13: Treatment of Helicobacter pylori

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Introduction

Historical notes

Even before the discovery of spiral gastric bacteria, bismuth therapy was commonly prescribed for gastrointestinal complaints and, as such, was probably the first therapy used for *Helicobacter pylori*. Kussmaul advocated bismuth subcarbonate for gastric ulcer [1], Ogle treated non-ulcer dyspepsia with bismuth subcitrate [2], and Osler sometimes offered bismuth subnitrate lozenges for acute and chronic gastritis [3]. In 1901, the forerunner of "Pepto-Bismol" (bismuth subsalicylate) was advocated for the treatment of infantile cholera, a disorder which in retrospect may have actually been *C. jejuni* gastroenteritis. The antispirochetal action of bismuth was subsequently proven by Robert & Sauton in 1916 [4], after which it was used extensively as an antispirochetal agent in human syphilis.

The first attempt to actually treat *H. pylori* infection was made by myself and Robin Warren in 1981. An elderly man, with suspected abdominal angina but normal endoscopy, was found to have *Campylobacter*-like organisms (CLO) and gastritis on biopsy. After 14 days' treatment with 500 mg q.i.d. of tetracycline syrup, the histology had improved, CLO could not be demonstrated, and the patient was asymptomatic.

The idea that *H. pylori* could be treated with bismuth arose in 1983, following the observation by Martin *et al.* [5] that duodenal ulcers healed with colloidal bismuth subcitrate (CBS) did not relapse as often as those treated with cimetidine. Investigating the cause of this effect, Gregory *et al.* [6] had studied duodenal ulcer borders and had shown circular profiles of CLO in pretreatment electron micrographs. I noted that the bacteria had disappeared in post-treatment illustrations. To see if CBS inhibited the bacteria, a disc was dipped in liquid "DeNol" and placed onto a culture plate of *H. pylori*, and 3 days later a large zone of inhibition was seen (Fig. 13.1).

As a result of that experiment, a controlled trial of duodenal ulcer therapy with either cimetidine or CBS was undertaken, with gastric biopsy to observe changes in gastritis and CLO. After treating 10 patients in each group, it became evident that CLO were suppressed, but not usually eradicated, by CBS therapy [7].

The first bismuth/antibiotic combination therapy for *H. pylori* was tried in 1983. A gastritis patient, treated with an 8-week course of CBS chewing tablets ("DeNol"), relapsed clinically and histologically 1 month later. On the second occasion, amoxicillin, 500 mg q.i.d., was added to the bismuth therapy causing eradication of the organism [8]. *H. pylori*, although not an anaerobe, is usually susceptible to bismuth/nitroimidazole combination therapy. I noted this when a patient developed a sore mouth while taking CBS. Suspecting periodontitis, I added metronidazole to his therapy. Long-term follow-up confirmed eradication of CLO and healing of gastritis. Experience in a large series of patients revealed a failure rate of 20–50% with both these regimens, causing Borody *et al.* to develop the present triple therapy regimens for *H. pylori* during 1986–87 in Sydney, Australia [9].

Table 13.1 lists *H. pylori* cure rates and minimal inhibitory concentrations (MICs) for most commonly used antibiotics. Data for Table 13.1 were derived from the references

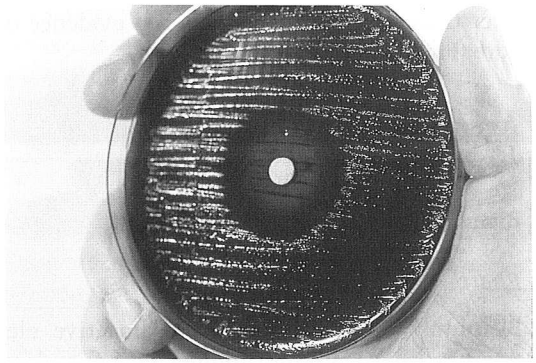

Fig. 13.1 Three-day-old culture of *H. pylori* inhibited by colloidal bismuth subcitrate ("DeNol"). The disc contains 50 μg of bismuth subcitrate.

cited in the text, and updated at the 1990 World Congress of Gastroenterology. More detailed information is available in papers by Bayerdorffer & Ottenjann [10], Glupczynski *et al.* [11], and McNulty *et al.* [12, 13]. It should be noted that only combination drug therapy has produced useful eradication rates.

