Helicobacter pylori: Good Side Complicates Efforts To Combat Bad Side

By Caroline McNeil

It sounds all too obvious: Screen people for Helicobacter pylori, a known cause of gastric cancer; then treat the infection with antibiotics and save hundreds of thousands of lives each year.

But it’s not that simple, and a debate about the pros and cons of population screening and treatment for H. pylori continues to simmer. In July, a new study in The Lancet added fresh fuel to the discussion. Masahiro Asaka, M.D., of Hokkaido University Graduate School of Medicine in Japan and colleagues in the Japan GAST Study Group studied 544 patients with early gastric cancer and H. pylori infection. The patients were randomized to receive either standard care for gastric cancer or standard care plus antibiotics to eradicate the infection. Among those who took the antibiotics, nine developed new cancers compared with 14 among those receiving standard care. The difference was statistically significant.

In an accompanying editorial, Nicholas Talley, M.D., Ph.D., of the Mayo Clinic in Jacksonville, Fla., wrote that the implications of the research extend beyond those with a history of gastric cancer to other high-risk groups.

“Population screening and treatment,” he wrote, “should be pursued by governments in populations at very high risk, and by [the World Health Organization]. … Preventing gastric cancer by eradicating H. pylori in high-risk regions should be a priority.”

His call echoes the recommendation of an Asia Pacific Consensus Conference, sponsored by the Asian Pacific Association of Gastroenterology in 2006. The consensus report, published in the Journal of Gastroenterology and Hepatology last June, states that “H. pylori screening and eradication in high-risk populations should reduce gastric cancer incidence and is recommended.”

However, complicating this view of H. pylori are data suggesting that the organism has some benefits for humans. Since it was discovered 26 years ago, researchers have discovered that it may protect against certain health problems, including esophageal adenocarcinoma (EAC) and probably childhood asthma.

“It’s not a simple story,” said Martin Blaser, M.D., at New York University School of Medicine. “It’s complex. It’s an organism that has two faces in humans—one beneficial and one deleterious.”

Pros

Arguments in favor of screening and treatment often start with the huge public health impact of gastric cancer, the fourth most common cancer in the world and the second-leading cause of cancer-related death. It kills 700,000 people annually. Many of those deaths are concentrated in high-risk areas, such as Japan, Korea, and China, so H. pylori screening programs in these countries could theoretically save many lives.

Second, the evidence linking H. pylori and gastric cancer is strong. “It is almost irrefutable that H. pylori causes the disease,” said Talley. The World Health Organization agrees, listing H. pylori as a carcinogen for gastric cancer. On the other hand, it is not the only cause of gastric cancer. Environmental factors such as high salt intake and host factors also play a role. H. pylori is a necessary, but not sufficient, cause of the disease, according to the consensus report.

Third, there is a body of research suggesting that screening and treating H. pylori in high-risk groups can reduce the risk of the disease. This is one place where the debate heats up, however. No randomized trial has yet shown a statistically significant benefit for population screening and treatment. A few studies have found that eradication of H. pylori could help prevent precancerous lesions from progressing. But to date, four randomized, placebo-controlled trials in general populations in high-risk areas of Asia have shown only a non–statistically significant trend toward risk reduction among those treated for H. pylori.

“There is no large, blinded, randomized, placebo-controlled trial,” Talley said. Nevertheless, he argued, the evidence is all in the right direction. And a meta-analysis conducted for the consensus conference, not yet published, has shown a statistically significant benefit, he said. It was on the basis of the studies to date plus the meta-analysis that the consensus conference experts concluded that H. pylori eradication in high-risk populations could reduce the risk of gastric cancer.

Cons

But even those convinced that screening and eradication would work admit that there are risks involved. One of these is the possibility of the organism developing increased resistance to antibiotics. The standard treatment for the infection is a 1- or 2-week course of several drugs, such as lansoprazole (which inhibits the production of acid in the stomach), and the antibiotics amoxicillin and clarithromycin. If patients do not finish the regimen, the bacterium could develop resistance to the medications.

“This is a real problem and a real possibility,” Talley said. On the other hand, the antibiotics to treat H. pylori are already...
commonly used, and some are sold over the counter. This means that there is probably already some resistance to them, he said, which is “unlikely to be aggravated by short-course triple or quadruple therapy.”

More troubling, Talley said, is the possibility that H. pylori could protect against EAC. Several studies have found an association between the infection and lower rates of EAC. Patients with EAC are less likely to have H. pylori than those without the disease. A large study led by Catherine de Martel, M.D., of Stanford University in Palo Alto, Calif., monitored nearly 129,000 patients prospectively for 5–35 years and found that H. pylori–positive people had an 80% lower risk of developing the disease. And a new meta-analysis by the Farhad Islami, M.D., of the University of Tehran in Iran and the National Cancer Institute’s Farin Kamangar, M.D., Ph.D., published online in October in Cancer Prevention Research confirms the inverse association between H. pylori and EAC.

