University HOSPITAL
Newark, NJ

Pharmacy News

Second Quarter 2022
Vol. XV, Issue 2

Special Points of Interest:

- Roles and Utility of Liquid Vitamin D
- Overview of Klinefelter Syndrome
- Kawasaki Disease
- Thalassemia
- Key Highlights to the 2022 AHA/ACC/HFSA Heart Failure Guidelines

P&T Update

Formulary Additions

1. ***Zynrelef® (bupivacaine and meloxicam)*** is an extended-release viscous solution containing bupivacaine and meloxicam, FDA approved for the soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty in adults after a single dose.
   – Formulary Addition- Approved conditionally as outlined in the discussion section

Formulary Deletions

1. ***Demeclocycline***
   No usage in the last one year, the entire supply has expired. – Formulary Deletion – Approved
2. ***Nephro-Vite Rx 1 mg***
   This product has been discontinued by the manufacturer. Being substituted with Nephro-Vite Rx 0.8 mg. – Formulary Deletion – Approved
3. ***Bacitracin 3.5 gm ophthalmic ointment***
   This product has been discontinued by the manufacturer. The Ophthalmology division has been informed. – Formulary Deletion – Approved
4. ***Gentian Violet 1% Topical Solution***
   No purchase history in the last 2 years. All the existing stock at hand has expired. Formulary Deletion – Approved
5. ***Benzoin Compound Tincture 10%***
   All the 5 bottles purchased in the last 24 months have expired. Formulary Deletion – Approved
6. ***Magnesium 12 g/500 ml NS***
   A formulary deletion is proposed to streamline the available strengths and chances of error. – Formulary Deletion – Approved
7. ***Amobarbital IV***
   No usage in the 2 years, no longer recommended for Wada Test. – Formulary Deletion – Approved.
8. ***Dextran 500 mL***
   Zero orders in 2020 and 1 order in 2021. – Formulary Deletion – Approved.
9. ***Dipyridamole 50mg/10mL***
   Product on backorder and zero orders in the last two years. – Formulary Deletion – Approved.
10. ***Ethanolamine***
    Zero orders in the last two years. – Formulary Deletion – Approved.
11. ***Promethazine Injection***
    ISMP recommendation due to safety concerns. OB, Anesthesia, Pediatrics, Pediatrics ICU aware and approve. Medicine aware and deferred to aforementioned departments.
    – Formulary Deletion – Approved
12. ***Famotidine 20 mg/50 mL IV NS***
    20 mg/2 mL vials in stock. No purchase in past 24 months. – Formulary Deletion – Approved.
13. ***Coretecorelin***
    Manufacturer discontinued, not available in US. Last purchase 2015. – Formulary Deletion – Approved.

P&T Update

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14. ***Methyldopa 250 mg, 500 mg, 500 mg/2 mL***
    Methyldopa injection is no longer available in the US. – Oral formulation is not available. – Formulary Deletion – Approved.

15. ***Ephedrine 25 mg/5 mL 503b compounded syringes***
    This concentration of ephedrine prefill syringe has sporadic availability. Higher cost than 50 mg/10 mL vials. – Formulary Deletion Approved. Confirmed with Dr. Bekker (Anesthesia) that 50 mg/10 mL vial is a reasonable alternative to prefilled syringes. – Formulary Deletion – Approved.

Formulary Line Extensions

Nimodipine Oral Liquid

Nimodipine is used primarily post subarachnoid hemorrhage to prevent vasospasm. It is available in the liquid filled oral capsule formulation (30 mg – formulary) and commercially available ready to use oral liquid (non- formulary) in a strength of 6 mg/ ml as unit dose cups or bulk oral liquid bottle. – Formulary Addition – Approved

Nephro-Vite 0.8 mg tablets

The current formulary option Nephro- Vite 1 mg has been discontinued by the manufacturer. Hence, the 0.8 mg strength formulation is being considered for the formulary addition. – Formulary Addition – Approved

Policies & Procedures/Floor stocks

Peripheral Administration of Vasopressors in the Critical Care Areas-New policy
A new policy has been drafted to allow the vasopressor administration through the peripheral access (PIV) in an effort to decrease the central line usage and the complications thereof (such as infection, vascular injury, embolism, misplacement, occlusion etc.). – Approved

Neonatal IVIG protocol
A protocol outlining the immunoglobulin administration for the treatment of neonatal iso-immune hemolytic disease as per the American Academy of Pediatrics is presented. – Approved

707-600-103 Automatic Stop Order and Renewal Policy- Revision
The policy is updated to change the automatic stop order time for the oxymetazoline nasal solution to 3 days based on the package insert. – Approved

Antimicrobial Stewardship policies/guidelines- Review

707-900-102 UH 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

707-600-181 UH Fecal Microbiota Transplantation Policy

University Hospital Guideline for Treatment of Community Acquired Pneumonia (CAP) and Health care–associated pneumonia (HCAP) in Adults

