Shaukat Khanum Memorial Cancer Hospital and Research Center

Pharmacy Newsletter

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The Team
Shahbaz Ahmad Khan, Saba Mazhar, Ehsan Elahi, Rehan Khan Niazi, Mariam Fatima, Faiqa Malik, Adeel Siddiqui ,Irfan Raza, Salman Azeem, Murryam Khalid, Saba Ashraf ,Eman Tahir, Salbia Shereen

Co-Editors:
Ghulam Mujtaba, Sidrah Andleeb, Omar Akhlaq Bhutta

Editor-in-Chief:
Muhammad Tahir Aziz

Get SMART: Reasons to quit using normal saline for resuscitation

Balanced crystalloids (lactated ringer) versus saline fluids (normal saline) for resuscitation have been an ongoing topic of discussion. Recent trials done in both critically ill (SMART) and non-critically ill patients (SALT-ED) are in favor of balanced crystalloids. Mortality benefit was observed in critically ill patients as well as major adverse kidney events were less in patients receiving balanced crystalloids. In light of these studies following reasons can be concluded that suggest avoiding normal saline as a resuscitation fluid.

1- There is no physiological rationale for using normal saline.

2- Saline exacerbates acidosis

3- Saline may be dangerous in hyperkalemia.

4- It causes hyper-chloremic metabolic acidosis

5- Saline causes renal injury

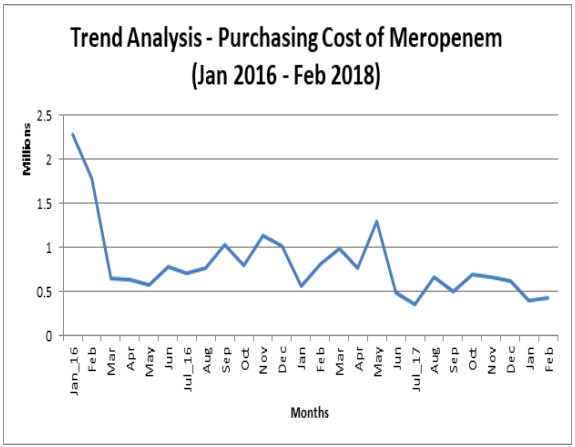
6- Saline may lead to increased levels of inflammation

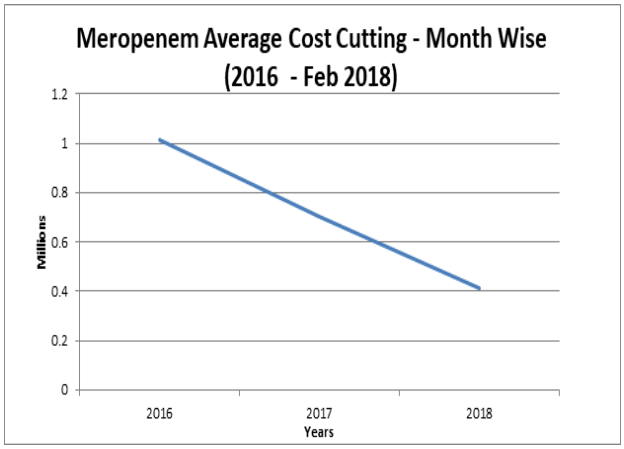
SMART Trial, SALT-ED in non-critically ill patients, Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis." Clinical Gastroenterology and Hepatology, 2018

Drug Product Selection & Cost Effectiveness Review

In our hospital, drug product selection is one of the main responsibilities of pharmacy and therapeutic committee (P&TC), which works efficiently to ensure appropriate and cost effective drug use. One way of saving the cost and ensuring quality of medications is selection of bio-equivalent drugs. Bio- equivalents are drug products which have same active ingredients and bioavailability with reference medicinal product. It means when it acts on its target - for example, a receptor in the brain - the research brand and the generic drug should deliver the same amount of active ingredient to the target site. Bio-equivalent drugs are included in the formulary after complete discussion over evaluation of response and cost. Here is an example of this process wherein 2017; drug utilization review was carried out for two brands of antibiotic Meropenem, brand 1 & brand 2. As per the available literature, no difference in clinical response was observed. However, there was a significant difference in their cost. Therefore, after complete clinical and pharmaco-economic evaluation by P&TC, Brand 2 was added into formulary in 2017.

Meropenem Brand Comparison 2016 - 2017						
Brand	No. of patients assessed (n)	Clinical Indicator	Clinical Response (n)			Remarks
		Clinical & microbiologic resolution	Improvement	Worsening	Static	
Brand 1 2016	30	Yes	30	0	0	Ok
Brand 2 2017	30	Yes	30	0	0	Ok





Co-Trimoxazole Desensitization Protocol

Desensitization is a process of drug re-challenge following an adverse reaction, starting with lower doses of the drug and gradual escalation.

Given the importance of co-trimoxazole and the lack of an equally effective and widely available alternative, desensitization is an important component of managing adults and adolescents with Pneumocycsits.carinii pneumonia prophylaxis in HIV experiencing allergic reaction. It can be attempted two weeks after a non-severe (grade 3 or less) reaction that has resulted in a temporary interruption of therapy. Desensitization should not be attempted in individuals with a history of grade 4 reaction to co-trimoxazole or other sulfa drug. It is recommended to commence an antihistamine regimen (e.g. pheniramine) one day prior to starting the regimen and to continue daily until completion of dose escalation. If a severe reaction occurs, the desensitization regimen is terminated. If a minor reaction occurs, repeat the same step for an additional day. If the reaction subsides, advance to next step; if the reaction worsens, desensitization regimen is terminated.

