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Population-based strategies for *Helicobacter pylori*-associated disease management: a Japanese perspective

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Abstract

The prevalence of *Helicobacter pylori* infection is decreasing gradually in Japan mainly owing to an improvement in sanitary conditions. The guidelines for *H. pylori* management by the Japanese Society for *Helicobacter* Research, initially established in 2000 and revised in 2003, were revised dramatically in January 2009. The new guidelines accepted the use of new drugs and recommended trying the second-line eradication regimen. Moreover, the revised guidelines reflected the recent knowledge in Japan that metachronous gastric cancer prevalence is decreased significantly by the eradication of *H. pylori* infection. The Japanese Society for *Helicobacter* Research proposed that the cure of *H. pylori* infection should be presupposed to prevent gastric cancer from active gastritis universally developed in the infected subjects. Overall, the most important and dramatic revision is that all infected people are recommended to receive eradication therapy irrespective of the clinical outcomes in the Japanese population.

Keywords

guideline; *Helicobacter pylori*; management; resistance; treatment

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The prevalence of *H. pylori* infection in Japan

The prevalence of *Helicobacter pylori* infection ranges widely between developed and developing countries. In developing regions, such as India, Saudi Arabia, Vietnam and Africa, the infection rate is high and approximately 80% of the population is infected by this bacterium by 20 years of age [1]. By contrast, the infection rate is as low as 10–20% in developed countries, and increases at a rate of approximately 1% per year [2]. It is supposed that the state of environmental hygiene, such as the development of a modern water and sewage system, is related to the *H. pylori* infection rate. In Japan, the prevalence of *H. pylori* infection is also believed to be related to social environment, especially during childhood [3].

The prevalence of *H. pylori* infection in Japan is very low in children under 10 years old (~5%) and it increases with age [4]. Interestingly, the younger generation have a similar pattern to that seen in developed countries, with low prevalence of *H. pylori* infection; whereas the older generation has the pattern seen in developing countries, with high prevalence. In 1992, Asaka *et al.* evaluated the prevalence of *H. pylori* infection among Japanese individuals undergoing an annual medical check-up (n = 426) and reported that prevalence increased with age [4] (Figure 1). The authors showed that *H. pylori* infection rates gradually increased up to 39 years of age (e.g., approximately 5% in patients 0–9 years old, 20% in those 10–19 years old, 25% in those 20–29 years old and 40% in those 30–39 years old); whereas the rate was dramatically higher (i.e., ≥70%) at 40 years of age and over. Overall, they concluded that the infection rate was higher among individuals born before 1950 and lower in those born thereafter. There was a rapid change in sanitary conditions and standard of living in Japan after World War II, and clean public water systems were introduced in Japan in the 1950s. This provided us with some evidence that *H. pylori* infection may be influenced by sanitary conditions. In our preliminary experiment, we also examined the prevalence of *H. pylori* infection using the urine antibody test (Otsuka Pharmaceutical Co., Tokyo, Japan) [5] for 4331 first-visited patients in Oita University hospital, Japan, between 2002 and 2006 (Figure 1). As expected, the prevalence of *H. pylori* infection increased with age. In our study, 10 years had passed since the report by Asaka *et al.*; therefore, as expected, when their results were simply shifted by 10 years, our results were in close agreement with theirs for those under 40 years old. However, they reported that the prevalence in patients aged over 40 years of age was over 70%; whereas we found a prevalence of 60% in patients aged over 50 years. There are several possibilities that may explain the discrepancies. For example, the *H. pylori* detection methods were different (i.e., they used serum antibody ELISA). Moreover, they chose a cutoff optimal density by themselves, which might have caused the high positive rate. Interestingly, Kumagai *et al.* reported that the *H. pylori* infection rate in those aged 9–70 years old decreased by 20% from 1986 to 1994 [6]. As the same population was examined longitudinally, a decrease in the prevalence was observed in every age group. The fall in the prevalence that occurred during the observation period reflected not only the changes in the rate of acquisition of *H. pylori* in childhood but also the higher rate of loss of the infection. This disappearance of *H. pylori* was thought to possibly be due to the use of anti microbials for other common infections. Thus, the *H. pylori* infection rate in Japan will probably continue to fall owing to the improvement of sanitary conditions and the use of antibiotics in the future.