University Hospital Adult Clostridioides difficile Infection (CDI) Guideline

UH Guideline for Treating Systemic Fungal Infections in Adults – Approved

Clozapine Policy- 707-500-119
Reviewed and updated to reflect authorized clozapine prescribers as outlines in the REMS program for clozapine. – Approved

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Polypharmacy and Antipsychotic Guidelines Policy -707-600-175
Reviewed and updated to include Abnormal Involuntary Movement Scale (AIMS) assessment and tardive dyskinesia monitoring
Dangerous Cautionary Drug-Drug Interactions Medication list reviewed

Antimicrobial Stewardship policies/guidelines-Review: UH Adult Staphylococcus Aureus Bacteremia (SAB) Guideline, ED Empiric Antibiotic Guideline. -Approved
SAB: Added pharmacokinetic data and cefazolin for MSSA CNS infections. ED Empiric Antibiotics: updated to reflect UH antibiogram changes

UH Anticoagulation Reversal Guidelines. -Approved
Updated based on Andexxa MUE
Apixaban/Rivaroxaban Reversal: Andexxa or Kcentra as first line options; Cost per dose added to guidelines

UH Buprenorphine Guidelines – Approved
No major changes

Medication Class Review 2022-2023. A. Antidepressants B. Antipsychotics C. Mood Stabilizers D. Dangerous Cautionary Drug-Drug Interactions
Yearly review of medication classes as recommended by the Joint Commission- Approved

Computerized order entry and verification of medication orders — Approved.

Ivenix Drug Library approval – Approved.

CADD- Solis Drug Library approval – Approved.

2022 Pharmacy Dept Policy and Procedure Table of Contents – Approved.

Medication Sample Addition Request

Nicotine patch/gum/lozenges- CINJ/UH Cancer Center
Reviewed proper procedures for sample medications. – Approved.
Approved pending that proper procedures are followed for these medication samples. – Approved.

Medication/Clinical Guidelines

Adult Skin and Soft Tissue (SSTI) Guidelines
Updated SSTI guidelines to provide antimicrobial recommendations for
Mild to moderate non-purulent cellulitis – Approved.
Mild to moderate purulent cellulitis – Approved.
Severe skin and soft tissue infections – Approved.
Diabetic foot infections – Approved.

Urinary Tract Infection (UTI) Guideline
Updated UTI guidelines to provide antimicrobial recommendations for
Uncomplicated cystitis – Approved.
Complicated cystitis or uncomplicated pyelonephritis – Approved.
Complicated pyelonephritis – Approved.
Asymptomatic bacteriuria – Approved.

University HOSPITAL Newark, NJ

Pharmacy News

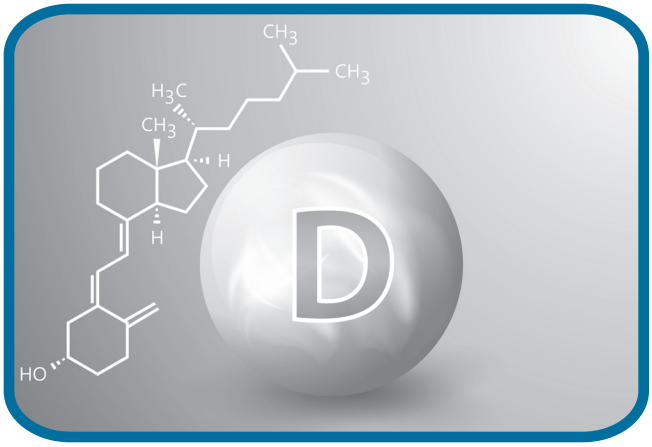
Roles and Utility of Liquid Vitamin D

Vitamin D insufficiency affects nearly 50% of the population worldwide.[1] Moreover, an estimated 1 billion people globally have a vitamin D deficiency.[1] Vitamin D is essential for the development, function, and maintenance of healthy bones.[2] The dosage form of oral drops offers a helpful solution for patients who have difficulty swallowing pills as well as infants requiring adequate Vitamin D.

Vitamin D is a fat-soluble vitamin produced endogenously when skin is exposed to ultraviolet rays from sunlight.[3] It is also naturally present in oil-rich fish such as salmon, tuna, and herring.[1,3] In order to improve Vitamin D intake, some foods are fortified with Vitamin D, including nearly the entire U.S. milk supply.[3] Another source of Vitamin D is dietary supplements, which are available as ergocalciferol (Vitamin D2) or cholecalciferol (Vitamin D3). Essential roles of Vitamin D include the promotion of intestinal calcium absorption as well as the maintenance of serum calcium and phosphate concentrations to allow for bone mineralization.[3] Vitamin D also has important functions in reducing inflammation in addition to modulating processes such as cell growth, glucose metabolism, and neuromuscular and immune function.[3]

