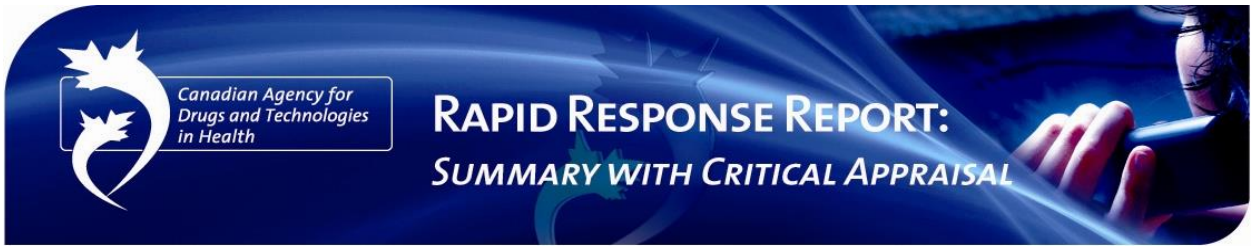


TITLE: Three- versus Five-Part Differential Complete Blood Count Testing for Patients in the Emergency Department: A Review of Comparative Diagnostic Accuracy, Safety, and Evidence-Based Guidelines

DATE: 09 August 2016

CONTEXT AND POLICY ISSUES

White blood cell (WBC) counts and their five subgroups of cell types (often called "differentials"), are common clinical measurements to diagnose and monitor a variety of pathologic conditions such as bacterial or viral infections, inflammation, leukemia, immunodeficiency states, and post-chemotherapy, or as part of a complete blood cell count in a routine health checkup.[1] The 5-part differentials that are usually performed in central laboratories using blood analyzers with blood collected by venipuncture are neutrophils, lymphocytes, monocytes, eosinophils and basophils. Three-part differentials consider granulocytes (neutrophils, eosinophils and basophils together as one group), lymphocytes and monocytes.[2]

Point of care (POC) analyzers of complete blood cell counts are being developed with the aim to reduce turnaround time and increase the chance that more timely medical decisions can be made in remote sites or in outpatient settings, with blood taken from a finger stick.[3] Currently, four main POC WBC systems are being used: Chempaq XBC (Chempaq A/S, Denmark), HemoCue WBC (HemoCue AB, Angelholm, Sweden), pocH -100i (Sysmex Corporation, Kobe, Japan), and ABX-MicrosCRP200 (Horiba Medical, Montpellier, France) (the last three systems are available for use in Canada).[2] The POC blood analyzers usually measure three-part differentials.[2] Three-part differentials can also sometimes be measured by lab-based tests.

This Rapid Response report aims to review the comparative diagnostic accuracy of three-part versus 5-part differentials and its risk, for patients presenting to the emergency department. Guidelines associated with the use of three-point differentials testing in emergency departments will also be examined.

RESEARCH QUESTIONS

1. What is the comparative diagnostic accuracy of three-part versus five-part differentials complete blood cell count tests for patients presenting to the emergency department?

2. What is the comparative risk of performing a three-part versus a five-part differentials complete blood cell count test for patients presenting to the emergency department?

3. What are the evidence-based guidelines regarding the use of three-part differentials CBC tests for patients presenting to emergency departments?

KEY FINDINGS

The use of Chempaq XBC in the emergency room setting showed good agreement with laboratory-based analyzers results for the granulocyte and the lymphocyte counts but not for the monocytes. This points to the potential risk of misdiagnosis for conditions where monocyte counts may be high (monocytosis) or low (monocytopenia). There are no evidence-based guidelines found regarding the use of three-part differentials CBC tests for patients presenting to emergency departments.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2001 and July 11, 2016.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Patients (adults and children) presenting to emergency departments and who are receiving complete blood cell count testing
Intervention	3-part differentials testing (POC, or lab based)
Comparator	5-part differentials testing
Outcomes	Comparative diagnostic accuracy Safety issues with using the 3-part vs 5-part differentials Evidence-based guidelines regarding the use of 3-part differentials tests in the emergency department
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), evidence-based guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2001, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included diagnostic accuracy trial was assessed using the QUADAS-2 tool.[4] Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 215 citations. After screening of abstracts from the literature search and from other sources, three potentially relevant studies were selected for full-text review. One study was included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