The background for the guidelines in 2009

In Japan, the first guidelines for management of *H. pylori* infection were constructed in 2000 [7,8] (Table 1). These aimed to prepare clinicians for the task ahead in view of *H. pylori* eradication therapy becoming available. Gastric and/or duodenal ulcer were the only diseases for which *H. pylori* eradication therapy was recommended. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma was recommended to receive eradication therapy only at specialist institutions where satisfactory histopathologic diagnosis, endoscopic diagnosis

(including endoscopic ultrasound) and genetic analysis can be performed, and where close follow-up is available.

The second guidelines in 2003 advanced the field greatly [9,10]. As the indication for cure of *H. pylori* infection, MALT lymphoma was recommended to receive eradication therapy in addition to active gastric and/or duodenal ulcer. In addition, the following three clinical outcomes were upgraded to advisable indications; early gastric cancer after endoscopic mucosal resection (EMR); atrophic gastritis; and gastric hyperplastic polyp. Thus, the 2003 guidelines included evidence-based recommendations for indication, diagnosis and therapy.

The guidelines were revised dramatically again in January 2009, 6 years after the second revision [11]. This revision was based on the approval of the Japanese national health insurance system for second-line eradication, the evidence for the relationship between *H. pylori* and gastric cancer and also the relationship with various extragastric diseases. The results from a large-scale multicenter study in Japan published in 2008 helped the revision greatly [12]. In the study, patients with early gastric cancer who received EMR were divided randomly into the eradication treatment group and the noneradication control group, and the development of metachronous recurrence was followed-up for 3 years. As a result, metachronous recurrence was significantly inhibited in the eradication group. That study clearly showed that the cure of *H. pylori* infection led to a decrease in the development of gastric cancer. This shows that even after the removal of gastric cancer by EMR, the subsequent development of gastric cancer was significantly inhibited by the cure of *H. pylori* infection, confirming the importance of careful management of *H. pylori*-related gastritis.

Guidelines 2009 Indications for *H. pylori* eradication therapy

The most important point in the new guidelines was that all '*H. pylori* infection' subjects were put into the 'level A' group for eradication therapy (strongly recommended based on strong evidence). This is based on the following evidence.

Helicobacter pylori infection is reported to cause various upper GI tract diseases, such as atrophic gastritis, gastric/duodenal ulcer, gastric cancer, gastric MALT lymphoma and gastric hyperplastic polyp [13-16]. Although not all infected people have the aforementioned diseases, an infected person is at a high risk of developing these diseases. Therefore, it is expected that successful eradication therapy will be connected with the improvement of histological gastritis and with the prevention of subsequent diseases. This may contribute to the prevention of gastric cancer development, which is one of the biggest health problems in Japan. For such reasons, the Japanese Society for *Helicobacter* Research (JSHR) concluded that all *H. pylori* infections should be considered as an indication for eradication irrespective of the background diseases.

Since all *H. pylori* infections were put into level A for recommendation of eradication, the new guidelines showed the level of evidence for each disease based on the evidence about the effect of the eradication (Table 2). The level of evidence for each recommendation is classified from level I to level VI (Table 3); however, an insurance system (approval of the Japanese national health insurance system) was not taken into consideration.

Gastric/duodenal ulcer (evidence level I)

There are many reports from all over the world showing that recurrence of the *H. pylori*-positive gastric/duodenal ulcers were inhibited by successful eradication therapy, and that complications such as bleeding were also decreased [17,18]. Therefore, *H. pylori* eradication therapy was initially selected as the first choice for gastric/duodenal ulcer treatment in the Japanese guideline in 2003 [9].

Although successful eradication therapy can reduce the development of peptic ulcers and the risk of bleeding accompanying NSAIDs and low-dose aspirin use, the effects were still limited [19-21]. For example, these high-risk patients need gastric acid control, such as proton-pump inhibitors (PPIs), even after successful eradication therapy [22].

