in March (preliminary information below). If you are a residency program director or a resident with an interest in presenting an ACPE presentation to the GCSHP chapter, please email us (gcshp.membership@gmail.com) for additional information.

UPCOMING CPE EVENTS

GCSHP Residency Grand Rounds
Title: Who Are We? The Pain Killers! Pain Management in the ICU
Presenter: Nhi Nguyen, PharmD
PGY-1 Pharmacy Resident at HCA Houston Healthcare Clear Lake
Date: Wednesday, March 11th, 2021

6:30 PM CST: general member meeting check-in
7:00 PM CST: general member meeting followed by Grand Rounds presentation



TEXAS CONTINUING PHARMACY EDUCATION REQUIREMENTS

According to Texas Board Rules §295.8, continuing education requirements for renewal period (except for initial renewal) are described below. For more information regarding renewal requirements, initial renewal requirements, and technician requirements, please visit the Texas Board of Pharmacy CE webpage at https://www.pharmacy.texas.gov/licensees/ce-pharmacist-faq.asp

A total of 30 hours are required per renewal period, which include the following:

2 Hours (1 hour annually)	Must be related to **pain management.** ***Special note:*** You must be sure to obtain at least one hour **annually** (as specified in House Bill 3285). For example, a single two-hour course would not meet requirements as outlined by House Bill 3285 or Board rule 295.8. Requirement must be met for all renewals received ***after*** August 31, 2021 and ***before*** September 1, 2023.
2 Hours	Must be related to **prescribing and monitoring controlled substances** (as specified in House Bill 2174). A pharmacist shoudl take the controlled substance CE ***no later than September 1 2021*** and submit this CE on the new renewal after September 1, 2021.
1 Hour	Must be related to **mental health awareness.** Requirement must be met for all renewals receiged ***after*** August 13, 2021 and ***before*** September 1, 2023.
1 Hour	Must be related to **Texas-specific pharmacy laws and/or rules.**
24 Hours	Can be **any subject**; can also consist of any **special certification CE requirements,** if applicable (for example, sterile compounding, immunization, preceptorship, etc.; see special CE requirements).

Source: pharmacy.texas.gov/files_pdf/pharmacist_CE_breakdown.pdf

SCHOLARSHIPS

The TSHP Research and Education Foundation is proud to offer several scholarship opportunities to students and pharmacists who meet the individual eligibility requirements. The application window is open as of January 2021 and closes in February 2021 so apply now here! Two notable scholarships are outlined below:

Gulf Coast Society of Health-System Pharmacists Leadership Scholarship

The GCSHP Pharmacists Leadership Scholarship was created in 2000 to recognize a pharmacist or pharmacy student in an undergraduate or graduate degree program based on leadership, service, and academic standing. A $500 scholarship will be awarded to the winner based on the following criteria:

- Current pharmacist or pharmacy student member of GCSHP
- Demonstrate leadership skills
- Active in health-system pharmacy organizational activities
- Active in school and community service
- In good academic standing (GPA may be considered in the selection process)
- Not a previous recipient of the scholarship in the past

Richard Cadle Mentoring Scholarship for Pharmacy Leadership

The Richard Cadle Mentoring Scholarship for Pharmacy Leadership was created in 2017 after the sudden passing of the scholarship's namesake. Dr. Richard Cadle cared deeply about mentoring the future pharmacy leaders of America as shown with his dedication to students, residents, colleagues, and his extensive involvement in TSHP and GCSHP. As a proud member of the United States Navy, he served his country by helping teach new generations of brave young men and women the value of hard work and perseverance. This scholarship is the first of its kind to be solely dedicated to helping pharmacy residents throughout Texas. A $1000 scholarship will be awarded to the winner based on the following criteria:

- Current pharmacy resident in Texas
- Member of their local TSHP Chapter Affiliate
- Demonstrate compassion and spirit of helping others by being active in community service
- Demonstrate leadership qualities as evidenced by their contributions to local, state and national organizations

RESIDENT'S CORNER

Demi Martinez, PharmD
PGY-2 Ambulatory Care Resident, Harris Health System
Preceptor: Jocelyn Thomas, PharmD, BCACP

Opicapone (Ongentys®) Monograph

Background

Levodopa remains the standard of treatment for Parkinson's; however, after years of treatment with levodopa, patients may notice the effects of the medication wearing off prior to the next scheduled dose. The time period where control of motor function is lost ("off period") increases with years of levodopa treatment and will require increasing the dosing interval. On April 24, 2020, the U.S. Food and Drug Administration (FDA) approved opicapone (Ongentys®), a peripheral catechol-o-methyltransferace (COMT) inhibitor indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease who experience "off" episodes.

