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Rapid Urease Testing of *Helicobacter pylori* in Gastric Biopsies Compared With Culture

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ABSTRACT

When an endoscopist takes gastric biopsies from a patient with dyspepsia, one of the first questions is whether *Helicobacter pylori* is present, and two very different tools are often applied to the same piece of tissue: a rapid urease test that gives a colour change within minutes to hours, and culture, which takes days and demands careful transport and microaerobic incubation. This narrative review asks how the two compare and how far published comparisons can be trusted. It draws on published work on the biology of the organism and its urease, on the principles of each method, and on the design of diagnostic accuracy studies, and it reports no new data. The rapid test detects enzyme activity in a biopsy and is quick, cheap and usually highly specific; culture detects viable organisms, is more demanding and less sensitive in routine hands, but is the only route to antibiotic susceptibility testing. Both depend on bacterial load, so recent acid suppression or antibiotics, bleeding, atrophy and a low number of biopsies can lower the yield of either. Comparisons between the two are weakened by the lack of a perfect reference standard, by selected patient groups, and by incomplete reporting of the interval before reading. The review concludes that the rapid test is a sound first-line aid at the time of endoscopy, that a negative result needs careful interpretation, and that culture keeps a defined role where resistance matters.

Keywords: *Helicobacter pylori*; Rapid urease test; Culture; Gastric biopsy; Diagnostic accuracy; Antimicrobial susceptibility; Narrative review

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Article Class: Narrative Review

1. Introduction

Few clinical questions in gastroenterology are asked as often as whether *Helicobacter pylori* is present in a patient's stomach. The organism was first cultured from gastric biopsies in the early 1980s (1, 2), was soon given its own genus (3), and is

now accepted as the main cause of chronic gastritis and a major risk factor for peptic ulcer and gastric cancer (4, 5, 6). Large consensus reports urge that infection be sought and treated in a growing list of situations (7). The practical question is which test to trust, and when.



Once a patient is on the endoscopy table, the question can be answered from the biopsies themselves. Two methods sit at opposite ends of the spectrum. The rapid urease test exploits the bacterium's abundant urease: a fragment of tissue is placed in a urea-containing medium with a pH indicator, and a colour change signals that urea has been split (8). Culture tries to grow the organism from the tissue, a slower and more fastidious process that nevertheless yields a living isolate (9). One is the fast screen; the other is the slow reference that can also say which antibiotics will work.

Papers comparing them are plentiful, and their conclusions look, at first, inconsistent. Some find the rapid test almost as informative as anything else on offer, others find it disappointing, and culture appears sometimes as a gold standard and sometimes as the weakest performer in the comparison. Part of the explanation lies in the patients, part in the technique, and part in the way studies are built (10). A clinician reading a comparison needs to know one thing first: who was tested, and why?

This article is a narrative review. It describes how each method works, what is known about the factors that change its yield, and what is wrong with many of the comparisons. The title may suggest a local diagnostic study, but no patient data of any kind are reported here, and nothing in the text should be read as a result obtained by the authors. The aim is to separate what is firmly established from what is merely repeated.

2. Literature Review

2.1 The Organism and Why Urease Matters

Helicobacter pylori is a spiral, microaerophilic Gram-negative bacterium that lives in the mucus layer of the

stomach, with a small proportion attached to the epithelium (11). Its survival in an acid environment depends on urease, an enzyme produced in unusual abundance. Microbial ureases as a group have been well characterised (12), and in this species the enzyme works together with a proton-gated channel that lets urea enter the cell when the surrounding medium is acidic (13). The ammonia that results buffers the immediate surroundings and helps maintain the internal pH of the cell (14).

That biochemistry is the foundation of the rapid test. If the organism makes so much urease, even a small fragment of infected mucosa should split enough urea to shift the pH of a small volume of indicator medium. The test therefore detects an activity, not an organism, and it will respond to anything in the sample that has the same activity, a point that matters for specificity. Other urease-producing bacteria can occasionally colonise an acid-suppressed stomach, and the literature on diagnosis has long noted this possibility (15, 16).

