University HOSPITAL
Newark, NJ

Pharmacy News

Second Quarter 2021
Vol. XIV, Issue 2

Special Points of Interest:

- P&T Update-Formulary Additions/Deletions
- Policy and Procedure Update
- Clinical Trials at University Hospital
- Teprotumumab (Tepezza®): An Eye-Opening Novel Therapy
- Cardiovascular Benefits with Low Dose Colchicine Use
- Guidelines for Naloxone Use
- Naloxone: Adult Dosing and Administration

P&T Update

Formulary Additions

1. ***Dextromethorphan***
   Dextromethorphan has been studied as an adjunct for postoperative pain due to its mechanism of action as an NMDA receptor antagonist. It has been approved for formulary addition with 48-hour duration limit for use in perioperative pain management.
2. ***Cabotegravir-Rilpivirine ER (Cabenuva®)***
   Cabotegravir-Rilpivirine ER IM injection is an integrase inhibitor and NNRTI HIV IM monthly treatment combination. This monthly injection is not approved for home injection by patient. The monthly injection must be provided by physician offices/clinic to patients. Infectious disease clinic will work on optimal patient selection to ensure prescription coverage via specialty pharmacy prior to starting regimen.
3. ***Capsaicin cream***
   Capsaicin is a topical cream used for requested indications of muscle and joint pain, diabetic neuropathy, and neuropathic pain.

Formulary Deletions

NONE

Formulary Restriction Modification

1. ***Sodium zirconium cyclosilicate (Lokelma®)***
   Sodium zirconium cyclosilicate is a potassium binder used to decrease the excessive potassium from the body. Currently restricted to the Cardiology/Nephrology services or a single dose is allowed through the order set. The Committee has voted to approve an unrestricted use in the hospital. Formulary restriction of Sodium zirconium cyclosilicate (Lokelma) to unrestricted – Approved.
2. ***Glucose Oral Gel 40% (Sweet Cheeks)***
   Line extension was requested and approved for the 40% oral glucose gel.

Policies & Procedures/Floor stocks

1. 707-500-115 Standard Concentrations for IV Infusion Medications- Update:
   The policy was presented to include the update on the neonatal intravenous drips concentration that have been worked on collaboratively between the Neonatology providers/PCS and the Pharmacy. – Approved
2. 707-500-110 High Risk High Alert & Look Alike Sound Alike Medications -Update:
   An update to the existing policy was presented to list the high alert high risk/ look alike sound alike (HRHA/LASA) medication list for the year 2021. – Approved
3. 707-500-101 Dangerous abbreviation policy- Update:
   The policy is updated with the year 2021 dangerous abbreviations. – Approved
4. Pharmaceutical Care Division Annual Policy/Procedure Approval
   The annual policy/procedure pharmacy manual was presented for approval. – Approved

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P&T Update

Continued from Page 1

Policies & Procedures/Floor stocks

5. Naloxone Rescue Kit Distribution Protocol
   A policy outlining the details on dispensing the naloxone rescue kit upon discharge to the patients at risk of opioid overdose, by the Emergency department was presented. – Approved
6. Annual Review of Updates to UH Anti-Infective Related Policies
   707-900-102 UH Antimicrobial Stewardship Program Policy
   707-600-176 Order Entry, Verification, and Provision of Restricted
7. Anti-Infectives
   707-800-104 Needle Stick Medication Starter Kits for HIV Post Exposure Prophylaxis

An annual review/update to the following policies pertaining to the anti-infectives was presented:

- 707-900-102 University Hospital Antimicrobial Stewardship Program Policy
- 707-600-176 Order Entry Verification and Provision of Restricted Anti-Infectives
- 707-800-104 Needle Stick Medication Starter Kits for HIV Post Exposure Prophylaxis: Recent formulary additions were added to policy to reflect the P&T committee approvals and explicit verbiage was added indicating scope of the policy.
- 707-900-102 University Hospital Antimicrobial Stewardship Program Policy
- The policies are available on the hospital's official policy website.
  Approved

8. 707-500-102 Automatic Route Change by Pharmacy:
   IV to PO/enteral interchange P&P revision presented for approval. UH TJC survey for comprehensive stroke in 2019 received an RFI on medication administered PO when patient had NGT - approved
9. 707-600-175 Poly-pharmacy antipsychotic Guideline reviewed, no changes – approved
10. 707-500-119 Clozapine Guideline update authorizing provider – approved
11. 707-300-101 University Hospital Formulary Addition policy revising the new UH logo- approved
12. 707-400-108 Resuscitation Equipment/Emergency Boxes Policy revision to include ET tube & Blakemore tube needed for neonates and new born
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Anti-Infective Subcommittee

Review of UH Antimicrobial Stewardship Program (ASP) Annual Report Summary CY 2020
Review of UH ASP Annual Goals and Strategic Action Plan for CY 2021
UH ASP Assessment of CDC Core Elements of Hospital Antibiotic Stewardship Programs
Review of Draft UH CY 2020 Antibiograms

Clinical Trials at University Hospital

What are Clinical Trials & Why are They Important?
Clinical trials are an essential component in advancing medical knowledge and finding new and better ways to prevent, screen for, diagnose, and treat certain diseases and conditions. These research studies can lead to the discovery of new treatments for unmet medical needs, or even find improvements in treatments and quality of life.[1] Each trial answers a specific scientific question and can also look for comparisons between new and existing treatments.[2] Thus, healthcare providers can use clinical trials to learn whether a new drug, treatment, or combination works and is safe to use for certain groups of people.[3]

