Early Sepsis Indicator (ESId) Application Addendum

UniCel DxH 900 Series with System Manager Software

Coulter Cellular Analysis System

Published Version: DxH 900 and DxH 690T - v1

IVD

PN C42014AC
April 2020

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BECKMAN COULTER

UniCel DxH 900 Series with System Manager Software
Coulter Cellular Analysis System
Early Sepsis Indicator (ESId) Application Addendum
PN C42014AC (April 2020)

The Early Sepsis Indicator (ESId) application is intended for use on the following instrument as an individual or workcell (connected) system:

- UniCel DxH 900 Coulter Cellular Analysis System

and the following instrument as an individual system:

- UniCel DxH 690T Coulter Cellular Analysis System

Find us on the World Wide Web at:
www.beckmancoulter.com

Symbols Glossary is available at **www.beckmancoulter.com/techdocs**. See Related Documents for the part number.

Rx Only in the U.S.A.

Original Instructions

Revision History

This document applies to the latest software listed and higher versions. When a subsequent software version affects the information in this document, a new issue will be released to the Beckman Coulter Web site. For labeling updates, go to www.beckmancoulter.com/techdocs and download the latest version of the manual or system help for your instrument.

Initial Issue AA, 4/2019
DxH 900 Software Version 1.1.1

Issue AB, 7/2019
DxH 900/DxH 690T Software Version 1.2

The following sections were modified:

- Added DxH 690T throughout this manual, as appropriate
- UniCel DxH 900 Series with System Manager Software Coulter Cellular Analysis System Early Sepsis Indicator (ESId) Application Addendum copyright page
- How to Use Your Manuals in Introduction
- Conventions in Introduction
- Intended Use in CHAPTER 1, System Overview and Operation Principles
- System Manager in CHAPTER 1, System Overview and Operation Principles
- Extended QC in CHAPTER 2, Quality Control
- Test Orders in CHAPTER 3, Sample Analysis and Data Review
- Processing Results in CHAPTER 3, Sample Analysis and Data Review
- Activating ESId in CHAPTER 4, Setup
- Added Deactivating ESId in CHAPTER 4, Setup
- Access Levels (Operator and Roles) in CHAPTER 4, Setup
- Restore Default MDW Rules in CHAPTER 4, Setup
- Enable MDW Decision Rules in CHAPTER 4, Setup
- Set Up Flagging Limits in CHAPTER 4, Setup
- Related Documents

Issue AC, 4/2020
DxH 900/DxH 690T Software Version 1.2.0

Note: Changes that are part of the most recent revision are indicated by a change bar in the left margin of the page.

The following sections were modified:

- Removed Effect of Time on MDW from CHAPTER 1, System Overview and Operation Principles
- Clinical Study in CHAPTER 1, System Overview and Operation Principles
- Added Automated VCSn Optimization in CHAPTER 2, Quality Control

Safety Notice

Read all product manuals and consult with Beckman Coulter-trained personnel before attempting to operate instrument. Do not attempt to perform any procedure before carefully reading all instructions. Always follow product labeling and manufacturer's recommendations. If in doubt as to how to proceed in any situation, contact your Beckman Coulter Representative.

Beckman Coulter, Inc. urges its customers to comply with all national health and safety standards such as the use of barrier protection. This may include, but is not limited to, protective eyewear, gloves, and suitable laboratory attire when operating or maintaining this or any other automated laboratory analyzer.

Alerts for Warning and Caution

Throughout this manual, you will see the appearance of these alerts for Warning and Caution conditions:

⚠ WARNING

WARNING indicates a potentially hazardous situation, which, if not avoided, could result in death or serious injury. May be used to indicate the possibility of erroneous data that could result in an incorrect diagnosis.

⚠ CAUTION

CAUTION indicates a potentially hazardous situation, which, if not avoided, may result in minor or moderate injury. It may also be used to alert against unsafe practices. May be used to indicate the possibility of erroneous data that could result in an incorrect diagnosis.

Safety Precautions

⚠ WARNING

Risk of operator injury if:

- **All doors, covers, and panels are not closed and secured in place prior to and during instrument operation.**
- **The integrity of safety interlocks and sensors is compromised.**
- **Instrument alarms and error messages are not acknowledged and acted upon.**
- **You contact moving parts.**
- **You mishandle broken parts.**
- **Doors, covers, and panels are not opened, closed, removed and/or replaced with care.**
- **Improper tools are used for troubleshooting.**

To avoid injury:

- **Keep doors, covers, and panels closed and secured in place while the instrument is in use.**
- **Take full advantage of the safety features of the instrument.**
- **Acknowledge and act upon instrument alarms and error messages.**
- **Keep away from moving parts.**
- **Report any broken parts to your Beckman Coulter Representative.**
- **Open/remove and close/replace doors, covers, and panels with care.**
- **Use the proper tools when troubleshooting.**

⚠ CAUTION

System integrity could be compromised and operational failures could occur if:

- **This equipment is used in a manner other than specified. Operate the instrument as instructed in the product manuals.**
- **You introduce software that is not authorized by Beckman Coulter into your computer. Only operate your system's computer with software authorized by Beckman Coulter.**
- **You install software that is not an original copyrighted version. Only use software that is an original copyrighted version to prevent virus contamination.**

⚠ CAUTION

If you purchased this product from anyone other than Beckman Coulter or an authorized Beckman Coulter distributor, and, it is not presently under a Beckman Coulter service maintenance agreement, Beckman Coulter cannot guarantee that the product is fitted with the most current mandatory engineering revisions or that you will receive the most current information bulletins concerning the product. If you purchased this product from a third party and would like further information concerning this topic, call your Beckman Coulter Representative.

Contents

Illustrations

Tables

Introduction

How to Use Your Manuals

This addendum to the Instructions for Use (IFU) for the UniCel DxH 900 Series with System Manager Coulter Cellular Analysis System covers the Early Sepsis Indicator (ESId) application. Modifications specific to the Early Sepsis Indicator (ESId) application are also included in this manual.

Use this addendum along with existing documentation (see Related Documents) for information on how to operate your system.

About This Manual

NOTE Screens and hardware depicted in this manual may differ slightly from the screens and hardware in your DxH System configuration.

The information in this Early Sepsis Indicator (ESId) Addendum is organized as follows:

- CHAPTER 1, System Overview and Operation Principles

  Provides the intended use of the application, the controls and supplies to use, performance, and method information.
- CHAPTER 2, Quality Control

  Provides information on running quality control.
- CHAPTER 3, Sample Analysis and Data Review

  Provides information on running test orders and processing results.
- CHAPTER 4, Setup

  Provides information on activating the application.

This manual also includes an appendix, references, a glossary, and an index.

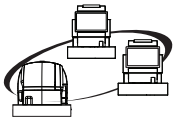
Conventions

This manual uses the following conventions:

- **Bold** font indicates buttons on the System Manager screen.
- *Italic* font indicates screen text displayed by the System Manager.
- The term *select* is used to indicate either one or both of the following actions:
  - to tap or touch with your finger (or a stylus on the DxH 690T screen)
  - to click with a mouse

IMPORTANT IMPORTANT is used for comments that add value to the step or procedure being performed. Following the advice in the IMPORTANT adds benefit to the performance of a piece of equipment or to a process.

NOTE NOTE is used to call attention to notable information that should be followed during use or maintenance of this equipment.

 indicates that the information following the graphic applies to DxH workcells.

The instructions in this manual are presented at the Lab Administrator level. For detailed instructions regarding other levels of operator access, see the Instructions for Use manual.

Graphics

All graphics, including screens and printouts, are for illustration purposes only. The appearance of your screens may differ slightly from the graphics in this document.

Symbols

The ≤ symbol in this addendum may appear as **<=** in the software. Both symbols mean *less than or equal to.*

The ≥ symbol in this addendum may appear as **>=** in the software. Both symbols mean *greater than or equal to.*

CHAPTER 1

System Overview and Operation Principles

Intended Use

The Unicel DxH 900 Series with System Manager Software Coulter Cellular Analysis System with Early Sepsis Indicator (ESId) application is the quantitative measurement of Monocyte Distribution Width (MDW). The Early Sepsis Indicator (ESId) is intended for use with adult patients presenting to the emergency department, on whom a white blood cell differential test has been ordered.

MDW is tested from a (K_2EDTA) whole-blood venous sample within two hours of collection. MDW results greater than 20.0 together with other laboratory findings and clinical information, aids in identifying patients with sepsis or at increased risk of developing sepsis within the first 12 hours of hospital admission.

MDW results greater than 20.0 should be interpreted in association with other clinical information and diagnostic testing as a proportion of patients without sepsis may have an elevated MDW result at baseline.

MDW results less than or equal to 20.0 cannot rule out sepsis or the development of sepsis within 12 hours of hospital admission. The Early Sepsis Indicator should not be used as the sole basis to determine the absence of sepsis.

The predictive value of the Early Sepsis Indicator (ESId) for identifying sepsis in patients with hematological abnormalities has not been established.

