Shaukat Khanum Memorial Cancer Hospital and Research Center

Pharmacy Newsletter

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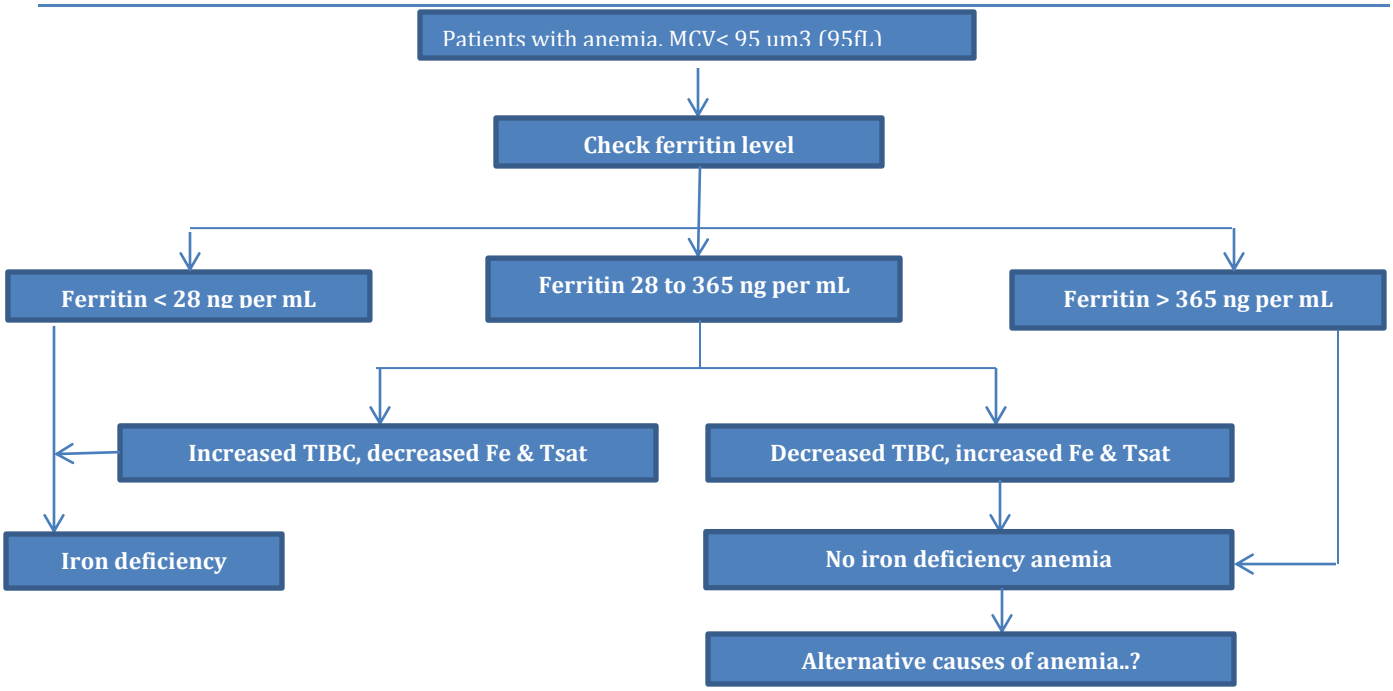
NEW ARRIVALS

Sugammadex, a modified gamma cyclo-dextrin, is the latest approved agent for reversing Rocuronium and Vecuronium induced neuromuscular blockade. It imparts the action by forming a complex with the neuromuscular-blocking agents in plasma thus reducing their available amount to bind with nicotinic receptors in the neuromuscular junction. Recommended dose for reversal of moderate and severe blockade is 2mg/kg and 4mg/kg respectively. For immediate reversal of Rocuronium induced blockade, it is to be given 16mg/kg as single dose. However use has not yet been evaluated in intensive care units. Furthermore, sugammadex is not to be used to reverse the effect of non-steroidal neuromuscular blocking drugs like Succinylcholine, or any other agents.

Ceftazidime-Avibactam: Ceftazidime (FDA approved in 1985) is vulnerable to a broad variety of beta-lactamases. The beta-lactamase inhibitor Avibactam extends its activity to ESBL and AmpC producing strains as well as to some carbapenemases such as KPC. In Feb 2015, Ceftazidime-avibactam was approved based on Phase II data from the company's clinical development program before the availability of Phase 3 study results. The submission was supported by in vitro data, by prior findings for the efficacy and safety of ceftazidime alone and extensive PK/PD analyses. It is given as 2.5g TID with metronidazole for complicated intra-abdominal infections and as 2.5g TID alone for complicated urinary tract infections as 2hrs intermittent infusion. Renal dose adjustments are recommended at GFR <50ml/min.

