

PROPOSAL: INTRODUCTION OF A NEW TEST

SUMMARY

Test description: Legionella Urinary Antigen Test

Sample type(s): urine

Procedure: ELISA or immunochromatography

Accreditation warranted: no

Can be ordered by: specialists

Pricing: B800 x 0,030811 = 24,.65 €

Estimated number of tests/year: 4.500 tests (= 25% of 18.000 adult patients hospitalized with pneumonia {= 60% of 30.000 patients hospitalized with pneumonia, in order to exclude children})

Estimated evolution over the next five years: no evolution

Proposed B value: B800

Estimated total budget/year: 800 x 0.030811 x 4500 = 110.920 €

Estimated cost savings/year: see withdrawal of “Legionellae, detection of antibodies against”

Tests that become obsolete and can be withdrawn from reimbursement: “Legionellae, detection of antibodies against”

Expected impact of (new) concurrent test ordering: suppression of Legionellae serology, saving of 119.192 € per year > final saving = 8.273 €

Access for other disciplines: no

Year report (with positive result percentage) warranted: no (positive cases are registered by IPH = WIV/ISSP, total number can be obtained from RIZIV/INAMI)

Nederlandstalige omschrijving prestatie

Legionellae antigen, opsporen in urine

Diagnose regel: enkel bij patiënten ouder dan 18 jaar
Maximum 1 test per ziekenhuisverblijf

Franstalige omschrijving prestatie

Antigène de Legionellae, recherche dans les urines

Règle diagnostique : seulement chez les patients âgés de plus de 18 ans
Maximum 1 test par séjour hospitalier

CLINICAL/DIAGNOSTIC SCENARIO

The diagnosis of Legionella pneumophila infection remains very difficult:

- *Culture has a low sensitivity (<50% when golden standard is serology), is slow (turnaround-time 3-7 days) and often not possible (<50% of patients produce adequate sputum).*
- *Direct fluorescent antigen staining on LRT secretions has a sensitivity of 25-70%, but is technically demanding.*
- *Serology is not useful for acute diagnosis, as more than 3 weeks up to 10 weeks are needed for a seroconversion or 4-fold increase in titers, and this with a sensitivity of 60-80%. Single titer results can be misleading.*
- *Molecular techniques are promising, but more evaluation and standardisation are needed before introducing in routine clinical diagnosis.*

Mandell, Douglas and Bennett's Principles of Infectious Diseases 2005, p 2718: "Urine antigen testing has revolutionized the laboratory diagnosis of legionnaire's disease, making it the most commonly laboratory test ordered for diagnosis of this disease."

- *In addition, it should be underlined that the BAPCOC uses the Legionella urinary antigen test as "key structural component of effective antibiotic stewardship programs" in its surveys about maturity of the Belgian antibiotic management groups (Struelens and Costers, 2008).*

APPRAISAL

1) Analytical performance characteristics (analytical validation report)

1.1 *Preanalytical considerations (patient variables, sample stability)*

- *Biological variation detection from day 1 after onset of legionellosis, but more reliable from day 3*
- *Interferences none*
- *Patient variables better sensitivity in severe disease, in travel associated-cases > community-acquired; lower sensitivity in nosocomial cases*
- *Sample stability BINAX: 24 u at roomT°, 14 days at 2-8°C, longer if frozen; no interference with boric acid*
- *Sample type urine*
- *Sample volume < 1 ml (more if concentration technique is used)*
- *Prevalence 90 cases reported by sentinel-laboratories in 2006; estimation about 500 cases*
- *Target population severe pneumonia*

1.2 *Analytical considerations (reproducibility, accuracy, correlation, linearity, reference range)*

- *(Im)Precision:*
- *Accuracy (bias): false positive reaction in serum sickness*
- *Correlation with current method/ standard Sensitivity only accurately studied for Legionella pneumophila type I: 50-90%; no good data for other serotypes, even*

if the EIA claims all serotypes are detected, it seems not to be the case; for IC: the fabricant claims only for detection of type I, but some cross-reactions are described, but the sensitivity remains low. CAVE: some newer kits seems to perform badly (low sensitivity)

- Reproducibility (*within run, between run*) *no data, but seems to be very good*
- Reference range
- Analytical range/Linearity
- Turn around time (TAT) (*POCT feasible, necessary, ...*) *Immunochromatography: within minutes; EIA: within hours*

1.3 Quality issues

- *CTL (clinical tolerance limits)*
- *Procedures available*
- *Follow-up internal quality control yes*
- *Does external quality control exist? (WIV, commercial, ...) no, but should not be difficult to organize*