The included study is a diagnostic accuracy study that evaluated the POC CBC analyzer Chempaq XBC (Chempaq A/S, Denmark) for hemoglobin, leukocyte counts and three-part differentials and compared the results with results from laboratory based Beckman Coulter LH750 analyzers.[5] Finger stick or a drop of venous blood sample were used for Chempaq, and venous blood specimens were used for Beckman Coulter analyzer from 420 in-patients from different clinical services. Precision of Chempaq was tested using low count and high count blood samples. The accuracy of Chempaq was tested using diluted high count blood samples. Precision and accuracy of POC three-part differentials and central lab five-part differentials at different clinical settings (emergency room, primary care, obstetrics and gynecology (Ob/Gyn), intensive care unit (ICU), pediatric clinics, hematology/oncology clinics, and in-patient wards) were reported.

Diagnostic accuracy was analyzed by evaluating the *precision* (the consistency of measurements when performed many times, as measured by coefficient of variation [CV]), and the *accuracy* (the agreement between POC and central laboratory methods results, as measured by linear correlation r; the closer r is to 1, the better the agreement).

A detailed summary of the included study design, population, interventions and comparators, and outcomes is provided in Appendix 2.

Summary of Critical Appraisal

The included diagnostic study[5] had the spectrum of patients representative of the patients who would receive the test in practice. The reference standard and index test were measured at the same time, eliminating the possibility that blood cell counts changed between tests. Because both the reference standard and the index test relied on an numerical value provided by the

analyzer, the possibility of bias in interpretation of results was minimized. The execution of the index test was described in sufficient detail to permit replication of the test. Uninterpretable/indeterminate results were not reported.

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4.

1. What is the comparative diagnostic accuracy of three-part versus five-part differentials complete blood cell count tests for patients presenting to the emergency department?

The included diagnostic accuracy study evaluated the POC CBC analyzer Chempaq XBC (Chempaq A/S, Denmark) for hemoglobin, leukocyte counts and three-part differentials and compared the results with results from laboratory based Beckman Coulter LH750 analyzers.[5] Venous blood specimens from 420 in-patients were used. Precision and accuracy of POC three-part differentials and central lab five-part differentials at different clinical settings including emergency rooms were reported.

The precision of Chempaq XBC, as measured by CV, showed acceptable between-assays variations of three-part differentials counts using high and low count blood samples.

For low count blood samples, the CV was 14.7%, 14.2% and for 13.8% for granulocytes, lymphocytes and monocytes, respectively. For high count blood samples, the CV was 9.2%, 12.7% and 19.8% for granulocytes, lymphocytes and monocytes, respectively. The coefficient of variation of repeated lab-based tests was not reported.

The accuracy of Chempaq XBC, as measured by linear correlation (r) showed good agreement with laboratory-based analyzers results in all clinical settings, except for monocyte counts. The correlations in the emergency setting were 0.95, 0.89 and 0.32 for granulocytes, lymphocytes and monocytes, respectively.

2. What is the comparative risk of performing a three-part versus five-part differentials complete blood cell count test for patients presenting to the emergency department?

The extent to which the low agreement between POC three-part differentials and laboratory-based five-part differentials in monocyte counts affects clinical outcomes was not reported. Evidence from the diagnostic accuracy study above pointed to the potential risk of using POC Chempaq XBC to evaluate suspected monocytosis and monocytopenia in the emergency room setting (this risk was applicable to all clinical settings evaluated in the study: emergency room, primary care, Ob/Gyn, ICU, pediatric clinics, hematology/oncology clinics, and in-patient wards).[5]

3. What are the evidence-based guidelines regarding the use of three-part differentials CBC tests for patients presenting to emergency departments?

There were no evidence-based guidelines found regarding the use of three-part differentials CBC tests for patients presenting to emergency departments.

Limitations

Evidence on the accuracy of three-part differentials is limited to data from one diagnostic accuracy study on one type of POC blood analyzer which is not available for use in Canada, thus limiting the generalizability of the evidence to a Canadian context. The extent to which the low agreement between POC three-part differentials and laboratory-based five-part differentials in monocyte counts affects clinical practice is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Very limited evidence on three-part differentials showed that the POC Chempaq XBC showed good agreement with laboratory-based analyzers results for the granulocyte and the lymphocyte counts but not for monocytes. This pointed to the potential risk of misdiagnosis for conditions where monocyte counts may be high (monocytosis) or low (monocytopenia).

