

HELICOBACTER PYLORI INFECTION IN PAEDIATRIC PRACTICE

BEST PRACTICE

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This article summarises the epidemiology and pathophysiology of *Helicobacter pylori* related disease in childhood, to enable the general paediatrician to develop an informed and evidence based approach to management.

H pylori is a unique bacterial pathogen:

- ▶ it is widespread, so that around 50% of people throughout the world are colonised
- ▶ it occupies an inhospitable niche (*H pylori* survives gastric acidity even down to pH of < 2)
- ▶ colonisation is chronic and may be lifelong.

H pylori was first conclusively identified as a human pathogen, and an aetiological agent of acute gastritis, in 1984.¹ The discovery that this bacterium is the cause of most peptic ulcer related disease in adult life has been arguably the most important advance in gastroenterology in recent decades. Approximately 0.5% of the UK population (around 290 thousand people, 20% of all general practice workload) are on long term acid suppression because of peptic ulcer related disease attributable to chronic *H pylori* infection.

PATHOPHYSIOLOGY

H pylori are Gram negative spiral organisms (fig 1) that live within and beneath the mucus layer of the human stomach. They do not invade the host and can only survive adherent to gastric type mucosa. *H pylori* utilises a urea splitting enzyme (urease) to neutralise gastric acidity, as it traverses the gastric lumen. Urease negative mutants do not readily colonise animal models of infection.²

Two complete genomes for *H pylori* have been described.^{3 4} Among the genes that have excited considerable interest (which include BabA, IceA, neutrophil activating protein, and various flagella and heat shock proteins) are two principle virulence determinants known to play a role in disease causation; the *cag* pathogenicity island (CagA PAI which codes for several genes including *cagA*) and *vacA* (coding for vacuolating cytotoxin A). Most isolates from patients with gastroduodenal disease from industrialised countries carry the *cag* PAI, while many strains from subjects with more benign colonisation do not. Approximately 26 kb of the 40 kb *cag* PAI encode components of a type IV secretion complex, which mediates translocation of CagA protein. This targets epithelial cells, where it is tyrosine phosphorylated, interacts with host regulatory factors, and disrupts cell signalling.⁵ The type IV secretion complex also induces cytokine IL-8 (also known as chemokine CXCL-8) synthesis.⁶ Despite being separated by a significant distance on the *H pylori* genome, there is an association between *cag* PAI and *vacA*. Most *cag*+ strains also carry toxigenic 's1'-type (signal sequence) alleles of *vacA*. Most *cag*- strains contain s2 *vacA* alleles, which produce a non-toxic protein. The product of *vacA* s1 exerts a toxic effect on certain epithelial cells, affecting plasma membranes, altering endolysosomal function, inducing apoptosis, and interfering with antigen presentation.⁷ While it seems likely that these virulence determinants are associated with the development of disease, many subjects with apparently pathogenic strains of *H pylori* within their stomachs remain symptom-free, and many ulcer patients harbour "non-pathogenic" isolates. The possible explanations for why apparently fully virulent forms of *H pylori* do not produce overt disease may include variations in the following host factors.

- ▶ *Host immune response*—Both peptic ulceration and gastric carcinoma appear to be associated with mucosal Th1 biased responses, resulting in high production of interferon γ (IFN γ), tumour necrosis factor α (TNF α), and interleukin 1 β (IL-1 β). Humoral responses are readily detectable, with polyclonal immunoglobulins directed against dominant epitopes such as *cagA*, *vacA*, and urease subunits⁸. The type of humoral immune response is affected by the age of the host, and the environment (tropical or industrialised societies).⁹ Host immune responses do not appear to be associated with clearance of infection, and may contribute to disease expression.
- ▶ *Small bowel immune activation*—Murine models of co-infection with virulent strains of *H felis*, and the small bowel with helminths such as *Nippostrongyloides*, indicate that polarised small bowel mucosal Th2 activity down regulates Th1 responses within the stomach.¹⁰

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Figure 1 Scanning micrograph of *Helicobacter pylori* on the gastric mucosal surface of a child.

