

PROPOSAL: TEST WITHDRAWAL

SUMMARY

Test description: Salmonellae, detection of antibodies against, (Maximum 4)
(Cumulregel 326)

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”

B80

Sample type(s): serum

Procedure: Slide and tube techniques with Salmonella (antigen) suspensions (ELISA), immunoblotting techniques, countercurrent immunoelectrophoresis

Can be ordered by: primary care physician and specialists

Estimated number of tests/year: 16.829 in 2008

Estimated total budget/year: 41.481 € in 2008

Estimated cost savings/year: 41.481 € annually

Expected impact of (new) concurrent test ordering: None

Nederlandstalige omschrijving voorstel

Schrap 551051 en 551062 Salmonellae, opsporen van antilichamen tegen

Franstalige omschrijving voorstel

Biffez 551051 et 551062 Salmonellae, recherche des anticorps

CLINICAL/DIAGNOSTIC SCENARIO

1. Diagnose van (para)tyfus

When facilities for culturing or antigen testing are not available, the Widal test if performed reliably and interpreted with care (with clinical findings), can be of value in diagnosing typhoid and paratyphoid (enteric fever) in endemic areas.

The value of the Widal test in diagnosing enteric fever in endemic areas remains controversial. It is of no value in the investigation of Salmonella food-poisoning. (2)

Quand à la sérologie, elle est souvent négative. Les anticorps anti-H sont sans valeur diagnostique. Les anticorps anti-O s'élèvent à 15 jours d'intervalle chez seulement 25 à 50 % des malades, même non traités. De plus, des faux positifs sont possibles notamment en cas de vaccination préalable ou au cours de nombreuses maladies fébriles, notamment dues à d'autres bacilles Gram négatifs. (3)

The Widal test, which measures agglutinating antibodies to the O and H antigens of Salmonella serotype Typhi, produces false-negative and false-positive reactions and does not provide a definitive diagnosis of individual cases of infection.

Two other rapid serodiagnostic tests have proved more useful than the Widal test for the serodiagnosis of typhoid fever:

Evaluation of rapid diagnostic tests for typhoid fever, J. Clin. Microb. 2004;42:1885-1889
Tubex; IDL Biotech, Sollentuna, Sweden

Typhidot; Malaysian Biodiagnostic Research SDN BHD, Kuala Lumpur, Malaysia (14)

Laboratorium diagnose van buiktyfus vereist isolatie en identificatie van *Salmonella enterica* serotype Typhi. De mogelijkheden van de laboratoria in de endemische gebieden zijn echter beperkt. Recente vooruitgang in de moleculaire immunologie hebben gezorgd voor gevoelige en specifieke merkers voor buiktyfus en de technologie om gemakkelijke en goedkope kits voor de snelle detectie te maken. 3 commerciële kits voor serologische diagnose van buiktyfus werden vergeleken. Patiënten met ≥ 4 dagen koorts werden ingeschreven in 2 ziekenhuizen in Zuid-Vietnam. Positieve gevallen waren patiënten met serotype Typhi geïsoleerd uit bloedstalen en controle gevallen waren patiënten met andere labo bevestigde ziekte (TBC, Dengue, malaria, andere bacteriële pathogenen). Multi-Test Dip-S-Ticks, TyphiDot (dot EIA) en TUBEX (agglutinatie, latex) op, respectievelijk, immunoglobulin G (IgG), IgG en IgM, IgM. De bijsluiters instructies werden gevolgd bij de analyses. Er werden 59 patiënten en 21 controles getest. De sensitiviteit en specificiteit waren 89 en 53 % voor de Multi-Test Dip-S-Ticks, 79 en 89 % voor de TyphiDot, 78 en 89 voor TUBEX, 64 en 76% voor Widal getest in ziekenhuizen en 61 en 100% voor Widal testen in het Pasteur Instituut. Voor alle assays was de sensitiviteit het hoogste gedurende de tweede week van ziekte. **De Widal test was ongevoelig en vertoonde interrun variabiliteit (deze kon echter niet getest worden voor de andere kits). Twee snelle kits, Typhidot en TUBEX vertoonde belovende resultaten. (kostprijs: Widal 0,5 US dollar/specimen, TUBEX 4 US dollar/spec., Typhidot 2.14 US dollar/specimen) (17)**

Meer dan 100 jaar na de introductie van de Widal test voor de diagnose van buiktyfus, is er nog steeds controverse over de test. Met de tijd is het meer en meer duidelijk geworden dat bacteriële agglutinatiesystemen (vooral Widal), hoewel ze heel simpel uit te voeren zijn, vaak resulteren in misleidende informatie omdat de antigenen betrokken polyvalent van aard zijn. In de bacteriële wereld zijn kruisreagerende antigenen sterk verspreid. **De sensitiviteit en specificiteit van bacteriële agglutinatie is niet voldoende om gebruikt te worden in serologische analyses bij mensen.** Volgende argumenten worden aangehaald om aan te geven dat Widal geen betrouwbaar diagnostisch resultaat kan geven in endemische regio's:

Inherente variabiliteit van de test

Moeilijkheden om een basistiter vast te leggen voor een populatie

Herhaalde blootstelling aan *S. typhi* in endemische regio's

**Kruisreactiviteit met andere niet-Salmonella organismen
Gebrekkige reproduceerbaarheid**

(18)

Single serologic tests, such as the Widal test, are of limited clinical utility in acutely ill patients because positive results may represent previous infection in endemic areas. In a study of healthy blood donors performed in central India, seropositivity for typhoid fever using the S. typhi O antigen or S. typhi H antigen was present in 8 and 14 percent, respectively. (9)

The Widal test has been used to detect anti-S.typhi antibodies for more than 100 years, but its role in the diagnosis of typhoid fever is limited.

A number of other assays have been used to detect antibodies against S. typhi antigens or circulating antigens themselves. They include an ELISA using a cell envelope antigen or lipopolysaccharide of S. typhi or purified Vi antigen.

Counter-current immunoelectrophoresis has been used to detect S. typhi antigens in blood or urine, but a lack of sensitivity and specificity has limited their use. (10)

Besluit: weinig of geen waarde in diagnose van (para)tyfus voor klassieke WIDAL, iets betere resultaten met Typhidot en Tubex in endemisch gebied.

2. Diagnose van reactieve arthritis?

The term reactive arthritis was introduced in 1969 as "an arthritis which developed soon after or during an infection elsewhere in the body, but in which the microorganisms cannot be recovered from the joint" [1]. In the most restricted sense, reactive arthritis has been used to refer to the triad of postinfectious arthritis, urethritis, and conjunctivitis, formerly called Reiter syndrome [2,3]...

Strictly speaking, reactive arthritis is still an evolving concept rather than an entity with validated diagnostic, or even classification, criteria.

Based upon the literature and on a 1999 consensus opinion derived from 34 specialists in the field of reactive arthritis and spondyloarthritis [5], the following parameters can be considered as being useful in identifying patients with reactive arthritis:

- Causative pathogens — The classical pathogens for reactive arthritis are: Chlamydia trachomatis, Yersinia, Salmonella, Shigella and Campylobacter, and perhaps Clostridium difficile and Chlamydia pneumoniae.
- Interval between preceding symptomatic infection and onset of arthritis — There should be a minimum of several days and maximum of several weeks between the preceding symptomatic infection and onset of arthritis.
- Typical arthritis pattern — The typical arthritis pattern is an asymmetrical mono- or oligo-arthritis, predominantly of the lower extremities.
- Distinguishing between acute and chronic reactive arthritis — Reactive arthritis of more than six months duration is regarded as being chronic instead of acute.

Reactive arthritis is an uncommon disease. The prevalence is estimated to be 30 to 40 per 100 000 adults, and the annual incidence from 5 to 28 per 100 000.

Infections can be identified in about 50% of patients diagnosed as possible or probable reactive arthritis by experts in this disorder when the presence of enteric and genitourinary pathogens or prior infection are sought using culture techniques or serologic studies.

Stool cultures — Stool cultures for a triggering pathogen are suggested even in the absence of gastrointestinal symptoms.

Screening for Chlamydia trachomatis — Chlamydia trachomatis infections are often asymptomatic. Tests based on DNA amplification, such as the ligase reaction, are rapid, non-invasive, and specific. They require only a urine sample.

Serologic testing — Infections by Yersinia, Salmonella, Campylobacter and Chlamydia cause strong antibody responses. Serological techniques have been used in epidemiologic studies to test for preceding infections [4,13]. However, in communities where these infections are endemic,

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and many times are clinically silent, serological testing will not be specific for recent episodes. There are as yet no internationally validated standard serological techniques or thresholds for antibody titers that can be recommended for diagnostic purposes. However, where national or regional validated reference ranges are available, such serologic tests may be used to support antecedent infection in individual cases.

(11).

The classical agglutination tests (by Widal technique) are still used in several laboratories for serodiagnosis of infections triggering ReA, especially when investigating salmonellosis and yersiniosis. In addition, many other techniques have been applied for this purpose including immunoblotting, haemagglutination, radio-immunoassay and immunofluorescence. However, none of these techniques have gained general acceptance. An enzyme immuno-assay (EIA) has proved to be useful in the serological diagnosis of many of these infections, including those caused by *Yersinia*, *Salmonellae* and *Campylobacteriae*. In EIA, antibodies of different immunoglobulin classes can be quantified separately, and this offers a large advantage compared with the classical methods.

