Shaukat Khanum Memorial Cancer Hospital and Research Center

Pharmacy Newsletter

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P&TC UPDATES:

A. New formulary approved medicines

1. ***Onabotulinum Toxin Type A.*** Regular formulary
2. ***Remifentanyl Inj.*** Regular formulary

B. Magnesium Sulphate Injection: Pharmacy will now dispense Magnesium Sulphate in multi dose bag (Normal Saline 100ml) as ward stock.

Pegasparaginase to Erwinaze dose conversion:

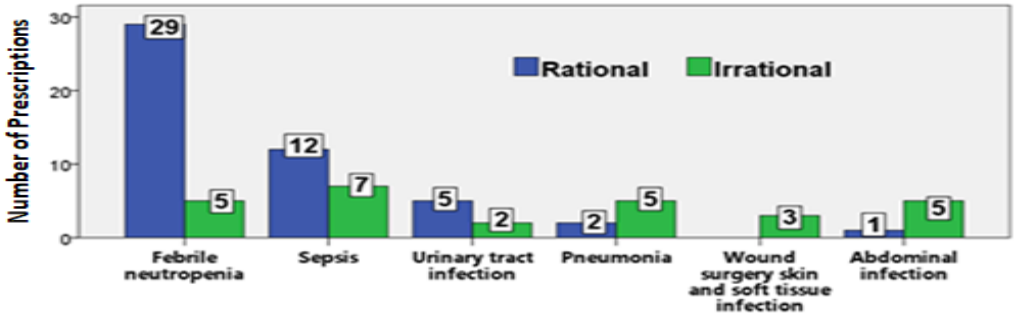
Dose Equivalence	Pegaspargase	Erwinaze
Dose	2500 international units/m² IM (preferred) or IV q14Days	Substitution for pegaspargase: 25,000 IU/m² IM/IV 3 times/week (Monday/Wednesday/Friday) for 6 doses (for each planned dose of pegaspargase) When substituting for native asparaginase *E. coli*, a dose of 25,000 IU/m^2 should be administered for each scheduled dose of native asparaginase *E. coli* (i.e. 1-to-1 dose replacement)
Administration	Administration is similar to that of Erwinaze.	**Intravenous Administration** Slowly inject in 100 mL of 0.9% NaCl over 1 to 2 hours within 4 hours of reconstitution.. **Intramuscular Administration**: 2 mL per injection site.
Adverse effects	Glucose intolerance, Pancreatitis, Fever, coagulopathy, Rash.	Hypersensitivity, Glucose intolerance, Pancreatitis, Fever, Coagulation abnormalities, Thrombosis.

1. Holle, Lisa M. "Pegaspargase: an alternative?" *Annals of Pharmacotherapy* 31.5 (1997): 616-624.
2. *Keating, Gillian M. "Asparaginase Erwinia chrysanthemi (Erwinaze®): A Guide to Its Use in Acute Lymphoblastic Leukemia in the USA." BioDrugs 27.4 (2013): 413-418.*

Drug Utilization Review of Piperacillin/Tazobactam at a Tertiary Care Hospital, Pakistan.

This retrospective, cross sectional study was conducted to estimate the rationality of Piperacillin/Tazobactam utilization in our hospital. The study aimed to involve all those patients who were admitted at SKM, and were prescribed Piperacillin/Tazobactam as an empiric therapy over a period of three months Apr to Jun, 2017. The medical records for 73 patients (76 prescriptions in total) were retrospectively reviewed and analyzed. Main indication for use of Piperacillin/Tazobactam was febrile neutropenia (34/76; 44.73 %). Overall percentage of rational use of empiric therapy was (49/76; 64.47 %) (p-value 0.001). Cases of wound/surgery/skin/soft tissue infections, abdominal infections and pneumonia and unit of palliative care, showed higher trends of irrational prescribing. Microbiology data was positive for 40/76 (52.63 %) prescriptions. Antibiotic de-escalation after culture sensitivity reports, was done in 12/24 (50 %) prescriptions.