Vitamin D requires two hydroxylations for activation. First, Vitamin D is hydroxylated in the liver to form 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. Then, Vitamin D is hydroxylated a second time in the kidneys to convert calcidiol to 1,25-dihydroxyvitamin D [1,25(OH)2D], commonly called calcitriol, which is the biologically active form of Vitamin D.[3] Inadequate supply of Vitamin D reduces its conversion to calcitriol, causing insufficient absorption of calcium. Furthermore, patients on a wide variety of medications, such as anticonvulsants and antiretrovirals, are at an elevated risk of Vitamin D deficiency, as these drugs enhance the catabolism of 25(OH)D and 1,25(OH)2D.[1] When the serum calcium level falls too low, the parathyroid glands release parathyroid hormone (PTH) into the bloodstream. PTH stimulates osteoclasts to release calcium from stores in the skeleton, weakening existing bones and preventing the formation of strong bones.[4]

In order to facilitate Vitamin D sufficiency, liquid Vitamin D provides unique benefits for people of all ages. For instance, infants may not acquire adequate Vitamin D from breast milk alone. Therefore, the American Academy of Pediatrics as well as the Dietary Guidelines for Americans recommend that exclusively and partially breastfed infants be supplemented with 400 IU per day of liquid Vitamin D beginning in the first few days of life.[5] In addition to helping infants, Vitamin D drops provide a convenient alternative for adults who have difficulty swallowing pills. At



optimal levels, Vitamin D can prevent rickets in children and osteomalacia in adults.[2,3] By enhancing intestinal absorption of calcium, Vitamin D can also prevent osteoporosis when combined with calcium.[3]

The high prevalence of Vitamin D insufficiency and deficiency is an important public health concern. Liquid Vitamin D offers both clinical and convenient benefits for individuals of all ages for whom it is indicated. Emerging research is uncovering the ever-growing and indispensable roles of Vitamin D in patient health.

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Submitted by:

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Overview of Klinefelter Syndrome

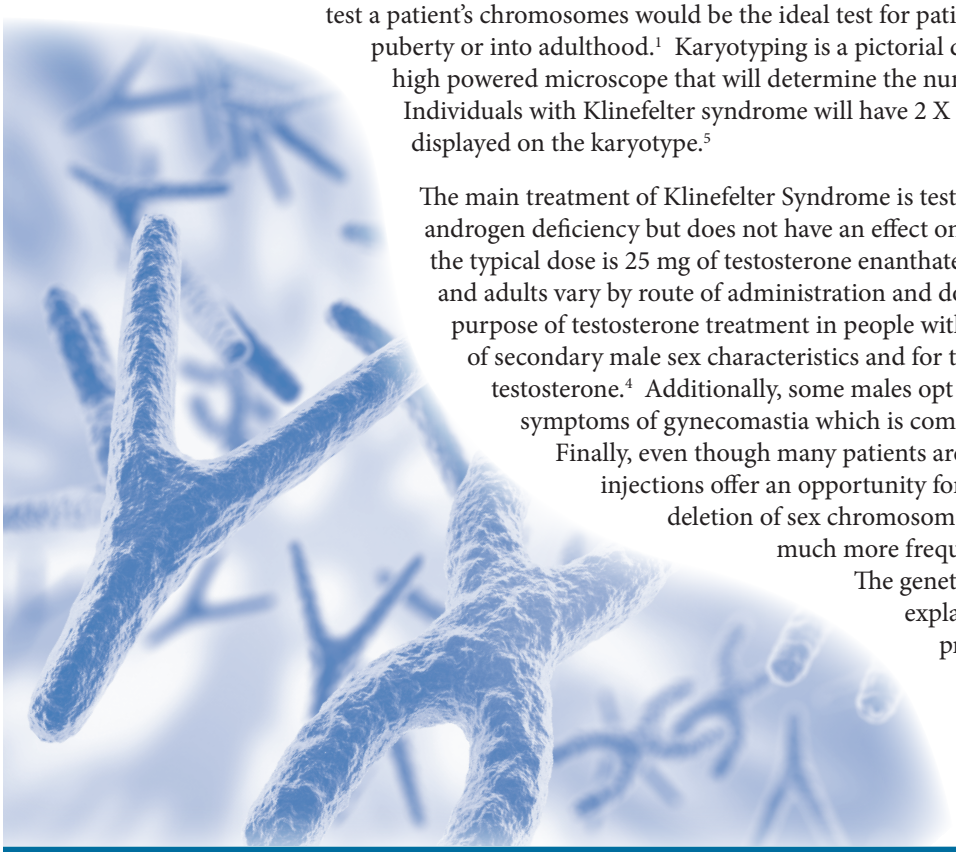
What is Klinefelter Syndrome ?

