Recurrence of *Helicobacter pylori* infection after eradication

C E EAPEN

Department of Gastrointestinal Sciences, Christian Medical College and Hospital, Vellore 632 004

**Definitions**

*Eradication*: Failure to detect *Helicobacter pylori* infection using gastric biopsy material (rapid urease test, cytology, histology or culture), or ¹⁴C or ¹³C urea breath test (UBT), at least four weeks after completion of antimicrobial therapy (the 'four-week rule').

*Recurrence*: Tests for *H. pylori* infection (e.g., biopsy or breath tests), which were negative four weeks after treatment, become positive again at a later stage. Recurrence can be due to recrudescence or reinfection.

*Recrudescence*: A pretreatment strain of *H. pylori* which was suppressed by treatment and was undetectable four weeks after treatment, becomes detectable at a later stage.

*Reinfection*: Infection by another strain of *H. pylori* or a genetically identical strain from a common original source at a later stage, after the original strain of *H. pylori* has been completely eradicated.

**Incidence of recurrence**

The recurrence rate of *H. pylori* infection has been reported as yearly rates, overall rates, or person-year rates. It is recommended to use cumulative recurrence rate as calculated below:

Cumulative recurrence rate (percentage) = previous recurrence rate (%) + (100 - previous recurrence rate [%] x current recurrence rate [%] / 100).

This includes the yearly rate and reflects the dynamics of the recurrence during the period of follow-up. This also allows comparison of results obtained by different studies.

**Western data**

Cumulative recurrence rate at six months post treatment = 0%-40%
Cumulative recurrence rate at one year post treatment = 0%-41.5%
Recurrence rate when recurrences during the first year were excluded = 0%-8.7% per year

In a meta-analysis of patients with duodenal ulcer who received anti-*H. pylori* therapy, 67% ulcer relapse rate was noted in patients in whom *H. pylori* was not eradicated compared to 6% in patients in whom it was.²

**Nature of recurrence**

In many studies, it is unclear whether recurrence of *H. pylori* after eradication was due to recrudescence or reinfection. Recrudescence is likely to be responsible for most cases because:

1. Techniques for detecting failure of eradication are not 100% sensitive;
2. Most cases of recurrence occur within the first 12 months after treatment;
3. Seroconversion of *H. pylori* infection is less than 1% per year in untreated adults;
4. Molecular techniques suggest that the isolates responsible for recurrence are usually identical to the original isolates.

**Factors associated with recurrence**

**Recrudescence**

1. Techniques for monitoring eradication and recurrence: Both invasive and noninvasive techniques for detecting *H. pylori* infection are highly sensitive and specific in untreated patients in whom the gastric infection is diffuse and the number of organisms is high. However, when these tests are used to monitor the short-term clinical efficacy of *H. pylori* eradication regimens using the four-week rule, their performance suffers because of reduced number of organisms, decreased urease activity, or delay in changes in immune responses.

Theoretically, the UBT alone should be sufficient to monitor recurrence of *H. pylori* during follow-up. However, in one study, 67% false positivity was noted with UBT after treatment.³ This may have resulted from overgrowth of urease-producing bacteria other than *H. pylori*, because of raised gastric pH after treatment with acid inhibitors. Thus, confirmation of recurrence of *H. pylori* infection should not be based on urease-based tests (UBT or the CLO test) alone.

2. **Sampling methods**: The number and site of biopsy specimens taken post-treatment may influence the sensitivity of detection of eradication, which varies inversely with later detection of 'recurrence'. Sampling gastric antral mucosa alone identified 'recurrence' in 41.5%.⁴ Increasing the sampling number to ≥4 seemed to slightly decrease the 'recurrence' rate.⁵ However, combining antral and corpus sampling reduced the 12-month recurrence rate to <3.5%.⁶

The sensitivity of antral biopsy specimens for detecting *H. pylori* can be considerably impaired in patients receiving a proton-pump inhibitor; biopsies taken from corpus and fundus should also therefore be included for assessment of eradication.⁷

3. **Efficacy of original treatment**: Recurrence is very rare when the original eradication rate is over 90%.⁸
Reinfection

i) Susceptibility of hosts to H. pylori infection: There are known genetic differences in the population in susceptibility to H. pylori infection.

ii) Recurrence to H. pylori infection: Heavy contamination of the environment, such as of drinking water, with H. pylori may play an important role in developing countries. People living in close contact have a high risk of transmission of infection. Family clustering of H. pylori infection may be mainly due to genetic hypersusceptibility to the infection, and it is believed that the role of transmission of the infection between family members in reinfection is limited.

Conclusions

i) Recurrence of H. pylori infection after apparently successful eradication occurs at a rate of 0% to 41.5% over 12 months.

ii) Recrudescence is most likely to occur during the first 12 months after apparent ‘eradication’ whereas reinfection may account for recurrence after this period.

iii) Techniques to detect H. pylori infection are not sensitive enough when used alone to monitor eradication. Sensitivity and specificity may be increased when biopsies for detection of H. pylori are taken from both gastric antrum and corpus (also fundus, if possible) and when more than one type of test is applied.

iv) ‘Recurrence’ is rare when eradication rate is over 90%.

v) Individual susceptibility and reexposure to H. pylori are suggested as two major causes of reinfection.