In 12/24 (50%) cases, required de-escalation was missing. Regarding the rationality as per criteria for dosing, dose adjustments and indications, 26/39 (66.66%) orders fulfilled the criteria for rational use. Piperacillin/Tazobactam use can be improved at our institute through strict surveillance on appropriateness of indication and duration of therapy with timely de-escalation. (Ehsan Elahi1* U. Z., 2017)



Rationality of Piperacillin/Tazobactam according to indication

Enoxaparin Dose Reduction for Thrombocytopenia

Development of thrombocytopenia in the setting of therapeutic anticoagulation for venous thromboembolic disease (VTE) is common in cancer patients. Memorial Sloan Kettering Cancer Center implemented the guidelines in this setting:

Platelet count	Enoxaparin therapeutic dose
> 50,000/mcL	Full dose
25,000-50,000/mcL	Half-dose
< 25,000/mcL	Stop enoxaparin

Validation of safety and efficacy of these guidelines was checked in 99 patients with 140 episodes of thrombocytopenia for 7 days. The median duration of thrombocytopenic episodes was 12 days. Enoxaparin dose was modified in 133 of the 140 episodes (95%), reflecting satisfactory adherence. There were no recurrent VTE events. In this cohort, there was only one trauma-associated retroperitoneal hemorrhage that occurred prior to enoxaparin dose modification. Lastly, 10 patients died during an episode of thrombocytopenia. Study supports the safety and efficacy of therapeutic enoxaparin dose modification.

Mantha, S., Miao, Y., Wills, J., Parameswaran, R., & Soff, G. A. (2017). Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. Journal of Thrombosis and Thrombolysis, 43(4), 514-518.

Effect of multidisciplinary team and an integrated follow-up electronic system on clinical pharmacist interventions in a cancer hospital.

The aim of drug therapy is to attain distinct therapeutic effects that not only improve patient's quality of life but also reduce the inherent risks associated with the therapeutic use of drugs. Pharmacists play a key role in reducing these risks by developing appropriate interventions. Whether to accept or reject the intervention made by the pharmacist is a relevant consultant's decision. Objective of study was to evaluate the impact of electronic prompts and follow-up of rejected pharmacy interventions by clinical pharmacists in an in-patient setting. This study was done at Shaukat Khanum Cancer Hospital & Research Center, Lahore, Pakistan. The study was conducted in two phases. Data for 3 months were collected for each phase of the study. Systematic and quantifiable consensus validity was developed for rejected interventions in phase 1, based on patient outcome analyses. Severity rating was assigned to assess the significance of interventions. Electronic prompts for follow-on interventions in phase 2 were then developed and implemented, including daily review via a multidisciplinary team (MDT) approach. Main outcome measure Validity of rejected interventions, acceptance of follow-on interventions before and after re-engineering the pharmacy processes, rejection rate and severity rating of follow-on interventions. Of a total of 2649 and 3064 interventions that were implemented during phase 1 and phase 2, 238 (9%) and 307 (10%) were rejected, respectively. Additionally, 133 (56%) were inappropriate rejections during phase 1. The estimated reliability between pharmacists regarding rejected interventions was 0.74 (95% CI of 0.69, 0.79, p 0.000). Prospective data were analyzed after implementing electronic alerts and an MDT approach. The acceptance rate of follow-on interventions in phase 2 was 60% (184). So, it can be concluded that electronic prompts for follow-on interventions together with an MDT approach enhance the optimization of pharmacotherapy, increase drug rationality and improve patient care.

Aziz, M. T., Rehman, T. U., Qureshi, S., & Andleeb, S. (2017). Effects of multidisciplinary teams and an integrated follow-up electronic system on clinical pharmacist interventions in a cancer hospital. International journal of clinical pharmacy, 39(6), 1175-1184.

A prospective evaluation of Intravenous (I/V) Fosfomycin in critically ill patients.

Fosfomycin, a phosponic acid derivative (acts primarily by disrupting bacterial cell wall synthesis) is a broad-spectrum antibiotic. Fosfomycin (I/V) is expected to achieve better blood levels and better activity than oral dosage form. A study was conducted in the ICU at 'Henry Dunant' Hospital, in Athens. The primary endpoint of the study was all-cause in-hospital mortality. Adult ICU patients who received IV fosfomycin were prospectively examined to assess its safety and efficacy as an adjunct to the antimicrobial therapy for life-threatening infections caused by carbapenem-resistant K. pneumoniae (CRKP). Fosfomycin was administered (2-4 g every 6 h) intravenously in 11 patients for treatment of hospital-acquired infections caused by CRKP. The mean ±SD duration of treatment was 14 ±5.6 days. All patients had good bacteriological and clinical outcome of infection. All-cause hospital mortality was two out of 11 (18.2%) patients. No patient experienced adverse events related to the administration of fosfomycin. Intravenous fosfomycin may be a beneficial and safe adjunctive treatment in the management of life-threatening ICU-acquired infections caused by CRKP. It is registered and available in Pakistan as 1g injection. Price: PKR 75 per 1 g vial.