Pharmacology/Pharmacokinetics

Opicapone is a selective and reversible inhibitor of COMT. COMT inhibitors – like tolcapone, entacapone, and opicapone – can reduce the levels of L-DOPA metabolite (3-OMD), which competes with L-DOPA for transport across the blood brain barrier. This would increase the bioavailability of L-DOPA, and thus reduce the "off period". The elimination half-life of opicapone is 1 to 2 hours and it primarily undergoes hepatic metabolism. Due to its metabolism, opicapone requires dose adjustment in patients with moderate hepatic impairment. Opicapone is contraindicated in patients with pheochromocytoma, paraganglioma, and other catecholamine secreting neoplasms.

Dosing

Opicapone is available as a once daily 50 mg capsule. In patients with moderate hepatic impairment, a recommended dose of 25 mg daily is recommended. Opicapone should be taken at bedtime at least 1 hour before or 1 hour after L-Dopa combinations. Food may interfere with absorption of opicapone and it should not be taken within 1 hour before or after eating food. In clinical trials, the mean peak plasma concentration of opicapone decreased by 62% when taken with a moderate calorie meal.

Clinical Trials

The efficacy of opicapone was evaluated in two double-blind, multinational, 14-15 week phase 3 trials. The primary endpoint of the studies was the change from baseline to end of the study in the absolute time in "off state". The trials concluded that adjunctive 50 mg/day opicapone significantly reduced motor fluctuations compared to placebo and percentage of time in the "off" state. [1] The trials also demonstrated non-inferiority of opicapone to entacapone. There were no between group differences between entacapone or opicapone in the secondary outcomes of percentage of patients achieving at least an hour or more in the absolute "off" state or an hour or more in the absolute "on" state. The most common side effects reported in both trials included constipation, hypotension, weight loss, and dyskinesia.

	Baseline Mean (SE)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)	Adjusted P-value
Placebo	6.17 hours (0.162)	-0.93 (0.233)	-	-
Opicapone 50 mg	6.20 hours (0.166)	-1.95 (0.233)	-1.01 (-1.620, -0.407)	P=0.002

Precautions and Contraindications

Patients who are on opicapone and additional drugs that are metabolized by COMT should be monitored for possible arrhythmias, increased heart rate, or changes in blood pressure.

Patients on dopaminergic medications or medications that increase levodopa, such as opicapone, have reported falling asleep during daily activities and sometimes without warning sign. Due to the potential to develop drowsiness, patients should take this medication at bedtime and be advised not to drive if drowsiness occurs.

Although the risk of hypotension was minimally seen in trials, patients should be monitored for hypotension (both orthostatic and non-orthostatic) and advised about the risk of syncope.

Opicapone has a risk of causing dyskinesia due to increasing the bioavailability of levodopa. Similarly, there is a risk of developing hallucinations and symptoms of psychosis including delusions, agitation, or aggressive behavior. Patient with major psychotic disorders should not be treated with opicapone because of the risk of exacerbating psychosis.

Precautions and Contraindications (continued)

Opicapone may place patients at risk of compulsive disorders or loss of impulse control. Around 1% of the patients treated with opicapone in clinical trials had increased urges to gamble, increased sexual urges, intense urges to spend money or to binge eat. Patients may not recognize these symptoms themselves, so it is important for prescribers to specifically ask patients or family members if they have noticed a loss of impulse control.

The rapid dose reduction or withdrawal of medications that increase dopaminergic tone may lead to symptoms that resemble neuroleptic malignant syndrome. There were no reports of neuroleptic malignant syndrome in patients discontinuing opicapone in clinical trials. It is recommended to monitor patients for signs of neuroleptic malignant syndrome during discontinuation of opicapone.

There is no data on the effects of opicapone in pregnant or lactating women. The developmental and health benefits should be considered along with the mother's need for opicapone. There is no data on safety or efficacy of opicapone in pediatric populations. No dose adjustment is required in the geriatric population; however, greater sensitivity to adverse reactions is still a possibility in this patient population and should be monitored.

Drug Interactions

Both opicapone and non-selective MAO inhibitors inhibit catecholamine metabolism. Concomitant use of both agents will lead to increased levels of catecholamines and increase the risk of possible arrhythmias, increased heart rate, and change in blood pressure.

