Shaukat Khanum Memorial Cancer Hospital and Research Center

# Pharmacy Newsletter

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***Contributors:***
*Shahbaz Ahmed Khan, Umar Zia, Saba Mazhar, Kiran Ibrahim, Azhar Khursheed, Saqiba Zulfiqar, Amna Khalid, Ehsan Elahi,Shoaib Shammas*

***Co-Editors:***
*Mariam Nawaz, Sidrah Andleeb, Omar Akhlaq Bhutta*

***Editor-in-Chief:***
*Muhammad Tahir Aziz*

## UPDATES

### Ceftazidime induced ESBL – A Marker of Resistance:

*P. aeruginosa* has an inducible, naturally occurring cephalosporinase that confers low-level resistance to amino-penicillin's and narrow-spectrum Cephalosporins such as Cephalothin and Cefoxitin. A prospective study was conducted to determine the prevalence of ceftazidime resistance in *P. aeruginosa* and the rate of ESBL, AmpC and MBL production among these strans isolated from the in-patients and out-patients of a tertiary care hospital. Of the 114 isolates of *P. aeruginosa*, ceftazidime resistance was observed among 65% isolates of in-patients and 44% from those of the out-patients. Ceftazidime slowly penetrates the gram-negative cell wall and accumulates in the bacterial peri-plasmic space. This allows time for the common beta-lactamases (TEM and SHV enzymes) to mutate by substituting one or more amino acids in the protein chain of the enzyme resulting in development of extended-spectrum beta-lactamase (ESBL). Both ceftazidime and cefotaxime appear to be responsible for inducing the class I chromosomal beta-lactamases into a hyper-production state leading to resistance during therapy. This problem is seen clinically in isolates of *Enterobacter* spp. and *Pseudomonas aeruginosa*. This type of resistance also leads to cross-resistance towards other extended-spectrum cephalosporins, penicillins, and aztreonam.

*Reference: Umadevi S, Joseph NM, Kumari K, Easow JM, Kumar S, Stephen S, Srirangaraj S, Raj S. Detection of extended spectrum beta lactamases, ampc beta lactamases and metallobetalactamases in clinical isolates of ceftazidime resistant Pseudomonas Aeruginosa. Brazilian Journal of Microbiology. 2011 Dec; 42(4):1284-8.*

## Acetaminophen – To use or Not to use

Acetaminophen use for treating fever in critically ill patients has been challenged by studies showing that fever may enhance immune function, inhibit pathogen growth and increase the efficacy of antibiotics. A randomized, multicenter blinded trial of Paracetamol 1g IV vs. D5W for up to 28 days was conducted by Australian and New Zealand Intensive Care Society Clinical Trials Group. Acetaminophen was associated with shorter ICU stay than placebo amongst survivors, and longer ICU stay amongst non-survivors, however, there was no significant difference in mortality at day 28 and 90. The observation of longer ICU stay amongst non-survivors is consistent with previous studies where physical cooling in mechanically ventilated patients of septic shock is associated with delayed mortality. However, since the study focused on short term (up to 28 days) use of acetaminophen, this effect may be evaluated further in future with prolonged use of the drug. As of the current study results, early treatment of fever with acetaminophen does not affect mortality or early discharge from ICU.

# MIRACLES OF ANTIBIOTIC LOCK THERAPY

Antibiotic lock is indicated as adjunctive therapy with systemic anti-microbials for patients

- With uncomplicated catheter related bloodstream infections [Gram-positive/Gram-negative organism (coagulase-negative staphylococcus, enterococcus, gram-negative bacilli)]
- Involving long- term catheters with no signs of exit site or tunnel infection
- Cases where catheter salvage is the goal. However, it should be used in conjunction with systemic anti-microbial therapy.