The driving components of a clinical trial include the protocol and principal investigator. A protocol is an action or research plan in a clinical trial. It is designed to answer specific questions and to safeguard the health of the participants in a clinical trial. It explains what will be done, how it will be done, and why each step in the trial is necessary.[2] Additionally, the protocol specifies who qualifies to join ("eligibility criteria"), any drugs or other treatments that will be given (including how they will be given, the dose, and how often), and whether there will be a control group or other ways to limit research bias.[1] The principal investigator is usually a doctor who prepares this protocol, submits it to the Investigational Review Board (IRB), and supervises all the data in the clinical trial. Their research teams are made up of doctors, pharmacists, nurses, social workers, and other healthcare professionals who will also be responsible for carrying out the protocol and recording of data.[2]

Phases of a Clinical Trial[1,3]

	Phase I	Phase II	Phase III	Phase IV
Purpose	To evaluate the drug's overall **safety** and determine the safest **dose** and route of administration of the drug after it has been tested in lab and animal studies.	To evaluate the drug's safety and efficacy. If results from this phase show that the new drug may be just as beneficial or more beneficial than the existing drug to treat the same or similar ailments, then researchers can move to Phase 3.	To confirm the drug's efficacy, monitor side effects, compare it to other commonly used treatments or to a placebo, and collect information to ensure safe use of the drug.	To evaluate the long-term risks and benefits of a medication after the drug has been approved by the FDA through the New Drug Application (NDA) process and available in the market (side effects, drug interactions, effectiveness).
Study Participants	20 - 100 healthy volunteers or people with the disease/ condition	Up to several hundred people with the disease/ condition	300 - 3,000 volunteers with the disease/condition	Several thousand volunteers with the disease/condition
Length of Study	Several months	Up to 2 years	1 to 4 years	Several years
Key Points	~70% of drugs move to next phase	~33% of drugs move to next phase	~25-30% of drugs move to next phase	This phase is completed post-market

Clinical trials can follow a typical series from small-scale, Phase 1 studies to large scale, Phase 3 and 4 studies.[1] Phases of clinical trials may also be broadly referred to as "early phase" or "late phase" studies as phases may overlap (i.e. 2/3 occur at the same time). More information regarding each specific type of trial can be found in the table below.

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Clinical Trials at University Hospital

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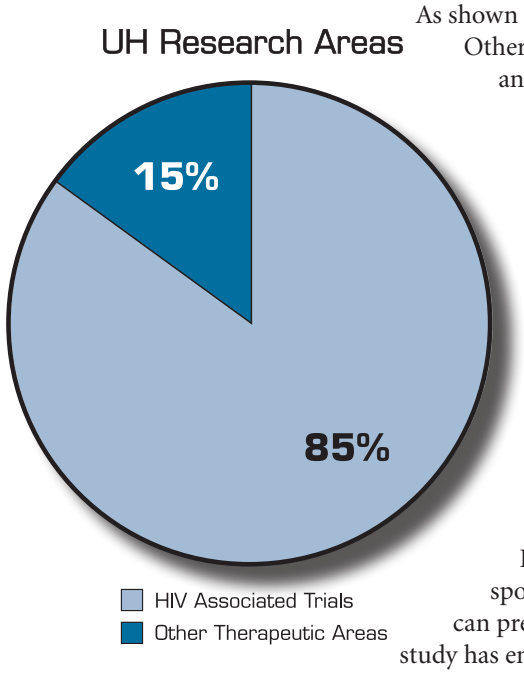
University Hospital Clinical Trial Highlights

Clinical trials first started at University Hospital (UH) more than 15 years ago in 2005. As of January 2021, there are a total of ~39 open studies of which ~35 are actively recruiting.



As shown above, the majority of trials at UH are for HIV and associated diseases/prevention. Other therapeutic areas (15%) include 6 COVID-19 studies, 5 oncology studies, and 3 transplant studies. There are a total of over 300 patients on these trials, predominantly being adults but also including special populations such as people post-incarceration, pregnant mothers, and geriatrics. These patients' medications are supervised by our IRB Pharmacist, Aidan Ziobro, and their general care by ~20 investigators at UH. The role of the pharmacist includes ensuring the right patient gets the right drug and dose (or placebo), properly storing and dispensing these investigational drugs, and maintaining the integrity of the trial in terms of randomization and blinded studies. All of this information must be documented for all trials at UH.

Currently UH is a part of Phase 2, 3, and 4 trials. Of the 39 total studies, 5 are focused on preventative treatment including vaccines for HIV (Janssen and HIV Vaccine Trials Network (HVTN), COVID-19 (Pfizer, Moderna (COVID-19 Prevention Network (COVPN)), and Regeneron), and RSV (Pfizer). These trials feature potential scientific breakthroughs which may benefit thousands of patients. For example, Mosaico is a large, double-blind, placebo-controlled, phase 3 study sponsored by Janssen that will try to prove whether an investigational vaccine regimen can prevent HIV infection in North America, Latin America, and Europe. To do this, the study has enrolled cisgender men and transgender people who have sex with cisgender men and/or transgender people.[4] Participants will receive either the Ad26.Mos4.HIV vaccine (at months 0, 3, 6, and 12) or the Bivalent gp140 vaccine (at months 6 and 12), both via IM injection into the deltoid muscle, or placebo.[5] The study vaccines are not made from live HIV, killed HIV, or HIV-infected human cells. Rather, the Ad26 vaccine is made from Adenovirus type 26. Bivalent gp140 is made of 2 man-made proteins called Clade C gp140 and Mosaic gp140, which are similar to a protein found on the surface of HIV. The Clade C gp140 protein is made to resemble an HIV protein most commonly found in southern Africa. The Mosaic gp140 is made to resemble a mix of many different HIV proteins found around the world.[4]