The infection itself is lifelong unless treated. Colonisation usually begins in childhood, its prevalence follows living conditions and socioeconomic background (17, 18), and the consequences range from silent gastritis to ulcer and malignancy (19, 20). Reviews of global patterns underline how uneven the burden is between regions and between generations (21, 22). A test that works well in a population with heavy colonisation may behave differently where the load is lighter, which is one more reason that accuracy figures do not travel freely.

2.2 The Rapid Urease Test

The rapid test exists in several formats, including gel, agar and paper-strip systems. All rely on the same principle and all require the biopsy to be placed in



contact with the medium; they differ in reagents, in the time they allow before a negative is declared and in how they are stored. A colour change that appears early generally points to a heavy load, while a late or faint change is open to interpretation (8). Reading too soon can miss a light infection, and reading far too late raises the chance of a spurious change. The attractions are obvious. The test is inexpensive, needs no laboratory, and returns an answer while the patient is still in the unit, so that treatment decisions need not wait (23). In most hands it has a high specificity, so that a positive result in an untreated patient is usually believed (8, 24). Its weakness is sensitivity, which tracks the number of organisms in the sample and therefore falls whenever the load falls. Differences in load that look trivial in a single sample matter across a service.

Table 1. Rapid urease test and culture compared on biopsy material.

Attribute	Rapid urease test	Culture
What is detected	Urease activity of the biopsy (8)	Viable organisms (9)
Time to result	Minutes to hours	Several days
Specificity	Usually high (8, 24)	High when growth is confirmed
Sensitivity	Depends on bacterial load (15)	Lower in routine practice (9)
Susceptibility data	None	Possible (9, 25)
Handling	Tube, gel or strip at bedside	Transport medium, special atmosphere

Note: Qualitative comparison of the two methods as described in the cited literature; no performance figures are given because they differ between studies and settings.

Table 1 summarises the contrast with culture. It is worth noticing that the two

methods answer different questions: one asks whether the tissue shows the enzyme, the other asks whether living organisms can be recovered. Neither question is identical to whether the patient is infected, which is what the clinician really wants to know.

2.3 Culture and Susceptibility Testing

The organism is fastidious. It needs a rich medium, a low-oxygen atmosphere with added carbon dioxide, high humidity and patience, since colonies may take days to appear (9). The biopsy must reach the laboratory promptly in a suitable transport medium, because the organism is sensitive to drying and to oxygen. In services without such logistics the practical sensitivity of culture can be disappointing, even though a positive culture is decisive proof of infection.

The reason to persist is that culture permits susceptibility testing. Resistance to clarithromycin and to metronidazole has become a serious obstacle to eradication in many regions, and surveillance in Europe has shown how closely it follows patterns of antibiotic consumption (26, 27). Treatment failures have been linked to resistance, which has prompted calls for susceptibility testing before or after the first attempt (25, 28). Only a living isolate, or in some laboratories molecular testing of tissue, can supply that information. A culture result that arrives after the patient has left the clinic is a different tool from one that arrives before.

Histology is the third member of the biopsy family. It shows the organism in the mucus and also records the inflammation, atrophy and intestinal metaplasia that accompany it, using a standard classification (29, 30). The role of the pathologist and the quality of the staining have been described elsewhere (31). For the present purpose, histology is important because it is often used as one of the



reference methods against which both the rapid test and culture are judged.

2.4 Other Diagnostic Tests

The urea breath test and the stool antigen test are the usual non-invasive options. They are discussed in guidelines as first-line choices when endoscopy is not otherwise needed (32, 33). Systematic reviews give the breath test a strong reputation for accuracy (34, 35), and the monoclonal stool antigen test has a good record in the diagnosis of untreated infection (36). Both tests report the state of the whole stomach, not of a sampled corner, and so are less exposed to sampling error.

These tests matter here for a practical reason. Whenever a biopsy-based result is doubtful, there is an independent test to fall back on, and many comparison studies use one of them as part of a composite reference. A review that set the rapid test and culture only against each other would miss how the wider diagnostic landscape shapes interpretation (23).

3. Materials and Methods

3.1 Scope and Question

The review asks a single question in two parts: how do the rapid urease test and culture compare when applied to gastric biopsies, and how reliable are published comparisons of the two? It does not attempt to rank the methods for any particular patient, and it gives no individual medical advice. The dates of the literature considered end with the year of the issue in which this article appears.

