

NATIONAL STANDARD METHOD

INVESTIGATION OF GASTRIC BIOPSIES FOR *HELICOBACTER PYLORI*

BSOP 55

Issued by Standards Unit, Evaluations and Standards Laboratory
Centre for Infections



Association of Medical Microbiologists
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National Standard Methods, which include standard operating procedures (SOPs), algorithms and guidance notes, promote high quality practices and help to assure the comparability of diagnostic information obtained in different laboratories. This in turn facilitates standardisation of surveillance underpinned by research, development and audit and promotes public health and patient confidence in their healthcare services. The methods are well referenced and represent a good minimum standard for clinical and public health microbiology. However, in using National Standard Methods, laboratories should take account of local requirements and may need to undertake additional investigations. The methods also provide a reference point for method development.

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AMENDMENT PROCEDURE

Controlled document reference	BSOP 55
Controlled document title	Investigation of gastric biopsies for <i>Helicobacter pylori</i>

Each National Standard Method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@hpa.org.uk.

On issue of revised or new pages each controlled document should be updated by the copyholder in the laboratory.

Amendment Number/ Date	Issue no. Discarded	Insert Issue no.	Page	Section(s) involved	Amendment
6/ 08.08.08	4.1	5	1	Front page	Redesigned
			10	4.5.2	Section added for user manuals
			14	References	Reviewed and updated
			All	All	PDF links amended to title of reference document

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INVESTIGATION OF GASTRIC BIOPSIES FOR *HELICOBACTER PYLORI*

Type of specimen: Gastric biopsy

SCOPE OF DOCUMENT

This National Standard Method (NSM) describes the primary diagnosis, processing and bacteriological investigation of gastric biopsies for *Helicobacter pylori*.

INTRODUCTION

Infection with *H. pylori* is associated with peptic ulceration and is a risk factor for gastric cancer. There is evidence that it may play an important role in non-ulcer dyspepsia. Acute symptoms of gastritis and epigastric pain, nausea and vomiting may occur and usually subside, but hyperchlorhydria may persist for much longer².

The detection and diagnosis of *H. pylori* infections has been of great interest. Initially invasive techniques (for example, tissue biopsies) were used. However, with progress in the diagnostic field, (especially molecular biology) non-invasive techniques have also been proposed. The most recent literature on diagnosis of *H. pylori* infections has focused on non-invasive methods³. Nevertheless the ideal method has yet to be proposed⁴.

Gastric biopsies – This is the specimen of choice for the culture of *H. pylori*. Attempts to culture from other specimens have a low success rate⁵.

Invasive techniques for examination of gastric biopsies taken at endoscopy include^{4,6,7}:

- Culture of the organism
- Histology
- Biopsy urease test
- Microscopy
- Polymerase chain reaction (PCR)

Culture of the organism is the most specific method and offers opportunity for conventional antimicrobial susceptibility testing if required. This is important in predicting and evaluating the efficacy of treatment, and in identifying re-infections.

Histological examination – This is as sensitive as culture when detecting *H. pylori*, and has a high degree of specificity⁸.

Neither culture nor histology will provide a rapid diagnosis.

The biopsy urease test – A rapid, sensitive and cost effective test. Positive results are often available within minutes but negative reporting may take a great deal longer, according to manufacturers' instructions. It is recommended for use in combination with either culture or histology, depending on local facilities. This test is often carried out in the endoscopy suite. Commercial kits are available which are highly accurate but also expensive.

Microscopy of tissue smears – organisms may be stained using Giemsa or Gram stains according to preference. Sensitivities of up to 90% have been reported if two biopsies are examined, but this method requires technical expertise. It is the only rapid method other than the biopsy urease test.

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PCR has been used for the detection of *H. pylori* in various samples, although its role in routine diagnosis remains to be established.

Non-invasive techniques (avoiding the need for expensive and invasive endoscopy) include:

- serology
- urea breath tests (UBTs)
- faecal antigen tests

Serology – ELISA-based tests have become more accurate in recent years. A large number of commercial kits are available⁹. IgG detection is commonly used and has the greatest published evidence in its support, but IgA is also available and inflammation markers are sometimes included. Several point-of-care tests using whole blood are available.

False positives have been shown to increase with the age of the patient¹⁰. The use of this technique to confirm eradication is limited by the variable but prolonged presence of immunoglobulins after clearance of *H. pylori*.