MANAGEMENT OF IRON DEFICIENCY

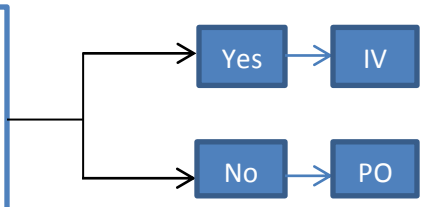


Iron deficit calculation :(Body weight (kg) x (target HGB - actual HGB) (g/l) x Factor) + Iron Store (mg)

Factor:	Adults: 2.4	Pediatrics: 0.24
Iron stores:	For ≥ 35Kg 500mg	< 35kg: 15mg/kg
Target Hgb:	For ≥ 35Kg: 15g/dl	< 35kg: 13g/dl

Patient's considerations:

- Intolerance to the gastrointestinal side effects of oral iron e.g., older individuals, pregnant women.
- Severe/Ongoing blood loss
- Anatomic or physiologic condition that interferes with oral iron absorption e.g., gastric surgery (bypass, resection).
- Co-existing inflammatory state that interferes with iron homeostasis.
- To avoid prolonged duration of use.



IV Iron supplements

Iron Salt	Elemental Iron (mg)	Dose (Adults)	Dose(Paeds)
Iron Sucrose	20 mg/mL	**CKD patients on HD:** 100 mg IV 3 times wkly (or every dialysis) x 10 doses (1 gram) **Not on dialysis** 200 mg IV x 5 doses over 14 days. Chemotherapy-related anemia:200 mg once every 3 weeks for 5 doses	**CKD patients on HD** 0.5 mg/kg/dose (max: 100 mg) every 2 weeks for 6 doses **Not on dialysis** 0.5 mg/kg/dose (max: 100 mg) every 4 weeks for 3 doses

Oral Iron supplements

Iron Salt	Elemental Iron mg per 100mg salt	Dose (Adults)	Dose (Paeds)	Cost
Ferrous gluconate	11.25	*100-200mg (2-3 divided doses)	*3 to 6 mg/kg/d in 3 divided doses	$$$
Ferrous fumarate	90			$$
Ferrous sulfate	20			$

**Doses in terms of Elemental iron*

MCV: Mean corpuscular volume, TSAT: Transferrin saturation, TIBC: Total iron binding capacity. Fe: Iron, Hgb: Hemoglobin, CKD: Chronic kidney disease

Instruction for patients:

- Iron should especially be taken separately from Calcium-containing foods and beverages (milk), Ca supplements, cereals, tea, coffee and eggs.
- Iron should be given two hours before, or four hours after, ingestion of antacids.
- Usually co-administer Ascorbic acid tablet or a half-glass of orange juice with iron to enhance its absorption.

New Armor against MDR-TB

As treating tuberculosis becomes tricky, there is emerging hope in recent times with newer anti-Tb drugs introduced in market.

Multidrug-resistant TB (MDR-TB): TB due to a strain of M. tuberculosis that is resistant at least to both isoniazid and rifampicin.

Rational MDR-TB treatment should include a minimum of four active drugs:
A later-generation fluoroquinolone (Levofloxacin/Moxifloxacin) + an injectable aminoglycoside + any first-line drug to which the isolate is susceptible + one of the following drugs:
Ethionamide (Eto), Prothionamide (Pto), Cycloserine (Cs), Terizidone (Trd), p-Aminosalicylic acid (PAS), p-Aminosalicylate sodium (PAS-Na)

Extensively drug-resistant tuberculosis (XDR-TB):

TB due to a strain of M. tuberculosis resistant to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

In case four active drugs from previous groups are not available, newer agents from following table may be considered:

Drug	Dose	Duration	Adverse effects	Interactions
Bedaquiline	400 mg daily for 2 weeks, then 200 mg three times a week for 22 weeks	6 months	QT prolongation	Simultaneous use of bedaquiline and delamanid is not recommended.
Delamanid	100-200mg BID	6 months	QT prolongation	In clinical trials no significant interactions were observed between delamanid and anti-retroviral drugs such as tenofovir, lopinavir/ritonavir, and efavirenz.
Pretomanid	100-200mg BID	8 weeks	No episode of QT interval exceeding 500 milli-sec was identified	Addition of pyrazinamide increased the activity of both bedaquiline and pretomanid
Linezolid*	300-600mg OD	6 months	Peripheral neuropathy, optic neuropathy, gastrointestinal disorders and myelosuppression	Clarithromycin + linezolid cause increased serum levels of linezolid
Meropenem /clavulanate	1000mg TID	3 months with linezolid containing regimens	Increased transaminase levels.	Probenecid may increase the serum level of meropenem.

*Available at SKMCH&RC Pharmacy

- When using injectable, the minimum duration of the intensive phase: 8 months
- Continuation phase lasting for 12–18 months, for total treatment duration of at least 20 months.
- As a rule, 18 months need to be added to the date of the first negative culture to define the final treatment duration.

News & Updates

First Dengue Vaccine Approved

Dengue fever burden in Asia countries is the highest globally, with an estimated 67 million people stricken annually. Sanofi Pasteur, the vaccine division of Sanofi has introduced the first Dengue vaccine approved by FDA in Asia, first in Philipines followed by Mexico. Dengvaxia is a tetravalent dengue vaccine that can prevent the disease caused by all four dengue types in individuals from 9 to 45years old living in endemic areas. Sanofi Pasteur's vaccine is the culmination of over two decades of scientific innovation and collaboration, as well as 25 clinical studies in 15 countries around the world. Dengvaxia successfully completed phase III clinical studies in 2014 to evaluate the primary objective of vaccine efficacy. Additional pooled efficacy and integrated safety analyses from the 25-month Phase III efficacy studies and the ongoing long-term studies, respectively, were recently published in *The New England Journal of Medicine* reconfirming the vaccine's consistent efficacy and longer-term safety profile in populations 9 years of age and older. This pooled efficacy analysis showed that vaccine prevented 9 out of 10 cases of severe dengue and 8 out of 10 hospitalizations due to dengue in this age group.

Villar L, Dayan GH, Arredondo-Garcia JL, Rivera DM, Cunha R, Deseda C et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med. 2015

Fixed combination of long acting insulin and GLP-1 receptor antagonist

Long-acting basal insulin can be given with a glucagon-like peptide-1 receptor agonist (GLP-1RA) Liraglutide for treating patients with type 2 diabetes. This combination, compared with long-acting insulin alone, improved glycemic control with less hypoglycemia. A comparative study has been conducted between a combination therapy and long acting insulin alone for treating patients with type-2 diabetes. In an open label trial 557 patients with mean age of 59 years, mean diabetes duration of 11years and mean HbA1C of 8.3% were treated with both for 26 weeks each. The results showed that combination had better control on mean HbA1C, lower dose requirement and lesser episodes of hypoglycemia. Combination caused weight loss while glargine alone caused weight gain. Nausea was more common with combination. Although this study showed benefits of combination therapy but doesn't include middle age and older patients. Also it didn't demonstrate overall clinical benefit from tight control in this patient population.

Fixed-combination is not yet FDA approved; the two components are available separately.

NEJM JW Gen Med Jul 1 2008 and N Engl J Med 2008; 358:2560 and 2545; NEJM JW Gen Med Jan 15 2009 and N Engl J Med 2009; 360:129

Aspirin Use & Cancer

Adding aspirin to immunotherapy could greatly improve cancer treatment, according to a study published online in *Cell*, September 3, 2015. Some cancers produce PGE2 as a way of escaping the immune system. The protective barrier can be diminished if the ability of cancer cells to make (prostaglandin E2) PGE2 is taken away, resuming the full power of immune system. Animal studies showed that aspirin combined with an immune checkpoint blocker (anti-PD-1 monoclonal antibody) substantially slowed melanoma and colorectal cancer growth, compared with immunotherapy alone. As aspirin's effects on overall cancer risk have not been clear, the researchers in the current study analyzed 32 years' worth of data from almost 136,000 participants in the Nurses' Health Study and the Health Professionals Follow-up Study. Participants who reported regular aspirin use (taking either a standard tablet at least twice a week or a daily low-dose aspirin) had a 3% absolute lower risk of any type of cancer than those who didn't take aspirin regularly.

http://www.mdlinx.com/oncology/article/142.