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Usefulness of Urinary Antigen Testing for Legionella in the Treatment of Community-Acquired Pneumonia: A Rapid Review

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Conflict of Interest Statement

All reports prepared by the Evidence Development and Standards branch at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Clinical questions are developed by the Evidence Development and Standards branch at Health Quality Ontario, in consultation with experts, end users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials and guidelines. Systematic reviews are evaluated using a rating scale developed for this purpose. If a systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies in the systematic review are retrieved and the GRADE criteria are applied to a maximum of 2 outcomes. Because rapid reviews are completed in very short time frames, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

About Health Quality Ontario Publications

To conduct its rapid reviews, Evidence Development and Standards and its research partners review the available scientific literature, making every effort to consider all relevant national and international research; collaborate with partners across relevant government branches; consult with expert advisory panels, clinical and other external experts, and developers of health technologies; and solicit any necessary supplemental information.

In addition, Evidence Development and Standards collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Disclaimer

This report was prepared by Health Quality Ontario or one of its research partners for the Ontario Health Technology Advisory Committee and was developed from analysis, interpretation, and comparison of scientific research. It also incorporates, when available, Ontario data and information provided by experts and applicants to Health Quality Ontario. It is possible that relevant scientific findings may have been reported since the completion of the review. This report is current to the date of the literature review specified in the methods section, if available. This analysis may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

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List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
CAP	Community-acquired pneumonia
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
SR	Systematic review

Background

As legislated in Ontario's *Excellent Care for All Act*, Health Quality Ontario's mandate includes the provision of objective, evidence-informed advice about health care funding mechanisms, incentives, and opportunities to improve quality and efficiency in the health care system. As part of its Quality-Based Funding (QBF) initiative, Health Quality Ontario works with multidisciplinary expert panels (composed of leading clinicians, scientists, and administrators) to develop evidence-based practice recommendations and define episodes of care for selected disease areas or procedures. Health Quality Ontario's recommendations are intended to inform the Ministry of Health and Long-Term Care's Health System Funding Strategy.

For more information on Health Quality Ontario's Quality-Based Funding initiative, visit www.hqontario.ca.

Objective of Analysis

This aim of this rapid review was to assess the sensitivity and specificity of urinary antigen testing for Legionella to determine its usefulness in treating patients with community-acquired pneumonia (CAP).

Clinical Need and Target Population

Legionella pneumophilia is a leading cause of CAP in both healthy and immunosuppressed individuals. (1) Early recognition of Legionella pneumonia can help prevent the development of more severe disease and even decrease mortality. (1)

Recently, new diagnostic and treatment strategies for Legionnaire's disease have been introduced, including commercially available urinary antigen tests, which can provide results in less than 15 minutes. (2) In Ontario, urinary antigen testing for Legionella is infrequently performed at present. An understanding of the characteristics of urinary antigen testing for Legionella is needed to better inform its possible use in patients with CAP.

Technology/Technique

Guidelines

International guidelines on the diagnosis and management of adults with CAP consistently recommend urinary antigen testing for Legionella (Table 1). However, the clinical usefulness of the test is often poorly defined, so while many guidelines agree that testing is beneficial, they do not all specify the situations in which testing should be performed. (3) As well, many guidelines do not cite the level of evidence on which they are basing their decisions.

Table 1: Urinary Antigen Testing for Legionella in Patients Hospitalized With CAP—Guideline Recommendations

Organization (Location)	Recommendation
CTS/CIDS (Canada) (4)	Testing should be part of the routine management of CAP
BTS (United Kingdom) (5)	Testing should be done in all patients with moderate- to high-severity CAP
IDSA/ATS (United States) (6)	Testing should be performed in all patients with severe CAP
SSID (Sweden) (7)	Testing is recommended
SWAB/NVALT (Netherlands) (8)	Testing should be performed in all patients with severe CAP
ERS/ESCMID (European) (9)	Testing should be performed in all patients hospitalized with CAP

Abbreviations: ATS, American Thoracic Society; BTS, British Thoracic Society; CAP, community-acquired pneumonia; CIDS, Canadian Infectious Disease Society; CTS, Canadian Thoracic Society; ERS, European Respiratory Society; ESCMID, European Society for Clinical Microbiology and Infectious Diseases; IDSA, Infectious Disease Society of America; NVALT, Dutch Association of Chest Physicians; SSID, Swedish Society of Infectious Disease; SWAB, Dutch Working Party on Antibiotic Policy.