More comparative evidence between three-part differentials and five-part differentials, and more studies on other POC blood analyzers that are available for use in Canada such as HemoCue WBC, pocH – 100i and ABX – MicrosCRP200 are needed to have an accurate evaluation of the accuracy of three-part differentials. The extent to which the low agreement between POC three-part differentials and laboratory-based five-part differentials in monocyte counts affects clinical practice needs to be addressed. There were no evidence-based guidelines found regarding the use of three-part differentials CBC tests for patients presenting to emergency departments.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Title 42: Public health, part 493: Laboratory requirements, sub-section 493.941: Hematology (including routine hematology and coagulation). In: Electronic code of federal regulations [Internet]. Washington (DC): U.S. Government Publishing Office; 2016 Jul 22 [cited 2016 Jul 25]. Available from: http://www.ecfr.gov/cgi-bin/text-idx?SID=1248e3189da5e5f936e55315402bc38b&node=pt42.5.493&rgn=div5#se42.5.493_1941

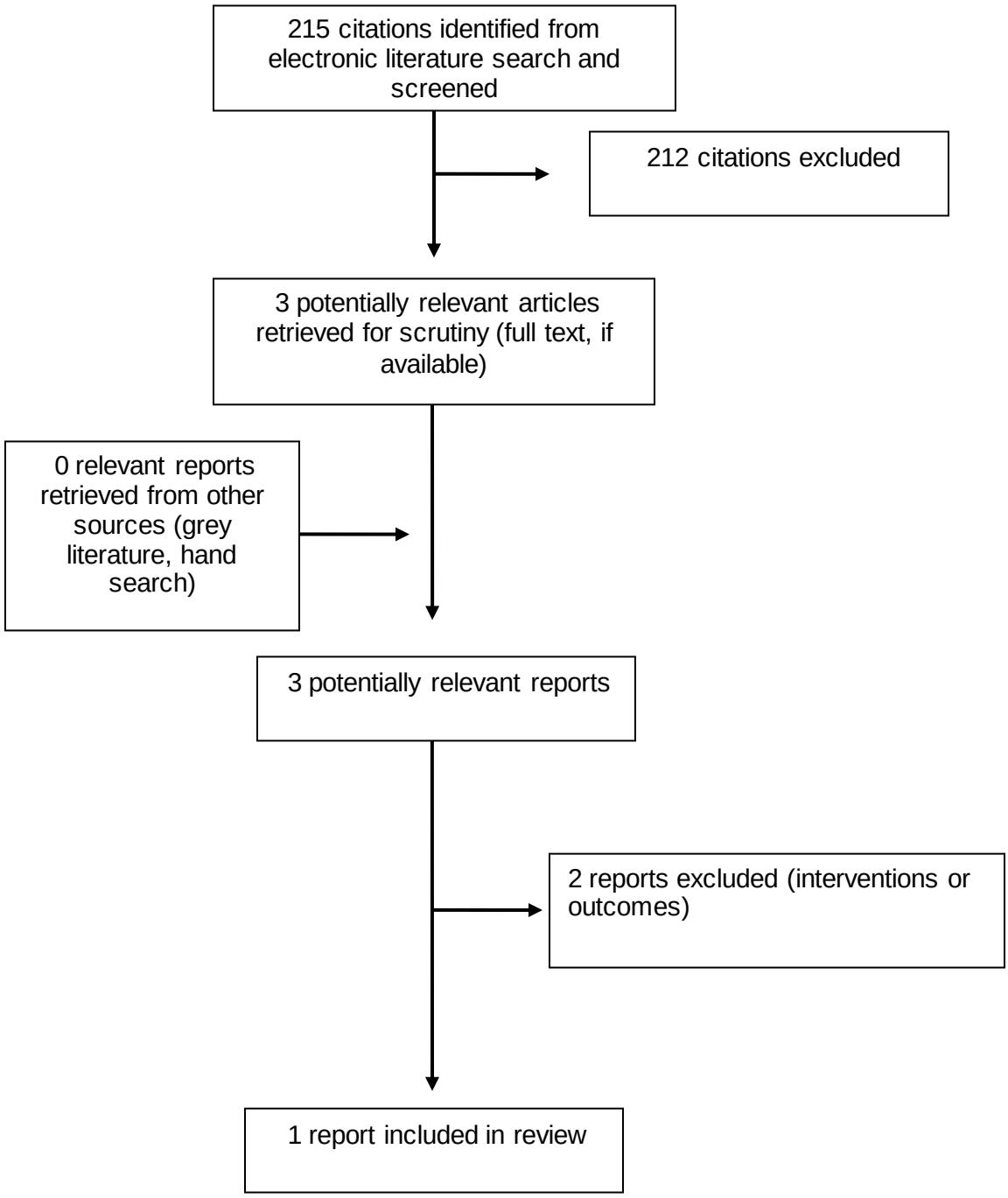
2. Point-of-care analyzers, coagulation; hematology; urine [Internet]. Plymouth Meeting (PA): ECRI Institute; 2015. (Healthcare Product Comparison System). [cited 2016 Jul 22]. Available from: https://www.ecri.org/ Subscription required.

