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November 2008

H58-A

Platelet Function Testing by Aggregometry; Approved Guideline

SAMPLE

This document provides concrete, standard procedures for using aggregometry to assess platelet function in patient specimens with the intent to achieve greater uniformity of results.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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Platelet Function Testing by Aggregometry; Approved Guideline

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Abstract

Clinical and Laboratory Standards Institute document H58-A—*Platelet Function Testing by Aggregometry; Approved Guideline* provides concrete, standard procedures for using aggregometry to assess platelet function in patient specimens and samples, with the intent to achieve greater uniformity of results by laboratories following these guidelines. Descriptions of light transmission aggregometry, whole blood impedance aggregometry, and shear-flow technologies are provided so both long-time and new users may establish consistent, reproducible platelet function testing programs in their laboratories.

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SAMPLE

Foreword

Platelets play a vital role in hemorrhagic, thrombotic, and vascular ischemic disorders. Antiplatelet therapy (APT) is regarded as “the cornerstone of treatment” for various coronary conditions,¹ giving dramatic rise to the introduction of new antiplatelet drugs. This in turn has increased the interest among clinicians and laboratorians to use various tests of platelet function. One such method is platelet aggregometry, a common technology that has been part of clinical laboratory practice for over 40 years. Yet, surprisingly, platelet aggregometry has largely been performed without globally accepted performance standards. Consequently, customized procedures and reagents are frequently used, often making it difficult to obtain consistent results.

This guideline provides concrete, standard procedures for using aggregometry to assess platelet function in patient specimens and samples with the intent to achieve greater uniformity of results by laboratories following these guidelines. Descriptions of light transmission aggregometry (LTA), whole blood impedance aggregometry, and shear-flow technologies are provided so both long-time and new users may establish consistent, reproducible platelet function testing programs in their laboratories. Laboratories are advised to consult the instrument manufacturer regarding country-specific registration and/or clearance, eg, US Food and Drug Administration 510(k) clearance, CE mark.

Key Words

Antiplatelet therapy (APT), impedance aggregometry, light transmission aggregometry (LTA), low and high shear, platelet activation, platelet aggregation, platelet function testing

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Platelet Function Testing by Aggregometry; Approved Guideline

1 Scope

This guideline specifies requirements/recommendations for specimen collection, preexamination considerations, patient preparation, sample processing, testing, result analysis, and quality control (QC) in relation to platelet function testing by aggregometry using light transmission aggregometry (LTA), whole blood impedance aggregometry as well as low and high shear technologies. It covers anticoagulants, specimen storage and transport temperatures, sample selection for various methodologies, establishment of reference intervals, result reporting, result analysis, assay validation, and troubleshooting. The intended users of this guideline are clinicians, hospital and reference laboratorians, manufacturers, and regulatory agencies. This guideline is not intended for use with global hemostasis, platelet counting, flow cytometry, home testing, point-of-care, or research systems. This guideline does not address therapeutic guidance or interpretive guidelines.

2 Introduction

Platelet function testing has been a part of clinical laboratory practice since early in the 20th century. Hundreds of publications have defined healthy and pathologic platelet activity using numerous methodologies, such as the *in vivo* bleeding time, platelet aggregometry techniques, measurement of granular content and release, assessment of membrane surface markers, evaluation of signaling pathways, and *in vivo* platelet survival. Yet, despite this vast wealth of information, no clear direction exists to guide setting minimum performance standards among laboratories performing platelet function testing. Establishing such a path is critical, given the role of platelets in both hemorrhagic and thrombotic conditions and the rising significance of antiplatelet therapy (APT) in controlling platelet function across a broad spectrum of vascular disorders. The goal of this guideline is to set minimum requirements for the performance of platelet function testing when using LTA, whole blood impedance aggregometry, and shear-flow technologies.

3 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to “standard precautions.” Standard precautions are guidelines that combine the major features of “universal precautions and body substance isolation” practices. Standard precautions cover the transmission of all infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the US Centers for Disease Control and Prevention.² For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to CLSI document M29.³

4 Terminology

4.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in CLSI, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all challenges to harmonization. In light of this,

CLSI recognizes that harmonization of terms facilitates the global application of standards and deserves immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In order to align the usage of terminology in this document with that of ISO, the term *accuracy*, in its metrological sense, refers to the closeness of agreement between a measured quantity value and a true quantity value of a measurand, and comprises both random and systematic effects. *Precision* is defined as the “closeness of agreement between independent test/measurement results obtained under stipulated conditions.” As such, it cannot have a numerical value, but may be determined qualitatively as high, medium, or low.

The term *measurand* (quantity intended to be measured) is used in combination with the term *analyte* (component represented in the name of a measurable quantity) when its use relates to a biological fluid/matrix.

