

PROPOSAL: TEST WITHDRAWAL

SUMMARY

Test description: Yersinia, detection of antibodies against, (Maximum 2)(Cumulregel 326) B80

Cumulregel 326: Serologie bacteriën: maximaal mogen 5 nummers aangerekend worden. Sommige nummers mogen meermaals worden aangerekend (zoveel maal als er verschillende antigenen worden gebruikt) voor zover het totale aantal van 5 niet overschreden wordt”

Sample type(s): serum

Procedure: Agglutination assays, enzyme-linked immunosorbent assays (ELISA) and immunoblotting techniques.

Can be ordered by: primary care physician and specialists

Estimated number of tests/year: 20.890 in 2008

Estimated total budget/year: 51.491 € in 2008

Estimated cost savings/year: 51.491 € annually

Expected impact of (new) concurrent test ordering: None to possibly a very slight increase in cultures (blood, faeces, fluids,...).

Nederlandstalige omschrijving voorstel

Schrap 551095 en 551106 Yersinia, opsporen van antilichamen tegen

Franstalige omschrijving voorstel

Biffez 551095 et 551106 Yersinia, recherche des anticorps

CLINICAL/DIAGNOSTIC SCENARIO

The genus *Yersinia* comprises 3 species that cause human pathology: *Yersinia enterocolitica*, *Yersinia pseudotuberculosis* and *Yersinia pestis*. Human infection with *Yersinia spp.* has become rare in Belgium (494 cases in 2004).

Pigs are the main animal reservoir and infection occurs through ingestion of contaminated food, milk or water. Feco-oral-transmission and blood transfusion are the main routes of transmission. Yersiniosis can be divided in an acute stadium (gastro-intestinal complaints, in rare cases sepsis) and a secondary stadium. The latter are immune mediated sequelae: reactive arthritis, erythema nodosum, Reiter's syndrome, glomerulonephritis and myocarditis.

1. Diagnosis of *Yersinia* infections (reference laboratories of UCL and KULeuven)

Consensus guidelines on the diagnosis of *Yersinia* infections do not exist. Diagnostic possibilities are: 1) Microbiological culture (mainly faecal samples) and 2) Antibody testing.

1. Microbiological culture

Different representative sample types can be cultured: peritoneal-, wound-, pleural fluid, abscesses, faeces,... When faeces are cultured, *Yersinia* specific media are systematically inoculated. In cultures positive for *Yersinia*, colonies will usually be serologically confirmed using agglutination techniques for serotypes O:3 and O:9 (the only pathogenic serotypes in Belgium).

2. Antibody detection

There several available techniques for *Yersinia* specific antibody detection: agglutination assays, ELISA, Immunoblotting, fluorescence techniques, complement fixation and radio-immuno assays (RIA).

Commercially available in Belgium:

Agglutination assays: Bio-Rad

ELISA: Viramed Labor Diagnostika (IgA-IgG), Mikrogen (recomWell *Yersinia* IgA-IgM-IgG, recomLine *Yersinia* IgA(IgM)-IgG), Dako (*Yersinia enterocolitica* O:3)

Immunoblotting: Mikrogen (recomBlot *Yersinia* IgM/IgA-IgG), Autoimmun Diagnostika GMBH (IgA-IgG)

2. Diagnostic value of *Yersinia* spp. antibody detection

2.1 Acute Phase Yersiniosis

There are no evidence based guidelines concerning this matter. Available information is based on "expert opinion".

Culture of faeces or other relevant specimens is the gold standard. Serology has the disadvantage that antibody titers are detectable only after a few days to one week. A maximum titer is usually achieved after 2 weeks.

- **CDC-guidelines** on the isolation of *Y. enterocolitica* and *Y. pseudotuberculosis* in food borne infections:

Culture of stool or vomitus should be done in the first place. Serology is less useful and available in reference laboratories (US situation).

