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New Diagnostic Guidelines for Myeloproliferative Neoplasms

Originally described by Dameshek in 1951, myeloproliferative neoplasms (MPNs) represent conditions characterized by excessive proliferation of hematopoietic precursors in bone marrow resulting in excessive production of mature blood cells (Dameshek W. *Blood*. 1951;6(4):372-375). MPNs generally occur in middle- or advance-age adults and are considered rare cancers because of the low incidence; <6 per 100 000 persons per year. MPNs include the following - chronic myeloid leukemia (CML), *BCR-ABL1+*; chronic neutrophilic leukemia; polycythemia vera (PV); primary myelofibrosis (PMF); essential thrombocythemia (ET); chronic eosinophilic leukemia, not otherwise classified; MPN, unclassifiable. The authors of *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues* recently revised the diagnostic criteria published in the 2008 edition for MPNs.

Clinically, PV and ET predispose patients to increased risk of thrombosis and/or bleeding. Disease progression and clinical outcomes are varied and related to the specific subtype. PV, for example, may progress to myelofibrosis and less commonly to blast phase/acute myeloid leukemia (AML), whereas ET may progress to more aggressive myeloid neoplasms. Within MPNs, PMF is associated with the most symptom burden and the worst prognosis and a variable risk of progression to AML. Diagnosis of MPNs involves fulfillment of a combination of major and minor criteria established in the *WHO* book. The major/minor criteria includes abnormal peripheral blood count, alterations of bone marrow morphology and genetic lesions. For example, erythrocytosis, as indicated by hemoglobin/hematocrit is one of the major criteria required for diagnosis of PV. Under the revised diagnostic criteria, the threshold values of hemoglobin/hematocrit required for the diagnosis

has been lowered to 16.5 g/dL/49% in men and 16.0 g/dL/48% in women.

After *BCR/ABL1* (Philadelphia chromosome), the next molecular anomaly discovered in 2005 involved a G to T somatic mutation at nucleotide 1849, in exon 14 of *JAK2*, a gene encoding Janus kinase 2, resulting in the substitution of valine to phenylalanine at codon 617 (*JAK2V617F*). The identification of *JAK2V617F* in approximately 70% of MPNs: 95% of PV and 50%-60% of ET and PMF provided a unifying genetic basis for these disorders, referred to as Philadelphia-negative classical MPNs. Demonstration of this mutation is the second major criterion in the diagnosis of PV. Subsequently, additional mutations were identified in *JAK2* exon 12, albeit at low frequency, in PV negative for *JAK2V617F*. The next big discovery came in 2013, with identification of frameshift mutations in the *CALR* gene involving significant number of *JAK2* ET and PMF (50%-60% ET and 75% PMF) cases. More than 50 mutations, mostly located in exon 9 of *CALR* have been reported to date. In the revised *WHO* criteria, demonstration of *CALR* mutation is now one of the major criteria required for diagnosis of ET and PMF.

Other genetic mutations identified in a minor population of MPNs include - thrombopoietin receptor gene (*MPL*) mutations (3% in ET and 5% in PMF) and exon 2 of *LNK* gene, reported in two patients (PMF and ET). Patients who meet other diagnostic criteria including abnormal complete blood cell counts and altered bone marrow morphology but lack a demonstrable driver mutation (*JAK2*, *CALR* or *MPL*) are referred to as triple negative. Approximately, 10% of ET and 5-10% of PMF fall under this category. According to the *WHO* criteria, clinicians should search for the most frequent accompanying mutations (eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*) to determine the clonal nature of the disease in triple negative disease.

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Heparin Monitoring and Potential Interference with Oral Factor Xa Inhibitors

Increasing numbers of patients are taking direct oral Factor-Xa inhibitors (apixaban, edoxaban, rivaroxaban). When these patients are admitted to the hospital they might be switched to parenteral anticoagulants (unfractionated heparin and low-molecular weight heparin). Heparin is usually monitored by anti-factor Xa assay (anti-Xa) but due to interference from direct oral Factor-Xa inhibitors, anti-Xa results are not reliable in such patients.