EIA methods have been evaluated most thoroughly in samples from patients with ReA triggered by *Yersinia* spp. or *Salmonella* spp. *Yersinia*-specific IgA antibodies⁶ and *Salmonella*-specific immunoglobulin M (IgM), IgA and IgG antibodies⁷ can be detected for months or even years in the serum of ReA patients. According to careful evaluation of relatively large patient samples, EIA results should only be regarded as positive if the levels of IgA or IgM, in addition to IgG, are positive by at least 2 standard deviations above that in a control population.⁸ However, it has to be kept in mind that the test results can be positive in approximately 10% of the healthy population, and the positivity rate may differ between countries.⁹

EIA has proved to be a sensitive method for the detection of both IgA and IgG class antibodies; if the sample only contains these antibodies, the agglutination reaction may be weak or totally negative. In acute *Yersinia*-triggered ReA, IgA and IgG antibodies can be detected in nearly 100% of patients and IgA is still detectable after 1 year in 84% of patients.⁶ In acute *Salmonella* infections, *Salmonella* lipopolysaccharide EIA shows 92% sensitivity compared with 64% sensitivity of Widal agglutination, which mainly detects IgM class antibodies.¹⁰ Two to five months after the beginning of the infection, EIA still gives a positive reaction in approximately 94% of patients, whereas Widal agglutination is only positive in 14% of patients.

(19)

**Besluit: EIA-testen scoren het best om eventuele infectieuze trigger op te sporen in het kader van ReA indien naast IgG ook IgM of IgA positief zijn.
De klinische impact van deze test (diagnostisch, therapeutisch en prognostisch) is zeer gering : zie punt 3.**

APPRAISAL

1. Analytical performance characteristics (analytical validation report)

1.1. Preanalytical considerations (patient variables, sample stability)

- Biological variation
- Interferences
- Patient variables
- Sample stability: store samples at 2 to 8 °C (8)
- Sample type: Serum
- Sample volume: minimum 300 ul
- Prevalence: (estimation of amount of positive test percentage): + 10% (ZOL, 2007)
- Target population

1.2 Analytical considerations

- (Im)Precision
- Accuracy (bias)
- Correlation with current method/standard
- Reproducibility (within run, between run)
- Reference range

The Widal test is reported by giving the titre for both O and H antibodies.

The antibody titre is taken as the highest dilution of serum in which agglutination occurs.

If no agglutination occurs the test should be reported as:

S. typhi O titre < 1/20

S. typhi H titre < 1/20 (2)

Information received from tropical and developing countries where typhoid is endemic suggest that active typhoid is associated with:

- Significantly raised H or O agglutinins or both (> 1/200); Raising the 'diagnostic' titer, e.g. to 1 in 320 increases specificity but may significantly reduce the sensitivity of the test.
- An early rise in antibody titre. Up to 70% of adult patients show a rise in antibody titre in the first week of infection. Some workers report that in a non-vaccinated patient the H titre is elevated earlier and more frequently than the O titre. Other workers report a rise in O agglutinins as having slightly greater diagnostic value.
- Only a two or three-fold rise in one or both agglutinins when the Widal test is repeated 7 - 10 days later. A four-fold rise rarely occurs, possibly due to the fact that titres are already significantly raised when a patient's serum is first tested. Up to 10% of patients with active typhoid show no rise in O or H titres (this may occur in some patients due to severe hypoproteinaemia). (2)

When paired acute and convalescent samples are studied, a fourfold or greater increase is considered positive. (10)

The minimal titers defined as positive for the O and H antigens must be determined for individual geographic areas and are higher in developing regions than in the United States. (10)

- Analytical range/Linearity
- TAT

1.3 Quality issues

- CTL (clinical tolerance limits)
- Procedures available
- Follow-up internal quality control
- Does external quality control exist?

2. Diagnostic performance

2.1 Sensitivity, specificity

The interpretation of the Widal reaction is full of difficulties and in many cases this test is of little use in diagnosis. (1)

The value of the Widal test in diagnosing enteric fever in endemic areas remains controversial. Some express the view that the test lacks standardization and adequate sensitivity and specificity to be clinical useful, while others consider the test to have a diagnostic value when judged with clinical findings and a knowledge of the 'normal' O and H agglutinin titre in the local population (baseline titres ?).

Example of the findings of a survey from a typhoid endemic area:

	H or O titres below 1 in 200	H or O titres over 1 in 200
% healthy persons	95.4	4.6
% of persons with non-typhoid febrile illness	92.5	7.5
% of persons with bacteriologically proven typhoid	24.8	75.2

Sensitivity: 75,2% max.