- **Guidelines Bottone et al.**

Serology is not useful in the diagnosis of gastro-enteritis of mesenteric adenitis. Elevated titers were detectable in patients with extra-intestinal complaints. Serology has an epidemiological value in outbreaks, since sensitivity and specificity of elevated monospecific titers are high.

2.2 Late phase Yersiniosis

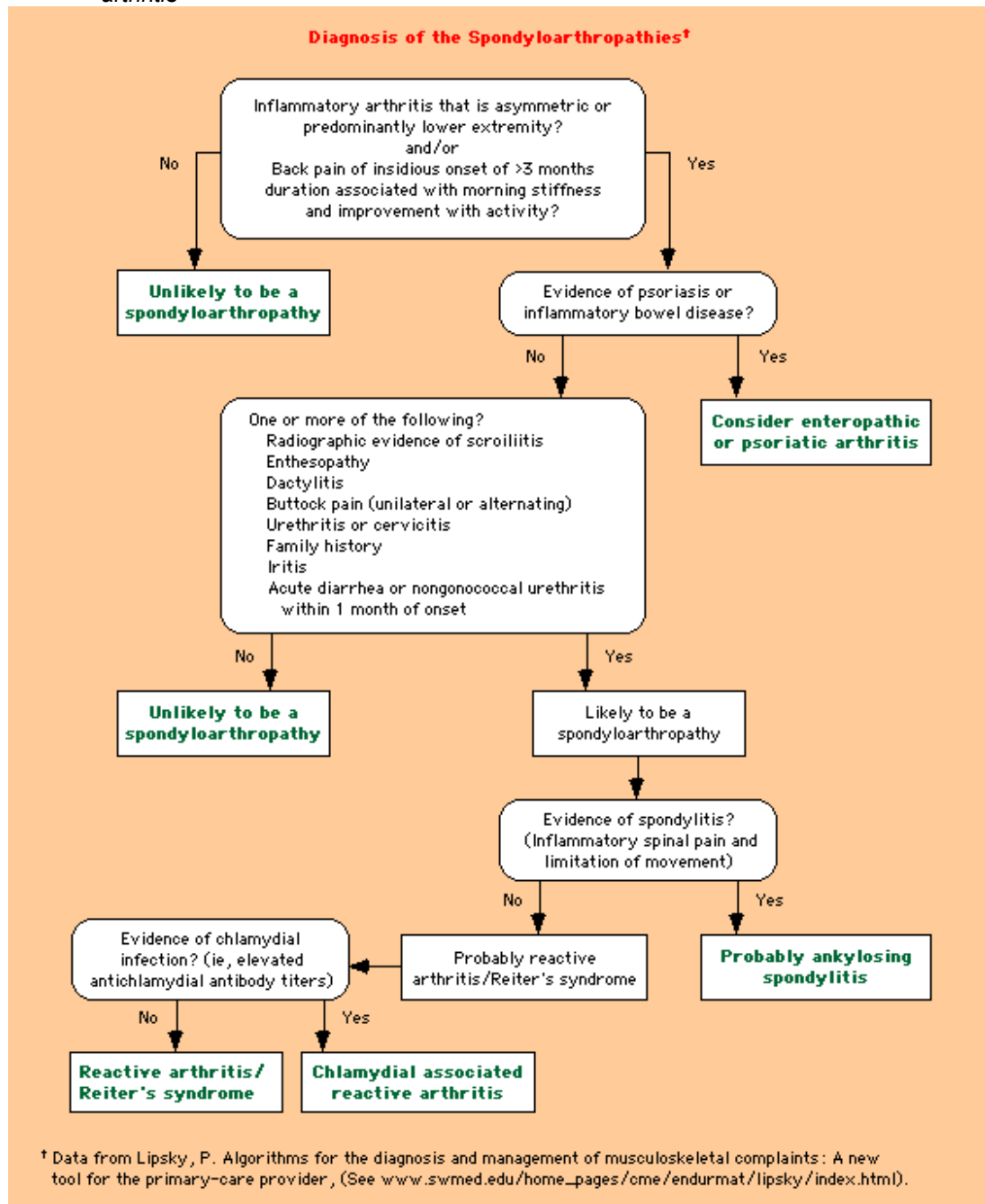
There are no evidence based guidelines concerning this matter. Available information is based on "expert opinion".