3.2 Literature Assembly

The review draws on peer-reviewed work in four areas: the biology of the organism and its urease; the principles and performance of rapid urease testing, culture and histology; consensus statements on diagnosis; and the

methodology of diagnostic accuracy studies. Sources were chosen by the authors for relevance and for their standing in the field.

We did not run a formal systematic search and we do not claim one. This is a narrative synthesis, and it carries the usual risk that the choice of sources reflects the preferences of the authors. Where we describe a finding, we describe it qualitatively, and we avoid quoting figures whose accuracy we could not check against the original. None of these steps is difficult, but each is easy to skip.

3.3 Appraisal Framework

To judge how far a comparison can be trusted, we used a short list of questions adapted from the standard tools for diagnostic accuracy research (37, 38). Who was tested, and were they consecutive? What was the reference standard, and was it applied to everyone? Was the interval before reading reported? Was treatment history recorded? These questions come from the bias literature (10, 39), and they are applied here to the field as a whole, not to individual studies. Table 2 and Table 3 set out the factors and the weaknesses that arose.

4. Results

4.1 How the Two Methods Handle a Biopsy

In practice a single biopsy cannot be used twice in the same way. A fragment placed in the rapid-test medium is exposed to the reagent and cannot then be reliably cultured, so most services take separate biopsies for each purpose, often from both the antrum and the corpus (Figure 1). That seemingly small point has consequences: two samples from the same stomach need not contain the same number of organisms, and a patchy infection can produce a positive result in one and a negative in the other (30, 31).

**Table 2.** Factors that lower the yield of rapid urease testing and culture.

Factor	Effect on the tests	Possible response
Recent proton pump inhibitor	Fewer organisms; false negatives (7, 33)	Stop beforehand if allowed
Recent antibiotics or bismuth	Suppressed load (7)	Respect the washout interval
Active bleeding	Lower rapid-test yield (40)	Confirm by another method
Atrophy, intestinal metaplasia	Patchy colonisation (29, 30)	Sample antrum and corpus
Few or small biopsies	Sampling error (31)	Take several biopsies
Poor transport	Dead organisms in culture (9)	Use suitable medium, send promptly

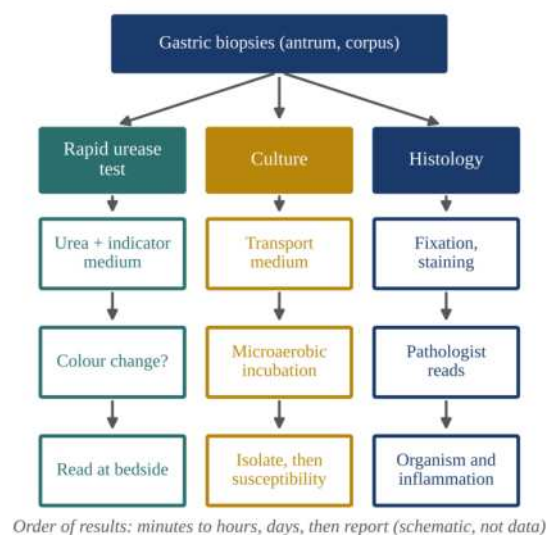
Note: Effects are those described qualitatively in the cited literature; direction rather than size is reported.

The workflow also differs in what happens next. The rapid test is read in the unit, culture waits for the transport, the incubation and the identification, and histology waits for the pathologist (9). Each route ends in a different kind of statement, and the statements are not interchangeable. When the three disagree, which is not rare, the disagreement is itself informative about load, distribution or handling.

4.2 Where the Rapid Test and Culture Diverge

Several situations lead to a positive rapid test and a negative culture. Transport delays can kill the organism before it reaches the plate. Overgrowth by other bacteria can mask it. A recent antibiotic course can leave enough enzyme activity to turn the indicator without leaving enough living cells to grow (7, 9). In these cases the culture, though sometimes

treated as the reference, is the less reliable of the two.