There are no reported cases of childhood *H pylori* associated gastric carcinoma, but histological changes in gastric biopsies in children such as gastric glandular atrophy and intestinal metaplasia have been described. These are both recognised risk factors for subsequent development of cancer, and may be present for many years before dysplasia and malignancy occur.

Most reports suggest that *H pylori* infection typically leads to a cell mediated gastritis with hypergastrinaemia and hyperacidity, although infected stomachs can exhibit normal acid secretory responses. Antral predominant disease tends to be associated with hypergastrinaemia and thus with duodenal ulceration and gastric metaplasia of the duodenum.¹¹ In adults approximately 20% of all cases of *H pylori* infection are associated with antral predominant disease. In children this proportion is probably higher.¹² Gastric malignancy, however, is more common in corporal predominant gastritis which is associated with hypochlorhydria and atrophy of parietal cells. Factors which influence whether *H pylori* causes an antral or corporal predominant disease are unclear, but may include host genotype^{13 14} and environmental and dietary factors (that is, smoked foods, high salt intake, infrequent fruit and vegetable consumption).

INFECTION

Transmission is thought to occur directly from an infected case via faeco-oral or oral-oral routes. The evidence for this comes from epidemiological studies (with deprivation and crowding being major risk factors)¹⁵ and micro-epidemiology¹⁶ (showing clustering of identical strains of *H pylori* on restriction fragment polymorphism analysis within long term care homes). *H pylori* has been cultured from faeces,¹⁷ showing that it passes through the digestive tract in a viable form (particularly when associated with diarrhoea), and has also been isolated from dental caries¹⁸ raising the possibility of oro-oral transmission.

Transmission rates vary enormously between populations, although in every situation prevalence increases with age. Prevalence rates vary from 40% in UK 50 year olds⁹ to 85% by

2 years of age in the developing countries.¹⁹ Prevalence can also vary between racial groups even within a geographical area.²⁰

DISEASE IN CHILDREN

H pylori causes acute and chronic gastritis, and can cause duodenal and gastric ulcers. There is strong epidemiological evidence to implicate *H pylori* gastritis in marginal B cell mucosal lymphomas^{21 22} and gastric non-cardia type carcinomas.^{23 24} Although these significant diseases are typically found among adults, there are clear parallels with gastro-duodenal disease in children. In particular, the following paediatric disorders have been associated with *H pylori*.

- ▶ *Peptic ulceration*—The strongest evidence for the role of *H pylori* in childhood disease is that of duodenal ulcer.^{25 26} The classic history of epigastric pain localised with two fingers, relieved by eating and waking the patient at night, is not reliable in young children. *H pylori* associated duodenal ulcers are only accurately diagnosed by endoscopy, but when treated with eradication therapy are likely to result in dramatic and long term improvement of the symptoms.^{26 27}
- ▶ *Abdominal pain in the absence of peptic ulceration*—In adult medicine this situation is described as non-ulcer dyspepsia. Although *H pylori* infection causes chronic gastritis (fig 2), the prevailing evidence is that eradication therapy tends not to improve symptoms in the absence of peptic ulcer. There is some uncertainty over the long term issues of treatment and symptomatic response, as much of this evidence is confounded by short term follow up.^{28 29} Long term histological follow up studies indicate that resolution of lymphonodular hyperplasia may take up to six months to resolve and inflammatory infiltrate may take up to four years.³⁰ It remains difficult to be sure whether *H pylori* has a major role in abdominal pain in the absence of peptic ulceration, when the temporal associations between infection and symptoms are so distant.
- ▶ *Gastro-oesophageal reflux disease*—Initial observational studies suggested there may actually be an increase in the incidence of reflux disease in people treated with *H pylori* eradication therapy,³¹ but subsequent studies have consistently failed to show an association.³²

The symptoms of the above three conditions can be very similar. Upper gastrointestinal (GI) endoscopy is the only reliable method of diagnosing peptic ulceration, and hence the likely response of symptoms to *H pylori* eradication.

