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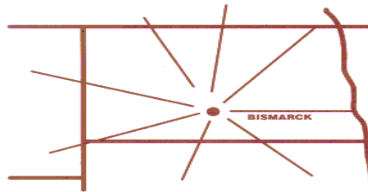

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Transfusion-Related Acute Lung Injury (TRALI)

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Transfusion-related acute lung injury (TRALI) is acute lung injury (ALI) that is temporally related to the transfusion of plasma-containing blood products and typically manifests with acute respiratory distress, hypoxemia, pulmonary edema, voluminous frothy airway secretions with elevated protein content, and fever. TRALI is a leading cause of transfusion-associated morbidity and mortality, with an estimated incidence of 0.02% to 0.05% per transfused blood product.[1]

An international consensus conference in 2004 established clinical criteria for TRALI: acute onset, hypoxemia, bilateral infiltrates on frontal chest radiograph, absence of left atrial hypertension, no preexisting ALI prior to transfusion, onset of symptoms during or within six hours of transfusion, and the absence of a temporal relationship to an alternative risk factor for ALI. If an alternative risk factor for ALI exists, the reaction is designated “possible TRALI.”[2]

Although the pathogenesis of TRALI is not definitively known, three possible underlying mechanisms have been identified. Antibody mediated TRALI is caused by an antigen-antibody reaction. In 60%-80% of cases, donor antibodies react with the recipient’s leukocytes; a minority of cases may involve recipient antibodies and donor leukocytes. In both cases, antibodies are thought to bind to and activate leukocytes, which then aggregate in pulmonary capillaries. The cumulative effect of the offending antibodies is increased pulmonary vascular permeability and edema. The causative antibodies in TRALI may be directed against class I or II human leukocyte antigens (HLA) or human neutrophil antigens (HNA).[1]

A second mechanism, non-antibody mediated TRALI, accounts for the 15% of TRALI cases where neither donor nor recipient antibodies are identified. This mechanism suggests that TRALI is caused by lipid products from cellular breakdown, which accumulate in stored blood products and prime and activate neutrophils. This theory is not readily applicable to acellular blood products and may work in conjunction with the “two-hit” hypothesis, described below.[1]

The two-hit hypothesis suggests that two separate events are necessary to cause TRALI. The first hit can include recent surgery, hypoxia, infection, trauma, malignancy, massive transfusion, cardiopulmonary disease, or bypass. These underlying conditions are thought to activate the vascular endothelium and ultimately result in pulmonary neutrophil priming. The second hit is the transfusion of blood products containing lipids, antibodies, or cytokines that stimulate previously primed neutrophils. The result is endothelial cell damage and noncardiogenic pulmonary edema.[1]

The diagnosis of TRALI is primarily clinical and radiographic and the majority of patients recover within days with only supportive care. If volume overload is excluded and TRALI

is suspected, evaluation of the donor serum can confirm the presence of anti-HLA or anti-HNA antibodies. Anti-HLA antibodies are a response to an immunologic challenge, and increased parity is known to be associated with increased antibody prevalence. Since the majority of donors associated with a TRALI reaction are multiparous females, many blood centers have moved toward using all-male plasma products and apheresis platelets. Research has yet to demonstrate a definitive reduction in the incidence of TRALI with the exclusion of multiparous donors. Donors involved in TRALI reactions, regardless of sex or antibody status, may be deferred from future donations.[1]

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Update on Cardiac Markers—Diagnosing AMI Using Troponin

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Since 1954, the search for a defining cardiac biomarker began as the breakdown products of myocardial ischemia were discovered[1]. The ideal marker would be effective and accurate would indicate how severe and when an acute myocardial infarction (AMI) has occurred. Thus far, no single marker can fulfill all criteria, but troponins can be very useful in making an important clinical decision to admit or discharge a patient in the ER or to treat a patient on the inpatient floor. Accurately deciding when an AMI has occurred can save both lives and resources.

Cardiac troponins are proteins that control the calcium-mediated interaction between actin and myosin, allowing contraction at the sarcomere level. Cardiac troponin is found almost exclusively in the heart, being composed of three subunits: I, T, and C. The clinically useful I and T subunits bind to tropomyosin and inhibit coupling of actin and myosin, respectively. These molecules have proven advantageous in clinical practice by providing a high specificity for cardiac damage in the presence of multiple injuries. Troponin levels peak at 18–24 hours and remain in circulation 7–14 days after an AMI (Table 1). Since troponin degrades slowly, clinicians have a large window for diagnosing a recent AMI. Newer high precision assays can now detect troponin elevations as early as two hours after the onset of ischemic symptoms, giving it an important role as an early marker.[2] Troponin is now the standard of care in most centers and is the preferred marker in defining an AMI.[3] At least three serial measurements are recommended

spaced at least three hours apart for detection of a cardiac event.[4] However, troponin is not the marker of choice to detect re-infarction, as it will be masked by the first event.[1]