System Parameters

The following parameters have been added:

Table 1.1 System Parameters for Early Sepsis Indicator (ESId) Application

Parameter	Whole Blood	Prediluted Blood	Body Fluids	Controls
MDW (Monocyte Distribution Width)	Venous Only	NA	NA	COULTER 6C Plus Cell Control and Patient Controls
LDW (Lymphocyte Distribution Width)	NA	NA	NA	COULTER 6C Plus Cell Control
D (V2)	NA	NA	NA	COULTER LATRON CP-X Control

Supplies

Reagents

No new or additional reagents are required for this application. See the System Help for the recommended reagents.

Required Controls

The required controls are:

- COULTER LATRON CP-X Control with new D(V2) parameter
- COULTER 6C Plus Cell Control - used with the Early Sepsis Indicator (ESId) application to monitor system performance

For more information, see the instructions for use for each individual control available on www.beckmancoulter.com.

Specimen Tubes

Specimen tubes with K_2EDTA whole-blood venous samples have been validated for MDW measurements with normal and abnormal whole-blood samples stored at room temperature (see Running Samples in CHAPTER 3, Sample Analysis and Data Review for storage time). Tubes must fit the dimensions for cassette size width and height restrictions. K_2EDTA tubes having a diameter of 8 mm and greater are acceptable for use on the DxH 900/DxH 690T. The recommended acceptable tube is based on the size which allows for proper mixing and is independent of a specific manufacturer. See the instrument's System Help for more information. Some cap materials may produce excessive coring. Tube types with intended use for capillary samples such as micro-collection devices are excluded from use with the Early Sepsis Indicator (ESId) application.

IMPORTANT Beckman Coulter does not guarantee the acceptability of the sample tube to produce quality results. Tubes that fit on the instrument systems must be verified before use in your laboratory.

System Manager

Contact your Beckman Coulter Representative for assistance in activating the MDW parameters, if applicable.

When MDW is activated, the new parameters will appear as indicated on screens, in printed reports, in transmitted data, and in export files as follows:

- PATIENT RESULTS: MDW appears as part of the differential parameter group for patient results, within the worklist, exports, and LIS transmission following NRBC. MDW results will be displayed for specimens from the intended use population which is defined as an adult patient

from the emergency department with an age ≥ 18 and ≤ 89 years of age, or the patient age is unknown.

- CELL CONTROLS: MDW appears as part of the differential parameter group following NRBC. LDW appears as part of the differential parameter group following MDW. MDW and LDW parameters appear in the control file, exports, and LIS transmission.
- PATIENT CONTROLS: MDW appears as part of the differential parameter group following NRBC. MDW parameters appear in the control file, exports, and LIS transmission.
- COULTER LATRON CP-X Control: D (V2) appears following D (V) in the control file, export, and LIS transmission.

When MDW is activated, the MDW parameter appears on screens, in printed reports, and in export files for the Repeatability and XM.

NOTE The location of MDW will follow the Basophil parameter if NRBC reporting is disabled. MDW follows percentage or absolute numbers parameters depending on the reporting configuration previously selected by the laboratory.

Performance

IMPORTANT All performance testing was conducted within the system's operating temperature range of 15.55° to 32.22°C (60° to 90°F). The information in this addendum is based on data collected from venous whole-blood specimens in K_2EDTA.

⚠ CAUTION

Risk of erroneous results. Do not refrigerate samples since this may increase the MDW results.

Accuracy - MDW

A multicenter pilot study established the optimal clinical cut-off for MDW at 20.0 units when used for the early detection of sepsis in the emergency department. MDW performance was established using Sepsis-2 criteria.

MDW values above 20.0 units should raise the level of suspicion that adult patients have or will develop sepsis within twelve hours of presentation to the emergency department.

Clinical Study

A blinded, prospective, observational, multicenter cohort study was conducted at three sites comprised of both academic and community hospital emergency departments in the United States. The study enrolled a total of 2,158 consecutive adult emergency-department patients (≥ 18 and ≤ 89 years of age) meeting inclusion criteria for:

- Having a CBC-DIFF performed upon presentation and
- Subjects remaining in the hospital (emergency department or in-patient) for at least 12 hours

The prevalence of sepsis as defined by the Sepsis-2 (ACCP/SCCM 2001 consensus criteria) was 17.8%. All subjects were adjudicated by two qualified physicians following the ACCP/SCCM 2001 consensus definition for Sepsis-2 and the recent Sepsis-3 definition. Discordant results were arbitrated by a third physician. No cases were excluded due to inability to arbitrate.

Clinical diagnosis was based upon medical information obtained with 12 hours of emergency-department presentation. The presence of infection was determined based upon retrospective chart review of clinical symptoms and tests performed within 12 hours of emergency-department presentation. Test results were obtained from the medical records 5 to 10 days later, including cultures, molecular tests, tissue pathology, etc. Additional blood cultures obtained after 12 hours of presentation were not considered in the determination of sepsis. For subjects to be considered for infection or sepsis diagnosis, evidence of a protocol-defined infection work-up was required in the data extracted from the medical charts. If an infection work-up was not performed within 12 hours or if the adjudicator believed that the infection work-up showed no evidence of infection, then the patient was classified as *Control* or *SIRS*. In order to categorize a patient as *Sepsis*, SIRS criteria and an infection work-up had to be fulfilled within 12 hours of presentation. The subject categories included:

- **Non-SIRS** - case controls, subjects having 0 to 1 SIRS (Systemic Inflammatory Response Syndrome) criteria and no infection
- **SIRS** - subjects having ≥ 2 SIRS criteria and no infection
- **Infection** - subjects having suspected or confirmed infection with 0 - 1 SIRS criteria
- **Sepsis** - subjects having infection plus ≥ 2 SIRS
- **Severe sepsis** - subjects having sepsis with one or more organ failures
- **Septic shock** - subjects having sepsis with severe hypotension

All sites were required to extract the same information to enable adjudication based on the case report form; however, the diagnostic evaluation for infection was not prescribed by the study, but rather followed the standard of care at the institution. Some subjects lacked cultures (87% had cultures drawn, 46% were positive as shown in Table 1.3, Microbiological Testing Results for Subjects Diagnosed with Sepsis) and empiric therapy was considered to be part of the infectious disease work-up. Some subjects (< 1%) may not have had any additional evaluation for sepsis besides the administration of antimicrobials, but may have had an infectious work-up conducted with a previous admission or physical exam findings suggestive of infection. Differences in diagnostic evaluations for infection might have led to some uncertainty in the clinical trial results.

The emergency-department population demographics based upon presenting clinical status are summarized in Table 1.2, Emergency-Department Population Demographics Based on Presenting Diagnosis.

Table 1.2 Emergency-Department Population Demographics Based on Presenting Diagnosis

Site	Category per Sepsis-2 Criteria				
	Case Control	**SIRS**	**Infection**	**Sepsis***	**Total**
1	320	111	95	139	665
2	440	222	60	115	837
3	328	108	89	131	656
Total	1088	441	244	385	2158

*Sepsis includes sepsis, severe sepsis, and septic shock.

The results of microbiological testing for subjects diagnosed with sepsis are summarized in Table 1.3, Microbiological Testing Results for Subjects Diagnosed with Sepsis.

Table 1.3 Microbiological Testing Results for Subjects Diagnosed with Sepsis

Microbiological Testing (Sepsis Positive N = 385) *				
Test(s)	**Performed**	**% Performed**	**Confirmed**	**Percent Confirmed**
All Microbial Testing	335	87%	155	46%
- Bacterial Tests (All Culture Sources)	330	86%	146	44%
--- Bacterial Blood Culture **	275	71%	45	16%
- Viral Tests	27	N/A	11	41%
- Fungal Tests	11	N/A	4	36%
- Serological Tests	8	N/A	0	0%
- Rapid Tests	11	N/A	1	9%
Not Performed	50	13%	N/A	N/A
Confirmed Cases	**Gram-Positive**	**Gram-Negative**	**Mixed Gram Stain**	**Gram-Positive and Gram-Negative from Different Cultures**
Bacterial Culture (All Sources/Subject)	43	59	34	10
- Bacterial Culture (Blood Only)	24	19	2	0

* Numbers do not add up to 385 as there were many cases of more than one microbial testing performed.

** Blood cultures are subset of bacterial culture total.

N/A - Not applicable

Monocyte Volume Width Distribution Testing

Whole-blood venous samples collected in K_2EDTA stored at room temperature were analyzed on the UniCel DxH Coulter Cellular Analysis Systems within two hours of venipuncture. MDW results were compared to the clinical adjudication of sepsis per Sepsis-2 criteria (defined as a documented or suspected infection together with two or more SIRS criteria).

Of the 2,158 subjects enrolled in the prospective clinical study, MDW trended upwards with sepsis and MDW values > 20 were highly prevalent in the sepsis group. However, a proportion of subjects

without sepsis also had elevated MDW values (see Table 1.4, Distribution of Elevated MDW Values in Prospective Clinical Trial).