Rapid Review

Research Question

What is the sensitivity and specificity of urinary antigen testing for Legionella in patients with CAP?

Research Methods

Literature Search

A literature search was performed on May 10, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EBM Reviews for studies published from January 1, 2003, until August 22, 2013. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 2003, and August 22, 2013
- health technology assessments, systematic reviews (SRs), and meta-analyses
- hospitalized adult patients with CAP
- studies where the sensitivity and specificity of the test could be extracted, either from exact reporting or from a combination of true positives, true negatives, false positives, and false negatives

Exclusion Criteria

- primary studies (randomized controlled trials, observational studies, case series, etc.)
- children (patients < 18 years)
- outpatients with CAP
- patients with hospital-acquired or ventilator-acquired pneumonia
- studies from which the outcomes of interest could not be extracted

Outcomes of Interest

- sensitivity
- specificity

Expert Panel

In April 2013, an Expert Advisory Panel on Episodes of Care for Pneumonia was struck. Members of the panel included physicians, nurses, allied health professionals, and personnel from the Ministry of Health and Long-Term Care.

The role of the Expert Advisory Panel on Episodes of Care for Pneumonia was to contextualize the evidence produced by Health Quality Ontario and provide advice on the appropriate clinical pathway for a patient with pneumonia in the Ontario health care setting. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of Expert Advisory Panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) tool was used to assess the methodological quality of SRs. (10)

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (11) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (11) For more detailed information, please refer to the latest series of GRADE articles. (11)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Rapid Review

The database search yielded 47 citations published between January 1, 2003, and August 22, 2013 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

One SR met the inclusion criteria. The SR by Shimada et al (2) captured 32 studies and conducted a meta-analysis to determine the sensitivity and specificity of urinary antigen testing for Legionella in patients with CAP. None of the studies reported on the severity of CAP in their populations. Characteristics of the included SR are summarized in Table 2.

Table 2: Summary of Included SR

Author, Year	Review Type	Search Dates	Inclusion Criteria	Number of Studies	AMSTAR Score
Shimada et al, 2009 (2)	SR	To August 2008	Studies where absolute numbers of true positive, false negative, true negative, and false positive observations could be obtained English-language only Studies with a reference standard	32	10

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

The SR rated the quality of the individual studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) method, which looks at the following domains: patient representativeness, selection criteria clarity, reference standard, duration between the test and the reference standard, consistency of verification, completeness of verification, blinding of reference, index test results, similarity to practice, uninterpretable tests, and withdrawals. Since the SR did not assess the level of evidence for the component studies using GRADE, details of the QUADAS scores were used to determine the GRADE level for both outcomes. Based on this information, the evidence base for both sensitivity and specificity was of low quality (Appendix 2).

Sensitivity

Table 3 shows the pooled sensitivity of urinary antigen testing for Legionella. The meta-analysis, however, showed considerable heterogeneity. A sensitivity analysis showed that 57% of the heterogeneity was due to the QUADAS scores of the individual studies; higher-quality studies were associated with significantly lower sensitivity.

Table 3: Sensitivity of Urinary Antigen Testing for Legionella

Number of Studies	Sensitivity (95% CI)	I^2 (Pooled)[a]	*P* (Pooled)[a]	I^2 (Control)[b]	*P* (Control)[b]
32	0.740 (0.680–0.810)	93.9%	< 0.005	86.8%	< 0.005

Abbreviations: CI, confidence interval; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.
[a]The I^2 and *P*-value for the pooled meta-analysis.
[b]The I^2 and *P*-value reported by Shimada et al (2) after the authors controlled for QUADAS scores.
Source: Shimada et al, 2009. (2)

Specificity

Specificity was much higher than sensitivity, but this result also showed very high heterogeneity. Unlike the results for sensitivity, however, stratifying by QUADAS score did not alter heterogeneity. Rather, 100% of the heterogeneity for specificity was found to be due to a single study; when this study was removed from the analysis, the I^2 dropped to 0.00% (Table 4).