***Antibiotics for Lock Therapy:***

| Antibiotic | Concentration (mg/mL) | Heparin (units/ml) |
|---|---|---|
| **Vancomycin** | 2.5 | 2500 |
| **Cefazolin** | 5.0 | 2500 |
| **Ceftazidime** | 0.5 | 100 |
| **Ciprofloxacin** | 0.2 | 5000 |
| **Gentamicin** | 1.0 | 2500 |
| **Ampicillin** | 10.0 | 5000 |

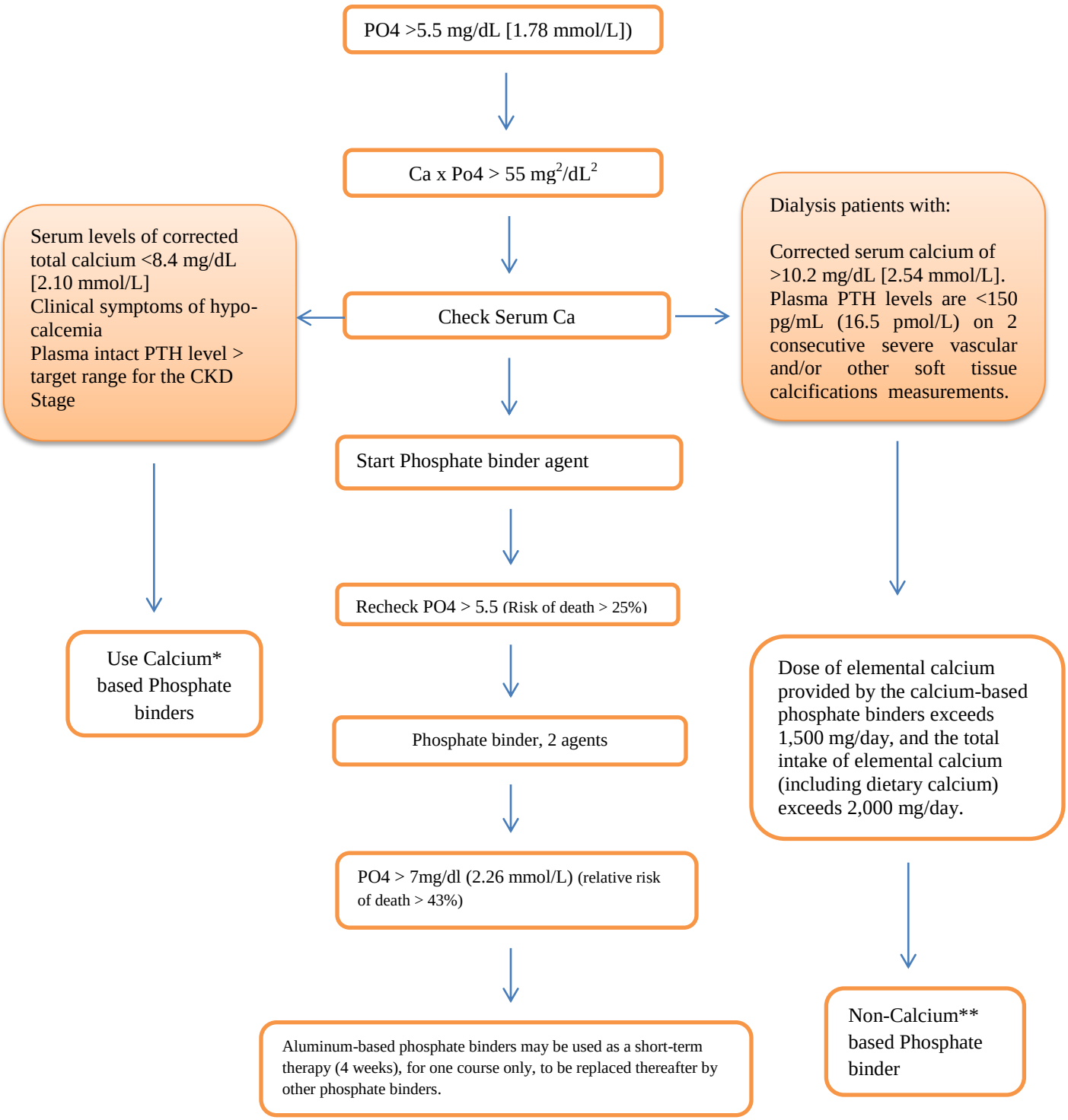
***Administration Instructions:***

1. Prior to installation of antibiotic lock, withdraw contents from catheter lumen and flush with normal saline.
2. Instill antibiotic lock solution to fill catheter lumen according to the permissible volumes for the catheter. Label the catheter: "DO NOT USE- Antibiotic Lock".
3. Allow lock solution to dwell for a period of time specified by the physician order. Usual treatment duration: 6-12 hours twice daily. Afterwards aspirate antibiotic lock solution from catheter lumen.
7. Flush catheter with normal saline before using line to administer medication.
8. Duration of antibiotic lock therapy is for 7-14 days.