References

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RESIDENT'S CORNER

Hannah Poquiz, PharmD
PGY-1 Pharmacy Resident, HCA Houston Healthcare Clear Lake
Residency Program Director: Laura Blackburn, PharmD, BCPS, BCCCP

Patient Case: Candiduria

Patient Case

DG is a 59 year old male who presented to the emergency department with weakness, fatigue and abdominal pain. DG was recently discharged from the hospital status post subtotal colectomy and recently completed a course of amoxicillin/clavulanate. He denies nausea/vomiting, diarrhea, cough, shortness of breath, dysuria, urinary frequency, and urgency. His vitals on presentation are: Tmax 38.6°C, blood pressure 124/58 mmHg, heart rate of 95 bpm, respiratory rate 26 breaths/minute, and 97% oxygen saturation on room air. He was found to have a white blood cell count (WBC) of 21,000 cells/mL. An abdomen/pelvis CT was performed showing loculated postoperative fluid collection in soft tissues of the abdominal wall adjacent to the ileostomy. Blood cultures were collected and finalized with no growth after 5 days. DG is started on empiric antibiotic therapy and is clinically stable awaiting surgical intervention to address the fluid collection. A urinalysis was performed reporting: urine appearance as amber and cloudy, 2+ leukocyte esterase, and a urine WBC >50 per HPF, prompting a reflex culture that grew: Yeast 10,000 – 50,000 CFU/mL.

Based on urinalysis and culture, does BG require treatment for a fungal UTI?

Candida spp. is the most common fungal organism isolated from urine. Patients at highest risk for candiduria are those who are elderly, female, diabetic, have an indwelling urinary device, are taking antibiotics, and have had prior surgical procedures. Presence of candida in the urine in patients who are asymptomatic almost always represents colonization. The 2016 IDSA Guidelines for the Management of Candidiasis recommend to eliminate predisposing factors, such as exchanging of the foley catheter or discontinuing unnecessary antibiotics, whenever feasible when patients present with candiduria.1 Similar to asymptomatic bacteriuria, the presence of pyuria and positive urine cultures with yeast is not diagnostic of a UTI and treatment of asymptomatic patients is not recommended unless the patient is at high risk (neutropenic, very low-birth

weight infants, will undergo urologic manipulation). A prospective study in renal transplant recipients found that treatment of asymptomatic candiduria did not improve outcomes and multiple studies have noted that candiduria in hospitalized patients does not commonly lead to candidemia.

It is important to note that while yeast is a common colonizer in urine, there are situations in which it may represent underlying infection. Isolation of candida spp. at multiple non-sterile sites in severely immunocompromised patients can be representative of disseminated infection which warrants further investigation and potentially empiric treatment.

Looking back at our patient, DG presented with systemic signs of infection but did not have any reported symptoms suggestive of UTI. His blood cultures were negative and an isolated yeast specimen was confirmed only in the urine. DG had a recent abdominal surgery and exposure to antibiotic therapy. These patient specific factors can explain DG's presenting symptoms and urine culture results. As discussed, the isolation of yeast in the urine alone is likely representative of asymptomatic colonization, which does not warrant treatment based on IDSA guidelines.

Key Summary Points:

- Common risk factors candiduria include: Prior exposure to antibiotic therapy, recent surgical procedures, advanced age, female gender, diabetes, presence of indwelling urinary device
- When candiduria is present, it is important to assess patient specific risk factors to establish if the presence of yeast is due to asymptomatic colonization or true infection.
- IDSA guidelines do not recommend treatment in asymptomatic patients with candiduria.

References:

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RESIDENT'S CORNER

Nhi Nguyen, PharmD
PGY-1 Pharmacy Resident, HCA Houston Healthcare Clear Lake
Residency Program Director: Laura Blackburn, PharmD, BCPS, BCCCP

Asymptomatic Bacteriuria

Patient Case

BH is an 88-year-old male with a past medical history of hypertension and hyperlipidemia who was brought to the Emergency Department (ED) by his daughter for altered mental status (AMS). He was admitted to the hospital one month ago for dehydration and acute kidney injury. Per his daughter, the patient lives in a nursing home and has not been eating or drinking well over the past few weeks since discharge. He recently experienced a fall and developed AMS, prompting the ED visit. BH's vitals include: Tmax 99.7°F, blood pressure 139/87 mmHg, heart rate 86 bpm, respiratory rate 22 bpm, and 95% oxygen saturation on room air. His white blood cell (WBC) count is 8,500 cells/microliter and a urinalysis (UA) with reflex urine culture is ordered. The UA shows amber, turbid urine with 2+ leukocyte esterase, WBC >50/HPF, 6-10 squamous epithelial cells, and 3+ bacteria. The culture grows E.coli (>100,000 CFU/mL) and BH is started on ceftriaxone 1g IV daily for 7 days for possible urinary tract infection (UTI).