UH has been a part of this trial for the past 2 years, currently with 6 patients. The estimated study completion date is in 2023 and if Mosaico shows that the study vaccine regimen works, it will be a very important step in finding the first safe and effective vaccine for the prevention of HIV/AIDS.[4,5]

The Future of Clinical Trials

Clinical trials are a key step in advancing new treatments from the research setting to the clinic. However, they are not always successful, and each study comes with a set of risks and potential benefits.[1] Many factors can contribute to study failure, and recruitment in clinical trials remains as one of the biggest issues. According to the National Institutes of Health (NIH), more than 80% of clinical trials in the U.S. fail to meet their enrollment timelines.[6] To address these types of concerns in Newark, the Rutgers New Jersey Medical School started an infectious diseases group called Research With a Heart. This group provides culturally competent research on HIV, Hepatitis C, and Influenza through community engagement, collaboration, and education. They spread awareness about the treatment and prevention of these diseases through campaigns on social media and talks on health equity.[7] This homegrown initiative is a prime example of utilizing platforms like Instagram and Facebook to reach more patients and create a lasting impact.

Furthermore, digital health tools are being integrated into trials to reduce patient travel burdens and improve convenience, making it more likely that a patient will enroll and stay. This has especially been helpful during COVID-19 as tools can be used to acquire patient consent virtually. There are also remote monitoring devices and devices patients can wear that collect data and monitor changes in key indicators (e.g., weight, blood pressure). Additionally, apps available on patients' mobile phones enable filling out questionnaires and completing tasks in seconds. Using Apple's ResearchKit framework, the Icahn School of Medicine at Mount Sinai in New York developed a free Asthma Health app. The app was downloaded by 50,000 people and enabled users with asthma to participate in a large-scale medical research study entirely through the iPhones in their pockets. The study enrolled more than 8,600 participants within six months without any in-person contact with researchers. The app also helped widen the geographic reach of the study as 87% of the participants enrolled did not live near the study site in New York. The FDA has also developed a similar app called the MyStudies App which creates a centralized, user-friendly platform where sponsors can monitor their patients. This data then gets linked to traditional clinical trials and registries, thus providing easier access to patient data and real-world evidence. The result of such apps is a much larger and more varied study group, more efficient and frequent data, and much more meaningful results.[1,6]

This recognition of the advantages of digital health has kick-started collaborations between pharmaceutical companies, healthcare providers, and health informatics which has led to increased patient recruitment and engagement in clinical trials. Today, people are living longer lives from successful treatments that are the results of past clinical trials and faster drug discovery and development.[6] Clinical trials are thus at the core of the healthcare industry and the key to making progress against any disease state for our patients.

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University HOSPITAL Newark, NJ
Pharmacy News

Teprotumumab (Tepezza®): An Eye-Opening Novel Therapy

Importance of Teprotumumab[1]

Teprotumumab is the first drug to be approved for the treatment of thyroid eye disease as of January 2020. It was contingently added to the University Hospital formulary in October 2020 for 6 months upon medication usage review through the white bag process only. This means the medication will be dispensed by an external specialty pharmacy and sent to the physician's office, hospital, or clinic for administration.

Pathophysiology and Epidemiology of Thyroid Eye Disease[2]

Thyroid eye disease is an autoimmune disorder of the retrobulbar tissue that is most commonly associated with Graves' hyperthyroidism; however, it may also be present in patients with hypothyroidism or normal thyroid function. An immune reaction is incited by the activation of autoantibodies against thyroid-stimulating hormone receptors (TSHR). These autoantibodies then attack TSHRs in the retrobulbar tissue, which are over-expressed in patients with Graves' hyperthyroidism, resulting in fluid accumulation between the muscle fibers and expansion of orbital adipose tissue.

Thyroid eye disease is more likely to affect women in their third to fifth decade of life with an incidence of 16 women per 100,000 persons per year. Other risk factors include cigarette smoking, older age at diagnosis of thyroid disease, longer duration of thyroid disease, uncontrolled thyroid dysfunction, and previous radioactive iodine treatment.

The diagnosis of thyroid eye disease is made based on patient history and physical exam. Symptoms can range in severity; mild symptoms include dry eye, and more severe symptoms include corneal ulceration and compressive optic neuropathy. Other symptoms can include blurry vision, orbital aching, eyelid or conjunctival swelling, diplopia, and bulging eyes (proptosis).

Current Therapies for Thyroid Eye Disease[2]

The primary goal of treatment is to achieve and maintain a euthyroid state with anti-thyroid drugs, thyroidectomy, or radioactive iodine. In about two-thirds of patients with mild thyroid eye disease, symptoms will improve spontaneously within 6 months; treatment beyond symptom management with lubricant eye drops is not necessary. However, selenium supplementation may be considered in patients with mild disease, as it has been shown to improve quality of life, reduce severity, and slow disease progression.