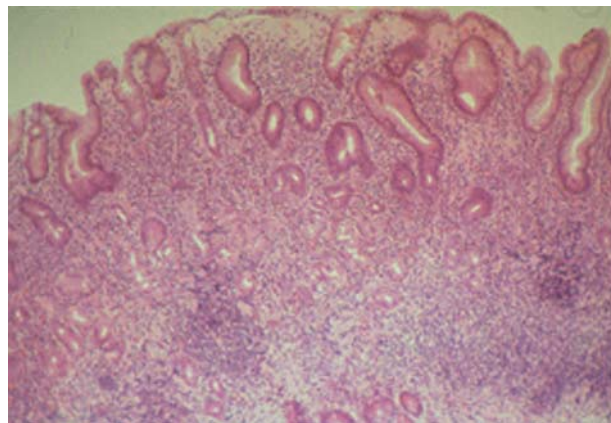


Figure 2 Haematoxylin and eosin stained high power section of a gastric biopsy showing *H pylori* associated gastritis.

It is also important to be aware that *H pylori* is relatively common among UK children (about 5% of 5–16 year olds are colonised). The overwhelming majority of these have no symptoms attributable to gastroduodenal disease. We therefore suggest the following approach to common clinical presentations.

Upper abdominal pain associated with dyspeptic symptoms

When presented with a child with epigastric pain, particularly if associated with mealtimes and occurring during the night, the question of *H pylori* infection status should be considered only of secondary importance compared to the likely pathology causing the symptoms. In practice, the key issue is whether the child has duodenal ulceration or not. It is still therefore advisable to investigate children with significant dyspeptic symptoms with upper endoscopy before embarking upon *H pylori* eradication therapy (especially if certain red flag symptoms exist, such as anaemia and family history of peptic ulcer disease).

Recurrent abdominal pain

It is tempting to hypothesise that *H pylori* associated chronic active gastritis could be a cause of recurrent abdominal pain (RAP) in childhood, and specific serology is often used as part of a screening investigation among children with RAP presenting to paediatricians. There is no consistent evidence that *H pylori* can cause recurrent abdominal pain among children without peptic ulcer. The most likely explanation for the finding of *H pylori* colonisation in recurrent abdominal pain is an epiphenomenon—the co-existence of two common, but unrelated conditions. There is convincing evidence that treating these children will not cure their symptoms.

Iron deficiency anaemia

Case reports and intervention studies show that *H pylori* can be associated with iron deficiency in asymptomatic children at puberty³³ and treatment results in increasing iron stores. Whether this is caused by increased iron loss or decreased iron absorption is not clear, but the relatively low iron stores of pubertal children make them vulnerable. It has been recommended, on a personal view basis, that if *H pylori* is identified in a case of iron deficiency, it should be eradicated.³⁴ This view is not currently supported by position statements from the European Society of Pediatric Gastroenterology, Hepatology and Nutrition/North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/NASPGHAN), and this finding does not imply that *H pylori* is a major cause of iron deficiency.

Childhood growth faltering

Some longitudinal studies have suggested that *H pylori* colonisation in childhood may lead to growth faltering, particularly among vulnerable populations.³⁵ Other cross sectional studies have produced conflicting results.^{36, 37} Potentially confounding variables such as socioeconomic status may contribute to both the development of malnutrition and early *H pylori* colonisation; early *H pylori* colonisation is simply a marker for socioeconomic deprivation. If, however, *H pylori* were found to be a significant cause of infant growth faltering then the implications for the health of children throughout the world are considerable. At present there is insufficient evidence to make such conclusions.

DIAGNOSTIC TESTS

In addition to examination of endoscopic biopsies, non-invasive tests are available for diagnosis of *H pylori* in childhood. These have been alluded to above, and are: immunoglobulin G (IgG) serology; urea breath tests; faecal antigen tests.

IgG serology is widely available. High concentrations of specific IgG in blood (or salivary IgA) are found in active infection; after successful eradication, these gradually fall to below empirically derived cut offs. The test is therefore not suitable for establishing short or medium term success of eradication therapy.³⁸ It should only be used as a diagnostic tool if there is evidence that *H pylori* eradication is likely to be beneficial.