Does BH have a UTI requiring antibiotic therapy?

Asymptomatic bacteriuria (ASB) is defined as ≥100,000 CFU/ml of one or more bacterial species in the urine without any signs or symptoms of UTI (urinary frequency, urgency, dysuria, costovertebral angle tenderness) and regardless of the presence/absence of pyuria. ASB is relatively common in healthy females, as well as in men and women with genitourinary (GU) tract abnormalities. The updated 2019 IDSA guidelines on the management of asymptomatic bacteriuria recommend against screening for and treating for ASB in most patients, except for pregnant women and patients undergoing urologic procedures with risk of mucosal trauma.

Elderly patients who present with AMS changes or after a fall are commonly screened for UTIs as a possible explanation of their symptoms. However, this is a huge area of opportunity for antimicrobial stewardship programs, as many of these patients do not have UTIs requiring antimicrobial therapy. Though observational studies suggest patients with AMS are at higher risk of having bacteriuria than those without AMS, a causal relationship between bacteriuria and AMS has not been established. Additionally, a cohort study of nursing home residents found that 80% of patients who experienced a fall did not have bacteriuria or pyuria.

The IDSA ASB guidelines recommend withholding antimicrobial therapy for elderly patients who experience altered mental status or a fall if the patient has no urinary or systemic signs of infection. Instead, the guidelines recommend careful observation and assessment of other causes which may explain the symptoms. This recommendation is due to the fact that the prescribing of antimicrobials for ASB can have unfortunate consequences for the affected patients. Studies have shown that the treatment of ASB does not prevent subsequent development of symptomatic UTIs, and in fact may actually increase the number of symptomatic UTIs that a patient experiences. Additionally, treatment of ASB has been associated with increased acquisition of antibiotic-resistant organisms, increased *Clostridioides difficile* infections, and worse functional outcomes for patients.

Looking back at our patient, BH presents without any classic UTI symptoms despite having pyuria and a positive urine culture. His clinical presentation is consistent with ASB, and since he does not have a fever or leukocytosis, it would be appropriate to withhold antimicrobial therapy and assess for other causes of his AMS. This particular patient's AMS can more likely be attributed to non-infectious causes such as dehydration and/or malnutrition given his reduced PO intake in the weeks prior to admission.

Clinical Pearls:

- ASB is a common condition in healthy females and men/women with GU tract abnormalities.
- ASB should only be screened for and treated in pregnant women or in patients undergoing urologic procedures associated with mucosal trauma.
- Antimicrobial therapy should not be initiated for elderly patients who fall or have altered mental status unless additional signs or symptoms of UTI or systemic infection are present
- Treatment of ASB does not reduce the risk of future UTIs and puts patient at risk for antimicrobial related adverse events such as C.difficile infection