2) Diagnostic performance

2.1 Sensitivity, specificity

- *What was used as gold standard: culture-proven legionellosis*
- *Why is expected the test under investigation performing better than the existing gold standard (if there is one) Culture has a low sensitivity (<50% when golden standard is serology), is slow (turnaround-time 3-7 days) and often not possible to perform (<50% of patients produce adequate sputum and bronchoscopy is generally only done after therapy failure).*
- *Health impact of false-positives and false-negatives: wrong antibiotic therapy with risk of therapeutic failure*
- *Economic impact of false-positives and false-negatives: prolonged hospitalization, mortality*
- *Proportion of tests than can not be interpreted, (are inhibited) and their impact on health and cost <1 %*

2.2 Likelihood ratio's (LR)

2.3 NND (number needed to diagnose)

2.4 Other

- ROC-curves (other methods)
- Are other results needed tot interpret this lab test? *no*

3) Clinical impact

3.1 Diagnostic

- *Can other (non)-laboratory examinations be avoided by this test? Very limited: some retrospective serological tests asked by health inspectors could be avoided; culture should always be performed with high suspicion (with positive test to obtain isolates for epidemiological studies, with negative test, as a complement for false-negatives)*

- *Does the test supply additional or more accurate information, not provided by other (non)-laboratory examinations? Yes, rapid diagnosis*

3.2 Treatment

- *Does the test allow (faster) starting of adequate therapy (or can useless therapy be avoided)? yes*
- *Is there a better guidance of therapy by this test? in the Belgian policies, antibiotic coverage is only proposed for CAPIV, or after 3 days without improvement in CAP III*
- *Can toxicity be avoided? no*
- *Does conditional reimbursement of medication exist, based on test results? (eg. HSV and acyclovir)? no*

3.3 Health outcome

- *Can illness, complications, morbidity, mortality be prevented? yes, if no antibiotic coverage is given for legionellosis, a positive rapid test leads to adequate therapy*

3.4 Other

- *Are there epidemiological interests to perform this test? Outbreak monitoring? Yes; even in isolated cases, the Health inspector will initiate a source investigation, that potentially can avoid many cases*
- *Is the test still in research faze? no*

4) Organizational impact

4.1 Impact in the hospital

- *Length of stay, ... shortened*

4.2 Impact outside the hospital

- *Patient transportation (POCT, ...) no*

5) Cost impact: in and outside the laboratory

5.1 (Activity-Based) Cost/test (reagents, personnel, overhead (housing, QC, ...))

- *R&D cost if applicable (in-house testing) no*
- *How many reagent kits have been sold? ??*

5.2 Reimbursement

- *Can other tests be withdrawn? yes, "Legionellae, detection of antibodies against"*

5.3 Profit elsewhere in the hospital? no

6) Decision making

6.1 Impact on the clinical decision making process and patient management high

6.2 *Overexploitation/underutilization are both important issues: we can fear overprescription of the test, limiting diagnosis rules are needed; underutilisation is a real concern in the present situation of no reimbursment*

6.3 Incorporated in Clinical Practice Recommendations/Guidelines?

RELEVANT EVIDENCE/REFERENCES

1) Guidelines and Recommendations (most recent topics on top)

Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG; Infectious Diseases Society of America; American Thoracic Society. **Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults** *Clin Infect Dis*. 2007 Mar 1;44 Suppl 2:S27-72.

Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Verheij TJ; **European Respiratory Society; European Society of Clinical Microbiology and Infectious Diseases**. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J*. 2005 Dec;26(6):1138-80.

British Thoracic Society. BTS guidelines for the management of community-acquired pneumonia in adults – 2004 update.

The Infectious Diseases Advisory Board. Consensus-tekst: Initiële diagnostische en therapeutische benadering van CAP bij de immunocompetente volwassene. 2002-2003.

British Thoracic Society. BTS guidelines for the management of community-acquired pneumonia in children. *Thorax* 2002; 57: i1-i24.

American College of Emergency Physicians. Clinical policy for the management and risk stratification of community-acquired pneumonia in adults in the emergency department. *Ann Emerg Med* 2001; 38: 107-113.

Canadian Infectious Diseases Society and Canadian Thoracic Society. Mandell LA, Marrie TJ, Grossman RF, et al. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and Canadian Thoracic Society. *Clin Infect Dis* 2000; 31: 383-421.

2) Systematic Reviews and Meta-analyses

3) Reviews

Diederens BMW Op zoek naar nieuwe diagnostische mogelijkheden voor patiënten met de veteranenziekte. *Tijdschrift voor Infectieziekten* 2008, 3:36-39.

