Laboratory and Clinical Issues in CLIA Waiver for CBC/ADCC Devices

Hematology and Pathology Devices Panel

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Laboratory and Clinical Issues -- Overview

- Scope and practical background for testing
- Preanalytical and analytical challenges
- Trade-offs between report detail and test cost or access
- Ranges of uses and interpretation of results
- Benefits and risks from waiver
- Seek input on how waiver criteria can be met

Automated Cell Counters 21 CFR 864.5200

- Complete Blood Count (CBC)
- Measure hematocrit, total hemoglobin
- Count the "formed elements": total RBC, total WBC, platelets
- Cell indices (not for discussion today)

Automated Differential Cell Counters 21 CFR 864.5220

- Distinguish and count subpopulations of RBC, WBC, platelets
- Neutrophils, lymphocytes, monocytes, eosinophils, basophils as “usual” analytes
- Will not address extended capabilities for distinguishing or counting cells with physiological or pathological implications, or cell phenotyping

Waiver Criteria

- Simplicity of the test
- Insignificant risk of an erroneous result
  - Analytical accuracy of the test
  - Pose no unreasonable risk of harm to the patient if performed incorrectly
- Adequate labeling

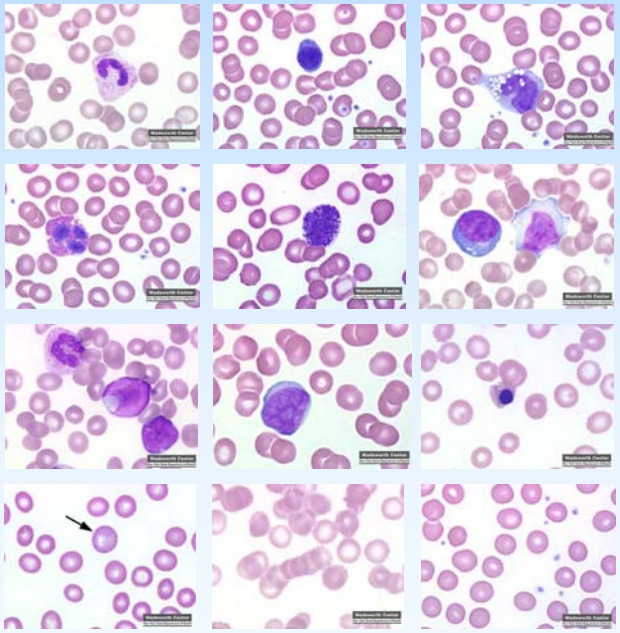
Historical and Practical Background

- Morphological recognition of the "formed elements" and their importance in health and disease
- Manual/visual counting methods, strengths and weaknesses
- Multiple analytes, with cross-checks and correlations

Manual/Visual Counting Methods

H20-A2
ISBN 1-56238-628-X
Volume 27 Number 4 ISSN 0273-3099

Reference Leukocyte (WBC) Differential Count (Proportional) and Evaluation of Instrumental Methods; Approved Standard—Second Edition



http://www.wadsworth.org/chemheme/heme/microscope/celllist.htm

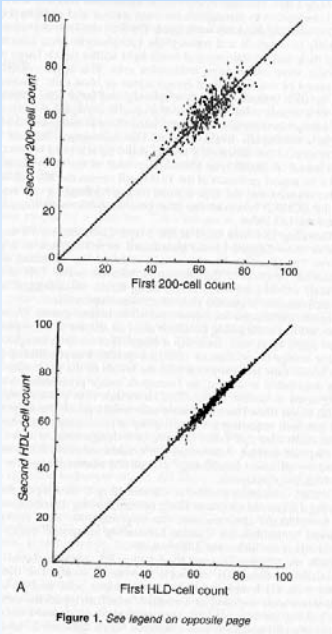


Figure 1. *See legend on opposite page*

RV Pierre, Clin Lab Med 2002

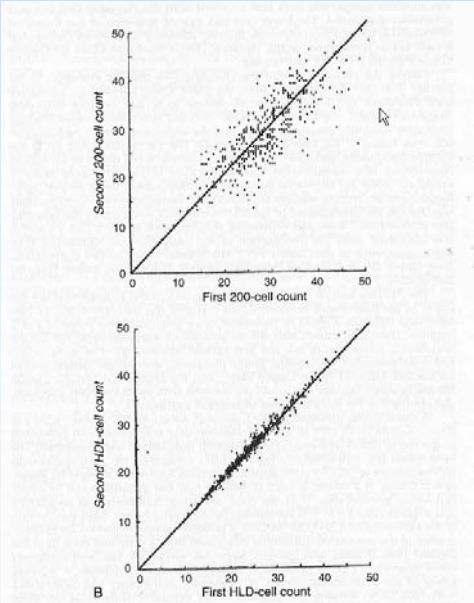


Figure 1 *(Continued).* Comparison of duplicate 200-cell eyecount differentials performed on the same slide by two observers versus duplicate 10,000 cell differentials performed on the same blood sample by the Hemalog D90. Results are shown for neutrophils *(A)* and lymphocytes *(B)*.