Urea breath tests (UBTs) – These are considered to be the diagnostic gold standard¹¹. The urea molecule used is labelled with either ¹⁴C or ¹³C. The former employs simple instrumentation, but the radioactive nature of the test inhibits its use. The latter uses a stable isotope, but requires complex instrumentation. Several ¹³C labelled tests are available commercially as postal services or by the use of dedicated in-house instrumentation. Local methods can be created if the laboratory has access to mass spectrometry.

UBTs allow the rapid assessment of eradication efficacy, however sample collection requires time and technical understanding.

Faecal Antigen Tests – The *H. pylori* stool antigen (HpSA) test is one of the newer developments in the range of diagnostic options¹². These tests can be performed remotely from the patient which allows batched processing.

The HpSA test is a non-invasive enzyme immunoassay (EIA) test that has shown high sensitivity and specificity¹²⁻¹⁴ and the ability to confirm eradication. The most widely used test involves a polyclonal anti-*H.pylori* capture antibody that is adsorbed to microwells, however a monoclonal antibody test has also been developed and is being evaluated⁹.

TECHNICAL INFORMATION/LIMITATIONS

Optimal growth requirements for the isolation of *H. pylori* are a moist, microaerobic atmosphere of 5-7% O₂ and 5-10% CO₂ at 35-37°C^{5,15}. Gas generating kits for microaerobic conditions are commercially available.

Homogenisation may be performed, but it is more time consuming and requires the use of a Griffiths grinder or an unbreakable alternative. Biopsies can be cut finely with a sterile scalpel.

Cultures should be incubated for up to 7 days, although colonies are usually visible at 3-5 days¹⁵.

Gram stain with a dilute carbol fuchsin counterstain enhances morphology.

There is currently no single medium that is best for the isolation of *H. pylori* although blood based media are preferred. Several have been described¹⁵⁻¹⁸.

Blood-free media, containing alternative supplements, may not be as good for primary isolation¹⁷.

Antimicrobial supplements may be added to media to inhibit overgrowth with contaminating bacteria and fungi¹⁹.

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H. pylori is sensitive to clindamycin, cephalosporins and sodium desoxycholate, none of which should be used in the selective medium¹⁷. Selective media for *Neisseria gonorrhoeae* may be used, although about 5% of isolates of *H. pylori* may be inhibited by colistin or polymixin B contained in the medium.

Contamination with moulds may be reduced by the incorporation of an antifungal agent to the medium such as cyclohexamide (100mg/L)⁵ and thorough cleaning of equipment before and after use. Autoclaving of jars previously contaminated with moulds is recommended.

Best results are obtained if both selective and non-selective media are used²⁰.

Confirmation of the organism relies on the characteristic "seagull" morphology in the Gram stained film, and positive oxidase and rapid urease tests.

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1 SAFETY CONSIDERATIONS²¹⁻³²

1.1 SPECIMEN COLLECTION

N/A

1.2 SPECIMEN TRANSPORT AND STORAGE

Sterile leak proof container in a sealed plastic bag

1.3 SPECIMEN PROCESSING

Containment Level 2

The above guidance should be supplemented with local COSHH and risk assessments

2 SPECIMEN COLLECTION

2.1 OPTIMAL TIME OF SPECIMEN COLLECTION

Before antimicrobial therapy where possible

2.2 CORRECT SPECIMEN TYPE AND METHOD OF COLLECTION

Gastric biopsy specimens are usually taken from the gastric antrum at endoscopy, and sometimes from the body depending on location of inflammation

2.3 ADEQUATE QUANTITY AND APPROPRIATE NUMBER OF SPECIMENS

At the discretion of the endoscopist as it depends on the individual patient

3 SPECIMEN TRANSPORT AND STORAGE

3.1 TIME BETWEEN SPECIMEN COLLECTION AND PROCESSING

Specimens should be transported and processed as soon as possible (preferably within 6h)¹⁵

3.2 SPECIAL CONSIDERATIONS TO MINIMISE DETERIORATION

It is important to maintain a moist atmosphere during transport

Where culture is to be carried out within 6h¹⁵:

The biopsy should be placed in a small, sterile container such as a bijou bottle, containing a small amount (approximately 100µL) of sterile isotonic saline to preserve moisture. Dent's transport medium can be used¹⁹. This is available from the Laboratory of Enteric Pathogens (Cfl).

Note: Sensitivity of the microscopy may be reduced if the biopsy is submerged in the saline, because mucus globules form and production of a satisfactory smear becomes difficult.

Where delays of >6h are expected^{15,20}:

The biopsy should be covered with approximately 1mL brain heart infusion broth in a small sterile container, such as a bijou bottle, and stored at 4°C for up to 48h. Dent's transport medium can be used. Organisms will remain viable in Amies, transport medium, but if this is used, care is required to ensure that the mucosa has not become detached from the rest of the biopsy¹⁹.