References

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STUDENT SECTION

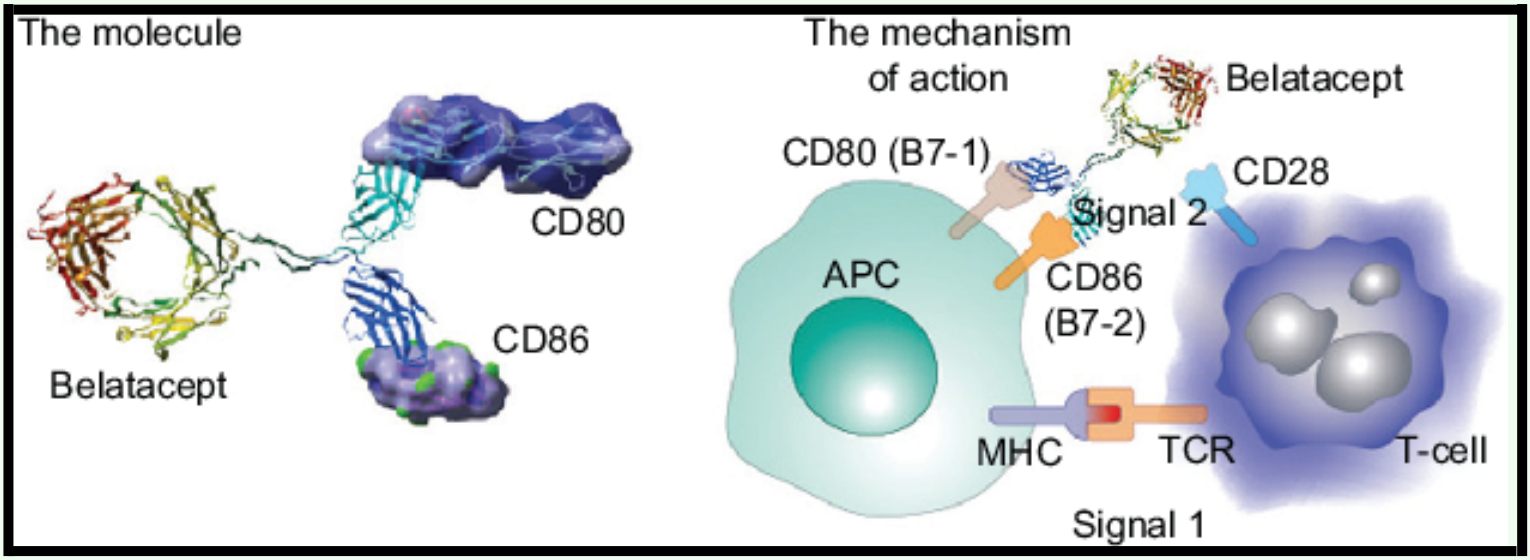
Emily Allen, PharmD Candidate 2021
The University of Texas at Austin
College of Pharmacy
Preceptor: Tracey Ellimuttil, PharmD

Amanda Gee, PharmD Candidate 2021
University of Houston
College of Pharmacy
Preceptor: Tracey Ellimuttil, PharmD

Belatacept: Unique Roles Both Pre- and Post-Transplantation

According to the World Health Organization, over 100,000 solid organ transplants are performed every year worldwide. Immunosuppressive regimens are key in improving overall graft function, preventing acute rejection, and improving patient survival post-transplant. Organ transplantation pharmacotherapy for immunosuppression consists primarily of an induction regimen followed by maintenance immunosuppression consisting of a calcineurin inhibitor (CNI), an antiproliferative agent, and corticosteroids. The biggest concern with the use of CNI post-transplant, especially in renal transplant recipients, is that CNIs have the potential to cause irreversible nephrotoxicity over time. This has led researchers to continue the search for an immunosuppressant with similar post-transplant success but without the risk of nephrotoxicity. As a result of this search, belatacept (Nulojix®) emerged as a potential CNI substitute in maintenance immunosuppression therapy.

Belatacept is a selective T-cell co-stimulation blocker that binds to CD80 and CD86 on the antigen-presenting cell and the T-cell, decreasing cytokine production and T-lymphocyte proliferation. It can be administered with other immunosuppressants with minimal drug interactions and is not affected by hepatic or renal dysfunction. Unlike CNIs, belatacept is an intravenous medication dosed monthly after completing the induction phase. The infrequent dosing of this medication allows this to be a possible alternative for patients struggling with medication adherence. Belatacept has a black box warning of increased risk for developing post-transplant lymphoproliferative disorder; therefore, Epstein-Barr Virus (EBV) serology should be tested before starting therapy.



Belatacept should be only administered to those with a positive EBV serostatus. The BENEFIT trial, a phase 3 study that compared belatacept-based immunosuppression with cyclosporine-based immunosuppression, showed that patient graft survival and mean estimated glomerular filtration rate (eGFR) were significantly higher with belatacept than with cyclosporine. This study showed that belatacept can provide similar graft survival rates while avoiding the nephrotoxic effects of calcineurin inhibitors. The biggest concern seen in these studies was the higher incidence of early acute cellular rejection (ACR) in the belatacept groups. For this reason, belatacept is not commonly used *de novo* post-transplantation. Since this study, belatacept's potential uses in specific patient populations and immunosuppressive desensitization therapies have been hypothesized.