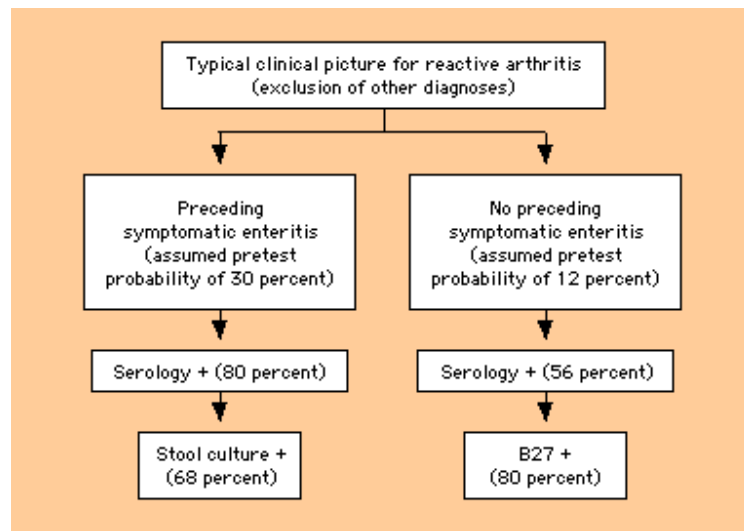
Stool culture is less useful in the secondary phase. Gastrointestinal complaints are usually not present. Culture is only useful if late phase symptoms are preceded by a gastro-enteritis or if the symptoms are still present. (review 11, original 46).

Culture or *Yersinia* specific PCR on synovial fluid is not useful. *Yersinia* bacilli do not penetrate the joint itself (they settle in the gut-associated lymphoid tissue (GALT)). In only one case, *Yersinia* DNA could be demonstrated in the joint (original 42).

Secondary sequelae are the main indication for the detection of *Yersinia* antibodies. This is supported by many experts (review 11, letter 8, originals 3,5,8,10,22,23,34,38,). Sieper et al. use the antibody titer in their algorithmic approach to the clinical diagnosis of reactive arthritis (figure 1):

Figure 1: algorithmic approach to the clinical diagnosis of spondyloarthropathies and reactive arthritis





Algorithmic approach to the clinical diagnosis of reactive arthritis The figure presents an algorithmic approach to the diagnosis of reactive arthritis based upon symptoms of enteritis and the results of serologic testing, stool cultures, and HLA-B27 testing. Reproduced with permission from: Sieper, J, Rudwaleit, M, Braun, J, van der, Heijde D. Diagnosing reactive arthritis: role of clinical setting in the value of serologic and microbiologic assays. *Arthritis Rheum* 2002; 46:319. Copyright ©2002 American College of Rheumatology. With permission of John Wiley & Sons Inc.

Sieper et al. also underscore in their study the importance of pre- and post-test probability. In the table below (table 1) they have calculated the post-test probability for a given pre-test probability. Serological tests used were ELISA directed against lipopolycaccharides (LPS) and Western Blot directed against *Yersinia* outer membrane proteins (Yops). Both tests have a sensitivity and specificity of 90%.

A clear association between HLA B27 and reactive arthritis (ReA) has been described. In this study, a sensitivity of 50% and a specificity of 85% for the HLA B27 test was used to calculate post-test probability (pre-test probability 40%).

