Mathur P, O'Brien J. 1-Minute Pearls/Pitfalls for the Clinician. *Brown Hospital Medicine*. Published online October 1, 2023. doi:10.56305/001c.87425

1-Minute Pearls/Pitfalls for the Clinician

Parijat Mathur, MD[1], Jennifer O'Brien, MD[1]

[1] Division of Hospital Medicine, Miriam Hospital

Journal of Brown Hospital Medicine

Article Information

Keywords: heparin resistance, antibiotic associated encephalopathy, antibiotics, delirium

https://doi.org/10.56305/001c.87425

Submitted: August 01, 2023 EDT

Accepted: August 15, 2023 EDT

QUESTION 1: DOES THIS PATIENT HAVE ANTIBIOTIC-ASSOCIATED ENCEPHALOPATHY?

A 63-year-old female with diabetes mellitus and Stage 3 chronic kidney disease is admitted with sepsis secondary to complicated UTI. She was started on IV Cefepime. Over the next 36 hours, she is noted to have significant improvement in her fever curve and leukocytosis. Her urine culture grew >100,000 colonies of E. Coli sensitive to cefepime. Blood cultures remain sterile. On day 5, she is noted to be encephalopathic, somnolent and inappropriately responding to vocal and tactile stimuli. She had no nuchal rigidity and no focal neurological deficits on bedside exam. She remains without fever and has no other complaints. What will be the next step in this patient's management?

A: This patient's clinical presentation is most likely due to antibiotic-associated encephalopathy, an underrecognized class of medications causing delirium in hospitalized patients. Antibiotic-associated encephalopathy(AAE) can be divided into three unique clinical phenotypes: encephalopathy commonly accompanied by seizures or myoclonus arising within days after antibiotic administration (caused by cephalosporins and penicillin-Type-I); encephalopathy characterized by psychosis arising within days of antibiotic administration (caused by quinolones, macrolides, and procaine penicillin-Type II); and encephalopathy accompanied by cerebellar signs and MRI abnormalities emerging weeks after initiation of antibiotics (usually caused by metronidazole as Type 3).[1]

While cephalosporins (especially cefepime) tend to cause seizures and myoclonus, quinolones, sulfonamides, macrolides, and procaine penicillin have psychosis-predominant symptoms. Electroencephalography (EEG) may be abnormal in greater than 70% of patients across all classes, with abnormalities ranging from epileptiform discharges in patients with cephalosporin/penicillin related AAE or can present with nonspecific findings of encephalopathy such as slowing and generalized periodic discharges with triphasic morphology (can be seen with both Type I and Type II class of antibiotics). Most patients with quinolone use also have abnormal nonspecific EEG findings.

Why is there a difference in clinical presentation across antibiotic classes?

Type 1 AAE (seizure/myoclonus): Type 1 AAE is thought to be caused by disruption of inhibitory synaptic transmission leading to excitotoxicity. The g-aminobutyric acid class A receptor ($GABA_AR$) is the most implicated receptor. B-lactams bind to $GABA_AR$ receptors, decreasing inhibitory synaptic transmission and translating clinically into seizure activity.

Type 2 AAE (psychosis-predominant): The distinct neuropsychiatric features found in type 2 AAE closely resemble drug-induced psychotic syndromes caused by perturbations of the D2 dopamine and N-methyl-D-aspartate (NMDA) glutamate receptors (e.g., cocaine, amphetamines, and phencyclidine).

Type 3 AAE (encephalopathy with cerebellar signs): Unlike the other subtypes of AAE, metronidazole toxicity results in characteristic reversible MRI signal abnormalities in the cerebellar dentate nuclei, dorsal brainstem, or splenium of the corpus callosum. Neurotoxicity is related to free radical formation and altered thiamine metabolism.

QUESTION 2: DOES THIS PATIENT HAVE HEPARIN RESISTANCE?

A 67-year-old patient with history of oxygen-dependent COPD, prior CVA, was admitted with dyspnea and palpitations. She was diagnosed with acute on chronic hypoxic respiratory failure due to pulmonary embolism

(right lower lobe segmental and subsegmental pulmonary emboli), complicated by new-onset Atrial fibrillation. She has no family history of hypercoagulable or autoimmune disorders. She has a history of ongoing tobacco use and over 20 pack/yr. She was started on IV heparin but was noted to have subtherapeutic PTT and anti-Xa levels even after multiple adjustments of her IV heparin based on standard protocol. Her anti-Xa levels range <0.04 to 0.06. Therapeutic range being (0.3 - 0.6: anti Xa U/ML). What will be the next steps in this patient's management?