Gastric MALT lymphoma (evidence level III)

The cure of *H. pylori* infection has been reported to improve the histological and endoscopic findings for approximately 60–80% of *H. pylori*-infected patients with gastric MALT lymphoma in European countries [23-25]. Thus, the cure of *H. pylori* infection was selected as a first choice in these countries. In Japan, a largescale multicenter clinical study for gastric MALT lymphoma was also completed [26]. The independent factors that can predict the effect of eradication therapy were the presence of *H. pylori* infection, clinical stage, depth of invasion and the API2–MALT1 chimeric transcript. However, conducting a placebo controlled randomized trial is difficult owing to the low frequency and the nature of this disease. Therefore, the evidence level was low, which was different from the recommendation level introduced by the Maastricht III guidelines, where the level of evidence was high (i.e., level Ic). Prognostic evaluation will be required over a long period of time in the future.

Idiopathic thrombocytopenic purpura (evidence level I)

Approximately 30,000 patients are known to have chronic idiopathic thrombocytopenic purpura (ITP) in Japan. Since Gasbarrini *et al.* initially reported the usefulness of the cure of *H. pylori* infection for chronic ITP patients in an Italian population [27], there have been many subsequent reports supporting the original findings. A meta-analysis of 17 papers showed that the platelet count increased significantly after the cure of *H. pylori* infection [28]. In Japan, it is also reported that the cure of *H. pylori* infection resulted in the increase in the platelet count by 40–60% compared with that in pretreatment or that of *H. pylori*-positive chronic ITP patients [29-31]. On the other hand, the effects of successful eradication therapy were unclear in the USA, Spain and France [32-36]. Although the reasons are not clear, it is reported that both bacterial and host factors are involved in the discrepancy [32-36]. However, successful eradication therapy is effective, at least in Japan; thus, the level of evidence in the new guidelines is I.

Following EMR for early gastric cancer (evidence level II)

In 1997 it was reported in Japan that the cure of *H. pylori* infection suppressed the development of metachronous gastric cancer after EMR for early gastric cancer [37]. Since this report was not a randomized controlled trial (RCT), a large-scale multicenter RCT was planned and successfully performed recently in Japan. Importantly, successful eradication therapy suppressed the incidence of metachronous gastric cancer [12]. Therefore, *H. pylori* eradication therapy is strongly recommended after EMR treatment for early gastric cancer.

Atrophic gastritis (evidence level I)

Atrophic gastritis was a ‘Class B’ (advisable) disease for *H. pylori* eradication in the 2003 guidelines. A meta-analysis showed that successful eradication therapy improved atrophic gastritis [38]. Moreover, successful eradication therapy against atrophic gastritis followed the suppression of the incidence of metachronous gastric cancer [12]. Thus, the level of evidence in the new guidelines is I.

Gastric hyperplastic polyp (evidence level II)

Randomized controlled trials showed that the effectiveness of the successful eradication therapy for gastric hyperplastic polyp was approximately 70% [39,40]. Thus, the level of evidence in the new guidelines is II.

Functional dyspepsia (evidence level I)

Since the eradication therapy was recommended by the Maastricht III Consensus report regarding functional dyspepsia [41], the level of evidence became I in the new guidelines. However, the effects are variable in reports from Japan [42-45]. We also examined the *H. pylori*-positive rate of patients who presented with dyspepsia. The *H. pylori*-positive rate in dyspeptic patients was approximately 20% in patients between 20 and 39 years of age, meaning that the remaining 80% were *H. pylori*-negative [46]. This suggested that factors other than *H. pylori* are related to the dyspeptic symptom in young people. Further studies may be necessary to evaluate the evidence levels for functional dyspepsia in Japan.

Reflux esophagitis (evidence level II)

An increase in the incidence and symptoms of reflux esophagitis rarely occurs after *H. pylori* eradication therapy [47,48]. Therefore, the guidelines suppose that the presence of reflux esophagitis will not be an impediment to performing *H. pylori* eradication therapy. However, these reports also showed that the risk of the incidence of reflux esophagitis was high in patients with hiatus hernia after *H. pylori* eradication therapy [48,49], thus it is necessary to explain this point to patients before eradication therapy. Therefore, the level of evidence in the new guidelines is II.

Iron deficiency anemia & chronic urticaria (evidence level III)

There is not enough evidence showing the effectiveness of eradication for these diseases, thus the level of evidence in the new guidelines is III.

Diagnosis of *H. pylori* infection & assessment of *H. pylori* eradication

There are currently six diagnostic methods recommended to detect *H. pylori* infection in the new guidelines. These include: culture, histology, rapid urease test, measurement of *H. pylori* antibody, urea breath tests and measurement of *H. pylori* antigen in feces based on enzyme immunoassay or immunochromatography. Fasting periods using PPIs before the test for preventing the false-negative results were shortened from 4 to 2 weeks [50-52]. Assessment of the successful eradication should be performed at least 4 weeks after the completion of treatment, which was unchanged from the previous guidelines in 2003.