In patients with moderate-to-severe thyroid eye disease, oral and intravenous corticosteroids are frequently used for their anti-inflammatory properties. Orbital radiotherapy or orbital decompression can be considered in patients not responding to steroids or with sight-threatening disease, respectively.

Pharmacokinetics and Pharmacodynamics of Teprotumumab[1]

- Mechanism of action: IgG1 monoclonal antibody directed against the insulin-like growth factor (IGF)-1 receptor
- Administration: IV infusion over 60-90 minutes given at 10 mg/kg for the first dose, followed by 20 mg/kg every 3 weeks for another 7 doses
  - Available in 500 mg vials of lyophilized powder for reconstitution
  - No dosage adjustments indicated for renal or hepatic impairment
- Distribution: estimated central V_d is 3.26 L and peripheral V_d is 4.32 L
- Metabolism: not fully characterized, but expected to undergo proteolysis
- Elimination: half-life approximated at 20 days
- Warnings: infusion reactions with increased blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscle pain; exacerbation of pre-existing irritable bowel disease (IBD); elevated blood glucose; and embryo-fetal toxicity
- Adverse events: muscle spasms (25%), nausea (17%), alopecia (13%), diarrhea (12%), and fatigue (12%)

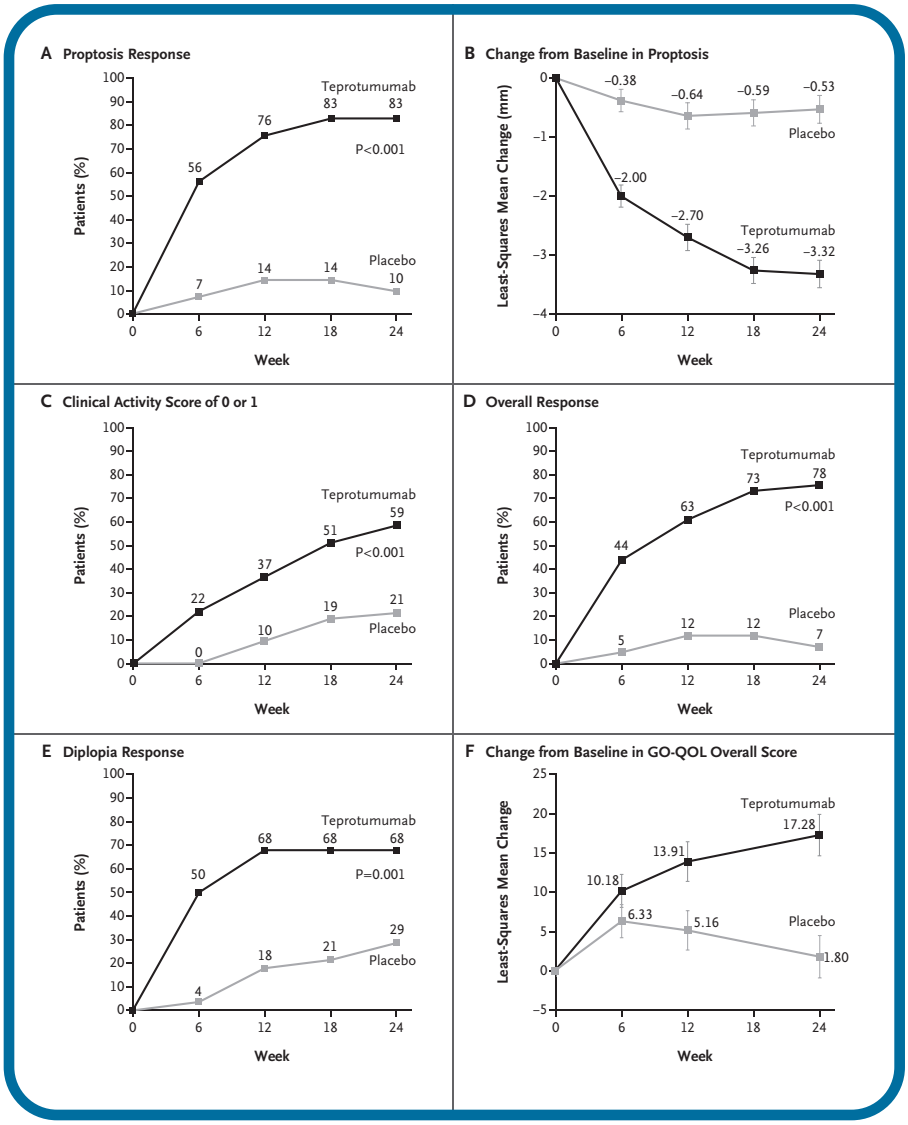
Efficacy Data for Teprotumumab[3,4]

In a randomized, double-masked, placebo-controlled phase 3 trial, Douglas et al. studied the effects of teprotumumab on patients with active, moderate-to-severe thyroid eye disease. The study included adult patients diagnosed with Graves' disease who had ocular symptoms beginning within 9 months of the baseline assessment. Patients were required to be euthyroid, with mild hypothyroidism or hyperthyroidism allowed. Patients who had undergone previous orbital irradiation or surgery for thyroid eye disease, as well as patients who received a cumulative dose of ≥ 1 g of methylprednisolone or glucocorticoid equivalent were excluded.