Klinefelter Syndrome is a genetic disorder that occurs in men and is a congenital disorder.[1] This means that it is present from the time of birth. Klinefelter syndrome is also considered fairly common, occurring in approximately 1 in 600 men.[1] Symptoms will also vary among men with some men experiencing very little symptoms while others have symptoms that are much more pronounced.[1,3,4] Even though Klinefelter syndrome is congenital it is not considered inherited.[1] This means that it is the result of an error that occurs during meiosis.[5] The mutation would be present after conception during division of sex cells.[5] People are not considered carriers for Klinefelter syndrome and there wouldn't be genetic sequences in parents that would show that their offspring is going to have Klinefelter Syndrome.[1]

Klinefelter Syndrome is also the most common genetic cause of infertility among men.[1,2,3,4] This disease occurs when males are born with 2 X chromosomes and 1 Y chromosome.[1,3,4,5] Most humans are born with 46 chromosomes consisting of 22 pairs of autosomes and 1 pair of sex chromosomes. Individuals with Klinefelter Syndrome are born with 47 chromosomes due to the extra X chromosome.[1,2,3] This results in diminished testicular growth and lower than normal production of testosterone. Lower levels of testosterone in men will present as reduced muscle mass, reduced facial and body hair and enlarged breast tissue.[3] Enlarged breast tissue or gynecomastia occurs during puberty and occurs in less than 10% of men with proper treatment.[5,4] It will also result in the production of little to no sperm which causes infertility.[1,3,4]

Diagnosis and Treatment

Diagnosis of Klinefelter syndrome can occur at any stage in life and signs and symptoms vary by age. Many boys will also only show few or mild symptoms and will go undiagnosed until adulthood.[3] However, Klinefelter syndrome can be diagnosed with either prenatal screening or when the patient is older. Prenatal screening will involve either taking samples from the placenta called chorionic villus sampling or taking a sample from the amniotic fluid which is called amniocentesis.[1,4] Conducting a karyotype to test a patient's chromosomes would be the ideal test for patients who are suspected of this condition at puberty or into adulthood.[1] Karyotyping is a pictorial display of chromosomes taken through a high powered microscope that will determine the number, type and appearance of chromosomes.[5] Individuals with Klinefelter syndrome will have 2 X chromosomes and 1 Y chromosome displayed on the karyotype.[5]



The main treatment of Klinefelter Syndrome is testosterone replacement which will help with androgen deficiency but does not have an effect on infertility.[1,4] In children ages 4-12 months, the typical dose is 25 mg of testosterone enanthate given as monthly injections.[4] Older children and adults vary by route of administration and dosing depending on the patient.[1,4] The main purpose of testosterone treatment in people with Klinefelter syndrome is for the development of secondary male sex characteristics and for the alleviation of feminization due to low testosterone.[4] Additionally, some males opt for breast reduction surgery to reduce the symptoms of gynecomastia which is common in patients with Klinefelter syndrome.[4] Finally, even though many patients are sterile for life, intracytoplasmic sperm injections offer an opportunity for procreation. However, the addition or deletion of sex chromosomes in a person's genome, or aneuploidies, are much more frequent in men with Klinefelter syndrome.[2,4] The genetic implications should be thoroughly explained to both the patient and their partner prior to procedure.[2,4]

Complications:

Patients with Klinefelter Syndrome are at increased risk for several complications

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Overview of Klinefelter Syndrome

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and should be monitored by primary care providers. Anxiety, depression as well as other emotional problems such as low self-esteem and emotional maturity exist with higher prevalence in this patient population.[3] Erectile dysfunction, osteoporosis and autoimmune disorders also occur more often in these patients due to lower than normal testosterone.[1,3] These patients are also at increased risk for breast cancer and metabolic syndromes such as Type 2 diabetes, hypertension and hyperlipidemia.[1,3] Heart complications such as myocardial infarction are more common and patients should be aware of the signs and symptoms of heart disease.[1]

Genetics:

Klinefelter syndrome is also known as a chromosomal aneuploidy which is a condition in which an individual has an abnormal number of one or more chromosomes.[5] Klinefelter syndrome occurs during meiosis which is the process when sex cells divide.[5] Nondisjunction occurs in the womb during division in which one of the eggs receives 2 X chromosomes while another egg receives 0 X chromosomes.[5] If the fertilized egg is Y0, which is 1 Y chromosome and 0 X chromosomes, that will be non-viable and the fetus would not survive.[5] If the father gives an X chromosome and the egg with 2 X chromosomes is fertilized, then a female is born is XXX and it is very rare to have complications with this syndrome.[5] However, if the egg with 2 X chromosomes is fertilized and the father gives a Y chromosome, then the patient will have Klinefelter syndrome.[5]

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Kawasaki Disease

What is Kawasaki Disease?