Urea breath tests are robust tools in children over the age of 2 years, and may be valuable in younger children.³⁹ They provide information on the presence or absence of *H pylori* on the gastric mucosa on the day of the test, and are useful in establishing *H pylori* eradication. ¹³C urea breath tests are non-radioactive, but require access to a mass spectrometer. These tests are widely available commercially.

Faecal antigen tests are also robust, comparable in price to urea breath tests, and require a single faecal sample tested using a simple enzyme linked immunosorbent assay (ELISA) kit.⁴⁰ They are a good guide to successful eradication, and because of the ease of use (a single faecal sample can be collected at home and brought or sent to the laboratory), it is likely that this will become the test of choice for assessing eradication in children.⁴¹

Endoscopy and histological examination of gastric biopsies remains the gold standard for diagnosis. Pre-pyloric biopsies have the highest yield (unless the patient is on proton pump inhibitors)⁴² and examination enables the investigator to identify the pathology associated with infection (for example, duodenal ulceration). Rapid urease tests have a high negative predictive value, but a poor positive predictive value in childhood⁴³ and need to be confirmed by histology. While in many situations haematoxylin and eosin stains are adequate to identify *H pylori*, further stains such as Giemsa will improve the detection rate (fig 3).

WHO SHOULD BE TESTED?

Testing for *H pylori* should be done in all situations which may influence management. Our simple advice is test only if you intend to treat. While approaches to treatment are discussed below, at the present time advice given by adult

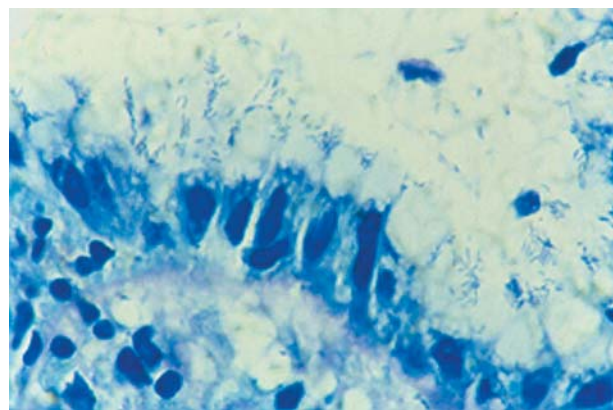


Figure 3 Appearance of *H pylori* on the gastric mucosal surface with Giemsa stain (high power view).

and paediatric gastroenterology professional bodies differs.^{44, 45} The “adult position” is that all cases of *H pylori* should be treated by eradication, regardless of the associated pathology, while NASPGHAN concludes that there is insufficient evidence to recommend this approach to treatment of *H pylori* in children. The National Institute for Health and Clinical Excellence (NICE) guidelines, entitled *Management of dyspepsia in adults in primary care*,⁴⁶ suggests a therapeutic strategy of treating dyspeptic patients without red flag symptoms (that is, rapid weight loss, GI bleeding, or anaemia) with empirical proton pump inhibitors for one month and eradicating those found to be *H pylori* positive. Endoscopy is only considered in those whose symptoms persist. There is a low threshold in investigating *H pylori* colonisation in adults, and even though non-ulcer dyspepsia is unlikely to resolve swiftly after eradication, the balance of risk to the individual patient is thought to favour empirical treatment.

TREATMENT

The principles for treatment are similar to those for any infectious illness, except that a more complete bactericidal effect is required than for most other infections. Even very small residual inoculae of *H pylori* will re-colonise the stomach, as they are relatively remote and protected from the body's own immune defences. The ability of surviving inoculae to re-colonise means that the emergence of antibiotic resistant strains is very likely. It is therefore important to ensure that when treatment is offered, complete courses are given, appropriate protocols that account for common local resistance patterns are followed, and treatment is reserved for those patients who will benefit from eradication. Antibiotic regimens are listed in table 1 and follow guidelines issued by NASPGHAN. It is recommended

that eradication is checked with a urea breath test or faecal antigen assay eight weeks after treatment. Failed eradication (with good compliance) should lead the clinician to consider second line treatment. Repeated treatment failures are an indication to undertake further endoscopy so that cultures of *H pylori* can be obtained for sensitivity testing. It is possible that non-invasive testing of all family members for *H pylori*, and treatment of all positive cases, may be useful in this situation, but there is little evidence to either support or refute this approach at present.