Specificity: 95,4% max. (2)

In a study of healthy blood donors performed in central India, seropositivity for typhoid fever using the S.typhi O antigen or S. typhi H antigen was present in 8 and 14 %, respectively. (9)

Single serologic tests, such as the Widal test, are of limited clinical utility in acutely ill patients because positive results may represent previous infection in endemic areas.

Newer serologic assays using ELISA and dipstick technologies perform somewhat better but still fail to attain sensitivity and specificity >95 %

An ELISA for antibodies to the capsular polysaccharide Vi antigen is useful for detection of carriers but not for the diagnosis of acute illness. (9)

Causes of raised O and H titres other than active typhoid:

- Previous Salmonella infections
- Chronic salmonellosis associated with shistosomal infection
- Vaccination with TAB or typhoid vaccine (following vaccination, H antibody titres remain elevated for 6 months or longer)
- Current infection with other Salmonella species
- Chronic liver disease associated with raised globulin levels
- Disorders such as rheumatoid arthritis, rheumatic fever, multiple myeloma, nephritic syndrome, ulcerative colitis

(2)

Although the test is relatively cheap and straightforward to perform, it lacks specificity and sensitivity.

1. In endemic areas low levels of antibodies are detectable in the healthy population, presumably because of prior exposure to the organisms.
2. Numerous non typhoid salmonellae share O and H antigens with S. typhi.
3. H antibody titres remain high for a long time after typhoid immunization.
4. In typhoid patients, titres often rise before the clinical onset, making it very difficult to demonstrate the diagnostic fourfold rise between initial and subsequent specimens.
5. A significant number of culture positive patients develop no rise in titre at all. (6)

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Cross-reactions occur with both non *S.typhi* group D salmonellae and salmonellae from other groups. (10)

The Widal test has been reported to be positive in 46 to 94% of patients with typhoid fever. The test is most reliable in areas in which data on the titers in control groups without enteric fever are available; the sensitivity of the test can be improved when diseases such as rheumatoid arthritis, which are associated with false positive reactions, are ruled out by other assays.

Although the criteria vary, a single elevated titer for O equal to or greater than (1:320) or H equal to or greater than (1:640) is considered positive.

A fourfold or greater titer rise demonstrated in paired serum specimens obtained 2 to 3 weeks apart is also diagnostic, but it is of no value in the acute setting.

The potential for either false-positive or false-negative responses limits the value of the Widal test in the diagnosis of typhoid fever. (10)

Het O-en H-antigen worden gebruikt in serologische testen (Widal). Vermits alle Salmonellae (niet alleen *S. typhi*) en ook aan Salmonella verwante kiemen gelijkaardige antigenen bezitten, zullen er vrij veel kruisreacties zijn (test is aspecifiek).

De test heeft ook een vrij lage gevoeligheid.

Een Widal test is slechts positief bij 50% bij het begin van de hospitalisatie en kan positief zijn door een vroeger doorgemaakte salmonellose. In een derde wereld situatie heeft dit dus meestal weinig zin, indien men dit routinematig vraagt. Wel kan men de test gebruiken indien men een stijgende titer kan aantonen (seroconversie). Antistoffen tegen het O-antigen zullen snel stijgen doch ook snel negativeren (vnl type IgM) Anti-H antistoffen zullen iets trager stijgen doch lang positief blijven (vnl type IgG).

Als men duidelijk vermoeden heeft dat iemand buiktyfus heeft en men doet éénmalige Widal (best O-antistoffen), dan is een hoge titer van deze antistoffen een vrij sterk argument om aan te nemen dat de patiënt wel degelijk buiktyfus heeft. Uit een negatief resultaat kan men niets besluiten. (5)

The ELISA established was used for the detection of *S. typhi* protein antigen in serum from 62 patients with typhoid, 30 patients with clinically diagnosed typhoid fever, 21 patients with paratyphoid, 17 patients with pyrexia caused by other bacteria, and 160 normal, healthy individuals. It was found that the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of this assay were 83.87, 89.04, 87.93, 67.53, and 95.31%, respectively. (12)

Considering PCR as the gold standard, the most appropriate diagnostic cutoff titer of TO and TH have been evaluated at the two different cutoff titers, i.e., 80 for O agglutinin, 160 for H agglutinin, and 160 for O and/or H agglutinins. It was found that specificity was significantly higher with the latter titer (13)

Test	Sensitivity (%)	Specificity (%)	PV+	PV-	LR+	LR-
Blood culture	32.0	100.0	100.0	21.7	infinite	0.67
Widal test (a)	79.2	30	85.7	21.4	1.13	0.69
Widal test (b)	69.8	60	90.2	27.2	1.74	0.50

(a) Cutoff titer of TO, >1:80; of TH, >1:160.

(b) Cutoff titer of TO, >1:160; of TH, >1:160.