Indian data

Reinfection rates

Data from India on reinfection are scarce. Four studies are available.

i) Patients with chronic atrophic gastritis were studied. H. pylori clearance (colonization status at the end of therapy) rather than eradication (colonization status 4 weeks after therapy) was studied. High incidence of recolonization (59%) at 3-6 months and no increase on subsequent follow-up suggest that these were possibly due to recrudescence.

ii) In three studies of 75 H. pylori-eradicated subjects, reinfection rate was 16% per patient-year follow-up (range 11%-40%).

iii) In one study, when infection in spouses was also eradicated, reinfection rate fell from 40% to 0%.

Ulcer relapse rates

i) In three studies, mean ulcer relapse rates were 17% among 99 patients who successfully eradicated H. pylori infection compared to 62% among 85 infected subjects during an average follow up of one year (weighted odds ratio 9.49, 95% CI 4.66-19.3). Other studies also reported lower ulcer relapse rates with anti-H. pylori therapy; however, the data were not stratified as per H. pylori eradication status. One study did not observe any ulcer relapse in patients who had or had not eradicated H. pylori, while they were on maintenance therapy.

Relatively higher reinfection and ulcer relapse rates reported from India could reflect the following factors:

Recurrent

i) H. pylori eradication not assessed properly as only one technique used to detect H. pylori, or due to error in obtaining specimens

ii) Efficacy of eradication therapy <90%

Reinfection

i) Genetic susceptibility

ii) Re-exposure to H. pylori

Data from other developing countries

Reinfection rates ranged from 0%-7% except in one study from Brazil (21%). Combined ulcer relapse rate was 4.5% per year. Thus, H. pylori eradication reduced the rate of ulcer relapse and infection rates in these high-prevalence areas.

Proposed guidelines

Design of clinical trials to determine recurrence rates in India

i) Anti-H. pylori therapy with efficacy of at least 90% should be used.

ii) Eradication should be assessed four weeks after therapy with a combination of two tests, e.g., CLO test and histology. However, both the tests should not be urease based. Biopsies for detecting H. pylori should be taken from the gastric antrum and corpus (and fundus, if possible).

iii) In case of recurrence of infection, molecular fingerprinting is required to identify whether it is recrudescence or reinfection.

iv) In case of recrudescence, culture and in vitro drug sensitivity of H. pylori needs to be done.

v) In case of reinfection, further studies are needed; for example, to determine a) the role of dental plaque as reservoir of infection; b) familial spread of infection; c) other environmental sources of contamination, like contaminated water.

When to assess eradication of H. pylori after therapy

i) Gastric MALT lymphoma.

ii) Gastric ulcers, where repeat endoscopy is required to monitor ulcer healing. If ulcer is still present H. pylori eradication needs to be monitored.

iii) Complicated duodenal ulcer.

References

1. Xia HX, Talley NJ, Keane TC, O’Morain CA. Recurrence of Helicobacter pylori infection after successful eradication.
H. pylori recurrence in India


Comments

K Mohandas: There are few studies from India on the true recurrence rate of Helicobacter pylori after eradication. The rapid urease test is likely to give false negative results soon after treatment.

A note of caution: It has been my observation that many gastroenterologists and oncologists offer anti-H. pylori therapy as first-line therapy for MALT lymphomas of the stomach irrespective of the stage, bulk and grade of the tumor. H. pylori eradication is effective only in early MALT lymphomas and not in high grade tumors or those with node-positive disease.

The converse is that many medical oncologists are using non-standard H. pylori regimens. We have found that eradication rates of H. pylori in MALT lymphoma patients are very low (40%-50%), probably due to their lower immunity, with a four-drug regimen for two weeks. Therefore, H. pylori eradication might be used only in selected cases of MALT lymphoma after joint consultation between the oncologist and gastroenterologist.

V Jayanthi: There is a need for an immunological test to confirm eradication.

Secondly, what protective factor determines reduction in recurrence rate especially when the individual gets back to the same environment is not clear.
Prabha Sawant: The drawback in Indian data is that most Indian studies are in the form of abstracts. However, the mean reported ulcer relapse rate in India is 17% in the first year, which is more than in the West. Hence, molecular fingerprinting is required to identify whether relapse is due to recrudescence or reinfection; unfortunately, this technique is not available in most centers in the country.

K Vinayan Chandra Nair: Though testing for H. pylori status is appropriate after eradication therapy, this is not practical. Repeat testing should be done a minimum of 4 weeks after therapy. The patient should not have received antibiotics, proton pump inhibitors or bismuth during this period. 13C urea breath test is the most appropriate test; it avoids the need for endoscopy. If, alternatively, endoscopy-based tests are done, a minimum of 2 tests should be used, with biopsies taken from both antrum and body.

The utility of the tests depends on the expertise at each center. What should be the approach in our country? Testing for eradication should be done in
1. patients with relapse of duodenal ulcer
2. patients with complicated duodenal ulcer
3. patients with gastric ulcer, when ulcer healing needs to be documented

Bajrang Pratap: Is it recurrence or reinfection? This is an important question and evokes controversy. We need DNA typing facilities to confirm whether reinfection was with another strain; this technique is not currently available even in the best centers.

Infection status should be assessed 2 months and 6 months after therapy or on recurrence of symptoms, whichever is earlier.

Though dental plaque as a reservoir for re-infection/recurrence of infection was highlighted by workers from Mumbai, these findings have not been reproduced. We have found H. pylori in dental plaque in only 25% of patients with low socioeconomic status.