The primary outcome measured the rate of proptosis response at week 24, defined as a reduction in proptosis of at least 2 mm. Of the 41 patients randomized to receive teprotumumab, 34 patients

(83%) demonstrated a proptosis response, while 4 of the 42 patients randomized to placebo (10%) achieved a proptosis response [$p < 0.001$].

Another measure of efficacy is the Clinical Activity Score that reports a sum score of symptoms of inflammation, consisting of pain, redness, swelling, and impaired function. For each symptom present, one point is added up to a possible 10 points. Scores of 0 or 1 are considered indicative of no or minimal inflammation. In this study, rates of overall response, defined as a composite outcome of both a reduction in proptosis and Clinical Activity Score, were significantly higher in the teprotumumab group (78% vs. 7% [$p<0.001$]). In addition, measures of inflammation were better in the teprotumumab group, with 59% of the teprotumumab group achieving a Clinical Activity Score of 0 or 1 compared to 21% of the placebo group [$p<0.001$]. Furthermore, scores on the Graves' ophthalmopathy-specific quality-of-life questionnaire improved significantly more in the teprotumumab group compared to placebo (13.79-point change vs. 4.43-point change [$p < 0.001$]).



Safety Data for Teprotumumab[3,5]

Adverse events are reported in clinical trials based on grades of severity of the adverse event; possible classifications range from grade 1 to 5, in which grade 1 is asymptomatic or mild symptoms, grade 2 is moderate, grade 3 is severe or medically significant, grade 4 is life-threatening, and grade 5 is death related to the adverse event. Among the adverse events reported in the teprotumumab group within 21 days of the final dose, most were grade 1 or 2 in severity. The most common adverse events reported more frequently in the teprotumumab group were muscle spasms (32% vs. 10% placebo), alopecia (20% vs. 12%), nausea (15% vs. 10%), fatigue (12% vs. 2%), dry skin (10% vs. 0%), and dysgeusia (10% vs. 0%). Overall, serious adverse events occurred in 5% of the teprotumumab group and 2% of the placebo group; the two incidents in the teprotumumab group included one case of pneumothorax likely unrelated to the drug and an infusion reaction that led to withdrawal from the trial.

Cost of Teprotumumab

It is estimated that 20-50 patients per year will be eligible for teprotumumab use in University Hospital. Though it has demonstrated efficacy via a significant reduction in proptosis and diplopia, the cost of the drug may prohibit use and limit availability to patients. The current average wholesale price of a single 500 mg vial of teprotumumab is $17,880.[6] Based on the dosing schedule, the cost of a complete regimen for a 70 kg patient would be more than $400,000. Therefore, it is important to identify patients with moderate-to-severe symptoms who would gain limited benefit from existing therapies in order to make this a cost-effective treatment option.

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Teprotumumab (Tepezza®): An Eye-Opening Novel Therapy

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Cardiovascular Benefits with Low Dose Colchicine Use

Colchicine's Anti-Inflammatory Properties

Colchicine is an anti-inflammatory agent that has an approved Food and Drug Administration (FDA) indication for gout while having other off label indications. Recently researchers have suggested that inflammation plays a role in the pathogenesis of cardiovascular disease and related complications, such as myocardial infarctions and ischemic strokes. Myocardial infarctions occur when blood vessels do not get enough oxygen, due to narrowing of the blood vessels caused by buildup of plaques and eventually leading to ischemia[4]. Studies have also suggested that mitigating inflammation may reduce the risk of such cardiovascular events. Previous trials have shown that Colchicine appears safe and effective for secondary prevention of cardiovascular disease on a small scale but a rigorous trial is needed to be completed to confirm the real impact it may have on the burden of cardiovascular disease.

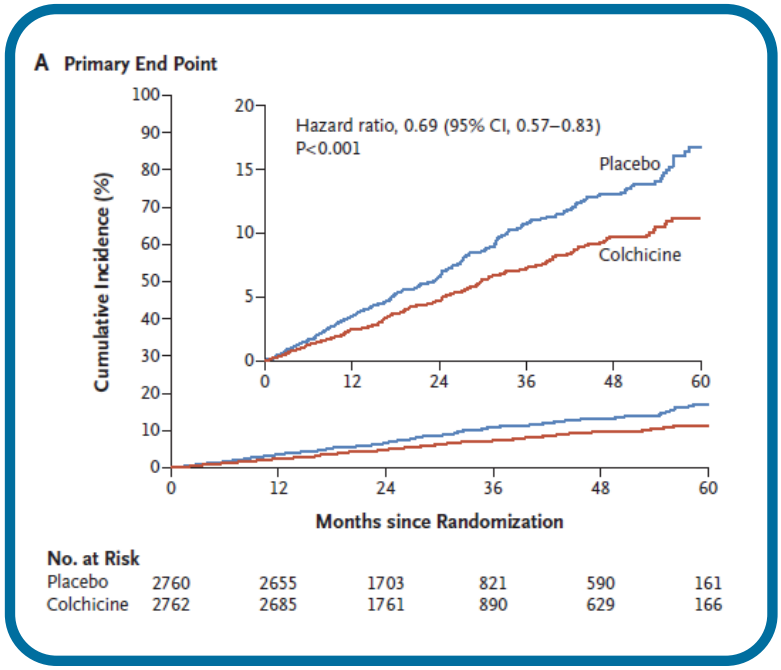
Low Dose Colchicine Phase II Trial[1]

This past fall, the New England Journal of Medicine published information regarding a randomized, placebo-controlled, double blind phase 2 study designed to determine the exact use of colchicine in patients with coronary artery disease (CAD). This study conducted in Australia and the Netherlands consisted of 5,522 participants who were randomized 1:1 to receive either low dose colchicine, colchicine 0.5 mg once daily, or placebo. The primary endpoint was a composite endpoint of cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization.

