

March 2018

Secondary "Safety Measure" Test for Platelets

Blood transfusion is a potential source of infection by a variety of known and unknown transmissible infectious agents. Over the last 20-30 years, significant reductions in the risk of viral infection via allogeneic blood transfusions have been achieved. HIV and hepatitis virus infections were as common as 1 in 1000 transfusions in 1980's. With stringent donor screening and infectious disease testing on collected blood, the current residual risk is 1 per 1,467,000 for Human Immunodeficiency Virus (HIV), 1 per 1,149,000 for Hepatitis C Virus (HCV) and 1 per 765,000-1,006,000 for Hepatitis B Virus (HBV).

Because of this success, bacterial contamination of blood products has emerged as the greatest residual source of transfusion-transmitted infections. The bacterial contamination risk is much higher for platelet transfusion compared to other blood components because unlike other components, platelets are stored at room temperature and thus are a great culture media for propagation of bacteria.

The sources of bacterial contamination of blood components are:

- Introduction of skin flora during collection
- Unrecognized asymptomatic bacteremia in donor
- Contamination during processing

The incidence of bacterial contamination is thought to be as high as 1 in 3000 units. 1 in 50,000 platelet transfusions can lead to a septic transfusion reaction and 1 in 500,000 RBC transfusions can lead to sepsis. Sepsis due to bacterial contamination of blood components can be fatal. Every year 3-5 patients die due to septic transfusion reaction in the US. Non-fatal infections due to contamination also

cause significant morbidity and extend hospital stay in many cases.

Preventive measures that decrease risk of bacterial contamination during blood collection include:

- Health history screening of donors
- Meticulous attention to cleansing of phlebotomy site
- Diversion of initial aliquot
- Bacterial testing (culture at 12 hour) of all platelet units as required by the AABB/CAP
- Removal from inventory of other products from the same donation if implicated in a septic reaction

Preventive measures hospitals can take to prevent septic reactions include:

- Examine unit prior to transfusion
- Change blood tubing every 4 hours
- Hang blood promptly (within 30 minutes of issue) and finish within 4 hours
- Prompt recognition and reporting of suspected septic reactions

Even after all these preventive measures, the bacterial contamination and septic reaction risk from platelets persists. FDA has therefore issued a draft guidance for industry for comment entitled "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion". To control the risk of bacterial contamination FDA suggests use of either Pathogen Reduction Technology or Secondary "Safety Measure" Tests.

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FDA approved Secondary "Safety Measure" Tests include:

- Rapid Bacterial Detection Tests (point of issue testing)
- Additional Culture-Based Testing (no sooner than Day 4 post-collection)

Negative results on days 4-6 of these safety measure tests also extends the shelf life of platelets to seven days.

Transfusion services at Saint Luke's Health System is closely following updates on FDA guidance on this issue. We are evaluating different methods to implement in the future as secondary safety measure tests for detection, prevention, and elimination of septic reactions from platelets.

Laboratory Aspects of Recent ACG Liver Enzyme Guidelines

In 2016, the American College of Gastroenterology (ACG) developed practice guidelines regarding evaluation of abnormal liver chemistries including alanine aminotransferase (ALT). These recommendations, intended for use by physicians and health care providers addressed establishing ALT normal reference ranges and threshold triggers for further evaluation. The ACG recommends establishing normal ALT reference ranges using a control healthy population with body mass index (BMI) of less than/equal to 25 kg/m². The proposed use of restricted BMI in the control population is due to the linear relationship with ALT levels. The second recommendation of determining the ALT threshold trigger is based on the assumption that the laboratory assay is standardized between facilities and a significant interlaboratory difference does not exist.

Aspartate aminotransferase (AST) and ALT are enzymes involved in the transfer of amino groups of aspartate and alanine, respectively, to ketoglutaric acid and are markers of hepat-cellular injury. ALT is primarily present in liver and thus is a more specific marker of hepatocellular injury. Albumin, bilirubin, and prothrombin time on the other hand are markers of hepatocellular function that can be influenced by

extrahepatic factors. One of the summary statements issued by ACG refers to the association of increased liver-related mortality in individuals with elevated ALT above the upper limit of normal (ULN) but without identifiable risk factors, arguing for a universally established ULN.

The ACG proposed a calculated ULN of 33 IU/L for men and 25 IU/L for women, which is based on a Korean study of 1,105 potential liver donors with normal liver biopsies. A multi center study fulfilling Clinical and Laboratory Standards Institute (CLSI) criteria to produce accurate reference ranges revealed higher ALT UNL of 59 IU/L for men and 41 IU/L for women (Ceriotti F., *et. al.* *Clin Chem Lab Med* 2010;48:1593-601). Further exclusion of individuals with BMI more than/equal to 25 kg/m³ in the same study still resulted in higher ALT UNL (49 IU/L for men and 33 IU/L for women) than those proposed by ACG.

The application of the latest ACG proposal of universal ALT UNL would result in approximately 13.7% of males and 10.9% of females classified as "abnormal". Moreover, establishing a threshold trigger based on the proposed ALT UNL can potentially result in "overdiagnosis" in many individuals, possibly requiring invasive procedures such as liver biopsy. In a recent published opinion, laboratory experts have advised not to use UNLs and threshold triggers/decision limits interchangeably, and more importantly synthesize the evidence behind these values while considering their clinical meaning (Panteghini M., *et. al.* *Clin Chem* 2017;63(7):1196-1197).

The National Institute for Health and Care Excellence (NICE) in the UK considering a similar scenario of nonalcoholic fatty liver disease (NAFLD) where ALT levels may not increase, reported in its evidence summary that there is only very weak evidence to support the use of ALT as a screening tool (<https://www.nice.org.uk/guidance/ng49>).

At Saint Luke's Hospital, ALT levels are performed on 0.5-1 mL serum or plasma specimen. The reference ranges are 13-69 IU/L, and were established using local healthy individuals as the control group.

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