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TOPIC HIGHLIGHT

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# Stool antigen tests for the management of *Helicobacter pylori* infection

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## Abstract

Stool antigen tests (SATs) are noninvasive diagnostic modules for *Helicobacter pylori* (*H. pylori*) infection. Two types of SATs exist for the diagnosis of *H. pylori* infection, one based on enzyme immunoassay (EIA) and another on immunochromatography (ICA). SATs do not require expensive chemical agents or specified equipment; hence, they are less expensive compared with the urea breath test. Both European and Japanese guidelines have shown that EIA-based SATs using monoclonal antibodies are useful for primary diagnosis as well as for the assessment of eradication therapy. ICA-based tests do not require particular equipment and are therefore useful in developing countries. SATs are also useful for the diagnosis of *H. pylori* infection in children and post gastric surgery patients. SATs performed via EIA can assess *H. pylori* infection in a large number of subjects, almost as well as serology. Thus, SATs would be useful or detecting current infection in such a survey to identify and eradicate *H. pylori* infection. The accuracy of SATs is lower when the stool samples are unformed or watery, because *H. pylori*-specific antigens in the stool samples are diluted. Temperature and the interval between stool sample collection and measurement also affect the results of SATs. The choice of test kit depends on the sensitivity and specificity in each region and the circumstances of each patient.



**Key words:** *Helicobacter pylori*; Stool antigen test; Diagnosis; Enzyme immunoassay; Immunochromatography

**Core tip:** Stool antigen tests (SATs) are relatively inexpensive noninvasive tests. Several guidelines on *Helicobacter pylori* (*H. pylori*) infection from around the world indicate that SATs using monoclonal antibodies are useful for primary diagnosis as well as for assessing the results of eradication therapy. SATs are also useful for diagnosing *H. pylori* infection in children and post gastric surgery patients. The choice of test kit depends on the accuracy in each population and the circumstances of each patient.

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## INTRODUCTION

Infection by *Helicobacter pylori* (*H. pylori*) has been implicated in the pathogenesis of gastro-duodenal diseases. Several guidelines on *H. pylori* infection from around the world indicate that eradication of *H. pylori* would result in a reduction of the incidence of gastroduodenal diseases, including gastric cancer, and would decrease new infections in future generations[1,2]. Following the recommendation of the Japanese guidelines for the management

of *H. pylori* infection (2009 revised edition), in 2013, the Japanese health insurance system approved the coverage of the diagnosis and eradication of *H. pylori* in all infected patients[3]. Consequently, an expansion in the role of *H. pylori* diagnostic tests will accompany the increased number of patients undergoing *H. pylori* testing and eradication.

Stool antigen tests (SATs) are noninvasive diagnostic modules for *H. pylori* infection and were introduced after the urea breath test (UBT). Early SATs used an enzyme immunoassay (EIA) based on polyclonal antibodies. While they provided reliable results in the diagnosis of *H. pylori* infection, controversial results were sometimes observed in the post-eradication assessment because of false-positives[4,5]. Monoclonal antibody-based techniques generally have higher specificity. SATs based on monoclonal antibodies have been developed, and have been found to be more accurate than those using polyclonal antibodies[6,7]. A meta-analysis also showed that the specificity of SATs based on monoclonal antibodies was 0.97 (95%CI: 0.96-0.98)[8]. Both European and Japanese guidelines have indicated that SATs using monoclonal antibodies are useful for primary diagnosis as well as for the assessment of eradication therapy[1,3].

Two types of SATs exist for the diagnosis of *H. pylori* infection, one based on EIA and another on immunochromatography (ICA). Although both types of tests are highly sensitivity and specificity, a recent study showed that currently available ICA-based tests provide less reliable results than EIA-based tests[9]. However, ICA-based tests are easy to perform and are useful for in-office rapid diagnoses of *H. pylori* infection[10]. ICA-based tests do not require specialized equipment; therefore, they would be useful in developing countries.

## DIAGNOSIS

### Comparison with UBT

Among non-invasive diagnostic tests, SAT and UBT have higher accuracy than serological or urinary antibody-based tests[1,3]. The American Gastroenterological Association recommends both SAT and UBT for the diagnosis of *H. pylori* infection in patients with dyspepsia[4]. While UBT has been considered the most reliable noninvasive test for the diagnosis of *H. pylori* infection, it has several limitations. The cost of UBT is still relatively high because of the price of $^{13}$C-urea (approximately 30.3 USD) and the cost of measuring $^{13}CO_2$. By contrast, SATs do not require expensive chemical agents and special equipment and hence are less expensive (1400 JPY; approximately 14.2 USD). In addition, patients are required to fast before UBT testing, but not before a SAT. Furthermore, proton pump inhibitor (PPI) administration modulates gastric pH, resulting in lower urease activity of *H. pylori* in the stomach. UBT detects gastric mucosal urease activity; therefore, false-negative results are noted in patients who have been taking PPIs[11]. It is therefore generally recommended that PPI administration be discontinued 2 wk before UBT testing[1]. PPIs can similarly influence SAT[12,13] results, but some monoclonal antibody-based SATs that are currently available are not affected by PPIs[14]. Such SATs, which do not require PPI discontinuation, are useful for the management of *H. pylori* infection in patients with gastroesophageal reflux diseases or those taking nonsteroidal anti-inflammatory drugs.

### Diagnosis in children and post gastric surgery patients

A systematic review and meta-analysis showed that SATs using a monoclonal antibody-based EIA are useful for the diagnosis of *H. pylori* infection in children[15]. UBT is also highly accurate in children older than 6 years, while studies from developed countries showed that its specificity was less than 90% in very young children[16,17]. By contrast, both monoclonal SAT and UBT were reliable in young children aged 6-30 mo in South American developing countries[18]. These results indicate that monoclonal antibody-based SATs are the most effective tests for children in populations with both high and low prevalences of *H. pylori* infection[18,19].

