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Pharmacy Newsletter

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Optimizing Management of Rheumatic Heart Disease Using Health Informatics Support

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Rheumatic heart disease (RHD) is one of the main causes of cardiovascular morbidity and mortality in young people, leading to about 250,000 deaths per year worldwide. Rheumatic fever (RF) is a rare and serious condition that has been known since 1812. In 1880 the association between sore throat infection causing RF and carditis was definitively linked. In 1960, RF was considered as one of the main leading reasons for death in children worldwide.

RHD is a worldwide public health concern as a chronic condition that results in valvular damage caused by multiple attacks by group A *Streptococcus* pyogenes. Despite the incidence of RHD that's significantly decreased in developed countries, it remains a major concern in developing regions such as Africa, south-central Asia and the Arabian Gulf, including Saudi Arabia.

Rheumatoid Fever is a consequence of throat infection caused by *Streptococcus* pyogenes. This organism can cause a damaging effect on susceptible untreated children. It was previously shown by molecular mimicry that the antigens of *S.* pyogenes and human proteins could result in autoimmune reactions, both humoral and cell mediated, leading to RF and RHD. It takes approximately 3 weeks post S. pyogenes infection to induce RF, resulting in inflammation affecting the brain, joints, skin and irreversible valve damage and heart failure.

Generally, primary prevention of RF using appropriate antibiotics to treat preceding S. pyogenes infection is considered the most effective method for preventing RHD. Moreover, RF can be prevented and controlled with prophylactic antibiotics by inhibiting the risk for further S. pyogenes infection and causing progression of valve damage. Hence, heart valve surgery to repair or replace damaged heart valves can be prevented or delayed through secondary prophylaxis antibiotics.

Epidemiology

RHD is the leading cause of heart failure in children and young adults living in low-income countries. Globally, RHD is estimated to affect 15.6 million people resulting in 233,000 deaths annually. Re-hospitalization and heart surgeries as a result of RHD are highly significant from 5 up to 20 years after diagnosis. In recent years, the global burden of RHD has dramatically declined in developed countries. Contrary to this RHD remains a major health concern in many endemic countries, and could affect up to 1% of all school children. Africa, Asia, Arab Gulf, and the Pacific and indigenous populations of Australia and New Zealand are mostly affected by RHD. Data on the prevalence of RHD amongst the Saudi population is limited. However, the percentage of children with RHD in Saudi Arabia remains above the global rate .

Antibiotic Selection and Duration of Therapy

All patients who have had rheumatic carditis, with or without valvular disease, are at high risk for RHD recurrence and should receive long-term antibiotics therapy. Secondary antibiotic prophylaxis is used to reduce the acquisition of new group A streptococcal strains that might induce repeated or chronic acute RF attacks, which is a major determinant of cardiac outcome. Medical intervention is based on the eradication of group A streptococcus with penicillin, which prevents the initial acute RF attack (primary prophylaxis) or disease recurrences (secondary prophylaxis). Treatment and route of administration is selected based on adherence to therapy (*see Table 1*). Guidelines can be accessed through the online hospital formulary.

Continued on Page 6

In this issue

Formulary & Therapeutics Committee Updates

The following are formulary changes by the Formulary & Therapeutics Committee (FTC) from Jul-Sept 2018 meetings. Please refer to the Online Hospital Formulary to check the status of the new medications and details on dosing and uses.

Approved New Formulary Addition

- **Interferon Alpha-2b (Peg-Intron®) 100 mcg Vial**

  Treatment of conjunctival neoplasia. Prescribing is restricted to Ophthalmology consultants in accordance with hospital guidelines.

- **Doxepin 10 mg Oral Tablet**

  Treatment of chronic idiopathic urticaria. Prescribing is restricted to Dermatology consultants in accordance with hospital guidelines. Form B is waived for this indication.

- **Ribociclib (Kisqali®) 200 mg Tablet**

  First and second line (in combination with fulvestrant) treatment of advanced breast cancer in pre– and peri-menopausal women with ER-positive and HER2-negative. Prescribing is restricted to Medical Oncology consultants in accordance with hospital guidelines.