Specific diseases such as duodenal ulcer require, in addition to eradication of *H pylori*, further antacid suppression and a three month course of a proton pump inhibitor would normally be used. Gastric mucosal B cell non-Hodgkin

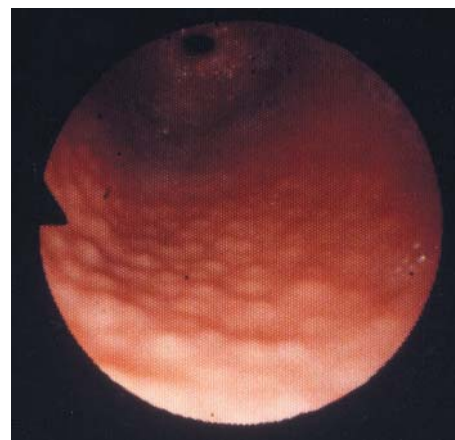


Figure 4 Endoscopic view of lymphoid nodular hyperplasia of the gastric antrum.

Table 1 Recommended eradication therapies for *Helicobacter pylori* in children

Options	Medications	Dosages
First line		
1	Amoxicillin Clarithromycin	50 mg/kg/day, up to 1 g day 15 mg/kg/day
2	Proton pump inhibitor (omeprazole) Amoxicillin Metronidazole	up to 500 mg twice daily 1 mg/kg/day up to 20 mg twice daily 50 mg/kg/day, up to 1 g day 20 mg/kg twice daily
3	Proton pump inhibitor Clarithromycin Metronidazole	up to 500 mg twice daily 1 mg/kg/day up to 20 mg twice daily 15 mg/kg/day up to 500 mg twice daily 20 mg/kg daily
4	Proton pump inhibitor (omeprazole)	up to 500 mg twice daily 1 mg/kg/day up to 20 mg twice daily
Second line		
4	Bismuth subsalicylate Metronidazole Proton pump inhibitor (omeprazole)	1 tablet (262 mg) four times daily or 15 ml (17.6 mg four times daily) 20 mg/kg twice daily up to 500 mg twice daily 1 mg/kg/day up to 20 mg twice daily
5	Plus an additional antibiotic: amoxicillin or tetracycline or clarithromycin Ranitidine bismuth-citrate Clarithromycin Metronidazole	50 mg/kg/day up to 1 g twice daily 15 mg/kg/day up to 500 mg twice daily 1 tablet four times daily 15 mg/kg/day up to 500 mg twice daily 20 mg/kg/day–500 mg twice daily

Adapted from Gold *et al.*⁴⁴

lymphomata require specialist oncological evaluation as well as eradication of *H pylori*, but are very uncommon in children.

INDICATIONS TO TREAT COLONISATION IN CHILDREN

There is complete agreement between adult and paediatric evidence that *H pylori* must be eradicated if it is detected in cases of duodenal or gastric ulcers and gastric lymphoma.²² Although the symptomatic response to *H pylori* eradication is poor in non-ulcer dyspepsia, in adult studies it still provides a good protection against development of gastric cancer (if the eradication is effective)²⁴ or duodenal ulcer.⁴⁷ A prospective observational study in Japanese adults has identified endoscopic warning signs that in an individual patient *H pylori* colonisation is at enhanced risk of inducing gastric carcinoma. These factors are gastritis associated with atrophy, gastric polyps, or corpus predominant gastritis.²⁴ The literature is also clear that antral lymphonodular hyperplasia (fig 4) regresses after *H pylori* eradication, but there is no consensus if this needs treatment in its own right in children.⁴⁸ While there is a rationale, however fragile the evidence base, to advocate eradication in any child with any of these histological abnormalities, most cases of *H pylori* diagnosed at endoscopy in the absence of peptic ulceration will have chronic active gastritis. In practice, virtually all parents of symptomatic children will opt for *H pylori* eradication regardless of whether their clinician feels it is likely to improve symptoms or not. Whatever the consensus statements may say, families will expect you to treat *H pylori* if you find it.