Biopsies may be stored for up to 6 months at -70°C in broth containing 20-25% glycerol although viability will be reduced.

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4 SPECIMEN PROCESSING

4.1 TEST SELECTION

The biopsy urease test is often performed in the endoscopy suite so only culture and microscopy may be required in the laboratory

The order in which any or all of the tests are performed will be in accordance with local protocol

4.2 APPEARANCE

N/A

4.3 MICROSCOPY

Carried out using carbol fuchsin or Sandiford's stain (See [BSOPTP 39 – Staining procedures](#))

4.3.1 STANDARD

Pick up the biopsy with a sterile swab and smear vigorously on to a clean microscope slide (a sterile slide is required if microscopy is performed before culture).

Staining and examination of the stained preparation need only be performed if the culture result is negative and the biopsy urease test positive. Gram or Giemsa stains are suitable.

Note: Methods for staining procedures are contained in [BSOP TP 39 – staining procedures](#)

4.4 CULTURE AND INVESTIGATION

4.4.1 PRE-TREATMENT

N/A

4.4.2 SPECIMEN PROCESSING

Culture

The same swab containing the biopsy that was used for microscopy (if performed) should be used to inoculate each agar plate (see [QSOP 52 – Inoculation of culture media](#))

For the isolation of individual colonies, spread inoculum with a sterile loop

Note: The simultaneous subculture of known control strains of *H. pylori* is recommended, especially if susceptibility testing is to be performed (see [BSOP 45 - Susceptibility Testing](#))

Metronidazole sensitive strain - NCTC 12822

Metronidazole resistant strain - NCTC 12823

Biopsy urease test

Squash the biopsy on the end of the swab into urease broth

The swab should be broken off in the broth and left *in situ* throughout the test

Incubate the urease broth at ambient temperature for up to 24h

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4.4.3 CULTURE MEDIA, CONDITIONS AND ORGANISMS FOR ALL SPECIMENS:

Clinical details/ conditions	Standard media	Incubation			Cultures read	Target organism
		Temp °C	Atmos	Time		
Gastritis Gastric biopsy	<i>H. pylori</i> selective agar*	35-37	microaerobic moist chamber	7 d	at 4-5 d and 7 d	<i>H. pylori</i>
	Blood agar	35-37	microaerobic moist chamber	7 d	at 4-5 d and 7 d	
For these situations, add the following:						
Clinical details/ conditions	Supplementary media	Incubation			Cultures read	Target organism
		Temp °C	Atmos	Time		
Biopsy urease test if not already performed in endoscopy suite	Biopsy urease broth	ambient	air	24 h	hourly up to 6 h and again at 24 h	<i>H. pylori</i>
*GC selective agar may be used in absence of <i>H. pylori</i> media						

4.5 IDENTIFICATION

4.5.1 MINIMUM LEVEL IN THE LABORATORY

[H. pylori](#) species level

4.5.2 REFERRAL TO REFERENCE LABORATORIES

For information on the tests offered, turn around times, transport procedure and the other requirements of the reference laboratory [click here for user manuals and request forms.](#)

Isolates with unusual or unexpected resistance and whenever there is a laboratory or clinical problem or anomaly that requires elucidation should be sent to the appropriate reference laboratory.

4.6 ANTIBIOTIC SUSCEPTIBILITY TESTING

Refer to NSM on Susceptibility Testing ([BSOP 45 - Susceptibility Testing](#))

5 REPORTING PROCEDURE

5.1 MICROSCOPY

Gram stain (if performed)

Report presence or absence of *H. pylori*-like organisms

5.1.2 MICROSCOPY REPORTING TIME

N/A

5.1.3 CULTURE

The following as appropriate:

Positive results: "*H. pylori* isolated"

Negative results: "*H. pylori* not isolated"

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Biopsy urease test: Report biopsy urease test result as positive or negative

5.1.4 CULTURE REPORTING TIME

Clinically urgent culture results to be telephoned or sent electronically

Written report: 24h for biopsy urease test (if not already performed in the endoscopy suite), stating that a further report on the culture will be issued

Culture result within 7 days

Supplementary investigations: up to 7 days for microscopy

5.2 ANTIMICROBIAL SUSCEPTIBILITY TESTING

Report susceptibilities as clinically indicated

6 REPORTING TO THE HPA³³ (LOCAL AND REGIONAL SERVICES AND CENTRE FOR INFECTIONS)

Refer to the following:

Individual NSMs on organism identification

Health Protection Agency publications:

"Laboratory reporting to the Health Protection Agency: Guide for Diagnostic Laboratories"

"Hospital infection control: Guidance on the control of infection in hospitals"

Refer to current guidelines on CDSC and COSURV reporting

Local guidelines

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7 ACKNOWLEDGEMENTS AND CONTACTS

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The National Standard Methods are issued by Standards Unit, Evaluations and Standards Laboratory, Centre for Infections, Health Protection Agency, London.