Table 4: Specificity of Urinary Antigen Testing for Legionella

Number of Studies	Specificity (95% CI)	I^2 (Pooled)[a]	*P* (Pooled)[a]	I^2 (Control)[b]	*P* (Control)[b]
32	0.991 (0.984–0.997)	77.4%	< 0.005	0.00%	< 0.005

Abbreviations: CI, confidence interval; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.
[a]The I^2 and *P*-value for the pooled meta-analysis.
[b]The I^2 and *P*-value reported by Shimada et al (2) after the authors controlled for QUADAS scores.
Source: Shimada et al, 2009 (2)

Conclusions

On the basis of a SR evaluating the sensitivity and specificity of urinary antigen testing for Legionella in patients with CAP, the following conclusions were reached:

- Low quality evidence indicated that urinary antigen testing for Legionella had high specificity.
- Low quality evidence indicated that urinary antigen testing for Legionella had a lower sensitivity, especially when the quality of the individual studies was taken into account.

Acknowledgements

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HQO's Expert Advisory Panel on Evidence-Based Episode of Care for Pneumonias Presenting to Hospitals

Panel Members	Affiliation(s)	Appointment(s)
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Dr John Jordan	Byron Family Medical Centre Western University	Professor of Family Medicine
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Dr Warren Wilkins	Peterborough Regional Health Centre	Medical Director, Internal Medicine Program Acting Lead Hospitalist
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Antimicrobial Pharmacy Specialist		
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Registered Nurse Educator (Emergency)		
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Charge Respiratory Therapist		
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Physiotherapist		
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Decision Support and Case Costing Specialist		
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Appendices

Appendix 1: Literature Search Strategies

Search date: August 22, 2013
Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; All EBM Reviews (see below)

Q: Does using urine antigen testing at the time of hospital admission provide adequate sensitivity and specificity for the diagnosis of community-acquired pneumonia in adult patients?

Limits: 2003-current; English
Filters: Meta-analyses, systematic reviews, health technology assessments

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 2013, EBM Reviews - ACP Journal Club 1991 to July 2013, EBM Reviews - Database of Abstracts of Reviews of Effects 3rd Quarter 2013, EBM Reviews - Cochrane Central Register of Controlled Trials July 2013, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 3rd Quarter 2013, EBM Reviews - NHS Economic Evaluation Database 3rd Quarter 2013, Embase 1980 to 2013 Week 33, Ovid MEDLINE(R) 1946 to August Week 1 2013, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 19, 2013

Search Strategy:

#	Searches	Results
1	exp Pneumonia/	256534
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	306293
3	or/1-2	421291
4	exp Antigens, Bacterial/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	136991
5	exp bacterial antigen/ use emez	35923
6	or/4-5	172914
7	exp Urine/	159443
8	exp Urinalysis/	66487
9	or/7-8	221130
10	exp Antigens, Bacterial/ur use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	542
11	((urin* adj3 (antigen* or test* or detect* or assay* or result* or kit* or sample* or analy*)) or BinaxNOW or Binax or pleural antigen assay* or (rapid adj3 (diagnos* or test* or method* urin* or antigen*))).mp.	198454
12	(6 and 9) or 10 or 11	198861
13	3 and 12	5135
14	Meta Analysis.pt.	50408
15	Meta-Analysis/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Technology Assessment, Biomedical/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	59527
16	Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez	86601
17	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	390537
18	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	5080
19	or/14-18	444385
20	13 and 19	84
21	limit 20 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	78
22	limit 21 to yr="2003 -Current" [Limit not valid in DARE; records were retained]	72
23	remove duplicates from 22	50

Appendix 2: Evidence Quality Assessment

Table A1: AMSTAR Score of Included Systematic Review[a]

Author, Year	AMSTAR Score	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
Shimada et al, 2009 (2)	10	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews.
[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al. (10)

Table A2: GRADE Evidence Profile for Urinary Antigen Testing for Legionella in Patients With Community-Acquired Pneumonia

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Sensitivity							
32 (observational)	Very serious limitations (–2)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Specificity							
32 (observational)	Very serious limitations (–2)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[a]All studies were observational; there was no allocation concealment, blinding, or adequate sequence generation.

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