REASONS NOT TO TREAT CHILDREN

Treatment failure is an increasingly frequently encountered problem, and is associated with emerging antibiotic resistance,⁴⁹ although other factors are involved. It has been observed that treatment of *H pylori* is associated with an increase in the carriage rate of resistant strains of *Enterococcus* species.⁵⁰ It is extremely difficult to establish whether recurrence of infection is caused by reinfection or by persistence of the original strain. In practice, recurrent infections are more difficult to eradicate, and frequently require prolonged courses of different antibiotics.

OTHER DISEASES PROPOSED TO BE ASSOCIATED WITH *H PYLORI*

Because of the high prevalence rate of *H pylori* it is susceptible to false association with other diseases. The following diseases have proposed links with *H pylori* infection, but all are contested: chronic urticaria,^{51 52} and immune thrombocytopenia. There is also increasing evidence to discount the proposed association between adult cardiovascular disease and long term *H pylori* infection.⁵³

CONCLUSIONS

At present, *H pylori* eradication can only be shown to be of benefit among the relatively small well defined groups of children with the disease states described above. The overwhelming majority of colonised children do not fall into any of these groups, and are unlikely to obtain symptomatic benefits from specific treatment. Some of them may go on to develop disease in adult life, but, as yet, we have no valid way of predicting who these may be. The bleakest estimate of risk for peptic ulcer is 20% from adult data, and the lifetime risk of developing gastric cancer rises by 4.9 fold in the context of

H pylori gastritis. As our understanding of the pathogenesis of *H pylori* associated disease improves, it is likely that our ability to predict at risk subgroups will also change and targeted treatment in childhood may be possible. The role of endoscopy is primarily for the assessment of gastroduodenal disease and should be performed in those children with a suspected peptic ulcer, rather than a non-ulcer cause of dyspepsia regardless of *H pylori* status.

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ARCHIVIST

Intramuscular ketamine in A&E

Ketamine was first developed over 40 years ago. It was used in the field by the US army in Vietnam and has been used extensively throughout the world (but not very much in Britain) since then. It produces anaesthesia, analgesia, and amnesia with preservation of respiratory protective reflexes. Reports of its use by non-anaesthetists for procedural sedation in children first appeared in the early 1990s. Now staff at two English accident and emergency departments have independently described their experience with intramuscular ketamine for children needing minor surgical procedures.

In Welwyn Garden City (DY Ellis and colleagues. *Emergency Medicine Journal* 2004;**21**:286–9) 89 children aged 1–10 years received intramuscular ketamine 4 mg/kg with atropine 0.02 mg/kg over the course of 1 year. In Lancaster (*Emergency Medical Journal* 2004;**21**:290–5) there were 500 patients aged up to 12 years (mean 3.6 years) over a period of 5 years and 9 months and the dose of ketamine was 2.5 mg/kg (190 children) or 2 mg/kg (310) with atropine 0.01 mg/kg. Both departments had protocols for the use of ketamine and provided parents with written and verbal information. Both used clinical and pulse oximetry monitoring and medical and nursing staff, including somebody with advanced paediatric resuscitation skills, were present throughout. Both departments encouraged parental presence. Four children (Welwyn Garden City) and 26 (Lancaster) received a second dose of ketamine of about half the first dose (about 5% in each centre). Adequate sedation was usually achieved within 10 minutes and few children needed to be restrained. Oxygen desaturation (<94%) did not occur in the WGC series and occurred in eight children in Lancaster. It was transient in all cases, responding to oxygen supplementation in one child with laryngospasm. The children were usually ready for discharge within 2 hours although recovery was slower in some. About 10% of patients vomited in the department and a further 10% after going home; it was more likely in children given a second dose. Some unsteadiness after returning home was fairly common and some agitation during recovery and later occurred in around 15–20%. Ninety-five per cent or more of parents were satisfied with the use of ketamine.

Both of these departments now use ketamine routinely but both emphasise the importance of staff training, adequate staffing levels, and careful monitoring.