**Figure 1.** Path of a gastric biopsy through rapid urease testing, culture and histology (schematic, not data).

The reverse pattern, a negative rapid test with a positive culture, points to a low load that is below the threshold of the colour change. Acid suppressants are the best-known cause, and the guidelines advise a washout period before testing where it is clinically safe (7, 33). A stomach that has recently been exposed to acid suppression behaves differently from one that has not. Bleeding ulcers form a second group, in which the rapid test is reported to be less sensitive (40). Atrophic mucosa is a third, as the organism retreats from areas where the stomach has lost its acid (29).

Figure 2 sketches what the approaches can and cannot tell the clinician. The rapid test is strong on speed and the signal of active infection; culture is strong on the isolate, and so on resistance. Histology sits between them. No single approach covers every row, which is the plainest argument for treating the tests as complementary rather than as rivals.

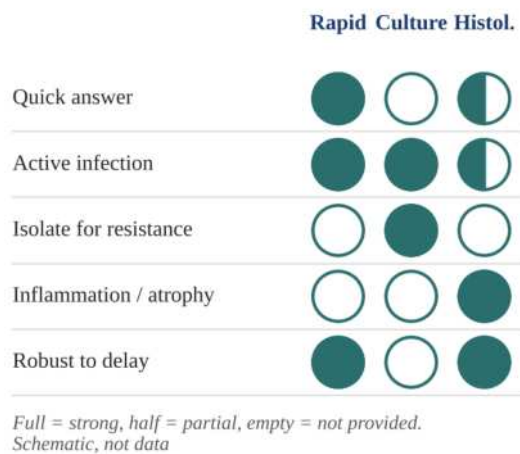


Figure 2. Qualitative matrix of what each approach can tell the clinician (schematic, not data).

4.3 The Problem of the Reference Standard

The first obstacle in any comparison is the choice of a standard. If culture is the standard, the rapid test is penalised for every case that culture misses, and the apparent sensitivity of the rapid test is capped by the sensitivity of culture. If histology is the standard, the same logic applies in reverse. The problem is well described in the general methodology literature (39, 41), and the usual response is a composite standard, in which a patient counts as infected if any of several tests is positive. The point is not that a study is poor, only that its result travels less far than its abstract suggests.

Composite standards bring their own difficulties. The definition of infection becomes dependent on the very tests being evaluated, and the number of tests chosen affects the answer. Even so, they are generally preferred to a single imperfect reference, and the better studies state their rule in advance (38). A reader who finds only a single reference in a comparison should read the reported sensitivities with reserve, and the choice of standard should always be stated openly.

4.4 Patients, Spectrum and Reporting

Studies enrol patients who were referred for endoscopy, and the people referred are not a random sample of the population. They have symptoms, a prior history, and often earlier drug exposure, and the mix differs between hospitals. Differences in the spectrum of patients are among the best-documented sources of variation in diagnostic accuracy (10, 39), and they help explain why one report finds the rapid test excellent and another does not. This is why the same test can look excellent in one report and unremarkable in the next.

Reporting is the other problem. Many accounts do not say how long the rapid test was observed before a negative result was declared, how many biopsies were taken, from where, or whether the patient had taken acid suppressants in the preceding weeks. Without these details a reader cannot judge whether a figure for sensitivity could apply elsewhere. Reporting guidelines for diagnostic studies exist for exactly this purpose (37, 38), but they are not always followed (Table 3).

Table 3. Common weaknesses in studies that compare the two methods.

Weakness	Consequence	Remedy
Imperfect reference standard	Errors in the standard distort accuracy (39, 41)	Use a composite standard
Selected patients	Results do not transfer (10)	Enrol consecutive patients
Reading time not stated	Sensitivity cannot be compared	Report the interval
Treatment history omitted	Hidden false negatives (32)	Record drug exposure
Incomplete reporting	Bias hard to judge (37, 38)	Follow reporting checklist

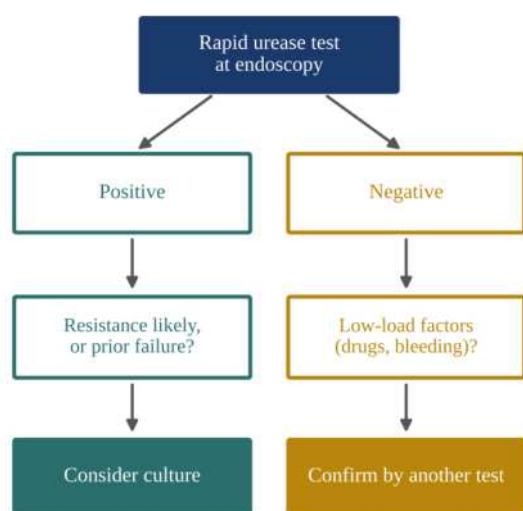
Note: Weaknesses are those discussed in the cited methodological literature; they are not attributed to any single study.