“The data are quite consistent that when H. pylori rates go down, gastric cancer rates go down and EAC rates go up,” said Blaser. “Obviously, it is a tradeoff.”

How H. pylori protects against EAC has not been established, but it may have to do with the infection’s suppressing acidity in the upper part of the stomach, Blaser said. When H. pylori is eliminated, the esophageal reflux is likely to contain more acid. That in turn raises the risk of the precancerous condition known as Barrett’s esophagus, which can lead to EAC.

H. pylori has also been associated with low rates of childhood asthma and other allergic conditions, according to recent studies. Blaser and colleague Yu Chen, Ph.D., also at New York University, have used data from two recent National Health and Nutrition Examination Surveys to examine the association between H. pylori infection and asthma, hay fever, and atopic dermatitis. In their most recent study, based on survey results from 1999–2000 and published in July in the Journal of Infectious Diseases, children between the ages of 3 and 13 were 59% less likely to have asthma if they had H. pylori.

Researchers have also found that H. pylori, an ancient and well-conserved colonizer of the human gut, is much less common now in developed countries than it was a century ago, probably because of better sanitation and antibiotics. Its decline coincides with the rise of childhood asthma in the United States and elsewhere.

Different Risks

The data pointing to H. pylori’s good side make the questions surrounding screening more difficult. “It is not clear that every time we find H. pylori in humans it is a problem,” said Andreas Ullrich, M.D., WHO’s medical officer for cancer control.

In fact, in some parts of Asia, such as India, Pakistan, and Thailand, H. pylori rates are high, whereas gastric cancer rates are low. The reasons for this incongruity probably have to do with both host and environmental factors, experts say. For instance, life expectancy in those countries is not as high as in countries such as Japan, and gastric cancer is a disease of old age. Diet, other common infections, and variations in strains of H. pylori could also play a role in different gastric cancer rates. In any case, it is clear that not everyone with H. pylori is at risk.

“I strongly agree that people at very high risk for gastric cancer need treatment for H. pylori,” Blaser said. “But the risk of gastric cancer is heterogeneous; it’s not the same in all populations or individuals.”

One way to manage the two sides of H. pylori may be to carefully select the populations to be screened and the individuals to treat. To that end, some researchers are searching for biomarkers that would tell them whether H. pylori was more likely to be a risk or a benefit in a particular patient. “If you had a biomarker that put you at high risk for gastric cancer, you would decide to get rid of H. pylori,” Blaser said. “But if you had a biomarker that said you were at greater risk of EAC, then you might keep your H. pylori.”

Another future scenario, he speculated, might include an engineered version of H. pylori that would protect against asthma and EAC but not increase the risk of gastric cancer. In that vein, he added, “I could envision a world in which doctors give H. pylori to children to help with normal development and to help prevent asthma and then at some age, 40 or 50 maybe, when the risk of gastric cancer is higher, get rid of it.”

Doing Something Now

Now, though, governments and public health groups are under increasing pressure to do something about the death toll from gastric cancer. Proponents of mass H. pylori screening argue that the risks of EAC and other problems are not as great as the risk of gastric cancer in parts of Asia. EAC, though more common than it used to be, is still a fairly rare disease, Talley said. “I think there is a relationship there, but eliminating the scourge of gastric cancer is worth the risk.”

In Japan, there may soon be more discussion about H. pylori screening, according to Asaka, who heads the Japanese Society for Helicobacter Research. “We are planning to appeal to the Japanese government to make a new system through which the prevention of gastric cancer by H. pylori eradication might be achieved,” he wrote in an e-mail. The society is also updating its guidelines for management of H. pylori and will recommend that it be eradicated in all persons with the infection, Asaka said. Other Asian governments have also been approached, according to Kwong Ming Fock, M.D., a professor at the National University of Singapore and one of the leaders of the consensus conference.

WHO has no policy regarding H. pylori screening, Ullrich said. “We are much more interested in prevention approaches
that focus on diet and physical activity for all cancers, including gastric cancer,” he said. Low salt intake and diets high in fruits and vegetables are associated with a lower risk of the disease.

One approach to the controversies could be a large, prospective, randomized trial to help sort out the benefits and risks of H. pylori screening and treatment. But such a trial would be extremely expensive, difficult to mount, and long, Talley said. “We thought we should do something now.”