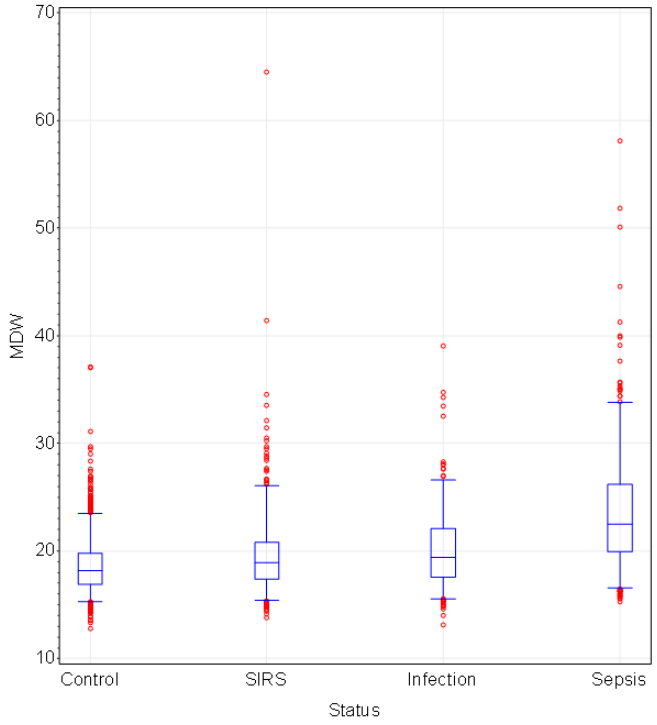
Table 1.4 Distribution of Elevated MDW Values in Prospective Clinical Trial

Clinical Population	Subjects with MDW Values > 20.0 (n [%])
Non-SIRS (Case Controls)	240/1088 (22.1%)
SIRS	151/441 (34.2%)
Infection	104/244 (42.6%)
Sepsis	284/385 (73.8%)

Clinical Performance

The distribution of MDW recoveries for the various sub-populations represented in the clinical study is illustrated by the box plot in Figure 1.1, Distribution of MDW Values for Various Sub-populations.

Figure 1.1 Distribution of MDW Values for Various Sub-populations



At a cut-off of 20.0 units, MDW effectively differentiated between sepsis and all other conditions in emergency-department patients. The MDW parameter upon emergency-department presentation is predictive of the development of sepsis within the first 12 hours of emergency-department presentation. Receiver Operator Characteristic Curve (ROC) analysis yielded an area under the curve (AUC) of 0.789 (95% CI 0.762 to 0.815). See Figure 1.2, Capacity of MDW to Differentiate between Sepsis (ROC Curve) and All Other Conditions.

Table 1.5, Performance of MDW for Sepsis-2 summarizes the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios with their respective 95% confidence intervals based on the established optimal cut-off of 20.0 units.

MDW values between 19.0 and 19.5 units have a higher sensitivity for predicting sepsis, but lower specificity (for example, more false-positive results). The impact on sensitivity and specificity for early detection of sepsis at different MDW cut-offs is provided in Table 1.6, Sensitivity and Specificity at Various MDW Cut-offs - Sepsis-2.

Figure 1.2 Capacity of MDW to Differentiate between Sepsis (ROC Curve) and All Other Conditions

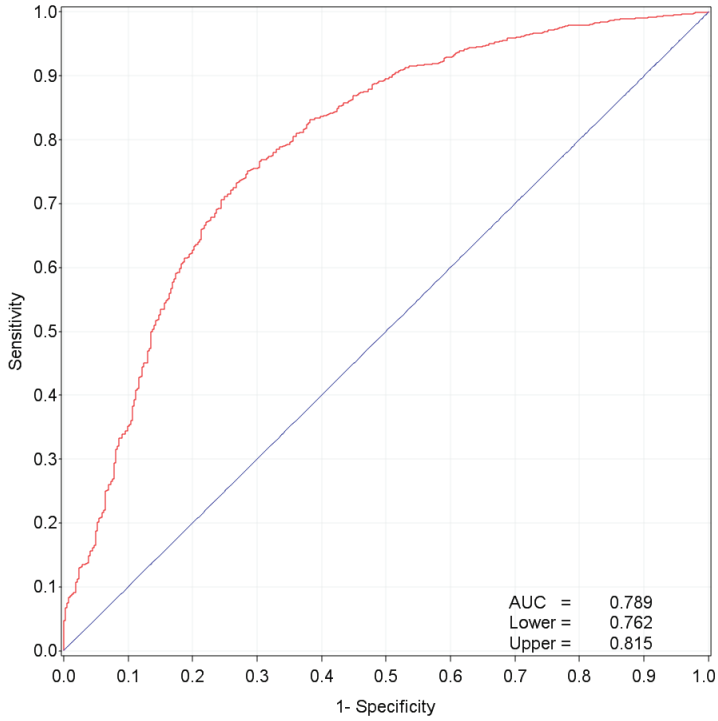


Table 1.5 Performance of MDW for Sepsis-2

MDW Cut-off at 20.0						
	Sensitivity	**Specificity**	**Predictive Values**		**Likelihood Ratios**	
			Positive	**Negative**	**Positive**	**Negative**
Estimate	0.740	0.720	0.365	0.927	2.646	0.361
Lower 95% Confidence Interval	0.694	0.699	0.332	0.912	2.406	0.304
Upper 95% Confidence Interval	0.782	0.741	0.399	0.940	2.911	0.428

Table 1.6 Sensitivity and Specificity at Various MDW Cut-offs - Sepsis-2

Cut-off	Sensitivity	95% Confidence Intervals		Specificity	95% Confidence Intervals	
		Lower	Upper		Lower	Upper
19.0	0.821	0.779	0.856	0.594	0.571	0.617
19.5	0.784	0.741	0.823	0.661	0.639	0.683
20.0	0.740	0.694	0.782	0.720	0.699	0.741
20.5	0.683	0.635	0.728	0.771	0.751	0.790

Added Value Analyses

The MDW parameter should be used in conjunction with the current standard of care for sepsis. In the following analyses, the current standard of care is represented by WBC which is a component of the SIRS criteria. Based on the data from the clinical trial, AUCs or ROC curves to detect sepsis are calculated for WBC as a single parameter and WBC+MDW combination.[10] Results are graphically presented in Figure 1.3, ROC Curves Comparison while AUC estimates along with their 95% confidence intervals are summarized in Table 1.7, AUC for WBC and Combined WBC+MDW. These results apply to this observational clinical trial and may not be generalizable to other patients in different institutions.

Figure 1.3 ROC Curves Comparison

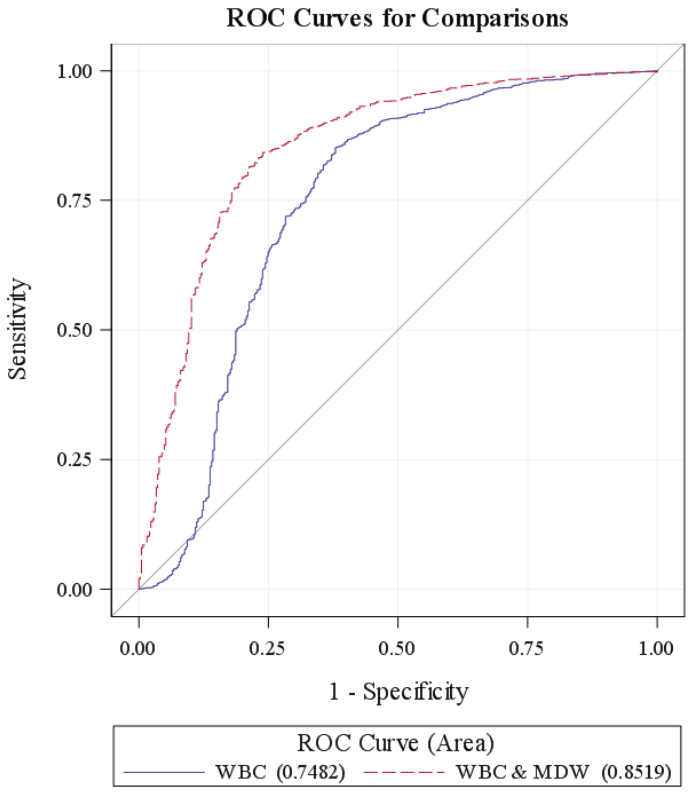


Table 1.7 AUC for WBC and Combined WBC+MDW

Parameter	AUC	SE	95% Confidence Limits	
			Lower	Upper
WBC	0.75	0.02	0.72	0.78
WBC+MDW	0.85	0.01	0.83	0.88
Difference	0.10	0.01	0.08	0.13

AUC for WBC+MDW is statistically greater than the AUC for WBC alone. The difference between the two models is statistically significant indicating that the implementation of MDW adds value to the current state of diagnosis for sepsis as represented by WBC.

The added value of MDW combined with WBC was integrated into an assessment for the probability of the disease. Pre-test and post-test probabilities for different combinations of tests are shown in Table 1.8, Pre-Test and Post-Test Probabilities for Different Combinations of Tests. This table summarizes the positive likelihood ratios and post-test probabilities for WBC only or when used in conjunction with MDW. The following decision rules are used for considering a result as abnormal:

- WBC > $12x10^3/\mu L$ is abnormal
- WBC < $4x10^3/\mu L$ is abnormal
- MDW > 20.0 is indicative of having or developing sepsis
- (WBC > $12x10^3/\mu L$ or WBC < $4x10^3/\mu L$) and MDW > 20.0 is a strong indication for sepsis

An abnormal WBC result increases the probability of a patient having or developing sepsis to 44.7% when the pre-test probability is 17.8%, based on the incidence of sepsis in the clinical study. The post-test probability increases to 63.5% when WBC is abnormal and MDW > 20.0. This represents an overall increase of 46% in the probability of being septic as a result of both tests being abnormal. This analysis includes patients who were not suspected of sepsis; therefore, results may not be generalizable.