According to the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, in addition to clinical symptoms of ischemia, detection of cardiac biomarkers (preferably serial troponin I or T) above the 99th percentile of the upper reference limit (URL) is required for diagnosis of AMI, although the WHO criteria differs by requiring above the 95th percentile.[4] Lower cutoff values for troponin may identify a population at risk for cardiac events, providing valuable risk stratification information rather than simple ”infarction or not” categories. A barrier to achieving these lower cutoff limits for troponin is the lack of standardization among the troponin I assays, due to: 1) different antibody configurations recognizing different epitopes, 2) assays with varying stabilities, and 3) different coefficients of variability. With this lack of standardization in assays, relaxing cutoff values could result in an increase of false-positives. The International Federation of Clinical Chemistry and Laboratory Medicine has a listing of troponin assays and their performances at lower concentrations that may be useful as a guide in AMI diagnosis.[5]

In the rapidly changing climate of medicine, cardiac biomarkers have evolved from curious laboratory findings into standards of care. Troponins now have the diagnostic power to detect subtle myocardial changes in a timely enough fashion to impact patient care and quality of life. A new set of challenges lies ahead in predicting the prognosis of AMI patients and screening those at risk for future cardiac events, thus making the advent of a new generation of markers an imperative.

Table 1. Characteristics of Cardiac Biomarkers after AMI in Hours[1]

Biomarker	Onset	Peak	Duration
Myoglobin	1–4	6–7	18–24 hours
Total CK	3–12	18–24	36–48 hours
CK-MB	3–12	18–24	24–36 hours
CKMB2/CKMB1	2–6	6–9	Unknown
Troponin I	2–12	18–24	7–10 days
Troponin T	2–12	18–24	10–14 days

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SNP Testing for Warfarin Sensitivity

Julie Katz Karp, MD

Pharmacogenomics is the study of genetic variation as it relates to a patient's response to a given drug. Single nucleotide polymorphisms (SNPs) are examples of such genetic variation and can serve as a guide for the therapeutic dosing of pharmaceuticals. Among other drugs, SNP testing has been used to predict warfarin sensitivity and estimate appropriate starting doses. According to the US Food and Drug Administration (FDA), warfarin is among the top 10 drugs with serious adverse event reports. In this setting, the goal of pharmacogenetic testing is to improve the safety and effectiveness of anticoagulant therapy.

The pharmacokinetics of warfarin is crucial to understanding the basis for pharmacogenomic testing. Unbound warfarin is absorbed by the liver, where the S-enantiomer of warfarin inhibits vitamin K epoxide reductase (VKOR). This interferes with the vitamin K-dependent carboxylation of coagulation factors and other vitamin K-dependent proteins. The S-enantiomer is subsequently metabolized by CYP2C9 and excreted in the bile. SNPs in the cytochrome P450 complex, specifically CYP2C9*2 and/or CYP2C9*3, have been associated with decreased warfarin metabolism. Consequently, patients who are homozygous for a SNP in vitamin K epoxide reductase, VKORC1, exhibit increased warfarin sensitivity and can have increased toxicity with “normal” doses of warfarin.

In response to these findings, in August 2007, the FDA approved an update to warfarin labeling that highlighted the use of genetic testing to improve initial estimates of warfarin dosing. Since that time, additional research has both supported and refuted these findings, and professional societies have responded in kind. While both the American Association for Clinical Chemistry (AACC) and the College of American Pathologists (CAP) support the use of pharmacogenomic testing for warfarin metabolism, the Association for Molecular Pathology (AMP), the American Society of Hematology (ASH), and the American College of Medical Genetics (ACMG) recommend additional research on the subject. More recently, in August 2009, the Centers for Medicare and Medicaid Services (CMS) issued a memorandum stating that pharmacogenomic testing would be covered only in patients enrolled in clinical studies and that the available

evidence does not support pharmacogenomic testing to predict warfarin responsiveness.

At the present time, pharmacogenomic testing for SNPs is largely limited to the direct-to-consumer setting. SNP testing can be used beyond the realm of pharmacogenomics to identify SNPs associated with genetically associated disorders, such as cystic fibrosis and sickle cell disease. SNP testing may eventually expand to include mainstream laboratories in the form of vendor-supplied technology or reference laboratory testing. Regardless, the pathologist will play an essential role in the development and implementation of SNP testing. Pathologists' understanding of molecular techniques will be instrumental in overseeing SNP testing and evaluating the quality processes used to establish results. Pathologists will also serve as a guide for clinicians in the appropriate use and interpretation of SNP testing.

Clinical trials focused on SNP testing are ongoing, and the medical community's understanding of pharmacogenomics will undoubtedly expand and change as a result. Pharmacogenomic testing is an initial step towards personalized medicine, a type of medicine that requires both diagnostic innovation and careful exploration before its promises can be realized.

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