Given the concern for early ACR post-transplant, Adams et al further explored the potential use of belatacept with transient use of CNI. In this study, 5 treatment groups (belatacept, tacrolimus, and 3 different combination regimens of belatacept and tacrolimus) were compared to determine the effects of these medication combinations on renal function, incidence of acute cellular rejection, development of donor specific antibody (DSA), graft failure, and mortality. The combination regimen of monthly belatacept dosing with a tacrolimus taper over eleven months was shown to reduce the risk of ACR while providing renal protection. Additionally, patients in the belatacept group had a significantly lower risk of DSA formation, which is associated with a lower incidence of antibody mediated rejection (AMR). The DSA reduction benefit shown in this study was consistent with the other published clinical trials leading to the evaluation of belatacept's utility in immunosuppressive desensitization therapies.

The DSA reduction benefit shown in this study was consistent with the other published clinical trials leading to the evaluation of belatacept's utility in immunosuppressive desensitization therapies.

Prior to transplant, patients undergo screening to determine their level of sensitization, or the number of antibodies they have against various human leukocyte antigens (HLA). The higher the sensitization, the less likely an adequate organ donor match may be found. Patients can become sensitized through previous pregnancies, blood product transfusions, or previous transplants. Desensitization therapies allow for the removal of these antibodies through immunosuppressive therapies. Two recent studies investigated the use of a proteasome inhibitor in combination with belatacept as desensitization therapy.

The biopsy results in the Ezekian et al trial showed a significant prolongation in graft survival and reduced antibody-mediated rejection (AMR) in all animal subjects. The study conducted by Alishetti et al investigated the use of this desensitization regimen in four highly sensitized heart transplant patients. The results showed that a belatacept-based combination regimen can significantly decrease HLA antibodies, B-cells, T-helper cells, and DSAs allowing patients a better chance at finding an optimal organ donor.

Overall, belatacept is a novel agent approved for renal transplant maintenance immunosuppression and is gaining increased use in other solid organ transplants. Due to belatacept's minimal adverse effect profile, it has shown promise as an alternative agent to the traditionally used calcineurin inhibitors. Finally, given its unique mechanism of action, belatacept has the potential to improve the success of desensitization therapies in highly sensitized patients awaiting transplantation.

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STUDENT SECTION

Taylor Jaramillo, PharmD Candidate 2021
University of Houston
College of Pharmacy
Preceptor: Jesse Harris, PharmD, BCCCP

Alyssa Chaplain, PharmD Candidate 2021
University of Houston
College of Pharmacy
Preceptor: Jesse Harris, PharmD, BCCCP

Treatment Modalities for Atrial Fibrillation

Atrial fibrillation (AFib) is the most common sustained cardiac arrhythmia and has significant effects on morbidity and mortality. According to the Centers for Disease Control and Prevention, AFib was mentioned on 175,326 death certificates and was the underlying cause of death in 25,845 of those deaths in 2018. The prevalence of AFib continues to increase as the population ages. It is estimated that 12.1 million people in the U.S. will carry a diagnosis of AFib in 2030.

Arrhythmias occur when there is a disruption in the normal electrical conduction of the heart, which interferes with the coordinated contractions of the atria and ventricles. Two mechanisms for the pathophysiology of AFib have been described. One mechanism is an abnormality in impulse generation from an area defined as an ectopic foci. Spontaneous impulse generation by foci may occur as a result of conditions such as hypoxia or electrolyte abnormalities. If the rate of spontaneous impulse generation exceeds that of the sinoatrial node, then a tachyarrhythmia known as rapid ventricular response may result. Another proposed mechanism is an abnormality in impulse conduction known as reentry. The reentrant mechanism involves indefinite propagation of the impulse and continued activation of previously depolarized tissue.

In addition to increasing age, patients with underlying heart disease including heart failure, valvular disease, hypertension, and coronary artery disease are at higher risk for developing AFib. These patients may present with shortness of breath, chest pain, palpitations, and fatigue. However, some patients may be

asymptomatic and AFib is found incidentally during routine workup. Treatment of AFib is indicated to reduce debilitating symptoms, decrease the risk of cardiomyopathy development, and prevent thromboembolisms associated with ischemic stroke. Currently, two pharmacologic treatment strategies exist for patients presenting with AFib, which are defined as rate and rhythm control strategies. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guidelines for the Management of Patients with Atrial Fibrillation suggest the initial use of rate control for most patients. However, the guidelines endorse rhythm control as a potential strategy for AFib caused by acute illness, unsuccessful treatment with rate control, presence of tachycardia-mediated cardiomyopathy, younger age, or first occurrence of AFib. Rate control as first line therapy is achieved with drugs such as beta blockers, non-dihydropyridine calcium channel blockers, digoxin, or amiodarone. Rhythm control therapy, when indicated, includes antiarrhythmic agents. Aside from pharmacologic treatment with antiarrhythmics, rhythm control may also be achieved via catheter or surgical ablation therapy. These procedures are used to treat AFib by scarring or destroying tissue in the myocardium to disrupt the abnormal impulse generation or conduction and utilize techniques such as radiofrequency or cryoablation. These ablation strategies are typically reserved for patients whose condition necessitates rhythm control yet have failed pharmacologic therapies.