Normal test results will reduce the probability of sepsis. The post-test probability of a normal WBC test is 7.9%, but this value goes down to 2.9% if both WBC and MDW are normal. Thus, the probability of sepsis in this clinical cohort, based on a sepsis incidence of 17.8%, is reduced when both tests are normal.

Table 1.8 Pre-Test and Post-Test Probabilities for Different Combinations of Tests

Test	Likelihood Ratio	Lower 95% Confidence Interval	Upper 95% Confidence Interval	Probability
Pre-Test	N/A	N/A	N/A	17.8%
Post-Test: Positive Test Results				
WBC Abnormal * and MDW Normal	1.48	1.15	1.90	24.3%
WBC Abnormal *	3.72	3.30	4.20	44.7%
WBC Abnormal * and MDW Abnormal	8.01	6.52	9.84	63.5%

Table 1.8 Pre-Test and Post-Test Probabilities for Different Combinations of Tests

Test	Likelihood Ratio	Lower 95% Confidence Interval	Upper 95% Confidence Interval	Probability
Post-Test: Negative Test Results				
WBC Normal and MDW Normal	0.14	0.10	0.19	2.9%
WBC Normal	0.39	0.34	0.46	7.9%
WBC Normal and MDW Abnormal	1.10	0.90	1.34	19.3%
* Abnormal White Blood Cells Range > 12 x 10^3/µl or < 4 x 10^3/µl				

Clinical Performance Differentiating Between Sepsis versus Non-Sepsis Per Sepsis-3 Criteria

MDW performance is lower for Sepsis-3 versus Sepsis-2. This is expected as MDW is intended to identify patients early in the disease progression prior to organ dysfunction.

Table 1.9 Performance for MDW Based on the Established Optimal Cut-off of 20.0 units per Sepsis-3 Criteria

	Sensitivity	Specificity	Predictive Values		Likelihood Ratios	
			Positive	Negative	Positive	Negative
Estimate	0.679	0.678	0.211	0.943	2.111	0.473
Lower 95% Confidence Interval	0.618	0.657	0.184	0.930	1.894	0.393
Upper 95% Confidence Interval	0.735	0.699	0.241	0.954	2.352	0.570

Table 1.10 Performance of MDW at Varying Cut-offs: Cut-offs, Sensitivity, Specificity, Lower and Upper 95% Confidence Intervals for Combined Sites versus Final Diagnosis per Sepsis-3 Criteria

Cut-off	Sensitivity	95% Confidence Intervals		Specificity	95% Confidence Intervals	
		Lower	Upper		Lower	Upper
19.0	0.774	0.717	0.822	0.557	0.535	0.579
19.5	0.724	0.665	0.777	0.620	0.598	0.642
20.0	0.679	0.618	0.735	0.678	0.657	0.699
20.5	0.630	0.567	0.688	0.731	0.710	0.750

Clinical Performance Differentiating Between SIRS versus Sepsis

An assessment was done to determine the ability of the MDW parameter to differentiate between adult patients with inflammation (≥ 2 SIRS) and infection (sepsis) from adult patients with inflammation only (≥ 2 SIRS). A total of 441 patients had ≥ 2 SIRS (see Table 1.2, Emergency-Department Population Demographics Based on Presenting Diagnosis) which represents 20% of the emergency-department population.

MDW effectively differentiated between SIRS and sepsis in emergency-department patients at a cut-off of 20.0 units. Receiver Operator Characteristics Curve (ROC) analysis yielded an area under the curve (AUC) of 0.756 (95% CI 0.723 to 0.789). See Figure 1.4, Capacity of MDW to Differentiate between SIRS and Sepsis (ROC Curve).

Table 1.11, Performance of MDW to Differentiate between SIRS and Sepsis summarizes the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios with their respective 95% confidence intervals based on the established optimal cut-off of 20.0 units.

MDW values between 19.0 and 19.5 units have a higher sensitivity for predicting sepsis from SIRS, but have a lower specificity. The impact on sensitivity and specificity for early detection of sepsis from SIRS at different MDW cut-offs is provided in Table 1.12, Sensitivity and Specificity at Various MDW Cut-offs to Differentiate between SIRS and Sepsis.

Figure 1.4 Capacity of MDW to Differentiate between SIRS and Sepsis (ROC Curve)

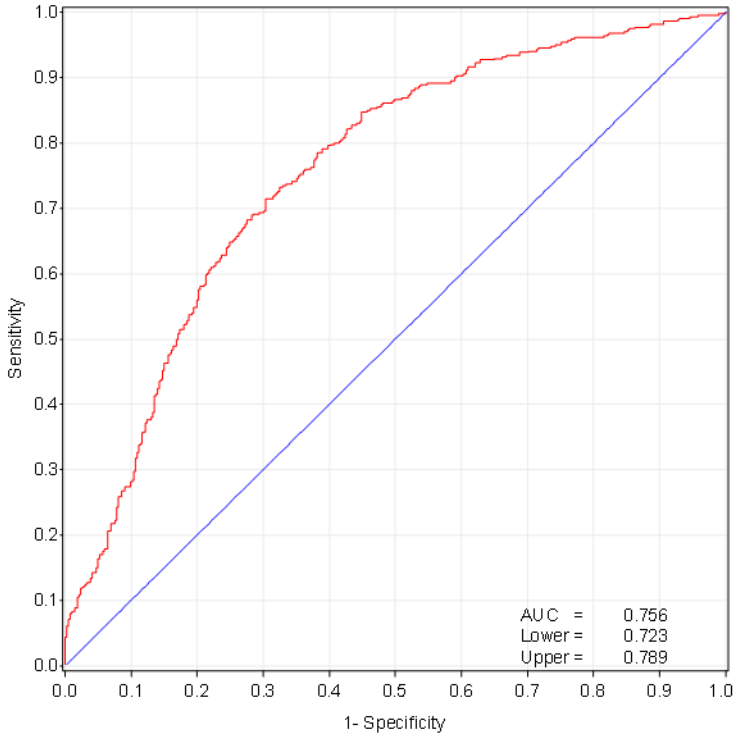


Table 1.11 Performance of MDW to Differentiate between SIRS and Sepsis

	MDW Cut-off at 20.0					
	Sensitivity	Specificity	PPV	NPV	Likelihood Ratios	
					LR+	LR-
Performance	0.740	0.658	0.654	0.744	2.162	0.395
Lower 95% Confidence Interval	0.694	0.612	0.608	0.698	1.875	0.329
Upper 95% Confidence Interval	0.782	0.700	0.697	0.784	2.492	0.474

Table 1.12 Sensitivity and Specificity at Various MDW Cut-offs to Differentiate between SIRS and Sepsis

		95% Confidence Intervals			95% Confidence Intervals	
Cut-off	**Sensitivity**	**Lower**	**Upper**	**Specificity**	**Lower**	**Upper**
19.0	0.821	0.779	0.856	0.517	0.470	0.563
19.5	0.784	0.741	0.823	0.601	0.555	0.646
20.0	0.740	0.694	0.782	0.658	0.612	0.700
20.5	0.683	0.635	0.728	0.719	0.675	0.759

MDW diagnostic ability is not statistically different for gender, race, or ethnicity and the same cut-off can be used for all groups. For more information, see Table 1.13, General Statistics of Gender Effects on MDW, Table 1.14, General Statistics of Ethnicity Effects on MDW, and Table 1.15, General Statistics of Race Effects on MDW.

Table 1.13 General Statistics of Gender Effects on MDW

						Non-Sepsis		Sepsis	
Gender	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**N**	**Mean**
Female	1125	20.02	4.19	13.31	64.52	935	19.28	190	23.69
Male	1033	19.66	4.11	12.78	58.11	838	18.77	195	23.48

Table 1.14 General Statistics of Ethnicity Effects on MDW

						Non-Sepsis		Sepsis	
Ethnicity	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**N**	**Mean**
Hispanic or Latino	125	19.13	3.68	14.14	33.58	102	18.00	23	24.13
Not Hispanic or Latino	1974	19.90	4.18	12.78	64.52	1625	19.11	349	23.57

Table 1.15 General Statistics of Race Effects on MDW

						Non-Sepsis		Sepsis	
Race	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**N**	**Mean**
American Indian or Alaska Native	4	16.16	31.31	21.39	7.13	2	19.00	2	23.77
Asian	53	14.88	33.53	19.62	3.76	42	18.80	11	22.76
Black or African American	459	13.15	64.52	19.87	4.11	377	19.18	82	23.02
Native Hawaiian or other Pacific Islander	2	19.79	20.86	20.33	0.76	2	20.33	0	0
Other	27	15.24	29.61	19.29	3.36	19	18.24	8	21.76
Not Provided	123	14.14	39.83	19.20	3.91	101	18.09	22	24.29
White	1490	12.78	58.11	19.91	4.21	1230	19.09	260	23.80

Whole-Blood Adult Reference Interval

A study was conducted to assess the normal reference interval for MDW on the Unicel DxH Coulter Cellular Analysis Systems. A total of 146 whole-blood samples were collected from apparently healthy adult males and females from three different geographic areas, representing the demographics of the United States population. The selection of donors was consistent with guidelines stated in *CLSI EP28-A3c*[3]. All subjects completed informed consent and were assessed for WBC and monocyte distribution (MO%, and MO# count) based on their respective laboratory's reference ranges. A non-parametric approach was used to calculate the lower and upper limits of the reference interval using 95% confidence. The 90% confidence intervals for the lower and upper bounds of the reference limits were also calculated. The reference interval for MDW on the UniCel DxH Coulter Cellular Analysis Systems across all participating sites is summarized in Table 1.16, Whole-Blood Adult Reference Intervals.