4.5 Choosing When to Add Culture

Because routine culture is demanding, most services reserve it for particular situations. The consensus literature suggests that susceptibility testing is most valuable after treatment failure and in regions where resistance is common or unknown (7, 28). Figure 3 sketches the logic in simple terms. The scheme is not a clinical guideline; it only shows how the extra information of culture is weighed against the burden of obtaining it.

It is also worth recalling what a negative rapid test does not exclude. In a patient with a recent history of acid suppression, with bleeding, or with atrophic change, the negative result may be a statement about the load, not about the infection, and confirmation by another method is commonly advised (23, 40). Read this way, a negative rapid test is a weak statement rather than a verdict.



Schematic of reasoning, not a guideline

Figure 3. Decision sketch for adding culture to a rapid test (schematic, not a guideline).

5. Discussion

5.1 Interpretation

The main finding is a conditional one. The rapid urease test is a sound, inexpensive first-line aid at the time of endoscopy, with

a high specificity, so that a positive result is generally reliable (8, 24). Its limits lie on the negative side, where sensitivity depends on bacterial load. Nothing here argues against using a rapid test; it argues for knowing what a negative result means.

Culture should be read differently. It is a demanding method whose practical sensitivity is often below that of a good rapid test, but it uniquely supplies an isolate, and so it is the route to knowing what will work (25, 27). Where resistance is common, that information can matter more than a few additional minutes saved.

A third point concerns how the evidence is presented. Comparisons that ignore treatment history, test timing or the reference standard are easy to find, and the headline figures they give are therefore hard to apply. These points apply with equal force to any rapid bedside test, not only to this one. The most useful sources are those that report enough detail for the reader to see how the numbers arose (37).

5.2 Limitations

This is a narrative review and shares the limitations of that form. The selection of sources is subjective, no formal search was made, and some relevant work will have been missed. Because we describe findings qualitatively, the review cannot say how large the differences between the methods are, and nothing in it should be used to estimate the accuracy of a particular test in a particular service.

The review also draws on evidence about related tests, on guidelines and on methodology, and not only on direct comparisons of the rapid test and culture, which a transferability argument can only partly justify. Reviews are more useful when they say where the evidence stops than when they smooth it over.



5.3 Future Work

Three needs stand out. First, a well-reported set of comparisons in consecutive, unselected patients, with a composite reference standard stated in advance, would be of real value. Second, studies that deliberately record the interval before reading, the number and site of biopsies and the patient's drug exposure would let others explain differences between settings. Third, work that links rapid-test results with local resistance patterns could show where adding culture is worth the burden. None of this requires new technology, only careful design and consistent, transparent reporting of what was actually done.

6. Conclusion

The rapid urease test and culture answer different questions about the same biopsy. The first reports an enzyme activity within minutes or hours and is usually specific; the second reports a living organism after days and is the route to susceptibility data. Both depend on bacterial load, and both can be misled by recent drugs, bleeding, atrophy and poor sampling or handling. That is a modest claim, but it is the one the evidence will currently bear.

For the practitioner, the message is practical. A positive rapid test in an untreated patient is usually trustworthy, a negative one deserves caution in the situations listed above, and culture earns its place where resistance is a concern. For the researcher, the opportunity is a set of carefully reported comparisons that make clear who was tested, when and with what reference. Until such reports are routine, comparisons between studies will remain more suggestive than conclusive, and readers should weigh them accordingly. It is a habit worth keeping even when the answer seems obvious.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

K.K. conceived the review and wrote the sections on the organism and on culture. C.Z. wrote the sections on rapid urease testing and on other diagnostic tests. C.U. wrote the sections on methodology and reporting. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No patients or animals were involved and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

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