Inclusion criteria for this trial consisted of patients between the ages of thirty-two and eighty-two, evidence of CAD such as coronary angiography or a coronary artery calcium score of greater than 400, and lastly, must be clinically stable for at least 6 months prior to starting treatment. Participants were excluded if they had moderate to severe renal impairment (serum creatinine > 2.0 mg/dL or estimated glomerular filtration rate < 50 mL/min/1.732 m^2), severe heart failure (stage 3 or 4), severe valvular heart disease, or known side effects from colchicine. Based on baseline characteristics, the average patient for this trial was about 66 years old, male, having stage 1 or 2 renal disease, having at least one comorbidity, and currently taking a lipid lowering agent and antiplatelet therapy.

After a median duration of 28.6 months, a primary end point event occurred in 187 patients (6.8%) of the colchicine group and in 264 patients (9.6%) of the placebo group, with a hazard ratio of 0.69 (95% CI, 0.57 -0.83) therefore resulting in a 31% lower relative risk of cardiovascular events for patients receiving colchicine[1]. As this was a composite endpoint, the breakdown of each individual endpoint

was also noted. Out of the three composite endpoints, the most benefit was seen in reduction of ischemic stroke. It is important to highlight one of the additional end points that was tested was death from any cause, resulting in hazard ratio of 1.21 when colchicine was compared to placebo. It was also recorded that when viewing adverse effects, noncardiovascular deaths were viewed to be in favor of placebo rather than colchicine, noting the hazard ratio was 1.51, which highlighted potential concern to the investigators. The most common adverse event reported by participants was gastrointestinal upset or irritation; due to colchicine providing a relatively favorable safety profile.



Critique of Findings

One limitation of this trial was the lack of representation in women with CAD as this does not truly represent the amount of women with chronic coronary disease in the general population. Another limitation to note is that baseline assessments, such as blood pressure, lipid levels, C-reactive protein levels, or any other laboratory indicators of inflammation, were not collected at baseline or any period during the trial therefore it is unknown if colchicine has any effects on the inflammatory state. It is also important to highlight the incidence rates of death from any cause and noncardiovascular death were higher with colchicine than with placebo. This finding in the trial makes it a concern of where colchicine may fit in guidelines and recommendations for patients with CAD. Additional studies on a larger scale may be needed to determine the exact implementation of this anti-inflammatory drug in the cardiovascular space although risk reduction has been established when compared to placebo.

The Future Possibilities

In the future, it is possible with more studies regarding the efficacy of colchicine for secondary prevention of stable and acute phases of coronary artery disease, the anti-inflammatory characteristics of this drug may translate into improving cardiovascular survival[2]. It is also important to be alert for colchicine uses other than gout and to not be surprised to see some cardiac indications for this drug. It is possible to see colchicine added to aspirin or NSAID regimes for up to 6 months for pericarditis as it may speed recovery and limit recurrence of inflammation around the heart[3].

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Guidelines for Naloxone Use

INDICATIONS
- Complete or partial reversal of opioid-induced ventilatory depression

CRITERIA FOR USE
- Patients should meet both of the following criteria prior to the administration of naloxone:
  - Suspected or documented exposure to an opioid agonist
  - Respiratory rate < 8 breaths/min for adults (< 50% age-appropriate rate for children) or clinical signs of hypoventilation/ respiratory failure
- Naloxone is not indicated to reverse sedation in patients without ventilatory depression

THERAPEUTIC CATEGORY
- Opioid Antagonist

MECHANISM OF ACTION
- Pure opioid antagonist that competitively inhibits binding of opioid agonists to opioid receptor

PHARMACOKINETICS
- Onset IV: ~2 minutes
- Duration: 20 – 90 minutes [dose/route of naloxone (IN > IM > IV duration)]
  - Be mindful of difference between duration of naloxone and duration of opioid, naloxone is generally shorter acting than the opioid
- Metabolism: primarily hepatic via glucuronidation

ADVERSE REACTIONS
- Signs of opioid withdrawal syndrome (e.g., yawning, irritability, agitation, lacrimation, diaphoresis, rhinorrhea, piloerection, mydriasis, vomiting, diarrhea, tachycardia, hypertension). Adverse effects are dependent on the dose and route of administration of naloxone and the patient's baseline degree of opioid dependence.
- Agitation, anxiety, and craving may be severe and lead to poor patient decision-making and difficult clinical and interpersonal situations.
- A large increase in catecholamine release occurs and may result in adverse effects such as pulmonary edema, myocardial ischemia, dysrhythmia, heart failure, or cerebrovascular changes.