Table 1.16 Whole-Blood Adult Reference Intervals

				MDW Range		95% Confidence Reference Interval			
Parameter	**N**	**Mean**	**SD**	**Minimum**	**Maximum**	**Lower Limit**		**Upper Limit**	
MDW	146	16.96	1.88	13.37	22.56	13.98		21.28	
						90% Confidence Interval for the Lower Bound		**90% Confidence Interval for the Upper Bound**	
						Lower Limit	**Upper Limit**	**Lower Limit**	**Upper Limit**
						13.37	14.57	20.38	22.56

NOTE These values are intended to be representative only. Each laboratory must establish its own reference ranges from the local population of normal donors.

Open-Vial to Closed-Vial Comparison

MDW was compared using a minimum of 40 normal and abnormal donors collected into K_2EDTA, analyzed at room temperature within four to 24 hours of collection. The difference between the open versus closed results was within the ± 1.00 comparability limit.

Operating Range

The operating range for MDW and LDW is 0.00 - 255.50.

Throughput

Throughput, as defined in the System Help for CD and CDR panels, is not impacted with the addition of the MDW parameter to the differential results.

Repeatability

Repeatability is assessed by replicate analysis of the same specimen (n=10). Repeatability is achieved with a %CV limit at or below 10.0. Specimens with system messages and/or suspect messages were not used for analysis.

Table 1.17 MDW Precision

Parameter	Range	Limit CV
MDW	0.0 - 255.0	≤ 10.00%

The precision profile was evaluated based on the CV% of ten replicates, from a total of 36 whole-blood samples analyzed. Analyzed samples recovered MDW values from 14 to 39. Results with MDW flags and/or messages were excluded. The repeatability CV% was estimated at different MDW levels around the 20.0 units cut-off.

Table 1.18 Repeatability

MDW Level	CV%	95% Confidence Limits	
		Lower	Upper
19.0	5.28	4.55	6.01
19.5	5.27	4.57	5.98
20.0	5.27	4.59	5.94
20.5	5.26	4.61	5.91

Limitations

Table 1.19 Limitations

Parameter	Limitations
MDW	• Clinical performance in patients receiving immune stimulants or those with alcoholism is unknown. • The MDW parameter is not intended to identify patients at risk of sepsis in patients outside the emergency department for whom a CBC has been ordered for other health care purposes. Additional clinical validation must be performed in alternative patient populations. • The clinical performance of the MDW has not been established in patients with hematological abnormalities, such as blast cells. • A secondary analysis was performed using Sepsis-3 criteria[11] to identify patients with organ dysfunction within the first 12 hours of hospital admission. The performance of MDW was decreased versus Sepsis-2 criteria. • Samples for MDW must be tested within two hours of collection. • Refrigerated samples should not be used for MDW testing. Characterization studies have shown an increase in MDW values when samples are refrigerated. • Testing was used to assess the effect of interfering substances (Hemolysis, Triglyceride, Bilirubin, and Hemoglobin) on the measurement of the MDW parameter. Table 1.20, Maximum Concentration with No Observed Interference provides the maximum concentration at which no interference was observed.

Table 1.20 Maximum Concentration with No Observed Interference

Interfering Substance	Maximum Concentration
Hemolysis	Up to 2.02 g/dL *
Triglyceride	1500 mg/dL
Conjugated Bilirubin	40 mg/dL
Unconjugated Bilirubin	20 mg/dL
Hemoglobin	Up to 1.87 g/dL
* 7.3% of hemolysate was used for the hemolysis study which corresponds to free hemoglobin.	

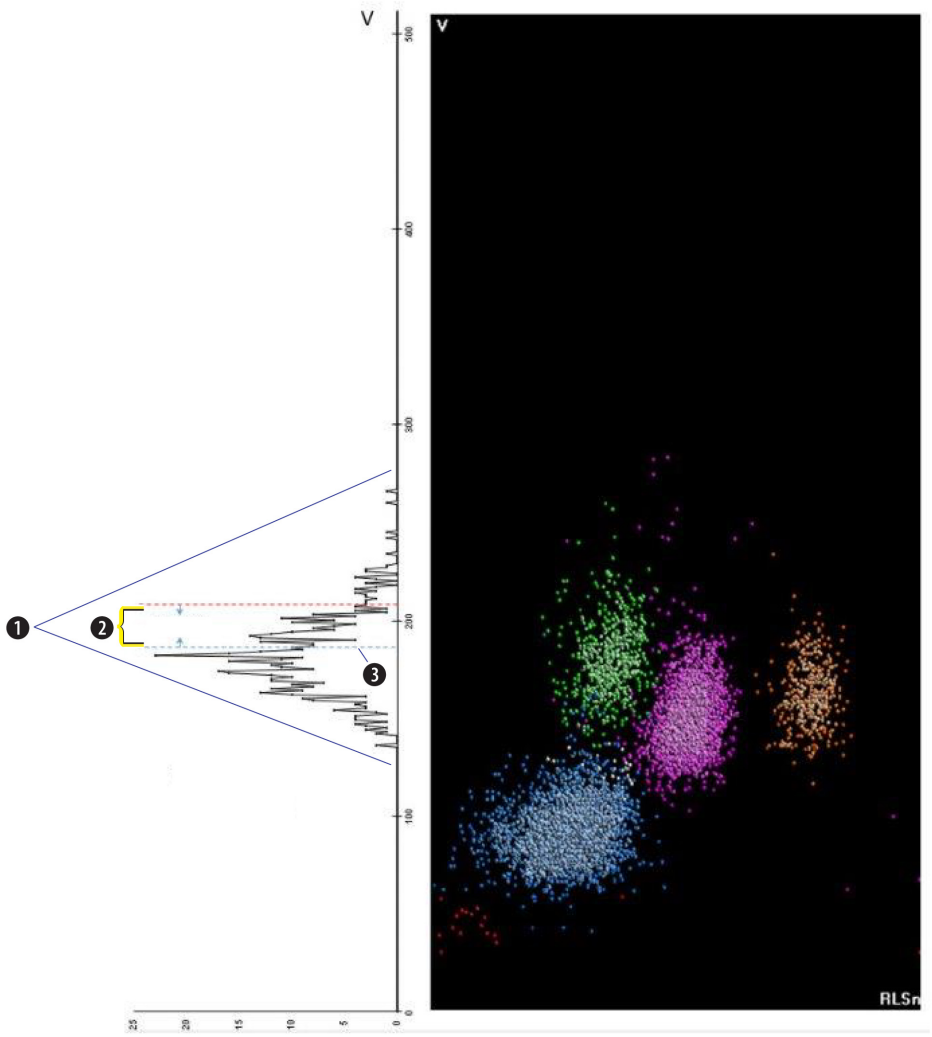
Operation Principles

Method/VCS 360 Analysis

The monocyte population is characterized using Volume (V), Conductivity (C) and multiple angles of Light Scatter (Sn). Volume measurements correlate to cell size.

Monocytes are identified in the Volume (V) versus Rotated Light Scatter (RLSn) dataplot. The MDW is calculated as the Standard Deviation (SD) of a set of monocyte cell volume values.

Figure 1.5 Monocyte Volume Distribution Width



Number	Description
1	Monocyte Volume Distribution
2	MDW
3	Monocyte Volume Mean

Parameter Measurement and Derivation

Table 1.21 Parameter Measurement and Derivation

Parameter	Method	Description
MDW	VCS 360 technology	Monocyte Distribution Width • The standard deviation of the volume component of the monocyte population derived from the differential dataplot • No reporting unit, independent of display reporting format • Applies to venous whole-blood samples, cell controls, and patient controls
LDW	VCS 360 technology	Lymphocyte Distribution Width • The standard deviation of the volume component of the lymphocyte population derived from the differential dataplot • No reporting unit, independent of display reporting format • Applies to cell controls
D (V2)	VCS 360 technology	Differential Volume 2 • Mean channel measurement for volume for the Early Sepsis Indicator (ESId) application • Applies to the COULTER LATRON CP-X Control

CHAPTER 2

Quality Control

Quality Control

COULTER LATRON CP-X Control

COULTER LATRON CP-X Control is used to monitor volume, conductivity, and light scatter measurements. To ensure minimal impact on size distribution used for MDW, a new parameter D (V2) and a new recovery limit was added.