Michalopoulos, A., Virtzili, S., Rafailidis, P., Halevelakis, G. H., & Falagas, M. (2009). Intravenous fosfomycin for the treatment of nosocomial infections due to carbapenem-resistant Klebsiella pneumoniae in critically ill patients. A prospective evaluation. Clinical Microbiology & Infection, 15(4), S183.

News & Updates:

Febuxostat: *New alert for increased CV death.*

Febuxostat is a potent non-purine selective inhibitor of xanthine oxidase, approved for treatment of gout by FDA in 2009. Drug label already carries a warning and precaution about cardiovascular events because the clinical trials conducted before approval showed a higher rate of heart-related problems in patients treated with febuxostat compared to allopurinol. These problems included heart attack, stroke, and cardiac disease associated mortality. FDA required an additional safety clinical trial after the drug was approved to better understand these differences. This trial includes over 6,000 patients with gout treated with either febuxostat or allopurinol. Primary cardiovascular (CV) end point for this trial is a combination of CV death, nonfatal myocardial infarction, nonfatal stroke, and unstable angina requiring urgent coronary revascularization. The preliminary results show that overall, febuxostat did not increase the risk of these combined events compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed a greater risk of heart-related deaths, nonfatal myocardial infarction, nonfatal stroke, and unstable angina. FDA advises health care providers to consider this safety information while deciding whether to prescribe patients with febuxostat or not. Febuxostat is added in the FDA's drug **"watch list"** for possible CV events.

Pontremoli, Roberto. "The role of urate-lowering treatment on cardiovascular and renal disease: evidence from CARES, FAST, ALL-HEART, and FEATHER studies." Current medical research and opinion 33.sup3 (2017): 27-32.

Axicabtagene Ciloleucel*: New Immunotherapy for DLBCL.*

On October 18, 2017, FDA granted regular approval to axicabtagene ciloleucel (YESCARTA, Kite Pharma, Inc.) for the treatment of adult relapsed or refractory large B-cell lymphoma, diffuse large B-cell lymphoma DLBCL, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma. It was approved following a priority review and under the FDA's breakthrough therapy program. Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T cell immunotherapy. Autologous T-cells are genetically modified to produce a CAR protein, allowing the T-cells to identify and eliminate CD19-expressing malignant cells (a protein expressed on the cell surface of B-cell lymphomas). The recommended dose is a single IV infusion with a target of 2 x 10^6 CAR-positive viable T cells per kg body weight (maximum 2 x 10^8).Approval was based on a single-arm multicenter phase 1/2 study (ZUMA-1) of 108 adult patients with aggressive B-cell non-hodgkin lymphoma. Of the 101 patients evaluated for efficacy, the objective response rate (ORR) as assessed by independent central review was 72%, with a complete remission (CR) rate of 51% (95% CI: 41, 62). *The most common grade 3 or higher ADRs include febrile neutropenia, cytokine release syndrome (CRS), encephalopathy, infections, hypotension and hypoxia.* FDA approved axicabtagene ciloleucel with a Risk Evaluation and Mitigation Strategy (REMS). The drug is a recent addition to the international medicine market and is unregistered in Pakistan so far.

Jain, M. D., & Davila, M. L. (2017). Concise Review: Emerging Principles from the Clinical Application of Chimeric Antigen Receptor T Cell Therapies for B Cell Malignancies. Stem Cells.

Daratumumab Multiple myelomas.

The combination of bortezomib, melphalan, and prednisone is a standard treatment for patients with newly diagnosed multiple myeloma ineligible for autologous stem-cell transplantation. Daratumumab has shown efficacy in combination with standard-of-care regimens in patients with relapsed or refractory multiple myeloma. Daratumumab containing regimen was associated with higher incidence of grade 3 or 4 infections. The primary end point was progression-free survival showing lower risk of disease progression or death than the same regimen without daratumumab. The drug is un-registered in Pakistan as yet.

Mateos, María-Victoria, et al. "Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma." New England Journal of Medicine (2017).