Step	Dose	
Day 1	80 mg sulfamethoxazole + 16 mg trimethoprim	(2ml of suspension)*
Day 2	160 mg sulfamethoxazole + 32 mg trimethoprim	(4ml of suspension)
Day 3	240 mg sulfamethoxazole + 48 mg trimethoprim	(6ml of suspension)
Day 4	320 mg sulfamethoxazole + 64 mg trimethoprim	(8ml of suspension)
Day 5	400 mg sulfamethoxazole + 80 mg trimethoprim	(10ml of suspension)
Day 6 onwards	800 mg sulfamethoxazole + 160 mg trimethoprim	(20ml of suspension)

***Each 1ml of suspension contains 8mg trimethoprim and 40mg sulfamethoxazole**

WHO-guidelines on Co-trimoxazole prophylaxis for HIV related infections (2006)

Carbapenem and Divalproate Drug-drug Interaction – An SKMCH&RC Case Study

Divalproate does not get along very well with carbepenems. Meropenem, imipenem or doripenem when given alongwith divalproate, reduce levels of divalproate, which may lead to therapeutic failure. The mechanism of this interaction is not well known with a few explanations. It was first identified in 2005 through a case study where patient suffered therapeutic failure for seizure control with combination of doripenem and divalproate due to low serum levels of the later.

We experienced a similar case in our hospital, where a patient with suspected bacterial meningitis was admitted in ICU with tonic clonic fits. Patient was on high dose meropenem 2g q8hrs, was loaded with phenytoin and put on maintenance dose of phenytoin and divalproate. Divalproate dose was doubled to 1g q12hrs on day 3 as seizures did not subside. Serum trough drug level drawn 96hrs on therapeutic dose of divalproate was 0 (target 50 – 100mg/L) while phenytoin level was in range. Divalproate was switched to levetiracetam 500mg q12hrs in view of the interaction. Seizures resolved 48hrs on therapy subsequently. It is suggested to use anti-convulsive drugs other than divalproate when required in patients on concomitant carbapenem therapy.

News & Updates:

Dealing with multi-drug resistant (MDR) HIV-1: What's New on FDA List?

Ibalizumab is a non-immunosuppressive monoclonal antibody, with a new mechanism of action thereby inhibiting the viral entry. It is the only treatment that does not require daily dosing. It is administered intravenously every 14 days in combination with other antiretroviral drugs. Clinical trial was conducted on 40 highly MDR HIV-1 patients being treated with at least 10 anti-retroviral drugs in past. HIV-RNA levels fell significantly one week after the addition of Ibalizumab to the failing antiretroviral regimens and after 24 weeks 43% of participants experienced HIV-RNA suppression, proving its pivotal success. The most frequently seen adverse effects were diarrhea, dizziness, nausea, and rash. Severe adverse effects included rash and immune reconstitution syndrome. The recommended dose is 2,000 mg single loading dose followed by a maintenance dose of 800 mg every 2 weeks, administered intravenously after dilution in 250 mL of 0.9% sodium chloride. Initial estimated annual treatment cost is PKR 15 million approx. Anticipated availability in international market is mid-April 2018.

Medscape - Mar 06, 2018.

Drug Recall – Daclizumab

Daclizumab is a humanized monoclonal antibody that acts on interleukin receptors and has shown therapeutic benefit in multiple sclerosis. The drug was approved by FDA for treatment in patients who have not responded to one or two prior therapies. However, under pharmacovigilance program carried out by European Medicine Authority, several cases of hepatic and brain injuries have been reported in patients being treated with daclizumab. A total of 8 cases of immune mediated brain inflammation induced by relapse multiple sclerosis treatment have been reported; 3 have proven as fatal. Consequently, manufacturer has decided to halt all the clinical trials of this drug leading to withdrawal of drug from the market.

EMA – Mar 08, 2018

Apalutamide for Non-Metastatic Prostate Cancer

U.S. Food and Drug Administration (FDA) have approved apalutamide for the treatment of non-metastatic castration-resistant prostate cancer. The drug binds directly to the ligand-binding domain of the androgen receptor (AR) and inhibits AR nuclear translocation, inhibits DNA binding and impedes AR-mediated transcription. Apalutamide approval follows phase 3 SPARTAN study, where patients were randomized to receive either active drug orally at a dose of 240 mg once daily, or placebo once daily. The study demonstrated a 72% reduction in risk of distant metastasis or death, and an increase in median metastasis-free survival by more than 2 years. Significant improvements were also observed in secondary endpoints including time to metastasis & progression-free survival. Precautions include seizure, falls and fractures. The drug is not registered in Pakistan. Estimated price for 30 tablets pack (60 mg) is PKR 340,000 approximately.

Smith, M. R., Saad, F., Chowdhury, S., Oudard, S., Hadaschik, B. A., Graff, J. N.,& Lopez-Gitlitz, A. (2018). Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer.New England Journal of Medicine