Automated Measurements

- Hematocrit and hemoglobin
  - Easily automated bulk physical or chemical properties
  - Spun Hct, single analyte Hgb waived by regulation with CLIA ’88
- Enumeration
  - Reliance on signature physicochemical properties (i.e., not morphology)
  - None waived to date

Analytical Challenges

- Clots (gross or micro), short draws
- Hemolysis or RBC resistance to lysis
- Bilirubinemia, lipemia, circulating mucin
- Matrix effects (non-EDTA anti-coagulant)
- Autoagglutination, rouleaux
- Giant platelets, platelet aggregation, microcytes, RBC fragments
- Nucleated RBC, megakaryocytes
- Atypical leukocytes or blasts
- Red cell inclusions

Comparison of Visual and Automated Cell Enumeration

- Morphology
  - Event detection (single vs overlapping cells)
  - Size
  - Shape
  - Color
  - Structure
- Phys/Chem detection
  - Event detection (“coincidence”)
  - Electrical (impedance, conductance, etc)
  - Light scatter
  - Light fluoresence or absorbance
  - Other

Trade-offs between report detail and test cost or access

Automated leukocyte count +/- differential as an example:

- No differential (i.e., total WBC only)
- Three-part differential (neutrophils, MID, lymphocytes)
- Three-part differential (granulocytes, lymphocytes, monocytes)
- Five-part differential, immature granulocytes, atypical lymphocytes, blasts

Cell Counts Alone Are Not the Whole Story

Conditions in which the blood count may be relatively unremarkable, but examination of the blood film will suggest or confirm the disorder[1]:

- Compensated acquired hemolytic anemia
- Hereditary spherocytosis
- Hemoglobin C disease
- Elliptocytosis
- Lead poisoning
- Macroglobulinemia, multiple myeloma
- Malaria, babesiosis
- Disseminated intravascular coagulation
- Hemolysis related to physical injury to red cells
- Severe bacterial infection
- Infectious mononucleosis

[1] From DH Ryan Hematology, 7th Ed, (McGraw Hill (2006)

How Often Is Peripheral Blood Film Examination Performed?

CAP Central Labs Study, 2006 n=95141		All Institution Percentiles		
	Mean	10th	50th	90th
Percent of automated complete blood counts with manual scan, review or differential count	29%	10%	27%	50%

Novas et al, Arch Pathol Lab Med 2006; 130:596-601.

Vancouver Outpatient Study, 1993 n=1600				
Specimens Flagged	Sens	Spec	PPV	NPV
35%	87%	97%	76%	98%

Brigden et al Am J Clin Pathol 1993; 100:618-625.

Generic Regulatory Descriptions

Identifications captured in regulations for automated cell counters and automated differential cell counters mainly address the analyte alone, and not the clinical indications:

- [Cell counters, 21 CFR 864.5200] "… used to count red blood cells, white blood cells, or blood platelets using a sample of the patient's peripheral blood…"
- [Differential cell counters, 21 CFR 864.5220] "… used to identify one or more of the formed elements of the blood. The device may also have the capability to flag, count, or classify immature or abnormal hematopoietic cells of the blood, bone marrow, or other body fluids…"

Range of Intended Clinical Populations and Uses

- Well person screening (any age)
- Differential diagnosis of disease
- Monitoring for adverse events
- Monitoring disease course, treatment effect

When is a Result Abnormal? Actionable?

- High physiologic variation for some analytes
- Variation across “normal” populations
- Differences across patient groups
- Device labels are usually generic with regard to reference intervals
- How can waived laboratories obtain suitable reference intervals?
- Are there critical/panic values for which informed follow-up by the laboratory is essential?

Benefits and Risks from Waiver

- Faster turnaround time (TAT)?
  - In office or clinic, at least for first round
  - TAT-driven treatment decisions
- Easier staffing, simpler quality assurance?
  - Training and retention of testing personnel
- Decreased test accuracy?
  - Instrumentation
  - Analytical process (personnel, QC, PT)
- Poorer clinicopathological correlation?
  - A la carte CBC/ADCC testing
  - Skill sets of the ordering and testing personnel

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