Greg Gousse Residency Conference
Clinical Pearl Proposal
SAMPLE #1

Title: Taking the Path of Least Resistance: Utilizing Argatroban in Patients with Heparin Resistance

Statement of Educational Needs Assessment:

Unfractionated heparin has been a cornerstone of initial treatment for venous thromboembolism (VTE) for decades.[1] Infrequent reports of patients requiring higher doses of heparin to achieve therapeutic concentrations have surfaced over the years. Despite several studies in the literature that have examined this phenomenon, the incidence, definition, monitoring, and treatment options for this effect are still controversial with no clear consensus.[1-2] Clinical pharmacists have a direct role in the monitoring and management of anticoagulant medications and play an integral part in recognizing heparin resistance and recommending alternative therapies for the treatment of VTE.

Planned Active Learning Assessment: A brief patient case will be incorporated into the presentation. Open response questions will be used with the audience to reinforce how to identify the clinical presentation of heparin resistance and select an appropriate alternative to achieve therapeutic anticoagulation.

HR is a 33-year-old male with a past medical history of atrial fibrillation who presented with a chief complaint of chest pain with palpitations and shortness of breath and was subsequently diagnosed with a pulmonary embolism and started on a heparin drip.

	Heparin Infusion on day 1			**Heparin infusion on day 2**		
Time	05:00	12:00	19:00	02:00	08:00	15:00-16:00
Heparin rate (units/kg/hr)	15	19	22	26	28	30
Total cumulative heparin given (units)	8,579	19,445	32,026	44,771	60,784	63,235
Anti-Xa levels	0.48	0.07	0.10	0.08	0.20	0.20

Abstract:

Unfractionated heparin (UFH) exerts its anticoagulant effect via binding of antithrombin (AT) through a high affinity pentasaccharide, causing a conformational change, and leading to inactivation of both factor Xa and thrombin.[3-4] It is commonly monitored with activated partial thromboplastin time (aPTT)

and anti-Xa heparin functional assays. An important distinction in functional assays is that the anti-Xa levels reflect only the plasma heparin level and are not influenced by variables that affect the aPTT such as Factor VIII.[3] One study found that in patients with acute deep vein thrombosis (DVT), pulmonary embolism (PE), or axillary vein thrombosis being treated with UFH, the patients in the aPTT group required a statistically significantly greater amount of heparin compared with the patients in the anti-factor Xa group.[5]

Heparin resistance is commonly defined as the need for high doses of heparin to achieve a targeted level of anticoagulation. One reported definition suggests that the need for more than 35,000 units per day to achieve therapeutic anticoagulation constitutes heparin resistance.[3] The proposed resistance mechanisms include the nonspecific binding of heparin, antithrombin deficiency, and increased heparin clearance.[3,6] There is a heavy reliance on small trials and literature reviews to identify the clinical presentation of heparin resistance and determine the most appropriate alternative treatments since there are no published guidelines on this topic, outside of the setting of cardiopulmonary bypass.[2] This presentation will summarize the available literature on heparin resistance and use of argatroban as a therapeutic alternative.[7] A patient case where argatroban was used to replace UFH in the setting of heparin resistance will be discussed.

Objective: Develop an appropriate alternative treatment regimen for patients requiring anticoagulation in whom there is clinical concern for heparin resistance

References:

1. Smythe MA, Priziola J, Dobesh PP, Wirth D, Cuker A, Wittkowsky AK. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016 Jan;41(1):165-86.
2. Spiess BD. Treating heparin resistance with antithrombin or fresh frozen plasma. Ann Thorac Surg. 2008 Jun;85(6):2153-60.
3. Levy JH, Connors JM. Heparin Resistance - Clinical Perspectives and Management Strategies. N Engl J Med. 2021 Aug 26;385(9):826-832.
4. Warnock LB, Huang D. Heparin. [Updated 2022 Jul 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538247/
5. Levine MN, Hirsh J, Gent M, et al. A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. Arch Intern Med 1994;154:49-56.
6. Durrani J, Malik F, Ali N, Jafri SIM. To be or not to be a case of heparin resistance. J Community Hosp Intern Med Perspect. 2018 Jun 12;8(3):145-148.
7. Treichl B, Bachler M, Lorenz I, Friesenecker B, Oswald E, Schlimp CJ, Pedross F, Fries D. Efficacy of argatroban in critically ill patients with heparin resistance: a retrospective analysis. Semin Thromb Hemost. 2015 Feb;41(1):61-7.