3. Diagnostic technology: point-of-care test for total white blood cell count. Oxford (GB): Nuffield Department of Primary Care Health Sciences, University of Oxford; 2010.

4. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36.

5. Rao LV, Ekberg BA, Connor D, Jakubiak F, Vallaro GM, Snyder M. Evaluation of a new point of care automated complete blood count (CBC) analyzer in various clinical settings. Clin Chim Acta. 2008 Mar;389(1-2):120-5.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included studies

First author, Year, Country	Study Objectives	Interventions/ Comparators	Patients	Main Study Outcomes
Rao,[3] 2008, US, Denmark	*"We evaluated a new POC CBC analyzer Chempaq XBC (Chempaq A/S, Denmark) for hemoglobin, leukocyte counts and 3-part differentials and compared the results with established laboratory based Beckman Coulter LH750 analyzers"* (p 120)	POC CBC analyzer Chempaq XBC Beckman Coulter LH750 analyzers	Venous blood specimens from 420 in-patients from different clinical services (ER, primary care, Ob/Gyn, ICU, Pedi clinic, hematology-oncology clinics, and in-patient wards). Blood samples separated for low count level and high count level	Precision (CV) Accuracy (linear correlation)

CBC: complete blood count; ER: emergency room; ICU: intensive care unit; CV: correlation coefficient

Appendix 3: Summary of Critical Appraisal of Included Study

Table A2: Summary of Critical Appraisal of Included Study

First Author, Publication Year	Strengths	Limitations
Critical appraisal of included accuracy study (QUADAS [4])		
Rao,[5] 2008	• Spectrum of patients was representative of the patients who will receive the test in practice (routine blood samples from a hospital) • The time period between reference standard and index test mentioned • The execution of the index test described in sufficient detail to permit replication of the test	• Uninterpretable/indeterminate results not reported

Appendix 4: Main Study Findings and Authors' Conclusions

Table A3: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (comparative diagnostic accuracy of three-part versus five-part differentials complete blood cell count tests for patients presenting to the emergency department)		
Rao,[5] 2008	Precision (coefficient variation, CV) For low count blood sample Granulocytes: 14.7% Lymphocytes: 14.2% Monocytes: 13.8% For high count blood sample Granulocytes: 9.2% Lymphocytes: 12.7% Monocytes: 19.8% Linear correlation to laboratory-based results (r) (Data from diluted high count blood sample) Granulocytes: 0.95 Lymphocytes: 0.89 Monocytes: 0.32	*"…the precision parameters using both high and low patient samples showed acceptable variations within the allowable total errors defined by CLIA guidelines"* (p 122) *"Overall, there was a good correlation observed at all the locations between Chempaq XBC and Beckman Coulter LH750 analyzers, except for the monocytes"* (p 124) "*The Chempaq XBC analyzer provides accurate hematologic results that can facilitate rapid quantitative assessment of CBC parameters and thus is clinically relevant, especially in outreach clinic settings and in critically ill patients*" (p 120)
Research question 2 (comparative risk of performing a three-part versus a five-part differentials complete blood cell count test for patients presenting to the emergency department)		
Evidence from the diagnostic accuracy pointed to the risk of using POC Chempaq XBC to evaluate monocytosis and monocytopenia in the emergency room setting (this risk is applicable to all clinical settings evaluated in the study: emergency room, primary care, Ob/Gyn, ICU, Pedi Clinic, hematology/oncology clinics, and in-patient wards)		
Research question 3 (evidence-based guidelines regarding the use of three-part differentials CBC tests for patients presenting to emergency departments)		
There are no evidence-based guidelines found regarding the use of three-part differentials CBC tests for patients presenting to emergency departments.		