The new D (V2) parameter and limit are set automatically by the software when the bar code is read from the COULTER LATRON CP-X Control assigned value sheet. If the fields for D (V2) mean and expected range are filled with zeros, assigned values should be manually updated. See the current assay sheet available on www.beckmancoulter.com.

The mean channel value for D (V2) is identical to that of D (V) used for the differential volume assessment. The new limit of ± 1 channel is applied to the D (V2) parameter and is only applicable to the MDW parameter. The D (V) parameter applies to all other differential parameters.

See *When a COULTER LATRON CP-X Control is Outside Its Expected Range* in the System Help when COULTER LATRON CP-X is out. COULTER LATRON CP-X Control must pass quality control before analyzing commercial controls and patient samples.

The MDW parameter cannot be reported if the D (V2) parameter fails for the COULTER LATRON CP-X Control. All other VCS 360 parameters can be reported as long as the D (V) parameter is within limits specified for the COULTER LATRON CP-X Control. Contact your Beckman Coulter Representative if the D (V2) parameter is outside of Expected Range. Follow other existing diagnostic and clinical methods for diagnosis of sepsis until the issue is resolved.

Automated VCSn Optimization

The new feature for Autogain Adjustment available in DxH 900 software version 1.1 and later (includes DxH 690T software version 1.2 and later) is set by default to occur automatically at shutdown after five successful Latron CP-X runs. This feature can only be disabled by a Beckman Coulter Service Representative. Confirm that all QC results are within limits prior to processing patient samples.

Commercial Control - COULTER 6C Plus Cell Control

COULTER 6C Plus Cell Control has been developed for use with the Early Sepsis Indicator application. Two new parameters, MDW and LDW, are contained in each of the three levels of the cell control, and represent dispersion values for different size populations of white cell subsets. The MDW parameter provides a larger dispersion value above the Sepsis cut-off value. The LDW

parameter provides a smaller dispersion value near or below the Sepsis cut-off value. Both values indicate that the UniCel DxH Coulter Cellular Analysis Systems are capable of calculating a range of clinical values for distribution width of cell populations.

NOTE LDW is designed to enhance control of population dispersion calculations; it is not designed as part of patient result evaluation. LDW is available in a CD panel for cell controls when Early Sepsis Indicator is activated.

Values for MDW and LDW parameters are similar but not identical across the three levels of controls. This gives the laboratory the ability to rotate control levels according to desired and flexible QC practices, while still maintaining adequate control of the MDW parameter.

The controls can be set up manually, or automatically by scanning the barcode label on the assigned value sheet, similar to COULTER 6C Cell Control. Configure the COULTER 6C Plus Cell Control for your system when the Early Sepsis Indicator (ESId) application is enabled.

See *When a Commercial Control is Outside of Its Expected Range* in the System Help.

Extended QC

Extended QC analysis is available for the MDW and LDW parameters. See the System Help for additional information on Extended QC.

Extended QC rules are derived from the German Quality Control Guidelines for the Medical Laboratory, known in Germany as Rili-BÄK (Guidelines of the Federal Chamber of Physicians). Extended QC only applies for WBC, RBC, HGB, HCT, and PLT, but it is available for the rest of the parameters including LDW and MDW.

Extended QC are additional QC rules for verification of the following:

- Random error or imprecision
- Systematic error or bias
- Total error, inaccuracy, or Root Mean Squared Error (RMSE)

RMSE is measured within a control file with Extended QC enabled. RMSE is a statistical result that is compared to the limits for Single Measurement Error. The software will perform the Extended QC calculations and flagging with runs N ³ 2 and < 15 (values exceeding limits are highlighted in yellow), but does not require acknowledgment of a QC Out condition until there are N ³ 15 runs (values exceeding limits are highlighted in red).

RMSE is $\Delta = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(x_i - x_0)^2} = \sqrt{\frac{n-1}{n}s^2 + \delta^2}$ where:

- Δ = RMSE
- x_0 = target value
- x_i = individual measurement value

- x_i = number of individual values
- s = empirical SD
- $\delta = \bar{x} - x_0$ = systematic error of measurement

RMSE is used to calculate Relative RMSE which is displayed in the software. Relative RMSE is $\left(\Delta / x_o\right) x100$ where:

- Δ = RMSE
- x_0 = target value

XM Analysis

XM analysis is available for the MDW parameter. See the system's Instructions for Use for more information.

CHAPTER 3

Sample Analysis and Data Review

Running Samples

Analyze the samples within two hours from the time of draw at controlled room temperature. Run the samples in cassette or single-tube presentation as described in your instrument's System Help section on Running Samples.

Test Orders

The MDW parameter is grouped with the differential parameter results as part of the CBC/DIFF (CD) or CBC/DIFF/Retic (CDR) panel when enabled for reporting. If selected, MDW will only be displayed for patients from the emergency department who are adults ≥ 18 and ≤ 89 years of age, and patients with unknown age. If the patient age is unknown, confirm that the patient age is within the intended use population (≥ 18 and ≤ 89 years) for the reporting of MDW.

Data Review

Processing Results

See the System Help for additional instructions for reviewing patient results. The system utilizes dataplot patterns for the differential and sophisticated statistical methods available for the sample analyzed. The Patient Result screen displays MDW as part of the differential parameters. Flags, codes, and messages that apply to the differential parameter also apply to the MDW parameter.

When there is inadequate data, the algorithm will suppress the reporting of the MDW parameter and display this code (.....) for incomplete computation. Incomplete computation applies to patient whole-blood results and patient controls:

- MDW results for patient samples will be shown as incomplete (.....).
- MDW results for patient samples processed as controls will be shown as incomplete (.....).

An incomplete computation is reported under the following conditions:

- When there are not enough (< 100) monocyte events for the reporting of results.
- When excessive debris is detected due to incomplete lysing.

NOTE Patients who receive an incomplete MDW result may not necessarily be excluded from the possibility of having sepsis.

For troubleshooting purposes, determine the cause for the incomplete computation by multiplying MO% x Displayed Count (located in the Additional Data screen - Diff tab):

- If the monocyte count is < 100 events, this is indicative of not enough events for the reporting of results.
- If the monocyte count is > 100 events in the presence of excessive debris, this is indicative of incomplete lysing.

Take action to rerun the sample. If you experience a significant increase in the frequency of incomplete computations (.....), contact your Beckman Coulter Representative for assistance.

Table 3.1, Lab Action Messages provides the appropriate messages associated with decision rules that may be used for patient result interpretations. See APPENDIX A, Flagging and Messages Available with Decision Rules for more information about flagging and the messages that will be displayed.

Table 3.1 Lab Action Messages

	Message
Decision Rule: Adults/Unknown age in the ED with elevated MDW	
Adults/Unknown Age	For adults in ED, MDW > 20.0 may be associated with a higher risk of sepsis during the first 12 hours of hospital admission.
Unknown Age	Confirm patient age is within intended use population (18-89 years) for MDW.
Decision Rule: Adults/Unknown age in the ED with elevated MDW and suspect flag (without Left Shift flag)	
Adults/Unknown Age	The predictive value of MDW for identifying sepsis in patients with hematological abnormalities has not been established.
Unknown Age	Confirm patient age is within intended use population (18-89 years) for MDW.
Decision Rule: Adults/Unknown age in the ED with elevated MDW and Left Shift flag	
Adults/Unknown Age	For adults in ED, MDW > 20.0 may be associated with a higher risk of sepsis during the first 12 hours of hospital admission.
	The predictive value of MDW for identifying sepsis in patients with hematological abnormalities has not been established.
Unknown Age	Confirm patient age is within intended use population (18-89 years) for MDW.
Adults/Unknown age in the ED with normal MDW	
Adults/Unknown Age	For ED adults patients suspected of sepsis, MDW ≤ 20.0 does not rule out sepsis or risk of sepsis.

⚠ WARNING

Risk of erroneous results. Flags, codes, and messages are evaluated when the sample is analyzed. Flags are reevaluated when results are manually edited or when new results are received for a pending sample. Flags (including Delta Checks) and decision rules are not reevaluated upon a change of flagging limits for results already in the database. Delta Checks settings have not been validated for use with the MDW parameter.

Beckman Coulter:

- **Does not claim to identify every abnormality in all samples. See the Flags and Codes information in the instrument's IFU.**
- **Suggests using all available options to optimize the sensitivity of instrument results.**
- **Recommends avoiding the use of one type of message or output to summarize results or patient conditions. There may be situations where the presence of a rare event may fail to trigger a suspect message.**

You should not rely upon instrument results alone to replace the need for clinical evaluation of the patient. Further diagnostic procedures and clinical methods must be evaluated for diagnosis.

Editing Patient Demographics and Active Test Orders

The system displays messages when you edit patient demographics.

For active test orders in the Worklist, messages will be displayed when you edit flagging limits and locations.

Table 3.2 Messages Displayed When Editing Patient Demographics and Active Test Orders

Scenario	Message Displayed	Action
Editing patient demographics (**Menu** > **Setup** > **Demographics**)	Flagging criteria may change as a result of these modifications. Select Yes to continue or No to cancel.	Select **Yes** to continue or **No** to cancel.