- **Fulvestrant (Faslodex®) 250 mg Vial**

  ⇒ Treatment of postmenopausal ER-positive, locally advanced or metastatic breast cancer following disease relapse on or after adjuvant antiestrogen therapy, or disease progression on therapy with an antiestrogen. Prescribing is restricted to Medical Oncology consultants in accordance with hospital guidelines.

  ⇒ First and second line (in combination with fulvestrant) treatment of advanced breast cancer in pre– and peri-menopausal women with ER-positive and HER2-negative. Prescribing is restricted to Medical Oncology consultants in accordance with hospital guidelines.

- **Osimertinib (Tagrisso®) 40 mg and 80 mg Tablet**

  Treatment of metastatic EGFR-T790M mutation-positive non-small cell lung cancer (NSCLC) in patients who have progressed on or after EGFR-TKI therapy. Prescribing is restricted to Medical Oncology consultants according to hospital guidelines.

Approved New Dosage Form Addition

- **Desmopressin (Stimate®) 1.5 mg/mL Nasal Spray**

  Treatment of Von Willebrand disease and Hemophilia A in adults and pediatrics > 11 months.

- **Quinine Sulphate 300 mg/10 mL Ampoule**

  Treatment of malaria as a second line treatment.

- **Venlafaxine 37.5 mg Capsule**

  For use as per formulary approved indications. Prescribing restricted to Psychiatry and Family Medicine departments.

Approved Extension of Prescribing Privileges

- **Cinacalcet Oral Tablet**

  Prescribing privileges expanded to include adult Endocrinology for new indications.

- **Hyperthermic Intraperitoneal Chemotherapy (HIPEC)**

  Prescribing privileges expanded to include Gynecology consultants who are privileged to perform HIPEC procedures.

- **Treosulfan 5 g Vial**

  Prescribing privileges expanded to include pediatric Hematology/Stem Cell Transplant.

Approved Expansion of Indication

- **Cinacalet (Mimpara®/Sensipar®) 30 mg, 60 mg, 90 mg Tablet**

  ⇒ Primary hyperparathyroidism
  - Inoperable hyperparathyroidism
  - Significant comorbidities that preclude surgery
  - Severe acute hypercalcemia secondary to primary hyperparathyroidism

  ⇒ Tertiary hyperparathyroidism

- **Treosulfan**

  Approved as an alternative to busulfan conditioning regimen for allogenic stem cell transplantation in pediatric patients, according to pediatric guidelines and its prescribing is restricted to pediatric Hematology.

FTC Updates *Contd…*

Approved Reinstatement

- **UW Solution 1000 mL bag for Organ Perfusion**

Approved Guidelines

- **Using Antidotes for Chemotherapy Extravasation**
  Updated recommendations and new items

Approved Miscellaneous

- **Prothrombin Complex Concentrate**
  Complete replacement of Beriplex® (1000 units and 250 unit vials) by Octaplex® (500 unit vial)
- **Sedation Protocol for Pediatric ICU**
  PICU sedation/Analgesia Protocol for Mechanically Ventilated Patients

For more information on the indications, age specifications, doses and guidelines please check the online hospital formulary:

http://online.lexi.com/lco/action/home

Accessing KFSH&RC via Smartphone Devices

⇒ For new users visit the **Lexicomp website**: https://www.lexi.com/account/ to register a new account or sign in as an existing user

⇒ After logging in, enter the individualized subscription code sent on request from the Drug Information Center

⇒ Download the Lexicomp application on your smartphone

⇒ Sign in to the application on your smartphone to synchronize with your personal account

⇒ Select **KFSH&RC Formulary and Drug Therapy Guide** and click the update button at the bottom of the application page

⇒ You are now ready to access the hospital formulary from your smartphone

KFSH&RC hospital staff (Riyadh) can email a request for smartphone access to the KFSH&RC Formulary to:

druginformationcenter@kfshrc.edu.sa

What is in the News

US-FDA Update Label Warnings of Fluoroquinolone Antibiotics on Glycemic and Mental Health Effects

The U.S. Food and Drug Administration (FDA) is strengthening the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects. This affects only the fluoroquinolone formulations taken by mouth or given by injection.