Kawasaki Disease (KD) is a rare but severe pediatric illness that is characterized by inflammation of the blood vessels; KD is the leading cause of acquired heart disease in children and infants.[1,2,3] The onset of KD is sudden and acute, where affected children develop several characteristic symptoms - a prolonged fever, a skin rash, and swollen lymph nodes in the neck (cervical lymphadenopathy). Patients may also develop redness in the whites of the eyes (conjunctivitis) as well as redness (erythema) of the lips, lining of the mouth, tongue, palms of the hands, and soles of the feet.[2,7] KD can lead to serious cardiac complications, but most children can fully recover if they are promptly and correctly treated.[7]

The exact cause of KD is unknown and is thought to be multifactorial. Evidence suggests that the KD has an infectious etiology and develops immunologically in genetically susceptible individuals.[3] Researchers have concluded that there is no link between KD and carpet cleaning chemicals; a theory which was promoted widely in the 1980's.[4] Although the inheritance pattern is unclear, siblings of children with KD have a significantly greater chance of acquiring the disease than do children of the same age in the general population.[2,7]

KD occurs worldwide but has the highest incidence in Japan, affecting 112 out of every 100,000 Japanese children under 5 years old.[3] In the United States, the incidence of KD is 25 out of every 100,000 children under 5 years old, or roughly 4200 cases per year in the USA.[3,4,12] More than 75% of KD cases occur in children younger than 5 years old and 50% of cases occur in children under 2 years old. In the United States, the incidence peaks in children aged 18-24 months, and in Japan the incidence peaks in children aged 6-12 months.[4,5] Cases of KD most commonly occur in winter and early spring in North America.[12]

Rarely, cases of KD have been reported in neonates, often presenting with atypical symptoms and arterial complications, including cerebral aneurysms.[2] Additionally, KD has been reported in adults, typically younger than 30 years old, but many reported cases in this age group have been misdiagnosed cases of toxic shock syndrome.[2]

Diagnosis and Management

KD symptoms usually appear in 3 phases. The symptoms of acute KD (Phase 1) include – a fever that is often ≥ 102.2 F (39 C) for ≥ 5 days, conjunctivitis without a thick discharge, a rash on the trunk on the body of the genitals, red, dry, cracked lips and an extremely red and swollen tongue (strawberry tongue), swollen, red skin on the sole of the feet and palms of the hands, and cervical lymphadenopathy. As well, plasma concentrations of brain natriuretic peptide (BNP) are increased during the acute phase of KD. The acute phase usually lasts 7 to 14 days.[1,8] Subacute KD (Phase 2) covers the period from the end of the fever until roughly day 25. It is characterized by peeling of the skin on the hands a feet, arthritis, diarrhea, vomiting, and abdominal pain.[1,8] The convalescent phase (Phase 3) begins when the clinical signs disappear and continues until the erythrocyte sedimentation rate becomes normal, usually six to eight weeks after the onset of illness.[8]

The diagnostic criterion for KD is a fever that lasts ≥ 5 days and at least 4 out of 5 of the following symptoms:

1. Cracked and erythematous lips, and strawberry tongue
2. Polymorphous rash on the extremities and perineal regions
3. Bilateral, non-purulent conjunctivitis
4. Erythema of the hands and feet
5. Cervical lymphadenopathy (>1.5 cm in diameter).[9]

Alternatively, a diagnosis can be made from a fever that lasts ≥ 5 days and coronary abnormalities on a transthoracic echocardiography.[9] Laboratory values that are commonly seen in KD include – elevated C-reactive protein (≥ 3 md/dL) and erythrocyte sedimentation rate (≥20 mm/hr.), elevated liver enzymes, hypoalbuminemia (≥ 3.0 g per dL), hyponatremia, platelets ≥ 450 X 103 per uL, sterile pyuria, and white blood cell count ≥ 15,000 per uL. [1,3,9]

To reduce the risk of coronary artery complications of KD, treatment should be initiated within 10 days symptom onset. While most KD patients will recover without any lasting heart cardiac complications, without treatment about 25% of KD patients will develop abnormalities of the coronary arteries.[1]

The treatment for acute KD, regardless of the risk of cerebral aneurysm (determined by echocardiograph findings), is a single intravenous immunoglobulin (IVIG) dose at 2 g/kg over 8-12 hours, and aspirin 3-5 mg/kg/day orally in four divided doses. [10] Aspirin should be continued until day 14 if febrile, and if afebrile for 48-72 hours; followed by 3 to 5 mg/kg/day orally for 6 to 8 weeks.[3] If the patient is at high risk for cerebral aneurysm, then they should also receive prednisone or prednisolone 2 mg/kg/day IV or orally in two divided doses for 10 days. [2,8,10]

Approximately 10% of patients will have refractory KD that does not respond to the initial therapy, and a fever will persist 36 hours after the initial IVIG dose. These patients may receive a second infusion of IVIG at 2g/kg. [1,8] Conversely, AHA guidelines explain the relative role of repeated use of IVIG and other adjunctive therapies (e.g., corticosteroids, TNF-α antagonists, plasma exchange, cyclophosphamide) are inconclusive for preventing KD complications. [1,8]

To prevent coronary thrombosis, Aspirin is used as an anti-platelet agent. After the acute phase treatment, aspirin may be used alone if the patient is asymptomatic, and the degree of coronary artery enlargement is low.[3] If the patient remains symptomatic or the coronary artery is enlarged, additional anti platelet agents, such as clopidogrel and dipyridamole, may be added for increased anti-platelet effects. Anti-platelet therapy can be continued for months to years.[3]