Table 3.2 Messages Displayed When Editing Patient Demographics and Active Test Orders *(Continued)*

Scenario	Message Displayed	Action
Specimen order is located in the Worklist Pending folder and the Flagging Set is edited.	You have chosen to override the system automatically selecting the flagging set based on patient age and location. Are you sure you want to proceed? Select Yes to continue or No to cancel.	Select **Yes** to continue or **No** to cancel.
Specimen results are located in the Worklist Review folder and the location in the patient demographics is edited, or patient demographics are edited from the detailed patient results.	**⚠ WARNING** **Risk of Delay in Results. Reflagging may occur for one or more of the following reasons, resulting in a masked MDW:** • **One or more of the following fields were modified: Date of Birth, Age, Gender, Patient Location.** • **Patient has been removed from the test order.** • **A new or existing patient has been added to the test order.** **Select Yes to continue or No to cancel.**	Select **Yes** to continue or **No** to cancel.

Partial Release

MDW results will be partially released along with the Differential group. See the information for releasing results in the System Help.

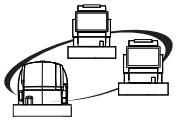
MDW Masking

Depending on the selected Flagging Limit, the MDW value will be displayed or masked. MDW result masking is done by displaying xxxxx in place of a result. For complete information on all available flagging and messaging-based decision rules and on when the MDW parameter is displayed or masked, see APPENDIX A, Flagging and Messages Available with Decision Rules.

CHAPTER 4
Setup

Activating ESId

The Early Sepsis Indicator (ESId) application is disabled by default at installation. When the Early Sepsis Indicator (ESId) application is activated, the MDW parameter is available for reporting. Previously run results prior to the activation of the MDW parameter will be displayed as xxxxx and flagging rules and limits will not apply to them.



When enabled, the Early Sepsis Indicator (ESId) application applies to an entire workcell, not just to an individual Sample Processing Module.

IMPORTANT The instrument(s) must be offline in order to activate or deactivate ESId. Follow the setup in the order indicated in this manual.

To activate the Early Sepsis Indicator (ESId) application, follow these steps.

1 Select **Menu > Setup > System > More > Configure Additional Features**.

2 Make a note of the hardware code displayed on the screen and follow the instructions in your license kit to request a feature password from your Beckman Coulter Representative. You need this feature password to activate the Early Sepsis Indicator (ESId) application.

3 Enter the feature password provided to you. The MDW checkbox will be displayed.

4 Select the **MDW** checkbox to activate the ESId application and select **OK**.

Deactivating ESId

IMPORTANT The instrument(s) must be offline in order to activate or deactivate ESId.

To deactivate the Early Sepsis Indicator (ESId) application from your system, follow these steps.

1 Select **Menu > Setup > System > More > Configure Additional Features**.

2 Deselect **MDW** and select **OK**.

3 On the next dialog box that informs you that to re-activate ESId, you must perform the activation process again, select **OK** to confirm the deactivation.

4 On the next dialog box that informs you that decision rules and flagging limits for MDW will no longer be triggered, select **OK** to continue.

NOTE If the system displays messages indicating that you must review QC Out runs or XM Diff batches with unreviewed conditions, review these items and then restart the deactivation procedure.

5 Delete MDW Rules 1-10:

- Select the **Decision Rules** tab or select **Menu > Setup > Flagging/Rules > Rules**.
- Select the **Active Decision Rules** tab.
- Highlight **MDW Rules 1-10**.
- Select **Delete Rule**. When the system displays *Delete selected decision rule?*, select **OK**.

Print and Save Configuration

The option to **Save Configuration** is not operational. **Print Configuration** is available. **Print Configuration** will detail whether MDW reporting is enabled or disabled.

Setting Up an Operator and Roles

A Level III operator is needed to set up the location, flagging limits, and decision rules. Use an existing Level III logon or create one following the steps in the DxH 900/DxH 690T IFU. See Related Documents for the part number.

NOTE If your institution has multiple emergency department locations, see Multi-Location Setup Scenario for more information.

1 Select **Menu > Setup > Operators and Roles > New Operator**.

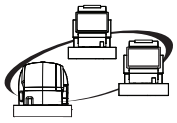
2 Enter the appropriate information.

3 Select **Access Level III** from the drop-down list.

4 Select **OK** to create the new operator. The password for a new operator is temporary. The new operator is prompted to change the password when logging on for the first time.

Access Levels (Operator and Roles)

A Level III operator is needed to activate the Early Sepsis Indicator (ESId) application and to set up locations, flagging limits, and decision rules. Use an existing Level III logon. The configuration setup requires the system or workcell to be offline.



The Early Sepsis Indicator application must be activated from the server for workcell configurations.

Decision Rules

IMPORTANT Follow the setup in the order indicated in this manual:

1. Restore Default MDW Rules.
2. Edit Default (ED) Location.
3. Activate Decision Rules.
4. Enable Decision Rules.
5. Set Up Flagging Limits.

Validate any new decision rules when you add or modify in order to ensure that the rules work as intended.

The MDW Rules are for the Early Sepsis Indicator (ESId) intended use population.

Ensure that the location in the MDW Rules reflects your institution's emergency department.

See Symbols in the Introduction for information on some of the symbols used in the software.

Restore Default MDW Rules

1 Select **Menu > Setup > Flagging/Rules > Rules.**

2 Select **Decision Rules Work Bench** tab > **Restore Default MDW Rules**. The system displays the following message: *The MDW Rules are for the Early Sepsis Indicator (ESId)™ intended use population. Ensure that the location in the MDW Rules reflects your institution's emergency department.*

3 Select **OK** to restore the Default MDW Rules.

Edit Default ED Location

IMPORTANT Follow the setup in the order indicated in this manual.

The ED location must be edited after Default MDW Rules are restored.

Ensure that the location entered reflects your institution's emergency department.

NOTE The Default Location (ED) can be edited, but not deleted.

1 Select **Menu > Setup > Flagging/Rules > Locations.**

2 Select **ED**.

3 Select **Edit**.

IMPORTANT Ensure that the location entered reflects your institution's emergency department.

4 Enter the name of your institution's emergency department for the location (Example: **ED**).

5 Select **OK**.

6 When the system displays the following message, select **OK**: *Changing the Location will also change it in decision rules, flagging limits, and test order, if applicable.*

7 Select **OK** then **Close**.

8 Select **Yes** to confirm the message:
Locations that will be used in Flagging Limits and Decision Rules including MDW must be within Early Sepsis Indicator (ESId)™ intended use population. Select Yes to continue or No to revert any changes made.

Activate Decision Rules

IMPORTANT The instrument must be offline in order to activate Decision Rule changes.

If Default MDW Rules are being activated, they must be inserted at the beginning of the Active Decision Rules list.

1 Select the **Active Decision Rules** tab or select **Menu > Setup > Flagging/Rules > Rules** > **Active Decision Rules** tab.

2 If active decision rules are available, ensure the first Decision Rule is highlighted.

3 Select **Activate Rules.** The system displays the following message: *If using Default MDW Rules, they must be inserted at the beginning of the Active Decision Rules list. Select Yes to activate Decision Rules or No to cancel.*

4 Select **Yes** to go to the Active Rules dialog screen.

5 Select all 10 MDW decision rules.

6 Ensure that **Insert at selected row** is selected.

7 Select **OK** to activate the rules

Enable MDW Decision Rules

1 Select the **Active Decision Rules** tab, or select **Menu > Setup > Flagging/Rules > Rules** and then select the **Active Decision Rules** tab.

2 Select all of the MDW Decision Rules (1 to 10).

3 Select **Enable Rule.**

4 When the system displays *You must validate any new decision rules that you add or modify in order to ensure that the rules work as intended.* Select **Yes** to continue or **No** to cancel. Select Yes to continue.

5 When the system displays E*nsure Decision Rules containing MDW use aH limit, Location and Ages that are within the intended use population for MDW. Are you sure you want to proceed?*, select **Yes**. The MDW Decision Rules are now enabled.

Set Up Flagging Limits

MDW is available as a test for use within action limits and within decision rules. Flagging limits and rules will not apply to the MDW parameter on samples run prior to the activation of the parameter. To set up flagging limits and rules, see the System Help for additional information.

IMPORTANT Follow the setup in the order indicated in this manual.

Ensure that the location entered reflects your institution's emergency department.

Validate any new flagging limits when you add or modify in order to ensure that the limits work as intended.

Two flagging limit sets are needed for the setup. Follow these steps to configure two sets of flagging limits:

1 Select **Menu** > **Setup** > **Flagging/Rules** > **Flags** > **Flagging Limits** tab.

2 Select **Add Limit**.

3 Create a new Emergency Department Flagging Limit Set 1:

- Specimen Type: Use the drop-down list to select **Whole Blood**
- Limit Name: Enter **ED Adult**
- Location: Select your institution's emergency department. Ensure the location reflects your institution's emergency department.
- Age Range: Enter **18 to 89 Years**

4 Select the **Display MDW** check box to display the MDW parameter.

5 Select **Copy Limit**.

6 Flagging Set Copy Source: Use the drop-down list to select the Laboratory's Adult Default Flagging Limits.

7 Select the **Copy All Available** check box.

8 Select **Copy**.

9 Select the **Action/Critical Limit** tab and enter **20.0** for MDW as *Action High*.

10 Select **OK** to save.

11 If you have selected **Display MDW**, select **OK** to continue to the following message:
MDW will be displayed for this Flagging Set. Ensure the MDW aH limit used, Location and Age Range setup are within the intended use population for MDW. Are you sure you want to proceed?
Select **Yes**.