Richtlijn LCI dec 2007 met wijziging juni 2008. <http://www.rivm.nl/cib/infectieziekten-A-Z/infectieziekten/legionellose/index.jsp> 2003; 9: 175-80

Murdoch DR. Diagnosis of Legionella infection. *Clin Infect Dis*. 2003 Jan 1;36(1):64-9.

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Murdoch DR. Nucleic acid amplification test for diagnosis of pneumonia. *Clin Infect Dis* 2003; 36: 1162-1170.

File TM. Community-acquired pneumonia. *Lancet* 2003; 362: 1991-2001.

Andrews J, Nadjm B, Gant V and Shetty N. Community-acquired pneumonia. *Curr Opin Pulm Med* 2003; 9: 175-180.

Carroll KC. Laboratory diagnosis of lower respiratory tract infections: controversy and conundrums. *J Clin Microbiol* 2002; 40: 3115-3120.

Saubolle MA and McKellar PP. Laboratory diagnosis of community-acquired lower respiratory tract infection. *Infect Dis Clin North Am* 2001; 15: 1025-1045.

Skerrett SJ. Diagnostic testing for community-acquired pneumonia. *Clin Chest Med* 1999; 20: 531-548.

Plouffe JF, McNally C, File TM. Value of noninvasive studies in community-acquired pneumonia. *Infect Dis Clin North Am* 1998; 12: 689-699

Stout JE, Yu VL. Legionellosis. *N Engl J Med* 1997;337:682-7

4) Original Articles

VOORSTEL WERKGROEP MICROBIOLOGIE/COMMISSIE KLINISCHE BIOLOGIE
LEGIONELLA ANTIGEN DETECTION (12/2009)

Helbig JH, Uldum, SA, Bernander, S, et al. Clinical utility of urinary antigen detection for diagnosis of community-acquired, travel-associated, and nosocomial legionnaires' disease. *J Clin Microbiol* **2003**; 41:838.

Trends in legionnaires disease, 1980-1998: declining mortality and new patterns of diagnosis. Benin AL; Benson RF; Besser RE *Clin Infect Dis* **2002** Nov 1;35(9):1039-46. Epub 2002 Oct 14.

Deforges L, Legrand P, Tankovic J, Brun-Buisson C, Lang P, Soussy CJ. Case of false-positive results of the urinary antigen test for *Legionella pneumophila*. *Clin Infect Dis*. **1999** Oct;29(4):953-4.

A recurrent outbreak of nosocomial legionnaires' disease detected by urinary antigen testing: evidence for long-term colonization of a hospital plumbing system Lepine LA; Jernigan DB; Butler JC; Pruckler JM; Benson RF; Kim G; Hadler JL; Carter ML; Fields BS *Infect Control Hosp Epidemiol* **1998** Dec;19(12):905-10

Dirven K, Ieven M, Peeters MF, van der Zee A, De Schrijver K, Goossens H. Comparison of three *Legionella* urinary antigen assays during an outbreak of legionellosis in Belgium. *J Med Microbiol*. 2005 Dec;54(Pt 12):1213-6.

Struelens MJ, Costers M. Hospital antibiotic management in Belgium – results of the ABS maturity survey of the ABS International group. *Wien Klin. Wochenschr* 2008; 10:284-288.

5) Reference Works, Handbooks and Databases

Isenberg H. *Clinical Microbiology Procedures Handbook*, 2nd edition, ASM:see section 3.11.4 RIVM

Murray P. *Manual of Clinical Microbiology*, ASM, **2007**

Mandell. *Principles and Practice of Infectious Diseases*. 6th Edition
(<http://www.ppidonline.com>)

Uptodate (online). Diagnostic approach to the patient with community-acquired pneumonia

6) Posters, “grey literature”, presentations

Evaluation of the Uni-Gold™ *Legionella* Urinary Antigen Test, a new immunochromatographic test in comparison with the Binax NOW test Abstract number: P1381 ESCMID **2008** Freydiere A.M., Lagrange N., Vandenesch F., Etienne J., Jarraud S.

Significance of the *Legionella* Urinary Antigen Test during an Outbreak. *WEVER PC, KUIJPER EJ, YZERMAN EP, SPEELMAN P, DANKERT J, VAN KETEL RJ; Interscience Conference on Antimicrobial Agents and Chemotherapy. *Abstr Intersci Conf Antimicrob Agents Chemother Intersci Conf Antimicrob Agents Chemother*. **1999** Sep 26-29; 39: 195 abstract no. 226