KD treatment is a rare exception for administering aspirin to patients who are under the age of 16.[3] Low-dose aspirin is given for six to eight weeks after disease onset and, if coronary abnormalities develop or persist, aspirin may be needed indefinitely.[8] Patients being treated for KD are typically observed for 24 hours following the completion of initial IVIG therapy to confirm resolution of fever. [10]

To promote blood flow and reduce the risk of cardiac ischemia and thrombosis, long-term therapy may be required.[3,11] Thromboprophylaxis and careful surveillance for coronary artery stenoses/obstructions and cardiac ischemia are the cornerstones of management.[1,3] Patients experiencing ischemia may be candidates for revascularization with catheter interventions or coronary artery bypass surgery or, rarely, cardiac transplantation.[3] The goals of long-term management are survival, optimal physiological outcomes into adulthood, and maintenance of good cardiovascular health. Longstanding KD patients are optimally managed by collaborative programs between pediatric and adult cardiology providers.[3] Evidence for the utility of beta-blockers, ACE-inhibitors, nitrates, and statins has been demonstrated for myocardial protection for patients with KD.[11] In general, KD patients do not significantly differ from the general population regarding CVD risk factors; however, they have an increased risk based on their thromboembolic complications.[11]

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Kawasaki Disease

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Potential Drug Interactions

Coadministration of IVIG and live vaccines such as MMR, Smallpox, and Rotavirus may diminish the effectiveness of the vaccines and any combination should be avoided while a patient is undergoing IVIG therapy.[10] As well, Ibuprofen antagonizes the aspirin-induced irreversible platelet inhibition and should be avoided in children with coronary aneurysms who are receiving aspirin therapy.[3] Patients with KD are best managed when pediatric, cardiac, and pharmacy specialists are in collaboration – this approach works best to avoid drug interactions when multiple drugs are being administered.

Pharmacogenomics

KD susceptibility, disease outcome, and the response to IVIG are influenced by single-nucleotide polymorphisms (SNPs) in several genes. Family linkage studies have implicated SNPs in FCyR2a, caspase 3 (CASP3), human leukocyte antigen class II, B-cell lymphoid kinase (BLK), inositol 1,4,5-triphosphate kinase C (ITPKC0 and CD-40. As well, variations in the genes that transcribe proteins in the transforming growth factor β (TGF-β) signaling pathway (TGFβ2, TGFβR2, and SMAD3) were associated with an increased risk of aneurysm development in patients of European ancestry.[11,12]

Furthermore, a lower percentage of CD4(+)CD24(+)FOXP(3)-regulatory T cells was observed in KD patients, and IVIG resistance has been shown to be related to the lack of CD4(+)CD24(+) FOXP(3)-regulatory T cells.[12]

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Thalassemia

What is Thalassemia?

Thalassemia is among the most common genetic disorders worldwide; 4.83% of the world's population carry globin variants, including 1.67% of the population who are heterozygous for α-thalassemia and β-thalassemia.[1] Thalassemia is an inherited blood disorder that affects the body's ability to produce normal levels of hemoglobin, the protein in red blood cells that carries oxygen. Hemoglobin is made of four protein chains, two alphas and two betas. Depending on which part of hemoglobin isn't being produced, a patient may suffer from alpha or beta thalassemia respectively. The purpose of hemoglobin is that it carries oxygen to the organs and tissues of the body and additionally transports carbon dioxide back to the lungs.[2] When an individual does not produce enough healthy red blood cells, the cells of the body become oxygen deprived, causing the individual to feel tired, weak, or short of breath.[3] This state of oxygen deprivation is known as anemia. Consequently, many patients who suffer from thalassemia may suffer from mild to severe anemia.

Types of Thalassemia

Alpha Thalassemia

There are four different types of Alpha thalassemia dependent on which genes are missing or damaged. An Alpha thalassemia silent carrier occurs when one gene is missing or damaged, while the other three genes are proper.[4] A patient with this type of thalassemia usually will have normal blood tests, however their blood cells may be smaller than those of normal individuals'. Being a carrier, an affected individual will not show signs of the disease but can pass on the damaged gene to a child.[4] With the second type, Alpha thalassemia carrier, an affected patient is missing two genes, and may have mild anemia. Third, Hemoglobin H disease is present when a patient is missing three genes. This individual

may have moderate to severe anemia, and would often require blood transfusions.[4] Lastly, in Alpha thalassemia major, all four genes are missing which causes severe anemia. Most often a newborn with this condition will die before birth.[4]

Beta Thalassemia

There are two types of Beta thalassemia both of which involve two specific genes. Beta thalassemia major (Cooley's anemia) is a condition where two genes are damaged, making it the most severe form of Beta thalassemia.[5] Individuals affected may not live normal life spans and will require frequent blood transfusions.[5] Beta thalassemia minor, is where only one gene is damaged, and which consequently results in a less severe anemia. Beta thalassemia minor is broken down into two further categories, Thalassemia minima and Thalassemia intermedia. In the former, there are few to no symptoms and in the latter, a patient will suffer from moderate to severe anemia.[5]