Treatment of *H. pylori* infection

The approved eradication therapy for the Japanese national health insurance system is shown in Box 1. Lansoprazol, amoxicillin (AMPC) and clarithromycin (CAM); omeprazole, AMPC and CAM (800 mg); and omeprazole, AMPC and CAM (400 mg) were approved for the Japanese health insurance system in 2000, 2002 and 2007, respectively. The effectiveness of rabeprazole for primary eradication has been established [53]; therefore, rabeprazole was newly added as the first-line eradication regimen in January 2007. Moreover, the great effectiveness (~90%) of the second-line eradication regimen (PPI, AMPC and metronidazole [MNZ]), recommended in the 2003 guidelines, was confirmed [54-57], and the therapy was also approved by the Japanese health insurance system in August 2007 (Box 1).

Clarithromycin-resistant *H. pylori* is the main cause of unsuccessful eradication therapy. In the JSHR, annual surveillance of CAM-resistant *H. pylori* was conducted for 5 years from 2002 [58]. As a result, the mean nationwide CAM resistance rates were increasing rapidly; 18.9% (2002), 21.2% (2003), 27.7% (2004), 29.0% (2005) and 27.2% (2006). The increase in CAM use in the fields of pediatrics, respiratory disease and otorhinolaryngology is considered to be the cause. In our institution, the successful eradication rate with lansoprazol, AMPC and CAM

(400 mg) tended to decrease between the years 2000–2001 and 2006–2007 (82.5 vs 75.7%, respectively; $p = 0.38$) [SHIOTA S, UNPUBLISHED DATA].

The successful eradication rate by the second-line eradication regimen is over 90%. Using the MNZ breakpoint of 8 µg/ml established by the European Study Group, resistance rates were not changed between 2002–2003 and 2004–2005 (4.9 and 3.3%, respectively) [58]. However, unsuccessful cases also exist and it is necessary to investigate an acceptable third-line eradication that will be useful in the Japanese population as soon as possible. The guidelines state potential third-line eradication programs, such as a PPI, AMPC and levofloxacin; or a PPI and high-dose AMPC. However, the evidence for these therapies is currently insufficient.

Box 1. Eradication therapy covered by the Japanese national health insurance system

First-line therapy

- Lansoprazole 30 mg twice daily, omeprazole 20 mg twice daily, rabeprazole 10 mg twice daily
- Amoxicillin 750 mg twice daily
- Clarithromycin 200 or 400 mg twice daily (for 1 week)

Second-line therapy

- All proton-pump inhibitors covered as first-line therapy
- Amoxicillin 750 mg twice daily
- Metronidazole 500 mg twice daily (for 1 week)

Expert commentary

We have described the concept of *H. pylori* infection as used in the Japanese guidelines in 2009, and shown a positive indication for eradication. Based on the evidence in Japan, the JSHR strongly recommend performing *H. pylori* eradication therapy for patients following endoscopic mucosal resection for early gastric cancer. This should be unique to Japan since most gastric cancer has been found at an early stage, whereas the prevalence of finding the disease at an early stage is usually rare in other countries. A successful eradication therapy leads to the improvement of histological gastritis, and the clinical outcomes that might be developed by *H. pylori* infection, such as peptic ulcer and gastric cancer, may be prevented. However, it is important to recognize that gastric cancer would develop after successful eradication therapy, especially with the case of strong atrophy in gastric corpus. This is currently a hot topic at the JSHR and we are now intensively researching the special characteristics of gastric cancer developed after the cure of *H. pylori* infection.

Another important concern is that the increase of CAM resistance has caused a decline in the successful eradication rate. A success of eradication therapy is been brought about by using MNZ in the place of CAM for patients failing primary eradication therapy. It is thought that successful second-line eradication therapy causes a lower *H. pylori* infection rate. However, MNZ-resistant anaerobic bacteria in addition to *H. pylori* may also increase, and surveillance is important.