(13)

3. Clinical impact

Betreffende (para)tyfus

3.1 Diagnostic

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

NO

The definitive diagnosis of enteric fever is made by isolating *S. typhi* or another *Salmonella* spp. from blood, bone marrow, stool, or urine. If multiple blood cultures are obtained, 73 to 97% of the cases will be confirmed. (cultures obtained before the initiation of antimicrobial therapy).

Culture of the blood clot after the serum is removed has been reported to yield more positive results.

Bone marrow cultures may be positive when blood cultures are negative, even after antibiotics have been administered.

Stool cultures are positive in less than half the patients, and urine cultures are even less frequently positive.

Cultures of biopsy specimens of rose spots have been reported to be positive in nearly two thirds of patients, including some who previously received antimicrobial therapy.

(10)

Additional laboratory tests that may be of value include the white blood cell count and differential, liver function tests, urinalysis, and chest radiograph. (10)

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

However, if the test is interpreted intelligently, bearing all these facts in mind, a significant number of patients will be correctly diagnosed by the Widal test, when all other methods have failed. (6)

3.2 Treatment

- Does the test allow(faster)starting of adequate therapy (or can useless therapy be avoided)?NO, on the contrary, risk of overconsumption of antibiotics.
- Is there a better guidance of therapy by this test? No
- Can toxicity be avoided? NO, on the contrary, risk of toxicity from antibiotics (chloramphenicol in tropical countries)
- Does conditional reimbursement of medication exist, based on test results? NO

3.3. Health outcome

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

Betreffende reactieve arthritis (ReA)

3.1 Diagnostic

Er bestaat geen algemeen aanvaarde set van criteria voor de classificatie of diagnose van ReA, noch één duidelijke diagnostische test.

DIAGNOSIS — Because a triggering pathogen frequently is no longer detectable at the time arthritis develops, and because some triggering infections may be asymptomatic, the diagnosis of reactive arthritis may be difficult to establish in some cases. In such situations, instead of making a clear-cut diagnosis, the clinician will have to resort to assessing the "probability" of a particular patient having reactive arthritis.

Estimating disease probability — There are no prospective studies to generate validated algorithms for assessing the degree of "probability" that a given patient has reactive arthritis.

However, algorithms derived from observational data are available, and can provide some guidance [14]. Limitations of the algorithmic approach should be noted, particularly that patients

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and controls resided in Germany and Scandinavia, and the estimates derived from these populations may not be applicable to other countries. In addition, since there is no "gold standard" for diagnosing reactive arthritis, the opinions of one group of experts was used to determine the presence or absence of reactive arthritis.

According to one published algorithm, an individual patient's likelihood of having reactive arthritis can be estimated in the following manner [14]:

First screen for two parameters:

- Does the patient have compatible arthritis pattern? — Is it a asymmetrical mono- or oligo-arthritis predominantly of the lower extremities?
- Have other diagnoses such as gout, osteoarthritis, and traumatic arthritis been excluded?

If the answer to both questions is "yes", the probability of reactive arthritis is about 40 percent.

If a patient has a typical presentation and other diagnoses have been excluded, is there evidence of a compatible prior (or ongoing) infection genitourinary or enteric infection with an organism that is associated with reactive arthritis?

- Chlamydia trachomatis — If there is a history of symptomatic preceding infection by Chlamydia trachomatis, the probability of reactive arthritis is increased to about 90 percent. If the patient does not have preceding symptomatic infection caused by Chlamydia trachomatis, but Chlamydia trachomatis can be detected in the urine, the probability of reactive arthritis is estimated to be roughly 60 percent.
- Enteric infection — If bacteria that are associated with reactive arthritis can be cultured from stool, the probability of reactive arthritis is 70 percent. As noted above, the usefulness of serological tests for preceding Chlamydia and enteric infections depend on the particular population being tested and the availability of validated tests with population-specific reference values.

Patients whose likelihood of having reactive arthritis is moderate, may be candidates for HLA-B27 testing. However, the diagnostic value of HLA-B27 testing has not been validated by large-scale community-based studies. (See "HLA-B27 testing" above).

(11)

Voor een inventarisatie van vroegere diagnostische schema's verwijzen we naar referentie (20):

Voorstel **Kobayashi and Kida** (21):

Classificatiecriteria:

Major criteria:

- asymmetrische artritis (mono- of oligo-) van de onderste ledematen
- symptomatische infectie (enteritis) drie dagen tot zes weken voor artritis

Minor criteria:

- evidentie van een trigger: positieve coprocultuur
- evidentie van persisterende synoviale infectie: positieve immunohistologie

Additionele classificatie:

- enterische ReA
- acuut (\leq zes maanden) en chronisch (\geq zes maanden)

Exclusiecriteria (andere reumatische aandoeningen uitsluiten):

- minimum aan uit te voeren testen: analyse synoviaal vocht (microscopie, cultuur en analyse kristallen), serologie (RF, ANA, anti-*Borrelia* en anti-streptokokken antistoffen) en radiologie (chondrocalcinosis? vernauwen gewrichtsspleet?)