Table 1. Pos-test probability of different diagnostic tests for Reactive Arthritis

Symptoms + diagnostics	Pretest prob. [%]	Sensitivity [%]	Specificity [%]	Posttest prob. + res.	Posttest prob. - res.
arthritis suggestive for ReA AND preceded by infectious symptoms & antibody detection	30	90	90	80	5
arthritis suggestive for ReA AND NOT preceded by infectious symptoms & antibody detection	12	90	90	55	2
Any arthritis/arthritis	1	90	90	8	21
arthritis suggestive for ReA & HLA B27-testing	40	50	85	69	28
arthritis suggestive for ReA AND NOT preceded by infectious symptoms AND positive antibody test & HLA B27-testing	55	50	85	80	42

Sieper et al. conclude that serology is **NOT USEFUL** in the absence of typical ReA symptoms and if other possible causes have not been excluded (too low pre-test probability). No single test has a post-test probability that is high enough to establish the diagnosis of ReA. Combination of different tests and good clinical investigation can raise the post test probability.

APPRAISAL

1. Analytical performance characteristics (analytical validation report) of serological tests

1.1. Preanalytical considerations (patient variables, sample stability)

- **Biological variation**

No data

- **Patient variables:** Childhood, malnutrition and immune suppression are factors that can impair antibody production (Bottone et al., guideline 1)

- **Interferences:**

- **Agglutination tests (Bottone et al., guidelines 1)**

- Prozone phenomenon
- Poor antigen stability can result in false negative reactions
- Cross reaction with *Brucella spp.*, *Salmonella spp.*, *Morganella spp.*, *Escherichia coli*, ... => Low specificity

- **ELISA**

- Cross reactivity with *Brucella spp.* (Benoit et al., original 32)

- **Immunoblot**

- Possible cross reactivity with *Borrelia spp.* (Rawlins et al, original 48)

- **Sample stability:** Store samples at 2 to 8 °C (no official guidelines)

- **Sample type:** Serum

- **Sample volume:** minimum 100 µl (agglutination test)

- **Prevalence:** (estimation of amount of positive test percentage): Depending on the technique used and on the cut-off value

- **Target population**

No data

1.2 Analytical considerations

- (Im)Precision

No data

- Accuracy (bias)

No data

- Correlation with current method/standard

For a comparison between different serological methods, cfr. 2.1 and 2.2 sensitivity and specificity.

- Reproducibility (within run, between run)

No data

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YERSINIAE ANTIBODY DETECTION (12/2009)

- Reference range

1. Agglutination tests:

Large variation in cut-off values according to different studies. Borg et al. (review 2), Hoogkamp-Korstanje et al. (original 31), Cafferkey et al. (original 17), Gripenberg et al. (original 6), Stolk-Engelaar et al. (original 33),... use a cut-off $\geq 1/160$. Fendler et al. (original 46) use 1/320. Stojek et al. A titer of 1/20(original 41), Larsen et al. (original 14) 1/80 and Shenkman et al. (original 1) 1/8. Every significant change in titer on paired sera is believed to be diagnostic.

2. ELISA

Positive reaction: at least 2 standard deviations (SD) above the mean of a healthy control population for IgG AND IgA or IgM. Fendler et al. (original 27) used a cut-off of 3 SD to raise specificity, but sensitivity dropped with 30%.

3. Immunoblot

According to the manufacturers instructions.

4. Fluorescence

A fluorescent signal can be called serotype specific if a dilution of at least 1/240 is still positive. At lower lower dilutions, slight cross-reaction with other serotypes is observed.

- Analytical range/Linearity

No data

- TAT

UZLeuven: the (agglutination) test is performed once weekly (Friday). After dilution and incubation, the titers are read on Monday (theoretically, 48 h incubation is enough). For EIISA and immunoblotting techniques, TAT vary from several hours to overnight.

1.3 Quality issues

- CTL (clinical tolerance limits)

No data

- Procedures available

No data

- Follow-up internal quality control

No data

- Does external quality control exist?

No data

2. Diagnostic performance of serological tests

2.1 Sensitivity, specificity

Comparison of different antibody tests as a tool for the diagnosis of *Yersinia* induced ReA is not easy for many reasons:

- There are no exact criteria for the diagnosis of *Yersinia* induced ReA.
- Different methods are compared.
- Homemade test are often used in different studies.
- (Agglutination) assays are prone to false negative and false positive results.