The major problem in Japan is that the diseases recommended by the guidelines are still not approved by the Japanese national health insurance system. Currently, peptic ulcer is the only 'approved' indication for *H. pylori* eradication therapy. Thus, most *H. pylori* infected-people, except those with gastric/duodenal ulcers, cannot receive the benefit of the eradication

treatment. Recently, some *H. pylori*-positive patients without gastric/duodenal ulcer have been able to receive the *H. pylori* eradication therapy in Japan, because some institutions have built special clinics for the diagnosis of and therapy for *H. pylori* where patients can be treated without the Japanese national health insurance system. It is expected that the diseases recommended by the guidelines will be approved by the Japanese national health insurance system in the future. If all the infected people are cured, the development of many peptic ulcers and gastric cancers will be controlled in Japan in the future.

Five-year view

The knowledge we consider to be required for the management of *H. pylori* infection in Japan over the next 5 years is as follows:

- The elucidation of a relationship between NSAIDs, low-dose aspirin and *H. pylori* infection;
- Identification of factor(s) that can predict the effectiveness of the eradication therapy for gastric MALT lymphoma, ITP and following EMR for early gastric cancer and atrophic gastritis, with long-term observation;
- RCTs with placebo for functional dyspepsia in Japan. Construction of further evidence regarding iron deficiency anemia and chronic urticaria;
- Investigation of the resistance rate to clarithromycin or metronidazole. Evidence of the effectiveness of the third-line eradication therapy;
- Development of a diagnostic method for other *Helicobacter* species, such as *Helicobacter hailmannii* related to gastric MALT lymphoma and *Helicobacter hepaticus* and *Helicobacter bilis* related to the hepatobiliary disease;
- Extending the approval of the Japanese national health insurance system of diseases that the guidelines recommend.

Key issues

- The *Helicobacter pylori* infection rate in Japan is falling gradually.
- We have described the concept of *H. pylori* infection, as used in the Japanese guidelines in 2009, and shown a positive indication for eradication. Based on the evidence from Japan, the Japanese Society for Helicobacter Research strongly recommends performing *H. pylori* eradication therapy for patients after endoscopic mucosal resection for early gastric cancer.
- It is important to recognize that gastric cancer would be developed even after the cure of *H. pylori* infection in the case of strong atrophy in gastric corpus.
- It is necessary to identify the factors that can predict the effectiveness of the eradication for gastric mucosa-associated lymphoid tissue lymphoma, idiopathic thrombocytopenic purpura and after early gastric cancer, atrophic gastritis and long-term observation is needed.
- Further evidence of functional dyspepsia, iron deficiency anemia and chronic urticaria is necessary.
- The increase of clarithromycin-resistant *H. pylori* has caused a decline in the successful rate of first-line eradication. The success of eradication therapy is achieved by using metronidazole in place of clarithromycin for patients failing first-line eradication therapy.

- The major problem in Japan is that the diseases recommended by the guidelines are not approved by the Japanese national health insurance system.