Rate vs. Rhythm Control

Trial	Objectives	Methods	Results [HR; (95% CI)]	Conclusion
AFFIRM[8] (2002)	– Determine mortality benefit between the long-term tx strategies of rhythm or rate control – PE: overall mortality – SE: composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, & cardiac arrest	– Randomized, multicenter comparison trial – IC: ≥ 65 yrs or presented with risk factors for stroke or death (included recurrent or newly dx AFib) – Rhythm control n=2033 – Rate control n=2027	– No sig difference found in the PE or SE between the two treatment arms – Rhythm control experienced more deaths compared to rate control – Rate control experienced less adverse side effects & hospitalizations when compared to the rhythm control	– Rhythm control strategy provides no survival benefit over the rate control strategy – Lower risk of ADE with the rate control strategy
ATHENA[9] (2009)	– Determine if dronedarone reduces rate of hospitalization from CV events or death in pts with AFib – PE: first hospitalization due to CV events or death from any cause – SE: death from any cause, death from CV causes, & first hospitalization due to CV events	– Randomized, double-blind, placebo-controlled trial – IC: paroxysmal or persistent AFib or atrial flutter & at least one of the following (≥ 70 yrs; arterial HTN; DM; previous stroke, TIA, or systemic embolism; left atrial diameter ≥ 50 mm; & LVEF ≤ 40%) – Dronedarone n= 2301 – Placebo n=2327	– PE: 32% of pts in dronedarone arm compared to 40% in placebo arm [HR 0.76; (0.69-0.84)] – Death from any cause was 5% in dronedarone arm versus 6% in placebo arm [HR 0.84; (0.66-1.08)]	– Dronedarone reduced the incidence of hospitalization due to CV events or death from any cause in pts with AFib

ADE: adverse drug events, CI: confidence interval, CV: cardiovascular, DM: diabetes mellitus, Dx: diagnosed, HR: hazard ratio, HTN: hypertension, IC: inclusion criteria, LVEF: left ventricular ejection fraction, PE: primary endpoint, pts: patients, SE: secondary endpoint, sig: significant, TIA: transient ischemic attack, Tx: treatment, yrs: years

The literature for management of AFib is rapidly evolving and given the high rate of morbidity and mortality associated with AFib, adequate treatment is necessary for patients presenting with this debilitating illness. Current clinical guidelines for the treatment of AFib are based on the results from the AFFIRM trial. While there have been several publications since this landmark trial, these studies are designed with various treatment modalities making it difficult to create a uniform approach to AFib management. Recently, the EAST-AFNET 4 trial was published, which has the potential to redefine the utility of rhythm control therapy in current practice guidelines. This trial was a product of previous hypothesis generating trials such as ATHENA, CASTLE-AF, and CABANA. EAST-AFNET 4 assessed an early rhythm control strategy versus standard of care (rate control) in patients with newly diagnosed AFib (diagnosis < 12 months from trial enrollment). The trial was stopped for efficacy at the third interim analysis after a median follow-up of 5.1 years per patient. The primary outcome was a composite of death from cardiovascular (CV) causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome, and it occurred less often in patients assigned to early rhythm control than in patients assigned to usual care.