In table 3 some examples are shown of studies that report on sensitivity and specificity of different serological assays. In most studies ELISA and blot techniques show better performance characteristics than agglutination assays: Benoit et al. (original 32), Gripenberg et al. (original 6), Chatzipanagiotou et al. (original 45), De Koning et al. (original 21), Fendler et al. (original 46) Hoogkamp-Korstanje et al. (original 31),...

2.1 Likelihood ratio's (LR): no data

2.2 NND (number needed to diagnose): no data

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YERSINIAE ANTIBODY DETECTION (12/2009)

	Population	Sensitivity (%)						Specificity (%)					
		Culture	Agglutination	ELISA	blot	IF	CF	Culture	Agglutination	ELISA	blot	IF	CF
Hoogkamp-Korstanje et al. (Ref. 16)	125 children with Yersiniosis (acute-chronic)	80 (97 bij enteritis)	24		98	85							
Fendler et al. (Ref. 27)	20 patients with <i>Yersinia</i> ReA		20	90					95				
Mäki-Ikola et al. (Ref. 45)	43 culture positive			93 (o.b.v Yops-LPS)									
Rawlins et al. (Ref. 47)	19 blot + en 21 blot -			95			26		82				95
Hoogkamp-Korstanje et al. (Ref. 15)	10 patients with chronic Yersiniosis	30	10		100	100							
Hoogkamp-Korstanje et al. (Ref. 48)	355 patients: 215 culture + en 140 culture -		18		83	94		29		82	93		

Table 2: (Some) examples of studies that report on sensitivity and specificity of different serological assays

3. Clinical impact

3.1 Diagnostic

- **Can other (non) –laboratory examinations be avoided by this test?**

NO

The result of an antibody test alone can not be used as a diagnostic tool, since there are no consensus guidelines on the diagnosis of *Yersinia* induced sequelae.

3.2 Treatment/prognosis

- Does the test allow (faster) starting of adequate therapy (or can useless therapy be avoided)?

NO

Several authors have investigated the impact of early antibiotic treatment (original 24, 30, 35). None of them could demonstrate a beneficial effect of (early) antibiotic treatment. Hoogkamp-Korstanje et al. (original 44) found a faster remission and a positive influence on complaints of pain of 2 x 500 mg ciprofloxacin therapy. Their hypothesis is that ciprofloxacin interferes with antibody production (only production of YopD antibodies, less YopH and no YopM antibodies). Whether this explains the impact on the complaints remains to be proven. On the other hand, early antibiotic treatment can result in over consumption of antibiotics.

- Is there a better guidance of therapy by this test?

NO

Is follow-up of antibody-titer indicated?

Available information is mainly based on expert opinion. *Yersinia*-specific IgG and IgA are generally present for 3 months and disappear after approximately 6 months. IgG can persist for several years. Persistence of IgA (mainly anti-YopD IgA) can indicate chronic Yersiniosis. This persistence is based on a chronic stimulation of GALT by *Yersinia* antigens.

Ganfors et al. (letter 2) investigated the persistence of IgA in ReA patients. They found persistence after 6 months of 80% in a group of 56 patients with ReA (39% in control group of 36 patients). Analysis after 1 year showed persistence of 85% (39 patients) versus 32% in the control group (22 patients).

Herlinger et al. (original 28) did a long term (mean: 10.7 years) follow-up of 22 patients after acute *Yersinia* arthritis. They concluded in their paper that there was no association between the persistence of IgA and/or IgG antibodies and prognosis of the disease.

- Can toxicity be avoided?