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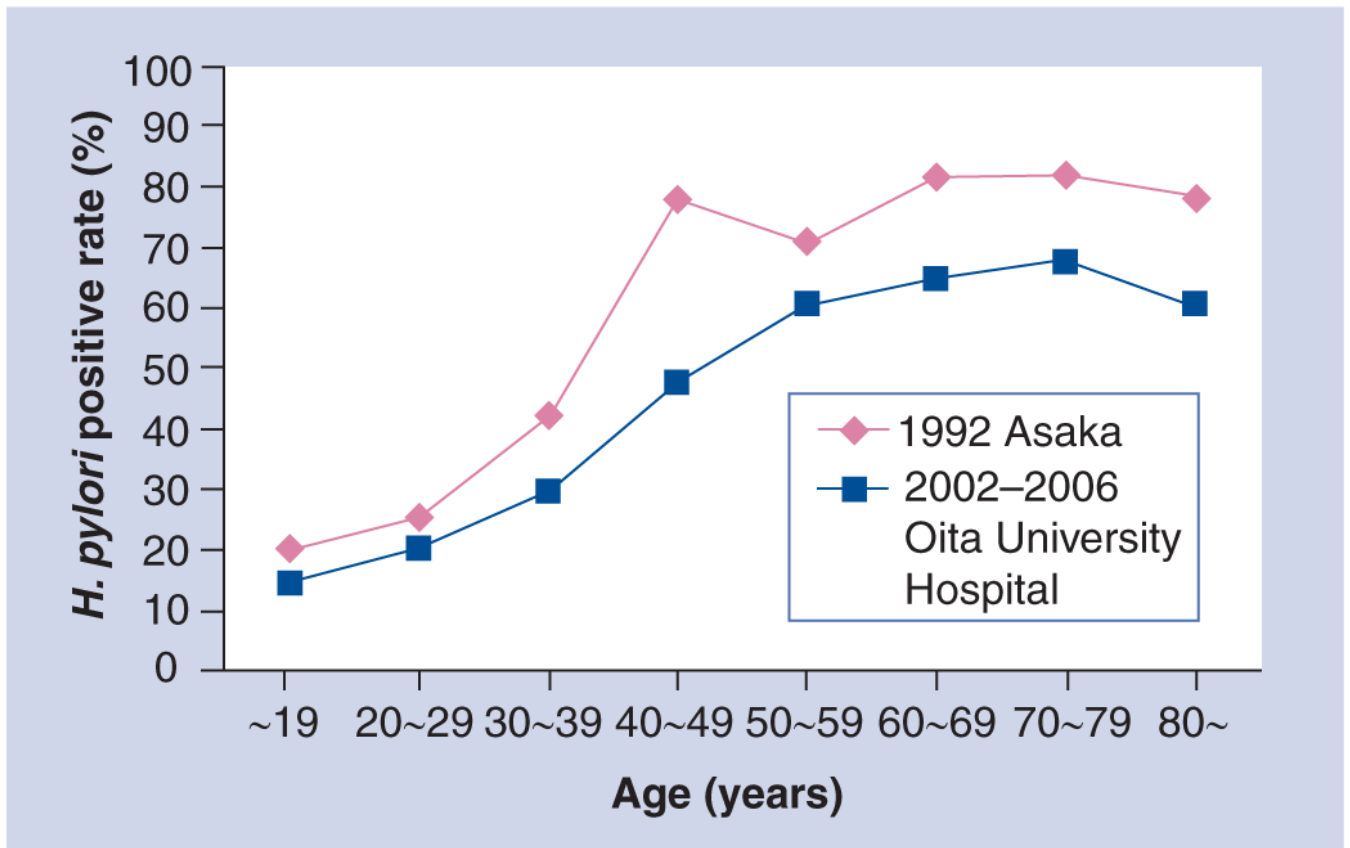


Figure 1.
Prevalence of *H. pylori* in Japan.

Table 1
Comparison of the 2000 and 2003 guidelines for *Helicobacter pylori* management

Parameter	2000	2003
Strongly recommended diseases	Gastroduodenal ulcer	Gastroduodenal ulcer Gastric mucosa-associated lymphoid tissue lymphoma
Diagnosis	Rapid urease test Histology Culture Measurement of <i>H. pylori</i> antibody Urea breath test	Rapid urease test Histology Culture Measurement of <i>H. pylori</i> antibody Urea breath test <i>H. pylori</i> stool antigen test
Treatment	Lansoprazole 30 mg twice daily Amoxicillin 750 mg twice daily Clarithromycin 200 mg or 400 mg twice daily (for 1 week)	Lansoprazole 30 mg twice daily Omeprazole 20 mg twice daily Amoxicillin 750 mg twice daily Clarithromycin 200 or 400 mg twice daily (for 1 week)

Table 2

Evidence level of *Helicobacter pylori* eradication

Disease	Evidence level
Gastric/duodenal ulcer	I
Gastric mucosa-associated lymphoid tissue lymphoma	III
Idiopathic thrombocytopenic purpura	I
Following endoscopic mucosal resection for early gastric cancer	II
Atrophic gastritis	I
Gastric hyperplastic polyp	II
Functional dyspepsia	I
Reflex esophagitis (<i>H. pylori</i> -positive)	II
Iron deficiency anemia	III
Chronic urticaria	III

Table 3

Classification of the levels of evidence

Level	Contents
I	Systematic review/meta-analysis
II	At least one randomized controlled clinical trial
III	Nonrandomized controlled clinical studies
IV a	Analytical epidemiologic study (cohort study)
IV b	Analytical epidemiologic study (case-control study, cross-sectional study)
V	Descriptive study (case report or case series)
VI	Opinion of an expert committee or individual specialist, not based on patient data