Activated partial thromboplastin time (aPTT) monitoring of heparin may be required in patients taking or with recent exposure to direct Factor-Xa inhibitors. A baseline anti-Xa, prothrombin time (PT), and aPTT levels should be drawn on all patients with suspicion of direct Factor-Xa inhibitor therapy. However, clinicians should note that a normal aPTT value DOES NOT RULE OUT presence of direct Factor-Xa inhibitor in blood. Abnormal anti-Xa levels are usually suggestive of presence of direct Factor-Xa inhibitor in the system. If anti-Xa levels are normal, parenteral anticoagulant monitoring can still be done using anti-Xa levels.

The following issues should be considered before switching patients on direct oral Factor-Xa inhibitors to heparin therapy:

- Is substitution to a parenteral agent necessary?
- Risk of thromboembolic event versus bleeding should be assessed prior to switch. In some cases of elective surgery/invasive procedures, it may not be necessary.
- How long has it been since the last dose of oral anticoagulant?
- How will current renal function impact the expected clearance of the oral agent?
- Should a bolus dose of heparin be given or not?
- If substitution to parenteral agent is deemed necessary, please use the following guidelines (developed in collaboration with SLHS Pharmacy) for conversion from anti-Xa to aPTT monitoring.

DVT/PE/AFib heparin dosing protocol:

- aPTT <34 seconds (secs): Give full IV BOLUS and INCREASE rate by 3 units/kg/hr. Recheck aPTT 6 hours (hrs) after dose change.
- aPTT 34-59 secs: Give half of IV BOLUS and INCREASE rate by 1 unit/kg/hr. Recheck aPTT 6hrs after dose change.

- aPTT 60-100 secs: NO BOLUS and NO RATE CHANGE. Recheck aPTT next morning (if this is the first level within range, then recheck in 6hrs).
- aPTT 101-120 secs: No bolus and DECREASE rate by 1 unit/kg/hr. Recheck aPTT level 6hrs after dose change.
- aPTT level >120 secs: No bolus and HOLD infusion for 1 hr, then RESTART infusion but DECREASE rate by 3 units/kg/hr (notify physician if aPTT >140 secs). Check aPTT in 6hrs.
- If repeat aPTT is ≤120 secs: refer to algorithm above. If aPTT still >120secs: hold infusion and notify physician.

Acute coronary syndrome heparin dosing protocol:

- aPTT <34 secs: Give full IV bolus and INCREASE rate by 3 units/kg/hr. Recheck aPTT 6hrs after dose change.
- aPTT 34-49 secs: Give half of IV bolus and INCREASE rate by 1 unit/kg/hr. Recheck aPTT 6hrs after dose change.
- aPTT 50-80 secs: NO BOLUS and NO RATE CHANGE. Recheck aPTT next morning (if this is the first level within range, then recheck in 6hrs).
- aPTT 81-100 secs: No bolus and DECREASE rate by 1 unit/kg/hr. Recheck aPTT level 6hrs after dose change.
- aPTT level >100 secs: No bolus and HOLD infusion for 1hr then RESTART infusion but DECREASE rate by 3 units/kg/hr (notify physician if aPTT >140 secs). Check aPTT in 6hrs.
- If repeat aPTT is ≤100 secs: refer to algorithm above. If aPTT still >100 secs: hold infusion and notify physician.

RBC Transfusions from Younger Donors doesn't Improve Survival

Fresher RBC (shorter shelf life) and younger donor RBC have been thought to provide revitalizing benefits to patients but scientific evidence is lacking to back this theory. A recent retrospective cohort study (Circulation 2016;134.21:1692-94) followed 968,264 RBC transfusion recipients for 10 years. After adjusting for the number of transfusions and taking into account non-linear relationships of variables, donor age and sex were not associated with mortality among RBC transfusion recipients.