Users of H58-A should understand, however, that the fundamental meanings of the terms are identical in many cases, and to facilitate understanding, terms are defined in the Definitions section of this guideline.

All terms and definitions will be reviewed again for consistency with international use, and revised appropriately during the next scheduled revision of this document.

4.2 Definitions

accuracy (of measurement) – closeness of agreement between a measured quantity value and a true quantity value of a measurand (VIM07).⁴

activation – when referring to platelets, a series of processes and events that change a discoid platelet into a spiny, spiculated entity with extension of pseudopodia that results in the initiation of signal transduction.

adhesion – the process by which platelets attach to surfaces or surface-bound proteins by certain glycoproteins, selectins, and integrins.

aggregation – platelet clumping, largely mediated by fibrinogen or von Willebrand factor binding to the platelet receptor, GPIIb/IIIa (integrin $\alpha_{IIb}\beta_3$), following activation of intact platelets by agonists or shear stress.

agonist – a substance or protein that can stimulate platelet activation (eg, collagen, adenosine diphosphate [ADP], epinephrine, thrombin, arachidonic acid, ristocetin).

analyte – component represented in the name of a measurable quantity (ISO 17511)⁵; **NOTE 1:** In the type of quantity “mass of protein in 24-hour urine,” “protein” is the analyte. In “amount of substance of glucose in plasma,” “glucose” is the analyte. In both cases, the long phrase represents the **measurand** (ISO 17511)⁵; **NOTE 2:** In the type of quantity “catalytic concentration of lactate dehydrogenase isoenzyme 1 in plasma,” “lactate dehydrogenase isoenzyme 1” is the analyte (ISO 18153).⁶

anticoagulant – an agent, natural or pharmacological, that inhibits clotting of blood or plasma.

blank – sample that does not contain the analyte of interest, or has a concentration at least an order of magnitude less than the lowest level of interest; **NOTE:** In the context of this document, in most cases, this is platelet-poor plasma (PPP).

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The approach is based on the model presented in the most current edition of CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*. The quality management system approach applies a core set of “quality system essentials” (QSEs), basic to any organization, to all operations in any health care service’s path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager’s guide. The QSEs are:

Documents & Records Organization Personnel	Equipment Purchasing & Inventory Process Control	Information Management Occurrence Management Assessments—External & Internal	Process Improvement Customer Service Facilities & Safety
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H58-A addresses the QSEs indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessments—External & Internal	Process Improvement	Customer Service	Facilities & Safety
				H03	X C28 GP29 H01 H03 H18 H21 M29	H01		GP29			H03 M29

Adapted from CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*.

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, CLSI/NCCLS document GP26—*Application of a Quality Management System Model for Laboratory Services* defines a clinical laboratory path of workflow, which consists of three sequential processes: preexamination, examination, and postexamination. All clinical laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information.

H58-A addresses the clinical laboratory path of workflow steps indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Preexamination				Examination			Postexamination	
Examination ordering	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
H03	X H01 H03 H21	X H03 H18 H21	X H03 H18	X H03 H18	H03			

Adapted from CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*.

Related CLSI Reference Materials*

- C28-A3** **Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (2008).** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests.
- GP29-A2** **Assessment of Laboratory Tests When Proficiency Testing Is Not Available; Approved Guideline—Second Edition (2008).** This document offers methods to assess test performance when proficiency testing (PT) is not available; these methods include examples with statistical analyses. This document is intended for use by laboratory managers and testing personnel in traditional clinical laboratories as well as in point-of-care and bedside testing environments.
- H01-A5** **Tubes and Additives for Venous Blood Specimen Collection; Approved Standard—Fifth Edition (2003).** This document contains requirements for venous blood collection tubes and additives, including technical descriptions of ethylenediaminetetraacetic acid (EDTA), sodium citrate, and heparin compounds used in blood collection devices.
- H03-A6** **Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Sixth Edition (2007).** This document provides procedures for the collection of diagnostic specimens by venipuncture, including line draws, blood culture collection, and venipuncture in children.
- H18-A3** **Procedures for the Handling and Processing of Blood Specimens; Approved Guideline—Third Edition (2004).** This document includes criteria for preparing an optimal serum or plasma sample and for the devices used to process blood specimens.
- H21-A5** **Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays; Approved Guideline—Fifth Edition (2008).** This document provides procedures for collecting, transporting, and storing blood; processing blood specimens; storing plasma for coagulation testing; and general recommendations for performing the tests.
- M29-A3** **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

* Proposed-level documents are being advanced through the Clinical and Laboratory Standards Institute consensus process; therefore, readers should refer to the most current editions.

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