Changes to the drug labels have been made for all the fluoroquinolone group due to a recent review of life-threatening reports of hypoglycemia side effects and additional mental health side effects. Hypoglycemia can result in serious harm, including coma, particularly in the elderly and patients with diabetes who are taking oral anti-hyperglycemic medications.

Despite both effects on blood sugar, high and low, documented with the use of fluoroquinolones, the label has now been updated to include hypoglycemia that can lead to coma. The mental health side effects were updated across all the fluoroquinolones to include disturbances in attention, disorientation, agitation, nervousness, memory impairment and delirium.

The US-FDA is investigating this new safety issue and will release an update as more information will be available.

SFDA Update Label of Darunavir/Cobicistat Products on Contraindication in Pregnancy

The pharmaceutical manufacturer in agreement with the Saudi Food and Drug Administration (SFDA), have updated the product information of darunavir/cobicistat to include the increased risk of treatment failure and an increased risk of mother-to-child transmission of HIV infection due to low exposure values of darunavir and cobicistat during the 2nd and 3rd trimester of pregnancy.

The pharmacokinetic data from a phase 3b study TMC114HIV3015 in 6 pregnant women demonstrated the mean exposure (AUC) of darunavir with cobicistat was 65% and 50% lower during the 2nd and 3rd trimesters of pregnancy, respectively, compared with 6 to 12 weeks postpartum. Mean darunavir C_{min} concentrations were around 90% lower during the 2nd and 3rd trimesters of pregnancy as compared to postpartum. Exposure of cobicistat was 63% and 49% lower during the 2nd and 3rd trimesters of pregnancy, respectively, as compared to postpartum. Low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the child. Healthcare providers should not initiate therapy with darunavir/cobicistat during pregnancy and switch all women who become pregnant during therapy with darunavir/cobicistat to alternative regimens.

US-FDA Warns Against Long-term Use of Azithromycin for Bronchiolitis Obliterans Syndrome (BOS) Prevention

The U.S. Food and Drug Administration (FDA) is warning that the antibiotic azithromycin should not be given long-term to prevent bronchiolitis obliterans syndrome (BOS) in patients with hematological malignancies who underwent hematopoietic stem cell transplantation (HSCT). Azithromycin is not approved for preventing BOS. Results of a clinical trial found an increased rate of relapse in hematological malignancies, including death, in these patients. The trial could not determine why the rates of cancer relapse and death were higher with azithromycin.

Health Canada Updates Label of Atezolizumab (Tecentriq®) on Increased Risk of Immune-Related Nephritis

Atezolizumab has been linked with the development of immune-related nephritis in oncology patients. A number of 28 patients were reported to have developed nephritis while on atezolizumab, 13 of whom with confirmed nephritis by biopsy. Two of the 28 cases were reported in Canada, but were not confirmed by biopsy. Both patients recovered with steroid treatment.

As a result of these findings, Health Canada, in collaboration with the pharmaceutical manufacturer, will update the product monograph to include information related to the risk of immune-related nephritis.

All drug safety alerts are communicated to the end-users of concern, as per the IPP MCO-CS-PCS-07-075: Dissemination and Action Related to Drug Safety Alerts at KFSH&RC. For more info access IPP via Unified KFSH&RC Portal.

Tip of the Issue

Biological and Biosimilar Taskforce

In the summer of 2017 the Formulary and Therapeutics Committee (FTC) established the Biological & Biosimilar taskforce under its auspices. The taskforce was to undertake class reviews of all biological and biosimilar agents (formulary & non-formulary) for the treatment of the following conditions:

- Psoriasis
- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Inflammatory Bowel Disease

The taskforce had representation from adult and paediatric gastroenterology, rheumatology and dermatology. There was additional representation from Supply Chain Management and Pharmaceutical Care Division. A consultant paediatric gastroenterologist was appointed as chairman of the taskforce and a clinical pharmacist was the designated coordinator.