PRECAUTIONS
- Use with caution in patient with pre-existing cardiovascular disease
- Excessive doses of naloxone in opioid-dependent patients (e.g. history of chronic opioid analgesic use, methadone maintenance, heroin/fentanyl use) may precipitate opioid withdrawal and/or exacerbate pain
- Duration of action of some opioids may exceed that of naloxone; therefore, patients must be closely observed for at least 2 hours after naloxone for re-emergence of ventilatory depression
- Clinical evaluation should be utilized to rule out other causes of ventilatory depression

SOURCES:

- Nelson LS, Howland MA (2015). Antidotes in Depth. In Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LS, Hoffman RS. Goldfrank's Toxicologic Emergencies, 11th Edition. New York, McGraw Hill, 2019. https://accessemergencymedicine.mhmedical.com/content.aspx?sectionid=210262002&bookid=2569#216812167 https://accessemergencymedicine.mhmedical.com/content.aspx?sectionid=210266395&bookid=2569#216816611
- Naloxone. In: Lexi-Tox Online. Hudson, OH : Lexi-Comp, Inc. https://online.lexi.com/lco/action/doc/retrieve/docid patch_f/7338?cesid=4YIJp4pZhUV&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dnaloxone%26t%3Dname%26va%3Dnaloxone#doa

Naloxone: Adult Dosing and Administration

Patients should be clinically monitored for at least 2 hours after naloxone is administered. Patients should optimally be monitored with capnometry and pulse oximetry if receiving oxygen or pulse oximetry alone without oxygen.

<u>Opioid Induced Ventilatory Depression in Opioid-Dependent or Unknown Patient</u>
(RR < 8 breaths/min or clinical signs of hypoventilation/respiratory failure)

- Provide ventilatory support and oxygenation
- Administer **naloxone 0.02-0.04 mg** IVP over 15 seconds, repeat dose in 2 minutes
  - If no response to 0.08 mg, administer 0.2 mg, 0.4mg, 2 mg, and finally 10 mg (rarely) as necessary until therapeutic response*
    - If no response is seen after the 10 mg dose, opioid is not likely responsible
  - Naloxone 0.4 mg diluted in 9 mL NS in a 10 mL syringe to yield a 0.04 mg/mL solution
- Note that with low-dose naloxone, patient arousal may be slow in onset and more subtle. Provide gentle stimulation before redosing.
- If patient develops withdrawal after bolus, allow effects of bolus to abate (typically about 30 minutes)
- If ventilatory depression recurs, redosing is suggested. If recurrent, see section on *Continuous Infusion*

<u>Opioid-Induced Ventilatory Depression in Known Opioid Naïve Patient</u>
(RR < 8 breaths/minute or clinical signs of hypoventilation or respiratory failure)

- Provide ventilatory support and oxygenation
- **Naloxone 0.4 mg** undiluted IVP over 15 seconds, repeat dose every 2 to 3 minutes as necessary for therapeutic response*.
  - If ventilatory depression is not reversed after initial bolus, administer increasing doses of 0.4 mg, 2 mg, and up to 10 mg of naloxone as IV bolus
- If ventilatory depression recurs, redosing is suggested. If recurrent, see section on *Continuous Infusion*

<u>Continuous Infusion</u>
(If repeated doses do not maintain adequate ventilation, consider a continuous infusion of naloxone)

- Provide capnometry and pulse oximetry with oxygen, or pulse oximetry alone without oxygen
- **Naloxone 2 mg/** 500 mL NS or D5W (4 mcg/mL)
  - If naloxone bolus successful, administer 2/3 of the effective bolus dose per hour by IV infusion
    - If patient develops withdrawal during infusion, stop the infusion and allow effects to abate
      - Restart the infusion at half of the initial infusion rate
    - If patient develops ventilatory depression during infusion, re-administer initial effective bolus dose and increase infusion by half (1.5x) the initial rate
      - Assess the patient for continued opioid absorption and other etiologies for ventilatory depression

**Therapeutic response defined as adequate ventilation with or without alertness (RASS- Richmond Agitation Sedation scale -1 to 0) without the onset of withdrawal or significant pain. Note that patients die from opioid poisoning primarily through ventilatory depression, and thus this is the endpoint for therapy. Patients may not wake up.*

Submitted by,
Dr. Lewis Nelson, MD
Nishat Faruqui, Pharm. D.

University Hospital Formulary Additions and Deletions for January 2019– December 2019

Generic Name	Brand Name	P&T Date	Approved	Denied	Deleted	Reason/Comments /Criteria
Bupivacaine Liposome Injectable Suspension	Exparel	Jan 2019		X		
Glimepiride 1mg and 4mg tablets		Jan 2019			X	
Atorvastatin 80mg tablets		Jan 2019			X	
Glipizide ER 5mg and 10mg tablets		Jan 2019			X	
Niacin 500mg tablets		Jan 2019			X	
Paroxetine 30mg tablets		Jan 2019			X	
Nadolol 40mg and 80mg		Jan 2019			X	
Medroxyprogesterone 10mg tablets		Jan 2019			X	
Haloperidol 20 mg tablets		Jan 2019			X	
Premarin 1.25mg tablets		Jan 2019			X	
Rasburicase	Elitek	Feb 2019	X			Restricted to approval by Nephrology/Oncology service
Eribulin	Halaven	Feb 2019	X			Restricted to the oncology service
Pembrolizumab	Keytruda	Feb 2019	X			Restricted to the oncology service
Ado-Trastuzumab Emtansine	Kadcyla	Feb 2019	X			Restricted to the oncology service
Paclitaxel Protein Bound	Abraxane	Mar 2019	X			
Rotavirus RV1	Rotarix	Mar 2019	X			Ambulatory Care clinic outpatient use
Dtap/IPV 0.5ml	Kinrix	Mar 2019	X			Line extension
MMR-V 0.5ml	ProQuad	Mar 2019	X			Line extension
Loperamide 1mg/7.5ml		Mar 2019	X			Line extension
Selzentry 150mg tablets		Mar 2019			X	
Phenol 89% bottle		Mar 2019			X	