IMPORTANT If you have not selected **Display MDW** and have not entered a value under *Action* for MDW, the system displays the following message:

⚠ WARNING

Risk of delay in results. MDW will not be displayed for this Flagging Set. Ensure the Location and Age Range setup are not within the intended use population for MDW. Are you sure you want to proceed?

If you have not selected **Yes** to confirm either message above, the Flagging Limit screen is displayed again where you can make changes.

12 Create a new Emergency Department Flagging Limit Set 2:

- Select **Menu > Setup > Flagging/Rules > Flags > Flagging Limits** tab
- Select **Add Limit**
- Specimen Type: Use the drop-down list to select **Whole Blood**
- Limit Name: Enter **ED Age Unknown**
- Location: Select your institution's emergency department. Ensure the location reflects your institution's emergency department.
- Age Range: Leave blank to indicate no age

13 Select the **Display MDW** check box to display the MDW parameter.

14 Select **Copy Limit**.

15 Flagging Set Copy Source: Use the drop-down list to select the Laboratory's Adult Default Flagging Limits.

16 Select the **Copy All Available** check box.

17 Select **Copy**.

18 For the Action/Critical Limit tab, leave the *MDW* field blank to indicate no value.

19 Select **OK** to save.

20 When the system displays *Are the From age and the To age blank because the flagging limit set is for unknown age?*, select **Yes**.

21 When the system displays: *MDW will be displayed for this Flagging Set. Ensure the MDW aH limit used, Location, and Age Range setup are within the intended use population for MDW. Are you sure you want to proceed?*, select **Yes**.

NOTE There is no aH limit for unknown age as intended.

IMPORTANT If you have not selected **Display MDW** and have not entered a value under *Action* for MDW, the system displays the following message:

⚠ WARNING

Risk of delay in results. MDW will not be displayed for this Flagging Set. Ensure the Location and Age Range setup are not within the intended use population for MDW. Are you sure you want to proceed?

If you have not selected **Yes** to confirm either message above, the Flagging Limit screen is displayed again where you can make changes.

IMPORTANT The System Manager alerts you when an overlapping unknown age with the same location is encountered meaning that another flagging set with a blank age range and the same location and specimen type already exists.

NOTE The System Manager alerts you when a blank age range is present and **View Age Range** is selected. Unless you are intentionally entering a blank age range, low and high age range values must be entered. Patient ages must be in the following ranges:

- 0 to 999 hours
- 0 to 999 days
- 1 to 999 weeks
- 1 to 999 months
- 1 to 150 years

The **From Age** must be less than the **To Age**.

Multi-Location Setup Scenario

IMPORTANT Follow the setup in the order indicated in this manual.

Ensure that the locations entered reflect your institution's emergency departments.

This procedure describes how to set up a facility with multi-location emergency departments (example: ER1, ER2, ER3).

1. Follow the steps in Setting Up an Operator and Roles.

2. Restore the default MDW rules. See Restore Default MDW Rules.

3. Set up the multiple locations (example: **ER1**, **ER2**, **ER3**). Ensure the locations reflect your institution's emergency departments.

4. Copy Decision Rules 4 to 10. The location will be assigned to these seven rules.

   NOTE For additional information on how to copy, edit, and delete decision rules, see Instrument Instruction for Use or System Help.

5. Delete the original MDW rules 4 to 10.

6. Edit the copied Decision Rules 4 to 10.

7. Edit the locations in the decision rules, remove ED, and add the multiple locations (example: **ER1**, **ER2**, **ER3**). Ensure the location reflects your institution's emergency department.

8. Activate the MDW Decision Rules. See Activate Decision Rules.

9. Enable the Decision Rules. See Enable MDW Decision Rules.

10. Follow the steps in Set Up Flagging Limits to add two Flagging Limits (one for Adult 18 to 89 years old and one for Unknown Age) for each of the emergency locations as created in step 3 above. Ensure the location reflects your institution's emergency department.

Custom Search

MDW is available as a test for use in custom searches. For more information, see the Custom Tab filter information in the Instructions for Use.

LIS Transmission

MDW will transmit to a host system for patient samples and patient controls. MDW and LDW will transmit to a host system for all COULTER 6C Plus Cell Controls. The D (V2) for COULTER LATRON CP-X Control will transmit to a host system. See the Early Sepsis Indicator (ESId) Application Host Transmission Manual (see Related Documents) for more information.

APPENDIX A

Flagging and Messages Available with Decision Rules

Flagging and Messages Available with Decision Rules

Table A.1 Flagging and Messages Available with Decision Rules

Adults[a] or Unknown Age in the Emergency Department (ED) with Elevated MDW[b]

Age Range	MDW Value	Flagged	Message
Adults	Displayed	Yes (aH)	For adults in ED, MDW > 20.0 may be associated with a higher risk of sepsis during the first 12 hrs. of hospital admission.
Unknown Age	Displayed	No	For adults in ED, MDW > 20.0 may be associated with a higher risk of sepsis during the first 12 hrs. of hospital admission.
			Confirm patient age is within intended use population (18-89 years) for MDW.

Adults[a] or Unknown Age in the Emergency Department (ED) with Elevated MDW[b] and Suspect Message(s)

Age Range	**MDW Value**	Flagged	**Suspect Messages**	Message
Adults	Displayed	Yes (aH)	Left Shift[d]	For adults in ED, MDW > 20.0 may be associated with a higher risk of sepsis during the first 12 hrs. of hospital admission.
			All[c]	The predictive value of MDW for identifying sepsis in patients with hematological abnormalities has not been established.
Unknown Age	Displayed	No	Left Shift[d]	For adults in ED, MDW > 20.0 may be associated with a higher risk of sepsis during the first 12 hrs. of hospital admission.
			All[c]	The predictive value of MDW for identifying sepsis in patients with hematological abnormalities has not been established.
			All[c]	Confirm patient age is within intended use population (18-89 years) for MDW.

Table A.1 Flagging and Messages Available with Decision Rules *(Continued)*

Adults[a] or Unknown Age in the Emergency Department (ED) with Normal MDW

Age Range	**MDW Value**	Flagged	Message
Adults or Unknown Age	Displayed	No	For ED adult patients suspected of sepsis, MDW ≤ 20.0 does not rule out sepsis or risk of sepsis.

Non-Adult in the Emergency Department (ED)

Age Range	**MDW Value**	Flagged	Message
< 18 years and > 89 years	Masked[e]	No	N/A

Any Age Outside the Emergency Department (ED)

Age Range	MDW Value	Flagged	Message
Any Age	Masked[e]	No	N/A

Represented in the table above:

a: Adult Age Range is ≥ 18 years and ≤ 89 years

b: MDW > 20.0 is considered elevated

c: This message will be present for LY Blast, MO Blast, NE Blast, Imm Grans, Variant LY, and/or Left Shift

d: This message will be present only for Left Shift

e: If a non-adult in the ED or a patient outside of ED, MDW will be masked and will appear as xxxxx

Glossary

This glossary is a collection of specialized terms and their meanings that are either used in this manual or related to the information in it. If a term has more than one meaning, all meanings relevant to this manual are included.

channel
Unit of measure for D (V2).

CI
confidence interval

cut-off
Threshold for detection. Values above and below the cut-off are positive and negative for conditions, respectively.

D (V2)
Mean channel measurement for volume for the Early Sepsis Indicator (ESId) application, using COULTER LATRON CP-X Control.

ED
Emergency Department

ESId
Early Sepsis Indicator

lymphocyte distribution width
(LDW) The standard deviation of the volume component of the lymphocyte population derived from the differential dataplot.

monocyte distribution width
(MDW) The standard deviation of the volume component of the monocyte population derived from the differential dataplot.

ROC
Receiver Operator Characteristic Curve

sepsis
A syndrome caused by the body's overwhelming and life-threatening response to infection which can lead to tissue damage, organ failure, and, ultimately, death.

A life-threatening condition that arises when the body's response to infection injures its own tissues and organs as per Sepsis 2 definitions[1].

SIRS

Systemic Inflammatory Response Syndrome

standard deviation (SD)

A measure of deviation from the mean. For example, a measure of the range of channel deviation within a measurement.

$$\mathrm{SD} = \sqrt{\frac{\sum \langle \bar{x} - x \rangle}{N}}^{2}$$

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Index

S

T

V

W

X

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- Data Review
- Workload
- Shutdown
- Setup
- Troubleshooting
- Quality Assurance
- Cleaning Procedures
- Replacement/Adjustment Procedures
- Appendices
- Abbreviations and Acronyms
- Glossary
- References
- Index
- Warranty

Symbols Glossary

PN C29230

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