*Reference: www. med.stanford.edu*

# MANAGEMENT OF HYPER-PHOSPHATEMIA

*By Mariam Nawaz*



| Ca- based PO4 binders | Elemental Calcium (1g = mEq) | Dose | Cost |
|---|---|---|---|
| Ca Citrate | 10.5 | 1.5-3 g | $$ |
| Ca acetate & Mg carbonate combo | 12.6 | 235mg /435mg<br>3-10 tablets daily | $$$ |
| Calcium Acetate | 12.6 | 2001-2668mg/day | $$$$ |
| Calcium carbonate | 19.9 | 3-6 g | $$$$ |

| Non- Ca based PO4 Binders | Dose | Cost |
|---|---|---|
| Al hydroxide | 1.425-2.85 g | $ |
| Mg carbonate | 0.7-1.4g | $$$ |
| Lanthanum carbonate | Initial: 1500mg/day, increase of 750mg daily every 2-3 weeks up to: 4500mg max | $$$$$ |
| Sevelamer-HCl | **Initial dose:**<br>>5.5mg/dl- 7.5mg/dl: 800mg TID<br>≥7.5 mg/dL - <9 mg/dL: 1200-1600mg TID<br>≥9 mg/dL: 1600mg TID<br>**Maintenance dose (based on serum PO4 level):**<br>>5.5mg/dL: ↑400-800mg TID at 2 weeks interval.<br>3.5-5.5 mg/dL: Maintain current dose<br><3.5mg/dL: ↓400-800mg / meal<br>Max: 14mg/ day | $$$$$$ |

*Reference: KDIGO 2013/14 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*

# NEW ARRIVALS

**Talimogene laherparepvec:** The US FDA has approved first of its kind genetically modified live oncolytic virus therapy, talimogene laherparepvec (Imlygic), for the treatment of melanoma lesions in the skin and lymph nodes. It is injected directly into melanoma lesions and replicates inside the cancer cells producing granulocyte-macrophage colony-stimulating factor (GM-CSF). The drug causes cell death and then lysis, which releases tumor-derived antigens and GM-CSF, promoting an antitumor response. The approval was based on the results of phase III OPTiM study, stating that talimogene laherparepvec showed a response lasting a minimum of 6 months. Of the patients achieving a durable response, 29.1% had a durable complete response and 70.8% had a durable partial response; median time to response was 4.1 months. Treatment with Imlygic involves a series of injections into the melanoma tumors. After the first injection, a second dose is given 3 weeks later, and then every 2 weeks, typically for at least 6 months. The most common side effects are fatigue, chills, fever, nausea, flu-like symptoms, and pain at the injection site. As it is a modified live virus, herpes virus infection can also occur. Imlygic should not be given to people with suppressed immune system or women who are pregnant. However, the FDA noted that talimogene laherparepvec was not associated with any improvement in overall survival and has not been shown to have an effect on melanoma spreading to the brain, bone, liver, lungs, or other internal organs.

**Antidote for Fluorouracil & Capecitabine:** In December 2015, FDA approved a new antidote for Fluorouracil & Capecitabine overdose/toxicity. Uridine triacetate reduces incorporation of fluorouridine triphosphate into RNA of hematopoietic progenitor cells and gastrointestinal mucosal cells to reduce fluorouracil & Capecitabine toxicity in normal tissues. Oral dose of 10g Q6 hourly for 20 doses, initiated as soon as possible (within 8 – 96hrs), has shown to reduce severity as well as incidence of overdose/overexposure of the offending drugs. Efficacy post 96hrs of chemo use has not been established yet. Uridine triacetate is not recommended for nonemergency adverse reactions associated with flourouracil or capecitabine because it may lessen the efficacy of these drugs.

**Cooling Cap to Reduce Hair Loss from Chemotherapy:** US FDA has approved marketing of a cooling cap to reduce hair loss in women being treated with chemotherapy for breast cancer. The Digni-Cap Cooling System is a computer controlled system which circulates a cooled liquid to a head-worn cap during chemotherapy treatment. The cooling cap is covered by a second cap made of neoprene, which holds the former in place and acts as an insulator. The cooling action causes vasoconstriction in the scalp, which, in theory, reduces the amount of chemotherapy reaching cells in the hair follicles. The cold also decreases the activity of the hair follicles, slowing down cell division so that they are less likely to be affected by chemotherapy.