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SAMPLE #2

Title: Revving the Immune Engine: The Safety and Efficacy of Immunotherapy in Patients Living With HIV

Statement of Educational Needs Assessment:

Fewer patients with human immunodeficiency virus (HIV) are dying of acquired immune deficiency syndrome (AIDS) related disease due to increased efficacy of antiretroviral therapy [1]. As a result, cancer has become the leading cause of death in patients living with HIV without AIDS related disease [1]. Immunotherapy has become a key player in the treatment of many different cancers. However, patients living with HIV were excluded from many initial studies using immunotherapy to treat cancer due to the fear of exacerbation of chronic HIV infection or development of immune related adverse effects [2]. Clinical pharmacists play a key role in assessing the safety and efficacy of immunotherapy for treatment of cancer in patients living with HIV.

Planned Active Learning Assessment:
A PowerPoint presentation will be utilized to present this topic. A brief patient case will be incorporated throughout the presentation to encourage participation and active engagement in the presentation. The patient case will be used to set the stage for the topic as well as discuss the real-life application of the topic.

Patient case:

- Non-small cell lung cancer (NSCLC)
- On previous chemotherapy – provider wants to switch to immunotherapy
- On antiretroviral therapy (ART) – last cluster of differentiation 4 (CD4) was above 200 with undetectable viral load

Abstract:
Immunotherapy has shown efficacy in many different cancers and become a breakthrough in cancer treatment. Immunotherapy includes agents that target the programmed cell death 1 (PD-1) checkpoint molecule that negatively regulates receptor signaling on T cells and down regulates the immune response. Immunotherapy blocks the interaction between PD-1 and its ligand, programmed cell death ligand 1 (PD-L1), and, programmed cell death ligand 2 (PD-L2), which blocks the down regulation allowing for the immune system to become upregulated and target cancer cells [3]. Clinical trials have excluded patients living with HIV due to the fear of exacerbation of chronic HIV infection or increased risk of developing of immune-related adverse effects as HIV infected cells have an increased expression of PD-1 [2]. Patients living with stable HIV on ART are less likely to die of AIDS defining conditions. Therefore, cancer is now the leading cause of death in 37 million people living worldwide with HIV [3]. There is a need for further evaluation of the efficacy and safety of immunotherapy in patients living with HIV.
Since the initial clinical trials, there have been a few studies published that evaluated the safety and efficacy of immunotherapy in patients living with HIV. An open label, non-randomized phase 1 multicenter study conducted at seven cancer immunotherapy trial network sites concluded pembrolizumab has acceptable safety in patients with cancer, HIV treated with ART, and a CD4 T cell count greater than 100 cells/microliter [3]. Additionally, a small observational study found the disease rate control observed in patients with HIV receiving immune checkpoint inhibitors was similar to the

general population [2]. A systematic review also determined that immune checkpoint inhibitors may be safe and effective in patients with HIV and advanced stage cancer [1].

This presentation will discuss the published literature on the safety and efficacy of immunotherapy in patients living with HIV in order for pharmacists to critically evaluate the role of immunotherapy in patients living with HIV.

Objective: Evaluate the safety and efficacy of immunotherapy for cancer treatment in patients living with HIV based on literature published since the initial clinical trials.

References:

1. Cook MR, Kim C. Safety and efficacy of immune checkpoint inhibitor therapy in patients with HIV infection and advanced-stage cancer. *JAMA Oncology*. 2019;5(7):1049. doi:10.1001/jamaoncol.2018.6737
2. Spano J-P, Veyri M, Gobert A, Guihot A. Immunotherapy for cancer in people living with HIV. *AIDS*. 2019;33(11). doi:10.1097/qad.0000000000002298
3. Uldrick TS, Gonçalves PH, Abdul-Hay M, Claeys AJ. Assessment of the safety of pembrolizumab in patients with HIV and advanced cancer—A phase 1 study. *JAMA Oncology*. 2019;5(9):1332. doi:10.1001/jamaoncol.2019.2244
4. Uldrick TS, Adams SV, Fromentin R, Roche M. Pembrolizumab induces HIV latency reversal in people living with HIV and cancer on Antiretroviral therapy. *Science Translational Medicine*. 2022;14(629). doi:10.1126/scitranslmed.abl3836
5. Castelli V, Lombardi A, Palomba E, Bozzi G. Immune checkpoint inhibitors in people living with HIV/AIDS: Facts and controversies. *Cells*. 2021;10(9):2227. doi:10.3390/cells10092227