

## Immature Platelet Fraction: Coming of Age of an Underutilized Test in the Setting of Thrombotic Thrombocytopenic Purpura

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Circulating immature platelets, also known as the immature platelet fraction (IPF), is the term that defines much larger platelets that have been recently released from the bone marrow. IPF have a greater RNA content, are measured by automated hematology analyzers equipped with a reticulocyte detection channel, and are reported as percentage of the total platelet count (%-IPF) [1]. It is well accepted that a high %-IPF is usually found in either consumptive or recovering thrombocytopenic disorders [2], while a low %-IPF is characteristic of bone marrow suppression disorders [3]. However, little was known until recently about their biology compared to mature platelets. A recent report by our group indicates that immature platelets differ from mature ones in that they have a longer lifespan, may be able to continue expanding during storage and that this expansion is significantly reduced by irradiation [4]. The latter is of major importance since it indicates that immature platelets are biosynthetically active and opens the possibility to research further these blood elements for transfusion support of patients needing platelets. Indeed in young pediatric patients who have received stem cell transplantations, a recent study reported that transfusion of IPF-rich platelet units significantly reduced the overall number of platelet transfusions required by these children compared to those receiving IPF-poor units [5]. Considering the increased longevity and distinct biology of immature platelets, these preliminary findings suggest that larger randomized trials ought to be performed to address if the concentration of immature platelets in a platelet product can further benefit patients requiring platelet transfusions.

Testing %-IPF and the absolute immature platelet count (A-IPC), which is obtained by multiplying the %-IPF by the optical platelet count, may also prove useful in the diagnosis and management of patients with thrombotic thrombocytopenic purpura (TTP) [1]. Current TTP diagnosis depends upon the presence of a thrombotic microangiopathy with hemolysis in the setting of ADAMTS13 deficiency [6]. ADAMTS13 testing is difficult to obtain promptly since it is sent out to centralized reference laboratories by most medical centers and results may take days to return. Therefore, therapeutic plasma exchange (TPE) usually starts in patients without a definitive diagnosis of TTP. We recently reported how %-IPF testing allowed us to successfully adjust therapy in TPE-refractory microangiopathic thrombotic presentation [7]. In this setting, a %-IPF that is inconsistent with a diagnosis of idiopathic TTP, and indicative of hypoproduction, may steer therapy especially in light of a normal bone marrow biopsy [7].

However, A-IPC may correlate better with real-time thrombopoiesis [4]. It was recently reported by our group that there is a positively-skewed bell curve in A-IPC production only in idiopathic TTP presentations that correlates with response to TPE, and seems to predict when procedures can be discontinued due to the restoration of platelet counts [8] [Hong et al., manuscript in preparation]. On the other hand, patients with HIV-associated TTP do not develop this A-IPC positively-skewed bell curve, fail to respond to TPE and only experience an increase in A-IPC once HAART therapy is initiated [8]. Of interest, we also found that an unexpected late increase of %-IPF/A-IPC in one of our idiopathic TTP patients whose platelet counts had normalized, and who had stopped receiving TPE appeared

to have predicted relapse 3 days prior to the decrease of platelet count.

A timely TTP diagnosis is important to minimize morbidity and mortality associated with the disease. Despite the importance of ADAMTS13 activity in the diagnosis of TTP, %-IPF/A-IPC provides a measure to rapidly ascertain the diagnosis and differentiate patients with TTP from those whose thrombocytopenic conditions are largely caused by bone marrow underproduction processes. Since the test can be obtained along with a CBC, this could prove essential during the clinical decision making to initiate TPE or other TTP-related therapy. Further, testing %-IPF/A-IPC may allow for real time management of idiopathic TTP patients undergoing TPE, as improvement and stabilization of %-IPF/A-IPC is consistent with responses to TPE and be predictive of platelet count recovery, whereas a late increase may indicate a relapse. Hence, testing %-IPF/A-IPC may prove valuable in the diagnosis and follow up of TTP.

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