A: Unfractionated heparin (UFH) is a heterogenous mixture of different length polysaccharide strands which bind to antithrombin, potentiating its anticoagulant effect, and thrombin, inactivating its thrombotic effect via subsequent impact on fibrin and coagulation factors IX, X, XI and XII. While UFH and low molecular weight heparin (LMWH) both inhibit thrombin and factor Xa, the difference in polysaccharide polymer length results in UFH influencing both thrombin and anti-Xa whereas LMWH primarily effects factor Xa. Due to a strong negative charge UFH attaches to macrophages, endothelial cells, and an array of heparin binding proteins. Monitoring for its therapeutic levels is by using activated partial thromboplastin time (aPTT), activated clotting time (activated CT), or more recently by using anti-Xa levels.

Heparin resistance should be considered in situations where progressively increased doses are required to achieve therapeutic levels of anticoagulation or the impossibility of achieving therapeutic aPTT or anti-Xa levels. A common accepted definition in current literature uses a threshold of UFH doses greater than 35,000 units/day, but the definition has not been validated.[2] Heparin resistance may be pseudo or real in nature.

- *Apparent or pseudo-heparin resistance* is detected by having a therapeutic anti-Xa level in the presence of sub-therapeutic aPTT levels, signifying a therapeutic heparin response by anti-Xa level. This is commonly due to elevated factor VIII and/or fibrinogen levels which reduce aPTT levels. Elevated VIII and/or fibrinogen levels are seen in systemic inflammatory states, malignancy, liver and renal diseases and in pregnancy. Identification and management of pseudo-resistance requires transitioning from aPTT to anti-Xa monitoring. This is particularly important to avoid hemorrhagic complications from *in vivo* supratherapeutic UFH.[3]
- *Real heparin resistance* is a low aPTT in confirmed by low anti-Xa levels despite escalated heparin doses. Evaluation of patients in this category includes checking anti-Xa and Antithrombin III levels.

The most common cause is antithrombin deficiency, which may be congenital or acquire. Congenital forms (Type I and Type II) are associated with early onset of thrombo-embolic phenomenon typically by the second decade of life. Acquired causes include disseminated intravascular coagulation (DIC), acute thrombosis, liver disease, nephrotic renal disease, asparaginase therapy for leukemia (ALL), sepsis, surgery, pregnancy and in particular pre-eclampsia and eclampsia, use of hemodialysis and extracorporeal membrane oxygenation (ECMO).[4] Heparin itself also can lower antithrombin levels. Due to the role of acute phase reactants, repeating antithrombin levels after resolution of acute illness may be considered.

Reduction in heparin bioavailability also results in heparin resistance. The strong negative charge of UFH is thought to result in increased binding to von Willebrand factor and other coagulation factors, interleukin-8, TNF-α, collagen, fibrinogen, glycoproteins and lipoproteins, microbial and viral proteins (with COVID-19 being an area of active investigation). UFH also has been noted to bind to cells such as leukocytes, endothelial cells and platelets (especially platelet counts>400,000IU), as well as platelet factor 4. Heparin-induced thrombocytopenia is itself a form of heparin resistance with development of antibodies to the heparin-platelet factor 4 complex.[5] Reduction can also be seen due to increased clearance with splenomegaly.

Management of real heparin resistance requires using increasing doses to achieve therapeutic anti-Xa levels in cases of where anti-Thrombin III levels are >40% or transition to an alternative agent such as a direct thrombin inhibitor or to direct oral anticoagulants as per patient's eGFR. Antithrombin supplementation and fresh frozen plasma has been used in cardiothoracic surgery and ECMO and is an area of active study for consensus use. Factitious heparin resistance should also always be considered and easily eliminated, as is seen in the case of line connection and other logistical administration issues.

Author Contributions

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures/Conflicts of Interest

The authors declare they have no conflicts of interest

Corresponding Author

Jennifer O'Brien MD
Division of Hospital Medicine
Miriam Hospital
164 Summit Ave
Providence, RI 02906
Ph: 401-793-2500

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