Over a seven months, the Biological and Biosimilar taskforce undertook extensive class reviews into the safety and efficacy of all biological agents, including biosimilars for the treatment of the aforementioned conditions. All recommendations were approved by the FTC with the exception of golimumab. The soon to be available biosimilar adalimumab made the addition of golimumab redundant. The recommendations of the taskforce also ensured that the addition of new agents was cost neutral. This was achieved by reduction in the cost current formulary agents as well as the expected reduction in utilization of formulary biological agents. Based on these class reviews the Biological and Biosimilar taskforce made the following recommendations to the FTC:

NEW FORMULARY & DOSAGE FORM ADDITIONS

Drug	Class	Approved Indications	Formulary Restrictions
ABATACEPT (ORENCIA®) 250mg vial and 125mg prefilled syringe	Selective T-Cell Costimulation Blocker	• Juvenile idiopathic arthritis • Rheumatoid Arthritis	IV: Pediatric and Adult Rheumatology SC: Adult Rheumatology
ANAKINRA (KINERET®) 100mg prefilled syringe	Interleukin-1 Receptor Antagonist	Juvenile idiopathic arthritis (systemic onset and poly-articular course). Waiver of form B	Pediatric Rheumatology
CERTOLIZUMAB-PEGOL (CIMZIA®) 200mg preffiled syringe	Anti-TNF	• Moderate/severe Crohn disease (≥18 years of age) • Rheumatoid arthritis in adults (≥18 years of age)	Adult Gastroenterology & Rheumatology
GOLIMUMAB* (SIMPONI®) 50mg & 100mg prefilled syringe		• Moderate/severe Ulcerative Colitis (≥18 years of age) • Rheumatoid arthritis in adults (≥18 years of age)	Adult Gastroenterology & Rheumatology
TOFACITINIB (XELJANZ®) 5mg Tab	JAK inhibitor	Rheumatoid arthritis in adults (≥18 years of age)	Adult Rheumatology
USTEKINUMAB (STELARA®) IV 130mg vial	Interleukin-12/23 inhibitor	• Expand indication to Crohn disease in adults (≥18 years of age) after failure of anti-TNF and/or conventional therapy • Add 130mg IV solution for infusion for loading dose	Adult Gastroenterology
VEDOLIZUMAB (ENTYVIO®) 300mg vial	Selective Adhesion-Molecule Inhibitor	• Crohn disease/ Ulcerative colitis patients ≥14 years of age after failure of anti-TNF and/or conventional therapy. • Waiver of form B for patients 14-17 years of age	Adult Gastroenterology

EXPANSION OF INDICATIONS/PRESCRIBING PRIVILIGE

Drug	Class	New Indications	Extended Prescribing Privileges
ADALIMUMAB	Anti-TNF	• Moderate to severe Ulcerative Colitis in patients ≥14 years of age. • Waiver of form B for patients 14-17 years of age	-
		Moderate/severe Crohn disease pediatric patients (≥6 years of age)	Pediatric Gastroenterology
		Plaque psoriasis	Dermatology
ETARNERCPT	Anti-TNF	Plaque psoriasis in paediatric patients	-
INFLIXIMAB	Anti-TNF	• Plaque psoriasis • Ulcerative Colitis (adults & paediatrics)	Dermatology & Pediatric Gastroenterology
USTEKINUMAB (Stelara®) 45 & 90mg Prefilled syringe	Interleukin-12/23 inhibitor	New dosing schedule 45mg-90mg Q8W in patients with plaque psoriasis in adult patients	-

DENIED ADDITIONS/EXPANSION OF INDICATION

Drug	Class	Indication	Reason for Denial
NATALIZUMAB (TYSABRI®) 300mg vial	Selective Adhesion-Molecule Inhibitor	Crohn disease in adults (≥18 years of age) after failure of anti-TNF and/or conventional therapy	Safety Concerns
TOFACITINIB (XELJANZ®) 5mg Tab	JAK inhibitor	Moderate to severe Ulcerative Colitis in patients ≥18 years of age	Limited clinical experience in Ulcerative Colitis
CANAKINUMAB (ILARIS®) 150 mg powder for injection	Interleukin-1 Receptor Antagonist	Systemic juvenile idiopathic arthritis	• Prohibitive cost inflation • Safety concerns with brodalumab
BRODALUMAB (SILIQ®) 210mg prefilled syringe	Anti-interleukin 17-Receptor Antibody	Plaque psoriasis in patients ≥18 years of age	
GUSELKUMAB (TREMFYA®) 100mg prefilled syringe	Interleukin-23 Inhibitor	Plaque psoriasis in patients ≥18 years of age	
IXEKIZUMAB (TALTZ®) 80mg prefilled syringe	Anti-interleukin 17-Receptor Antibody	Plaque psoriasis in patients ≥18 years of age	

Pharmacy Newsletter

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Continued...

