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1-Minute Pearls/Pitfalls for the Clinician

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Abstract

This article explores important insights and potential challenges in managing patients with candidemia and prolonged QTc. It also offers guidance on managing patients with VTE and prolonged APTT.

QUESTION 1: HOW TO MANAGE PATIENTS WITH CANDIDEMIA AND PROLONGED QTC?

A 45-year-old female with a history of Crohn's disease s/p ileostomy on Infliximab, a history of depression, and chronic pain syndrome is admitted with fevers, chills, and abdominal pain. She reports no cough, shortness of breath, chest pain, increasing ostomy output, or dysuria. No tenderness is noted at her Port-A-Cath site. Her other medications include Citalopram and Methadone. A CT scan of the abdomen and pelvis revealed the absence of an abscess. Her blood cultures revealed budding yeasts. The Port-A-Cath is removed, and she is started on an echinocandin (Micafungin), with the plan to transition to an azole based on clinical course and laboratory data. Speciation reveals she has fungemia due to candida albicans species. Repeat cultures are negative on day 5 of her admission. She is eager to go home. What are her options?

A: Management of candidemia is based on the following principles:

- Use of a broad anti-fungal regimen and adjusting regimen based on culture results
- Source control in applicable cases: removal of lines, ports, and infected devices.
- Evaluation for evidence of metastatic disease, such as endophthalmitis, endocarditis
- Evaluation for hepatosplenic disease in high-risk patients.
- Obtaining negative repeat cultures to exclude occult metastatic infection
- Appropriate use of Azole in the setting of potential QT prolongation.

She has responded well to the use of Micafungin, and her Port-Cath has been removed. In this patient with negative repeat cultures, it is unlikely she has metastatic disease. Even in the absence of a history of abdominal pain, it is prudent to obtain a CT scan of her abdomen and pelvis to exclude hepatosplenic candidiasis, given her history, and use immunosuppressive agents. In deciding on the use of Azole, her current medications pose a concern for QT prolongation, which can result in polymorphic ventricular tachycardia- Torsades de pointes

How Long is Too Long?

A normal QTc is less than 500 ms. QTc prolonging drugs should be avoided when the baseline QTc is >500 ms or if there is significant concern for prolonging the QTc to >500 ms. The risk of Torsades de Pointes increases when QTc >500 ms or there is an increase from a baseline of >60 ms. Prior to starting a QT-prolonging agent, a baseline ECG is recommended. Consult Cardiology if there is any uncertainty of ECG; the QTc interval can be difficult to interpret in certain rhythms, such as a bundle branch block or atrial fibrillation. At least half of the patients admitted to the hospital have or are prescribed QT-prolonging agents.

Close ECG monitoring is required in the inpatient setting to detect increasing QTc intervals early when two or more QTc interval-prolonging medications are used. Fluoroquinolones and Macrolides are commonly used antimicrobials in this category. In the ambulatory setting, it is best to avoid such drug-drug interactions as much as possible. Currently, this patient is on both Methadone and Citalopram (SSRI), which carry the highest risk of QTc prolongation leading to Torsades on their own, so concomitant use would increase risk even further.

Methadone and Citalopram are not usually recommended together; these two medications are considered a major drug-drug interaction. Her QTc interval is 500 ms. She has an ileostomy, so she is at higher risk of electrolyte disturbances, which can further increase QTc. This patient is not currently reporting any increased ostomy output, but ostomy patients will often be put on high-dose loperamide to manage high output.

Loperamide at higher doses can also induce Torsades. With the QTc of 500 ms, a change of Citalopram to an alternative SSRI with lower risk could be considered. In the inpatient setting, consider dose-reducing Citalopram to no more than 20 mg. This patient's risk of Torsades is high without Azole treatment. The use of an Azole or any other medication that can further prolong QTc interval for more than 2-3 days, as will be required in this patient, increases her risk for Torsade de pointes. Fluconazole and voriconazole are associated with the greatest risk of QTc prolongation.[1-9]

In this patient, it will be best to use Isavuconazole, which does not prolong the QTc interval. Isavuconazole has a high oral bioavailability of 98% and is absorbed primarily in the upper small intestines. Her QTc of 500 ms, current medication regimen, IBD (inflammatory bowel disease), and risk for electrolyte abnormalities pose additional concerns about the use of the other azoles. Cost prohibition may be a concern with the Isavuconazole (Cresemba); it is expensive and not a preferred agent on many insurance plans, so it may require prior authorization.