Catheter Ablation as Form of Rhythm Control				
CASTLE-AF[10] (2018)	– Determine the utility of catheter ablation for AFib in pts with HF who are receiving appropriate tx – PE: composite of death from any cause or hospitalization for worsening HF – SE: death from any cause, unplanned hospitalization related to HF, death from CV disease, stroke, unplanned hospitalization for CV disease, & any hospitalization	– Multicenter, open label, randomized, controlled trial – IC: paroxysmal or persistent AFib; an absence of response to, unacceptable side effects from, or unwillingness to take antiarrhythmic drugs; and NYHA class II, III, or IV HF & a LVEF ≤ 35% – Catheter ablation n=179 – Medical therapy n=18	– PE occurred in 28.5% of pts in ablation arm & 44.6% of pts in medical therapy arm [HR 0.62; (0.43-0.87)] – Death from any cause was 13.4% in ablation arm & 25% in the medical therapy arm [HR 0.53; (0.32-0.86)] – CV deaths occurred 11.2% in the ablation arm & 22.3% in the medical therapy arm [HR 0.49; (0.29-0.84)]	– Use of ablation therapy in pts with HF sig lowered the composite outcome of death and hospitalization – CV death was sig lower with ablation therapy
CABANA[11] (2019)	– Determine if ablation tx for AFib is more effective than drug therapy in pts with symptomatic and inadequately treated AFib – PE: composite of death, disabling stroke, serious bleeding, or cardiac arrest – SE: all-cause mortality	– Investigator-initiated, multicenter, prospective, randomized, open-label – IC: ≥ 65 yrs or < 65 yrs with ≥ 1 risk factors for stroke (HTN, HF, history of stroke, DM, or other heart problems), had ≥ 2 episodes of paroxysmal AF or 1 episode of persistent AF in previous 6 months	– PE occurred in 8.0% of pts in the catheter ablation arm & in 9.2% in drug therapy arm [HR 0.86; (0.65-1.15)] – 5.2% of pts in the catheter ablation arm & 6.1% in the drug therapy arm died during follow-up [HR 0.85; (0.60-1.21)]	– Provides further evidence for the efficacy of ablation in achieving rhythm control in pts with symptomatic AFib although it didn't show a sig reduction in the PE

CV: cardiovascular, DM: diabetes mellitus, HR: hazard ratio, HTN: hypertension, IC: inclusion criteria, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, PE: primary endpoint, pts: patients, SE: secondary endpoint, sig: significant, yrs: years

When comparing previous published literature on AFib, the AFFIRM trial included both patients with recurrent AFib and first-time occurrence whereas the EAST-AFNET 4 trial only included patients who had an early diagnosis of AFib. Therefore, the timing after a patient is diagnosed with AFib should be considered

when determining rate or rhythm control therapies given the significant cardiovascular benefits displayed in the EAST-AFNET 4 trial. In the ATHENA trial, patients on rhythm control with dronedarone had a reduction in first hospitalization due to CV events or death when compared with placebo. Similarly, 16.7% of patients in the EAST-AFNET 4 trial were on dronedarone for rhythm control and displayed beneficial outcomes. Aside from pharmacotherapy, EAST-AFNET 4 also included patients treated with catheter ablation therapy as a form of rhythm control. The CASTLE-AF trial showed benefit with the use of cardiac ablation as a method for rhythm control specifically in patients with heart failure. Although the results of the CABANA trial did not show a significant difference in death, disabling stroke, serious bleeding, or cardiac arrest when using catheter ablation compared to pharmacologic therapy, this trial does support the utility of non-pharmacologic rhythm control in AFib patients.

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation				
EAST-AFNET 4[12] (2020)	– Determine whether a strategy of early rhythm-control therapy would have better outcomes in pts with early AFib than usual SOC – PE: composite of death from CV causes, stroke, or hospitalization with worsening of HF or ACS – SE: number of nights in hospital per year	– International, investigator-initiated, parallel-group, randomized, open, blinded outcome-assessment trial – IC: ≥ 18 yrs with early AFib (AFib ≤ 12 months from enrollment) & were > 75 yrs, had previous TIA or stroke, or had CV conditions with CHA_2DS_2VASC score of ≥ 2 – Rhythm control n=1395 – Usual care n=1394	– PE occurred less often in pts assigned to early rhythm control than in pts assigned to usual care [HR 0.79; (0.66-0.94) – No statistical differences between the groups for the number of nights in hospital per year	– When initiated early after AFib diagnosis, a rhythm-control strategy is superior to usual care in improving CV outcomes among pts with recent diagnosis of AFib and concomitant CV condition

ACS: acute coronary syndrome, CV: cardiovascular, HF: heart failure, HR: hazard ratio, IC: inclusion criteria, PE: primary endpoint, pts: patients, SE: secondary endpoint, SOC: standard of care, TIA: transient ischemic attack

Although a large amount of data is available, there is a lack of consistency to support or refute one treatment strategy over another for AFib. Clinicians should consider many factors when treating these patients such as specific patient characteristics, institutional protocols, and physician preference. With the newly published EAST-AFNET 4 trial, a shift in direction for future literature and updates to clinical guidelines will likely be reflective of the substantial outcomes from this study.

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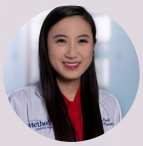

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