Diagnosis and Management

Diagnosis

Hemolytic anemia is a disorder in which a patient's red blood cells are destroyed faster than they are replaced. Symptoms of hemolytic anemia can be observed immediately after birth in Alpha thalassemia, or several months after birth in Beta thalassemia.[6] At a basic level, blood tests can reveal not only the numerosity of red blood cells within the body but also abnormalities in their shape, size, and color. Blood tests can also be used to perform a DNA analysis in which mutated genes can be flagged. Complete blood count (CBC) can also measure the hemoglobin in the body. Patients with thalassemia will have fewer healthy red blood cells in their body and a lessened hemoglobin count as compared to an unaffected individual. Dependent on the type of thalassemia, a plethora of tests such as hemoglobin electrophoresis, reticulocyte count, and iron level counts can be used in diagnosis. Prenatal tests such as chorionic villus sampling and amniocentesis can also be conducted.[6]

Management

Mild forms of thalassemia usually do not require treatment, and many individuals can go through life without an awareness they have the disease.[6] For moderate to severe forms of thalassemia (dependent on type), treatments such as blood transfusions, iron chelation therapy, and folic acid supplements can be utilized.

Potential Drug Interactions

There are several drugs used for treatment of thalassemia, principally to raise hemoglobin levels. The drugs that have the most potential are, Hydroxyurea (inhibitor of Ribonucleotide Reductase), Sodium Butyrate (inhibitor of Histone Deacetylase), and 5'-Azacytidine (DNA Methylating agents).[7] Studies on the complications that may arise from the usage of these drugs are still underway, and need to be conducted.

Pharmacogenomics

Thalassemia is an autosomal recessive disorder. Alpha Thalassemia is caused by genetic changes in the HBA1 and/or HBA2 genes while Beta Thalassemia is caused by changes in the HBB gene. Hydroxyurea, Sodium Butyrate, and Azacytidine help to improve the α:β ratio in erythroid progenitor cells and thus improve a major complication amongst transfusion dependent thalassemia major patients.7 Several drugs used for the treatment of Thalassemia have known carcinogenic and mutagenic effects.[7] In regards to iron chelators, Deferoxamine may cause neurotoxicity, growth retardation and visual problems after prolonged use.[7] Being as there is no cure for thalassemia, the effects of other drugs must be further studied as they are most likely to be utilized for long-term use by patients.

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Key Highlights to the 2022 AHA/ACC/ HFSA Heart Failure Guidelines

In April 2022, the American Heart Association (AHA) and the American College of Cardiology (ACC) released updated guidelines for the management of Heart Failure. The new guidelines replace 2013 ACCF/AHA Guideline for the Management of Heart Failure and the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. While the guidelines are extensively detailed, areas of focus include:

- Prevention of HF
- Management strategies in stage C Heart Failure, including:
  - New treatment strategies in HF, including sodium-glucose cotransporter-2 inhibitors (SGLT2i) and angiotensin receptor-neprilysin inhibitors (ARNi).
  - Management of HF and atrial fibrillation (AF), including ablation of AF.
  - Management of HF and secondary MR, including MV transcatheter edge-to-edge repair.
- Specific management strategies, including:
  - Cardiac amyloidosis
  - Cardio-oncology

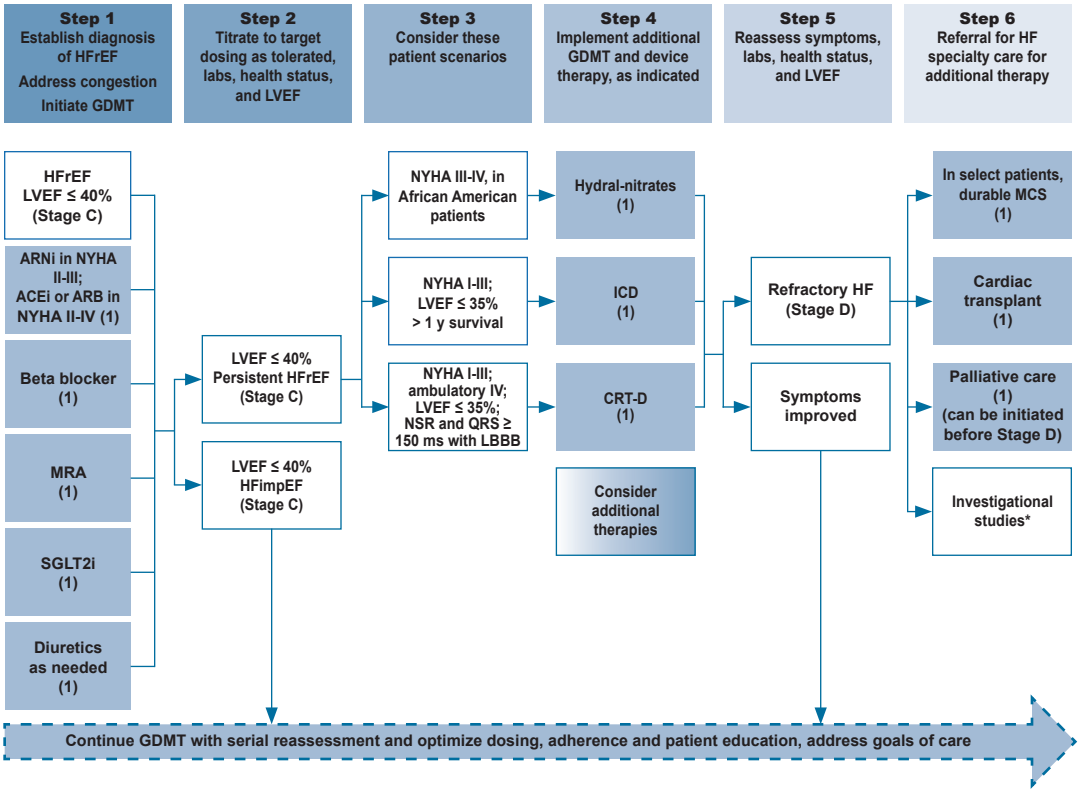
A major highlight of the guidelines are updates in the classification of Stage C Heart Failure, which is seen in the table below:

Type of HF According to LVEFCriteria	
HFIEF (HF with reduced EF)	■ LVEF <40%
HFimpEF (HF with improved EF)	■ Previous LVEF -40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	■ LVEF 41% 49% ■ Evidence of spontaneous or provokable increased L' filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	■ LVEF =50% ■ Evidence of spontaneous or provokable increased LI filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

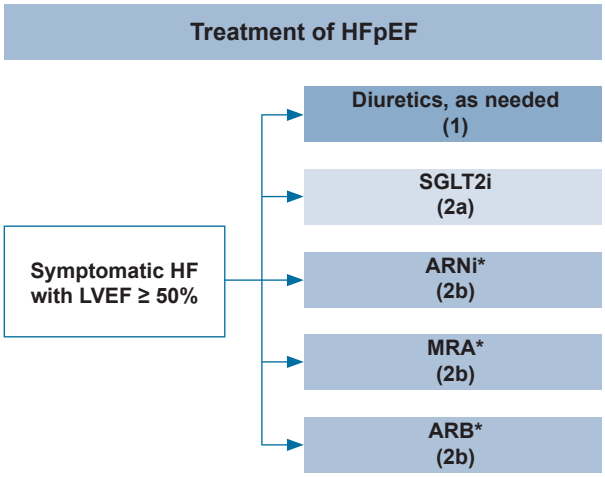
Significant updates in the pharmacological treatment for Stage-C HF were also included in the guidelines. Angiotensin receptor-neprilysin inhibitors (ARNis) are now considered first-line therapy for de novo treatment in hospitalized patients with acute HF. They are also recommended over ACEi or ARBs in patients with chronic symptomatic HFrEF with NYHA class II or III symptoms who have previously tolerated these classes of medications. These recommendations are based on the improvements in morbidity and mortality seen with ARNis when compared to ACEi or ARBs in RCTs.

Pharmacy News

A 4th class of medications in the treatment of HFrEF, sodium-glucose cotransporter 2 inhibitors (SGLT2i) has been added to the new guidelines. Two SGLT2i, Dapagliflozin and Empagliflozin, have been shown to reduce the risk cardiovascular death or HF hospitalization by approximately ~25%, irrespective of diabetes status. The use of SGLT2i therapy has also been shown to reduce all-cause mortality and cardiovascular death. Below is a table depicting the full scope of treatment of HFrEF stages C & D:



New recommendations for the treatment of Heart Failure with preserved ejection fraction (HFpEF) were also made with this update. SGLT2 inhibitors were given a class 2a recommendation for those with HFpEF, as they have been shown to reduce HF hospitalizations and mortality. These recommendations are based on the findings from the EMPEROR-Preserved RTC (Empagliflozin), which demonstrated a 21% reduction in time to HF hospitalization or cardiovascular death. Mineralocorticoid receptor antagonists (MRAs), such as Spironolaconte and Eplerenone, as well ARNi's received a weaker 2b recommendation.



Other important takeaways from the new guidelines include:

1. Value statements were created for select recommendations where high-quality cost-effectiveness studies of the intervention have been published. A high-value is defined as < $ 60,000 and a low value is > $ 180, 0000 per quality-adjusted life year (QALY) gained.

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Key Highlights to the 2022 AHA/ACC/HFSA Heart Failure Guidelines

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2. Adjustment of HF stages (A,B,C,D) to identify risk factors for HF and those at risk for HF, with Stage A being defined as "at risk", stage B as "pre-HF", stage C as "symptomatic HF" and stage D as "advanced HF".
3. Those patients with advanced HF who wish to prolong survival should be referred to a team specializing in HF.

Here at University Hospital's Healthy Heart Program, we have already begun to implement these new changes to the HF guidelines. More patients are being initiated on ARNi's and SGLT2i's, where appropriate, and we continue to enroll new patients into our HF program for more intensive monitoring and management of their disease and therapies.

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