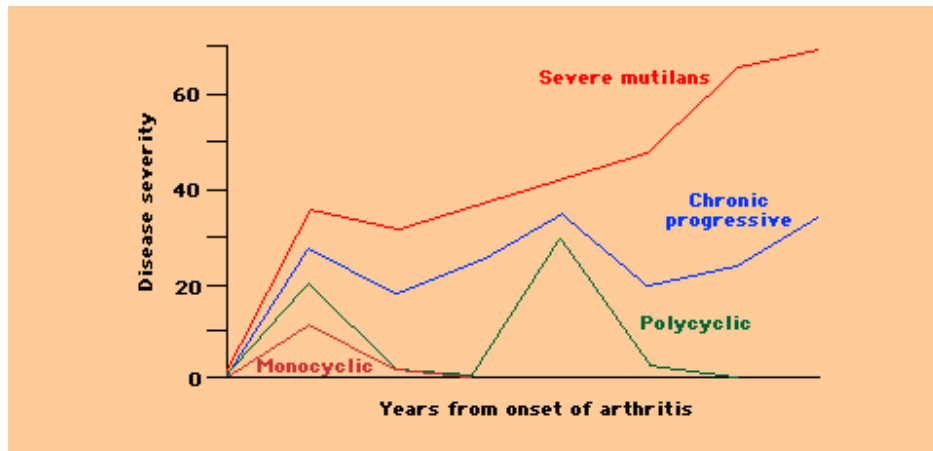
NO

On the contrary, risk of toxicity from antibiotics.

GENERAL REMARK:

Correct diagnosis of ReA (with *Yersinia* as a possible causative agent) can lead to less aggressive therapies that are used to treat other forms of spondyloarthropathies (SpA). The prognosis of ReA is generally good (figure 2)

Figure 2: Prognosis of reactive arthritis



Course of Reiter's syndrome Schematic representation of the four clinical patterns in Reiter's syndrome: monocyclic, in which the attack is self-limiting (usually less than six months) and never recurs (35 percent of cases); polycyclic, which is characterized by initial remission with intermittent recurrences (35 percent); chronic progressive, in which the initial attack never subsides completely and continues with a waxing and waning course (25 percent); and severe mutilans, in which severe inflammatory disease persists for many years and may even progress to destructive arthritis in multiple joints (five percent). Courtesy of Craig Wiesenhutter, MD.

- Does conditional reimbursement of medication exist, based on test results?
NO

3.3. Health outcome

- Can illness, complications, morbidity, mortality be prevented?

No data

3.4 Other

- Are there epidemiological interests to perform this test? Outbreak monitoring?

The sensitivity, specificity and positive predictive value of a raised titer of a monospecific antibody is high in an "outbreak setting" (cfr. Pre-test probability). Serology can have an epidemiological value (Bottone et al, guideline 1)

- Is the test still in research phase?
NO

4. Organizational impact

4.1. Impact in the hospital?

- Length of stay... NO

4.2 Impact outside the hospital

- Patient transportation (POCT,...) NO

5. Cost impacts: in and outside the laboratory

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

Agglutination test: (UZ Leuven data):

Total cost of €6.53/test.

Immunoblot:

According to “diagnostisch kompas” (The Netherlands): €38.80/test

5.2 Reimbursement

- Can other tests be withdrawn?
NO

5.3 Profit elsewhere in the hospital

NO

6. Decision making

6.1 Impact on the clinical decision making process and patient management?
NO

6.2 Overexploitation: YES/underutilization: NO

6.3 Incorporated in Clinical Practice Recommendations/Guidelines? Yes, cfr. Sieper et al. (figure 1).

Yersinia antibody detection: conclusions

- Antibody detection is **NOT USEFUL** in the acute phase of a *Yersinia* infection
- For the diagnosis of secondary sequelae of a *Yersinia* infection, especially reactive arthritis, there is an added value to the detection *Yersinia* specific antibodies. Nevertheless, there are no evidence based guidelines concerning this matter and pre-test probability is a very important issue. There is neither a proven impact on therapy and prognosis.
- ELISA and Immunoblot are the preferred techniques, because of better performance characteristics

Because of the unclear diagnostic value of antibody testing, the fluctuating quality of the assays and the difficult interpretation of the different tests, a withdrawal of reimbursement of antibody testing is proposed. Further testing may be done in a “reference laboratory setting”.

RELEVANT EVIDENCE/REFERENCES

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