In patients who received distal gastrectomy, the accuracy of UBT was lower than that of a biopsy urease test[20]. However, in Japanese patients who underwent distal gastrectomy, the specificity of SAT was 90.5% while that of UBT was only 59.1%[21].

### Mass survey and screening

In mass surveys, with regard to technique and cost, serology has generally been used despite its lower specificity[3]. SATs performed *via* EIA can assess *H. pylori* infection in a large number of subjects, almost as well as serology. In 994 healthy Japanese adults who participated in a mass survey, concordance of the results of SAT and serology was over 90%[22]. However, in that study, the positivity of SATs was significantly lower than that of serology in 303 subjects with severe atrophic gastritis. In the gastric mucosa of patients with severe atrophic gastritis and intestinal metaplasia, colonization by *H. pylori* is decreased or non-existent. Therefore, in the setting of a mass survey, serology is useful for the detection of both current and past infection. SATs should be used to detect current infection in such a survey to identify and eradicate *H. pylori* infection for the prevention of gastric malignancies.

## ASSESSMENT OF ERADICATION

To date, many studies have demonstrated the usefulness of SATs in the evaluation of the results of eradication therapy. Recent guidelines of the European Helicobacter Study Group (EHSG) recommend both UBT and laboratory-based monoclonal SAT[1]. After eradication therapy, the amount of *H. pylori* colonization in the stomach would be reduced, even when eradication therapy was unsuccessful. Therefore, SATs should be performed to detect the reduced number of bacteria. Among laboratory-based monoclonal SATs, the Premier Platinum

HpSA Plus (HpSA ELISA Ⅱ; Meridian Diagnostics, Inc., Cincinnati, OH, United States), which uses multiple murine monoclonal antibodies, seems to be accurate. We previously demonstrated the significantly higher sensitivity of HpSA ELISA Ⅱ to that of the Testmate Pylori Antigen EIA (TPAg EIA; Wakamoto Pharmaceutical Co. Ltd., and Kyowa Medex, Tokyo, Japan), which uses a single monoclonal antibody[23]. HpSA ELISA Ⅱ produced a higher positive predictive value, although the TPAg EIA provided efficient results[24].

In the guidelines of the EHSG, laboratory-based tests, but not in-office tests, are recommended for the evaluation of treatment results[1]. However, recent observations indicate that some in-office monoclonal antibody-based tests can accurately evaluate the results of eradication treatment[9,25]. In-office tests allow physicians to evaluate the results of eradication therapy in a single visit and the next eradication therapy can be started on the same day in non-eradicated patients. In-office tests do not require specialized equipment; therefore, they would be suitable in institutes that cannot measure $^{13}CO_2$.

PPI administration should be discontinued 2 wk before evaluating treatment results by UBT or SAT[1]. However, as described above, the results of certain SATs are not affected by PPIs[13]. Actually, in a small series of 22 Japanese patients, we showed that the results of eradication therapy assessed by TPAg EIA during PPI administration were the same those determined by UBT 4 wk after discontinuing PPI in 21 patients[26].

In several guidelines, evaluation of the results of eradication therapy by SATs should be performed at least 4 wk after finishing the treatment[1,3]. However, relapse after eradication is considered to be mainly recurrence of the same infection rather than reinfection. Therefore, proposals have been made to extend the timing to 6 or 8 wk after finishing treatment. A monoclonal antibody-based EIA test could determine the treatment results at 6 wk after finishing the treatment as well as 8 wk[26].

## TO BE MENTIONED WHEN PERFORMING SATS

Several factors influence the results of SATs. The accuracy of SATs is lower when the stool samples are unformed or watery, because *H. pylori*-specific antigens in the stool samples are diluted. Therefore, watery stools should not be used, particularly in the determination of the results of eradication therapy. The sensitivity of SATs is also lower in patients with upper gastrointestinal bleeding[27].

Temperature and the interval between stool sample collection and measurement also affect the results of SATs. Such information is available for two kits. Querioz *et al*[18] examined the results of HpSA ELISA Ⅱ and showed a remarkable reduction of the OD value when stool samples were maintained at 37 ℃ for 48 h. They also retested a stool sample with an OD value of 0.183 after 6 h of incubation at 37 ℃ and found that the OD value fell below the cutoff (0.120). In samples tested by TPAg EIA we found that the OD values of initially negative stool samples increased and were almost similar to the cutoff level if the samples were maintained at 40 ℃[9]. However, OD values were unchanged for up to 7 d at -5 ℃-25 ℃ when stool sample suspensions were stored in their particular collection devices. Therefore, stool samples should be stored at a low temperature and be tested over a short period if the collection devices are not available. To maintain the antigenicity over a longer term, stool samples should be stored at -80 ℃.

Differences in the antigenicity of *H. pylori* strains sometimes affect the accuracy of SATs in different populations[28]. Therefore, sensitivity and specificity of SATs should be tested in each population before use in the management of *H. pylori* infection.

## CONCLUSION

In summary, SATs are relatively inexpensive noninvasive tests. SATs using monoclonal antibodies are useful for primary diagnosis as well as for the assessment of eradication therapy. SATs are also useful in the management of *H. pylori* infection in children and post gastric surgery patients. In the future, SATs should be used in mass surveys to identify and eradicate *H. pylori* infection for the prevention of gastric malignancies. The choice of test kit depends on the sensitivity and specificity in each region and the circumstances of each patient.

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