Definities:

- ReA: aanwezigheid major criteria en een relevant minor criterium
- mogelijks ReA: aanwezigheid major criteria, maar geen minor criteria of eerste major criterium en één of meerdere minor criteria

Labo-testen aan te vragen door reumatoloog:

Bij voorafgaandelijke, symptomatische gastro-intestinale infectie:

- verplicht: coprocultuur en *Yersinia*-serologie
- facultatief: HLA B27?

Bij geen voorafgaandelijke, symptomatische infectie:

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- *Yersinia* serologie, geen stoelgangculturen
- facultatief: HLA B27?

Voorstel **Fendler et al.** (22):

Voor de diagnose van ReA moet één van de volgende criteria voldaan zijn:

- positieve coprocultuur
- antistoftiters ELISA > 3 SD boven normale controlepopulatie voor IgG en IgA of IgM
- antistoftiters ELISA > 2 SD boven normale controlepopulatie voor IgG en IgA of IgM en symptomen van enteritis

Voor de diagnose van mogelijks ReA:

- antistoftiters ELISA > 2 SD boven normale controlepopulatie voor IgG en IgA of IgM
- agglutinatie > 1/320 (normaal < 1/160)

Een voorwaarde om deze criteria te kunnen toepassen is de aanwezigheid van een asymmetrische artritis van de onderste ledematen.

Tevens zijn er geen algemeen aanvaarde criteria voor de diagnose van een SpA. De diagnose wordt gesteld op basis van klinische bevindingen, fysische informatie, laboratoriumuitslagen en beeldvorming. Ook hier werden door enkele groeperingen voorstellen geformuleerd.

ESSG-criteria (European Spondyloarthritis Study Group) (23):

Minimum één van de twee volgende criteria moet aanwezig zijn:

- inflammatoire spinale pijn. Inflammatie is aanwezig wanneer vier van de vijf criteria zijn voldaan: rugpijn bij een persoon jonger dan 40 jaar, een insidieus begin, problemen gedurende minimaal drie maanden, associatie met ochtendstijfheid en pijn die verbetert met oefening.
- asymmetrische synovitis voornamelijk van de onderste ledematen. Synovitis betekent hier: weke delen zwelling, warmte, effusie, reductie in de actieve en passieve range en voornamelijk klachten na een periode van rust.

Wanneer één van de twee criteria aanwezig is, worden volgende criteria nagekeken:

- zijn er nog familieleden aangetast?
- psoriasis?
- inflammatoire darmaandoening (Crohn-CU)?
- urethritis, cervicitis of acute diarree minder dan één maand voor ontwikkelen gewrichtsklachten?
- pijn zitknobbel? pijn alternerend tussen de zitknobbels?
- enthesopathie?
- sacro-iliitis?

In de ESSG-criteria zijn geen bloedtesten (m.i.v. HLA B27) inbegrepen, enkel een RX van de sacro-iliacale gewrichten. De ESSG-criteria zijn immers niet ontworpen omwille van diagnostische redenen, maar voor classificatiedoeleinden.

Amor-criteria (criteria van de French Society of Rheumatology)

- lumbale of dorsale pijn 's nachts of ochtendstijfheid = 1
- asymmetrische oligo-artritis = 2
- pijn zitknobbel = 1 (alternerend pijn rechts en links = 2)
- 'sausage-like' teen of vinger = 2
- hielpijn = 2
- iritis = 2
- niet-gonokokken urethritis of cervicitis minder dan één maand voor het ontwikkelen van de gewrichtsklachten = 1
- diarree minder dan één maand voor het ontwikkelen van de gewrichtsklachten = 1
- psoriasis/balanitis/inflammatoire darmaandoening = 2
- sacro-iliacale aantasting op RX = 3
- HLA B27 positief of familiale ankyloserende spondylitis of Reiter of uveïtis of psoriasis of chronische enterocolopathie = 2
- verbetering binnen de 48 uur bij inname NSAID of relaps van de pijn binnen de 48

uur bij stop NSAID = 2

Volgens de Amor-criteria leidt een persoon aan een SpA als hij minimum zes punten scoort.

Besluit: Geen plaats voor opsporen Salmonella-antistoffen in de diagnose/classificatie van reactieve arthritis (op één referentie na).

3.2 Treatment

Heeft de identificatie van de trigger (dmv serologie) enige invloed op de therapie?

Dienen antibiotica opgestart te worden afhankelijk van de identificatie van de trigger?