The duration of secondary prophylaxis depends on several factors including, age, date of last attack, and most importantly the presence and severity of rheumatic heart (*see Table 2*).

Clinical Decision Support System (CDSS) and Antibiotics Selection for RHD

In order to provide the best care for patients, supporting prescribers through health informatics systems improves healthcare processes and outcomes. Integrating guidelines in CDSS aids clinicians to optimize patient care. CDSSs are programs that provide clinical data or medical knowledge designed to support healthcare professionals in making informed clinical decisions. These systems are intended to identify and reduce the rate of errors, inappropriate or inefficient actions, and adverse events. It provides support in a timely manner, either before, during or after decisions are made. KFSH&RC uses Integrated Clinical Information System (ICIS).

There is no published data reflecting the use of CDSS in management of RF or RHD. However, health information technology has the potential to assist in disease management by applying a CDSS designed to assist in clinical decision-making on an individual basis, and consequently resulting in optimized patient care. The customized evidence-based tool on the management of RHD supports prescribers to make more accurate decisions on the choice of antibiotics post valve replacement. By standardizing practice, the incidence of RF/RHD can be minimized. In light of this, a tool was developed in the hospital system whereby every patient admitted to KFSH&RC with RF or RHD will be assessed for antibiotics use as a prevention strategy. Implementation of the CDSS improved adherence within one year by 32% (p-value <0.001, NNT of 18).

This intervention highlights the potential for developing and implementing integrated, evidence-based, clinical decision support tools which work to considerably improve adherence to appropriate antibiotic prescribing, as secondary prevention for RHD patients.

Table 1: Treatment Regimens for Secondary Prophylaxis of Rheumatic Fever and RHD

Antibiotic	Child ≤ 27 Kg	Adult or > 27 kg	Route of administration
Agent of Choice (refer to management pathway for appropriate selection)			
Benzathine benzylpenicillin G[1]	600,000 units[2]	1,200,000 units	Single IM injection every 4 weeks [3]
Penicillin V	250 mg q12h		Oral
For individuals allergic to penicillin			
Sulfonamide: "sulfadiazine"	500 mg q24h	1000 mg q24h	Oral
For individuals allergic to Sulfonamide			
Erythromycin	250 mg q12h		Oral
Azithromycin	6 mg/kg q24h (up to 250 mg)	250 mg q24h	Oral

Table 2: Duration of Therapy for Secondary Prophylaxis of Rheumatic Fever and RHD

Category of patient	Duration of prophylaxis
Rheumatic fever with carditis and residual heart disease (persistent valvular disease)	>10 years since last episode and at least until age 40 years, sometimes lifelong prophylaxis [4]
Rheumatic fever with carditis but no residual heart disease (no valvular disease)	For 10 years after the last attack, or at least until 21 years of age (whichever is longer)
Rheumatic fever without carditis	5 years or until 21 years, whichever is longer
More severe valvular disease[5]	Lifelong
After valve surgery	Lifelong

Footnotes:

1. IM injection should be avoided in all individuals receiving oral anticoagulantion.
2. Dose in small children and infants of benzathine benzylpenicillin: 25,000 units per kg.
3. In high-risk population, administration every 3 weeks is justified and recommended in populations in which the incidence of RF is particularly high and those who have recurrent acute RF despite adherence to an every-4-week regimen.
4. Patients who are at high risk and likely to come in contact with populations with high prevalence of streptococcal infection, i.e. teachers, day-care workers, clinical or echocardiographic evidence.
5. Valve severity is diagnosed according to the following ECHO criteria:
   a. Valve area (cm2) < 1 in aortic, mitral and tricuspid valve
   b. Mean gradient (mmHg): aortic >40, mitral >10, pulmonic >64, tricuspid >5

References available on request