QUESTION 2: HOW TO MANAGE VENOUS THROMBOEMBOLISM IN PATIENTS WITH AN ABNORMAL ACTIVATED PARTIAL THROMBOPLASTIN TIME LEVEL?

A 31-year-old man with a relatively benign past medical history is admitted with painful swelling of the left lower extremity. He denies fevers, chest pain, shortness of breath, or any preceding trauma to the affected site. He was adopted and unsure of his biological family history. Doppler study reveals a non-occlusive deep vein thrombosis (DVT) of femoral veins' left popliteal and distal aspect. No extension to the iliac veins is noted. He has normal CBC, Renal function, BNP, and Troponin levels, and his PTT level is 48 secs (Normal: 24-37 secs), but INR is 1.0. He is discharged within 24 hours on Apixaban (a direct oral anticoagulant: DOAC) for management of his unprovoked left lower extremity DVT. He returns within 48 hours with a sudden onset of shortness of breath and right-sided chest pain. He is not hypoxic; his blood pressure is 135/67mmHg, but his heart rate is 100-117/min. CT angiogram of his chest reveals evidence of segmental and subsegmental pulmonary emboli (PE). His lab data showed normal CBC, Renal function, troponin, and BNP levels. He reported compliance with the Apixaban regimen. Additional lab data from his first visit reveals a positive lupus anticoagulant and elevated anticardiolipin antibodies and beta-2 glycoprotein 1 antibodies. He started on Enoxaparin. He is eager to go home. What are the therapeutic options for his condition?

A: His serology laboratory data pattern is suggestive of triple-positive (high-risk APLAS -Antiphospholipid antibody syndrome). Diagnosis of APLAS is made based on thrombotic (VTE, arterial thrombosis, noninfectious cardiac vegetations) or obstetric events in combination with laboratory findings). Laboratory testing includes the anticardiolipin antibodies, anti-β2-glycoprotein antibodies, and lupus anticoagulant.

For diagnosis, laboratory findings must be positive for either lupus anticoagulant or medium- or high-titer antiphospholipid IgG antibodies (anticardiolipin or anti-β2-glycoprotein-I antibodies) on two or more occasions at least 12 weeks apart. Retesting is very important at 12 weeks or greater due to the risk of false positivity in certain conditions such as infections, lupus flare, or cancer. DOACs can also show a false positive lupus anticoagulant. Confirmation of this condition, a family history of thrombophilia and/or personal history of recurrent episodes of DVT, and repeat labs in 12 weeks showing the same pattern noted above will necessitate the need for him to be transitioned from heparin to warfarin (Vitamin K antagonist) for management of this episode of DVT complicated by PE, and long-term prophylaxis.

Triple positive APLAS and higher titer laboratory findings carry the highest risk of thrombosis. In most patients, warfarin is the standard of care for long-term anticoagulation. In studies, triple-positive APLAS patients have a higher risk of thrombosis on DOACs when compared to warfarin. Any patient who was initially treated with a DOAC who is then confirmed with triple positive APLAS should have their anticoagulation changed to warfarin. Of note is that in patients who experience arterial thrombosis, the INR goal may need to be higher. In this patient, the INR goal would be 2-3. If warfarin is contraindicated, the recommendation would be Enoxaparin for anticoagulation.[10-13]

Treatment options for this patient case:

- He may be discharged on Enoxaparin with a bridge to Warfarin (INR goal 2-3) and a plan to repeat labs in 12 weeks. If the laboratory data pattern remains unchanged, he will need to continue the long-term warfarin regimen.
- He may also be discharged on Enoxaparin with a plan to repeat labs in 12 weeks and then transition to a DOAC or warfarin based on the results.

He is not a DOAC failure since the episode of PE is likely a sequel of his newly diagnosed DVT. He, however, has a high chance of recurrence of thrombo-embolic phenomena on Apixaban if he has triple positive APLAS.

The antibodies associated with APLAS interfere with phospholipids and increase the coagulation times, such as activated partial thromboplastin time (aPTT). Elevated aPTT in the absence of unfractionated heparin is a marker for this condition. Vitamin K deficiency and liver disease can also elevate aPTT, however, in this patient, the INR was not elevated.

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

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