Up to date (11): Antibiotics are not used to treat the arthritis specifically, though they may be indicated if there is evidence of ongoing genitourinary infection or carriage of potentially pathogenic organisms.

Antibiotics for acute infections — With regard to antibiotic therapy in reactive arthritis, several scenarios must be considered:

Active enteric or genitourinary infection — Treatment of active enteric infections should follow the standard practice of infectious disease specialists in that particular locality. In general, antibiotics are not indicated for uncomplicated enteric infections. Therapy may be indicated, however, in patients with severe disease, the elderly, or immunocompromised host. ([See "Approach to the adult with acute diarrhea in developed countries"](#) and [see "Travelers' diarrhea"](#)).

In contrast, patients with acute C trachomatis infection, and their sexual partners, should receive a currently recommended regimen. Appropriate regimens are presented elsewhere. ([See "Genital Chlamydia trachomatis infections in men"](#) and [see "Genital Chlamydia trachomatis infections in women"](#)).

Prevention of Chlamydia-induced arthritis — Prompt treatment of acute Chlamydia infections in both patients and partners may lower the probability of developing reactive arthritis. (This has not been proven definitively because a placebo-controlled trial in Chlamydia-infected patients would be unethical.) Patients with an episode of Chlamydia-induced arthritis should be evaluated for recurrent genitourinary infection and treated with antibiotics if this is found.

Chronic arthritis with no evidence of active infection — An initial report suggested that long-term antibiotic therapy with lymecycline might be an effective therapy for chronic arthritis following Chlamydial infection [9]. However, the consensus from subsequent studies [15,19-23] is that long-term antibiotic treatment does not improve the outcomes of patients with reactive arthritis.

This consensus is supported by the following two studies:

- 152 patients received a single dose of [azithromycin](#) 1 gram and were then randomized to either weekly azithromycin or placebo for three months [15]. There were no statistically significant differences between the two groups in the change in swollen and tender joint count or back pain.
- 32 patients were randomized to either ten days or four months of [doxycycline](#) [23]. Only two patients in both groups achieved disease remission, and there were no differences in the number of tender or swollen joints, the intensity of pain, and the patients' global assessment.

In summary, antibiotics are perhaps effective in preventing reactive arthritis in patients infected with Chlamydia. However, long-term antibiotics are not effective for established cases of reactive arthritis. We recommend not using long term antibiotics to treat reactive arthritis in patients with established disease.

Fryden et al. (24) toonden aan dat een kortdurende antibioticatherapie (één tot twee weken) het verloop en duur van de arthritis niet beïnvloedde.

Ook **Toivanen et al. (25)** vonden geen voordeel in het gebruik van antibioticatherapie. Hun patiëntenpopulatie bestond echter wel uit patiënten met reeds vijf jaar artritisklachten (laat stadium).

Sieper et al. (26) deden een studie op 39 patiënten met *Yersinia*- of *Salmonella*-geïnduceerde arthritis en stelden geen betere outcome vast bij therapie gedurende drie maanden met ciprofloxacin en dit zowel bij een groep met korte als lange ziekte duur.

Hoogkamp-Korstanje et al. (27) onderzochten het nut van 2 x 500mg ciprofloxacin per dag gedurende drie maanden bij *Yersinia*-getriggerde ReA. Zij stelden als enige (in tegenstelling tot al

de vorig uitgevoerde studies) een snellere remissie en pijnvrij worden vast in de behandelde groep.

Besluit: Geen plaats voor opsporen Salmonella-antistoffen in de behandelingscriteria van reactieve arthritis (op één referentie na).

3.3. Health outcome

Heeft de identificatie van ReA en zijn trigger (d.m.v. serologie) enige invloed op de prognose?

PROGNOSIS — The course of reactive arthritis probably varies considerably depending on the triggering pathogen, the genetic background of the host, and whether patients are identified in specialty rheumatology clinics or other settings. Most patients remit completely or have little active disease six months after presentation. Chronic persistent arthritis, lasting more than six months, occurs in only a small proportion of patients. As an example, reactive arthritis that lasted for more than one year occurred in 4 to 19 percent of patients in Finland whose arthritis was induced by Yersinia, Salmonella, Shigella and Chlamydia [6], it is difficult to know whether this proportion of patients who develop chronic disease can be generalized to other parts of the world. HLA-B27 testing has been associated with a worse prognosis in some, but not all studies [15,16].

Besluit: geen plaats voor opsporen Salmonella-antistoffen bij inschatten prognose van reactieve arthritis

3.4 Other

- Are there epidemiological interests to perform this test? Outbreak monitoring? Use of serology in the search for typhoid carriers, for example in the routine examination of food handlers and waterworks employees, is of doubtful value. (4)

An ELISA for antibodies to the capsular polysaccharide Vi antigen is useful for detection of carriers but not for the diagnosis of acute illness. (9)

- Is the test still in research phase?