For further information please contact us at:

Standards Unit
Evaluations and Standards Laboratory
Centre for Infections
Health Protection Agency
Colindale
London
NW9 5EQ

E-mail: standards@hpa.org.uk

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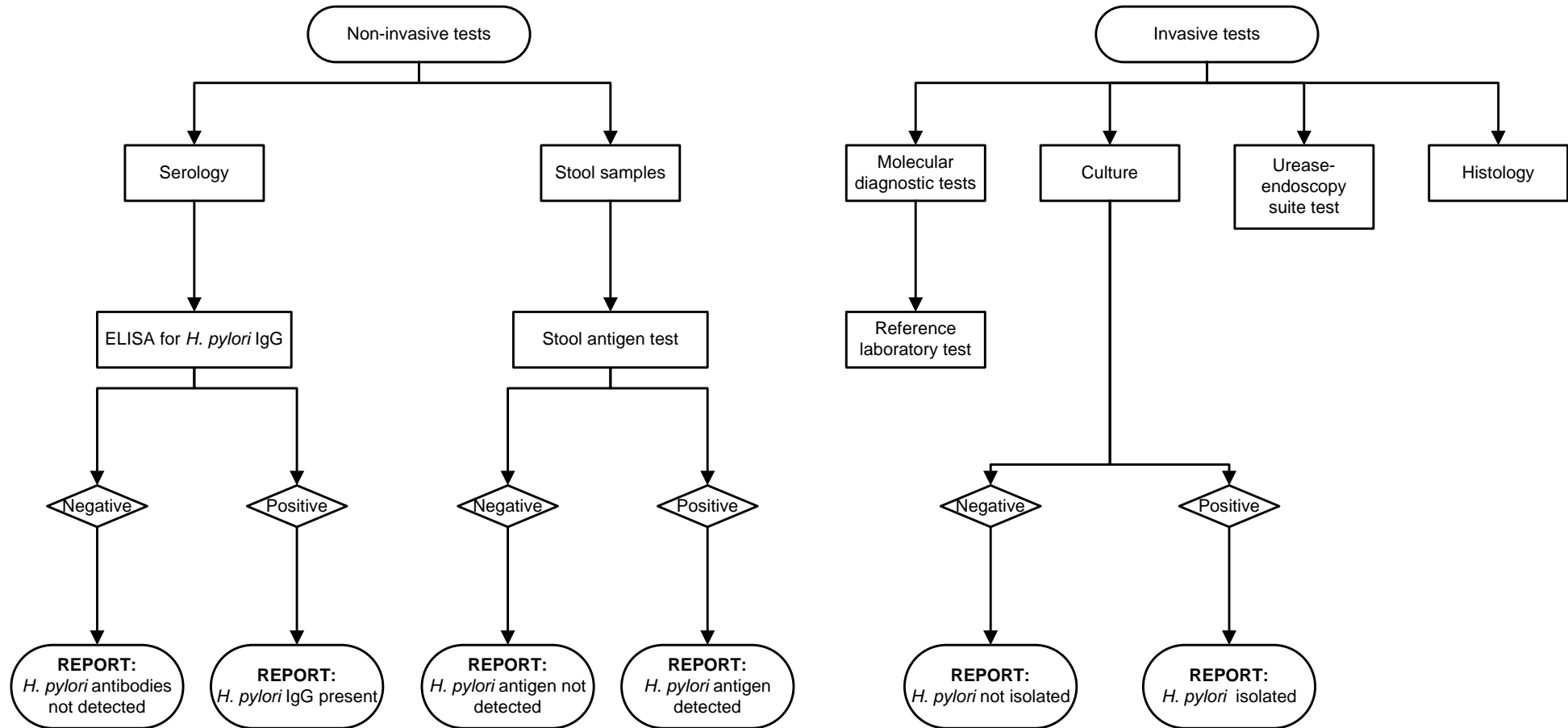
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APPENDIX 1. TESTING ALGORITHM: GASTRIC BIOPSIES FOR *HELICOBACTER PYLORI*



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