Cefotaxime Injection		Mar 2019			X	
Loperamide 1mg/5ml		Mar 2019			X	Discontinued by manufacturer
Epoprostenol	Flolan	April 2019	X			Line extension
Hydrocortisone 0.5% ointment		April 2019			X	Discontinued by manufacturer
Hydrocortisone 1000mg injection		April 2019			X	
Desipramine 50mg		April 2019			X	
Methylprednisolone 2000mg injection		April 2019			X	
Sodium Zirconium Cyclosilicate		May 2019	X			Limited to Nephrology and Cardiology Services
Torsemide		May 2019	X			
Dalbavancin	Dalvance	June 2019	X			Restricted to Hblue Observation unit patients and to approval by infectious disease services
Carfilzomib	Kyprolis	June 2019	X			Restricted to the oncology service
Emtricitabine and Tenofovir alafenamide	Descovy	June 2019	X			
Degarelix	Firmagon	Sep 2019	X			Restriction to oncologists only
Brentuximab	Adcetris	Sep 2019	X			Restriction to hematologist/oncologist only
Del Nido Cardioplegia		Sep 2019	X			Line extension
Gentamicin 120 mg/100 mL NS		Oct 2019			X	
Sodium zirconium		Nov 2019	X			Formulary line extension approved for unrestricted one time dose through order-set, maintenance dose will require cardiology and nephrology approval
Aspirin 325 mg, aspirin EC 81 mg, aspirin EC 325 mg		Nov 2019			X	
Activated charcoal with		Nov 2019			X	

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University Hospital Formulary Additions and Deletions for January 2019 – December 2019

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sorbitol						
Allopurinol IV		Nov 2019			X	
Melatonin		Nov 2019	X			
Abciximab		Nov 2019			X	
Sodium Phenylacetate/Sodium Benzoate		Dec 2019	X			
Dantrolene	Ryanodex	Dec 2019	X			Line Extension
Acetaminophen 325mg Rectal Suppositories		Dec 2019	X			Line extension

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University Hospital Formulary Additions and Deletions for January 2020– December 2020

Generic Name	Brand Name	P&T Date	Approved	Denied	Deleted	Reason/Comments/Criteria
Entecavir	Baraclude	Feb 2020	X			
Bacitracin IV		Feb 2020			X	FDA requests withdrawal from market
Brolucizumab		May 2020	X			Approved with re-evaluation in months
Rantidine		May 2020			X	Contaminant has been found, returned stock
Rifaxamin		May 2020	X			Restriction Modification
Quinidine Gluconante IV		June 2020			X	No longer manufactured in USA
Ceftolozone-Tazobactam	Zebraxa	July 2020	X			Approved with restriction for use to the Infectious Disease Service and Antimicrobial Stewardship Team Evaluation

Dofetilide	Tikosyn	July 2020	X			Approved for Formulary Addition with restriction to Clinical Cardiac Electrophysiology Specialist for use for In-patient
Ibutilide	Corvert	July 2020	X			Approved with restriction to Clinical Cardiac Electrophysiology Specialist for use In-Patient
Atazanavir/Cobicistat	Evotaz	July 2020			X	Lack of use
Magnesium/Aluminum Hydroxide	Gaviscon	July 2020			X	Lack of use
Bimatoprost Ocular Impant	Durysta	Aug 2020		X		
Rasburicase		Aug 2020	X			Formulary restriction expansion to include intensivists besides the Oncology/Nephrology services
Teprotunumab	Tepezza	Oct 2020	X			Further re-evaluation needed in 6 months
Tranexamic Acid 1g/100 mL premix		Oct 2020	X			Line Extension
Remdesivir	Veklury	Nov 2020	X			Restriction to ID consult or Stewardship team for approval no consult required
Cefiderocol	Fetroja	Nov 2020	X			Restriction to ID or Stewardship team
Dapaglifozin	Farxiga	Nov 2020	X			
Benzocaine Spray 20%		Nov 2020			X	

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Pharmacy News

University Hospital Formulary Additions and Deletions From January to April 2021

Generic Name	Brand Name	P&T Date	Approved	Denied	Deleted	Reason/Comments/Criteria
Tretinoin		Jan 2021	X			Oral, Restricted to oncology services/home medication restricted to second sign
Cardioplegia Solution		Jan 2021			X	
Methacholine Kit		Jan 2021	X			Line Extension
Methacholine 100 mg Vial		Jan 2021			X	Deletion due to ready to use Kit
Methylene Blue 0.5%		Jan 20201	X			Line extension due to 1% on back order for years
Sodium Zirconium Cyclosilicate	Lokelma	Feb 2021	X			Approved for restriction status changed to being unrestricted
Insulin Lispro aabc 100 unit/mL kwikpen and multidose vial	Lyumjev	Feb 2021	X			Medication sample addition to the ACC clinical F level
Dextromethorphan		Mar 2021	X			Approved for Formulary addition with 48 hour duration limit for Use in Perioperative Pain Management
Capsaicin Cream		Mar 2021	X			
Cabotegravir-Rilpivirine ER	Cabenuva	April 2021	X			ID clinic will determine optimal patient selection
Glucose Oral Gel 40%	Sweet Cheek	April 2021	X			Line Extension

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