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...)

WIDAL (Salmonella typhi as)

Aantal analyses in 2007: ZOL

Widal H-ag antistof:	51	criterium: <1/80
Widal O-ag antistof:	51	<1/40

Aanvragers: Pediaters, internist - gerieters, huisarts, neo-natologen, gastro-enteroloog.....

Aantal positieve resultaten in 2007:

Widal H-ag antistof:	2	>1/320
Widal O-ag antistof:	3	2 x >1/320, 1 x >1/40

Kostprijs reagens - controles op jaarbasis: 210 €/jaar

Tijdsinvestering van een MLT per negatief resultaat: 5 min.
Tijdsinvestering van een MLT per positief resultaat: 15 min.

Totale werkingskost (reagens - MLT indirecte en directe kost) per gemiddeld uitgevoerde test:

€ 8,00

(ZOL, laboratory)

Aantal analyses in 2007: VJZ

Widal B-ag antistof:	30	criterium: <1/20
Widal C-ag antistof:	30	<1/20
Widal D-ag antistof:	30	<1/20
Widal H-ag antistof:	30	<1/20
Widal TM-ag antistof:		<1/20

Aanvragers: internisten, hematologen-oncologen, reumatologie

Kostprijs reagens: +/- 30 €/5 mL (flesje) = 100 testen 0.3 €/test

Tijdsinvestering van een MLT per negatief resultaat: 5 min.
Tijdsinvestering van een MLT per positief resultaat: 15 min.

Totale werkingskost (reagens - MLT indirecte en directe kost) per gemiddeld uitgevoerde test:

€ 4-5

Salmonella typhi-H Flagellar antigen d Stained Suspension (code SS01)

Salmonella typhimurium-H phase 1 Flagellar antigen i Stained Suspension (code SS07)

Salmonella typhi-O groep D Somatic antigens Stained Suspension (code SS09)

Salmonella paratyphi B-O Group B Somatic antigens Stained Suspension (code SS12)

Salmonella paratyphi C-O Group C+ Somatic antigens Stained Suspension (code SS13)

5.2 Reimbursement

- Can other tests be withdrawn? No

5.3 Profit elsewhere in the hospital

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? Almost no clinical impact

COMMENTS

Besluit betreffende opsporen van anti-salmonella antistoffen in patiëntenserum

Geen nut in de acute fase van Salmonella infectie:

S. typhi-paratyphi infecties:

- De diagnose van (para)tyfus in de acute fase wordt gesteld met hemoculturen, het dragerschap wordt opgespoord met een cultuur van stoelgang. PCR biedt toekomstperspectieven
- Widal heeft een onaanvaardbare lage gevoeligheid en specificiteit voor het opsporen van S. typhi-paratyphi. Ook nieuwere ELISA technieken scoren eerder laag.
- Zeer lage ziekteprevalentie in België waardoor zeer lage positieve predicatieve waarde van een positieve test (1 à 2 %) indien geen sterk klinisch vermoeden (rol bij importpathologie?).
- Sommige experts zien een bescheiden rol voor de test vooral in situaties waar culturen niet mogelijk zijn (ontwikkelingslanden) en indien intelligente interpretatie. In dit geval scoren nieuwere testen (Typhidot en Tubex) beter dan de klassieke Widal (agglutinatie).
- De interpretatie van het resultaat (bij welke titer TO en TH is test positief) is niet gestandaardiseerd en afhankelijk van de endemiciteit van de ziekte. Eventueel verdere studie betreffende standaardisatie waarde resultaten zinvol in ontwikkelingslanden?

Salmonella gastro-intestinale infecties:

- De diagnose wordt gesteld met een cultuur van stoelgang.

Geen of zeer bediscussieerbaar nut in de diagnose van reactieve arthritis (ReA):

- Widal zeker ongeschikt: enkel de O en H antigenen van Salmonella serotype Typhi worden opgespoord, terwijl ReA kan veroorzaakt worden door verschillende serovars van Salmonella enterica.
- Beter maar nog beperkte gevoeligheid en specificiteit bij gebruik van EIA met gelijktijdig opsporen van IgM, IgG, IgA tegen Salmonella.
- Geen klinische impact van de test aantoonbaar in literatuur op gebied van diagnose, therapie en prognose

Voorstel voor nomenclatuurnummer Salmonella-antistoffen:

551051 – 551062 *Opsporen van antilichamen tegen Salmonellae*

De test wordt geschrapt uit de nomenclatuur.

Het opsporen van Salmonella-antistoffen (IgG, IgA, IgM) zal idealiter uitgevoerd worden door het Belgische referentiecentrum mits een gemotiveerde vraag of in studieverband.

TO DO ACTIONS

ATTACHMENTS

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