Rules for assessing *H. pylori* therapies

In an early study [7], we noted the disappearance of *H. pylori* with therapy, but reappearance of the bacterium in 85% of patients 6 weeks later. Restriction endonuclease analysis of relapsing patients by Langenberg *et al.* [14] demonstrated that apparent reinfection in their patients was usually bacteriologic relapse with the original

Table 13.1 Antibiotics used in the treatment of *H. pylori*

	Notes	MIC ($mg\ l^{-1}$)	Eradication (%)	
			Single agent	Combination therapy
Bismuth subcitrate	abck	4–30	0–40	70–90
Bismuth subsalicylate	abck	4–30	0–10	70–90
Metronidazole	degk	1–4	5	70
Tinidazole	degk	1–4	5	70
Amoxicillin	abdk	<1	10–20	30–40
Ampicillin	abdfhk	<1	20	?50
Penicillin	ai	0.01–0.1	?0	—
Tetracycline	abcfk	0.5–2	10–20	70–90
Minocycline	acf	0.5	?0	—
Doxycycline	abcdi	0.1–3	5	5
Erythromycin	adgk	0.01–1	10	40–60
Clindamycin	ag	2–8	?10	?
Gentamicin	afg	0.1–1	?	—
Furazolidone	abcg	2–12	20–40	30
Nitrofurantoin	abcg	2–12	15–30	30
Rifampicin	afh	0.2–4	?	—
Ofloxacin	bdfgh	0.1–2	13	30
Ciprofloxacin	dfgh	0.1–8	0	—
Cefalexin	abfh	0.5–8	0	—
Cefoxitin	afh	0.1–0.5	?	—
Imipenem	afh	0.12–2	?	—
Thiamphenicol	ai	2–8	0	—
Sulfonamides	j	—	—	—
Vancomycin	j	—	—	—

a, *H. pylori* is (almost) always sensitive *in vitro*; b, monotherapy may be effective in some patients; c, seems to act by a topical effect; d, seems to act by a topical and/or a systemic effect; e, resistant organisms very common in some countries; f, not evaluated fully *in vivo*; g, *H. pylori* quickly develops resistance *in vivo*; h, potentially a useful agent; i, very poor eradication results *in vivo*; j, *H. pylori* is not inhibited *in vitro*; k, effective in double or triple therapy (see text).

strain. This implied that the infections had been inadequately treated, and that a negative biopsy immediately after therapy was useless as an indicator of bacteriologic cure. The explanation for this phenomenon is that reappearance of the organism may be in a patchy fashion, so that biopsy sampling of mucosa results in false-negative specimens in the first month post-treatment.

In a double-blind trial of cimetidine versus bismuth/tinidazole therapy for duodenal ulcer [15], we observed disappearance of *H. pylori* in 29 patients biopsied 2 weeks after completing therapy. During a 12 month follow-up period, relapse of infection occurred in two (14%), and apparent reinfection occurred in one. This suggested that biopsy 2 weeks after therapy was also too soon, since false-negative biopsy results still occurred in 14% of patients. Rauws *et al.* [16] studied patients treated by several different therapies, and found that a negative biopsy 1 month after completing therapy was proof of cure. Reappearance of the bacterium after 1 month was due to reinfection.

For the above reasons, discussion of eradication of *H. pylori* must be based only on studies in which follow-up biopsy was performed more than 28 days after completing therapy. In these studies, the test used to prove eradication should be sensitive, and should detect a component of the bacterium rather than an immunologic response. Currently, biopsy of the gastric mucosa for histology is still the most sensitive means of detecting *H. pylori*. At least two biopsy specimens should be tested by staining, urease tests, immunologic methods, or culture (see Chapter 12). Alternatively, the urea breath test may be used [17]. If the above methods are unavailable, serial antibody titers [18], which show falling titers 1 and 6 months after treatment, are circumstantial evidence of cure (Fig. 13.2).

Agents used in the treatment of *H. pylori*

Bismuth

Pharmacology of bismuth salts

Bismuth is the heaviest non-radioactive element, with an atomic number of 83, and an atomic weight of 209. It is chemically related to phosphorus, arsenic, and antimony, which occur in the same group of the periodic table.

The primary bismuth salt, bismuth nitrate, is produced by the action of concentrated nitric acid on bismuth metal. This may be hydrolyzed to bismuth subnitrate in boiling water. Bismuth nitrate will react in solution with soluble basic salts such as carbonates, salicylates, and citrates to form bismuth subcarbonate, bismuth subgallate, bismuth subsalicylate (BSS) or bismuth subcitrate. With the addition of ammonia, bismuth subcitrate forms a colloidal solution in which the trivalent bismuth atom links to trivalent citrate moieties to produce large complexes in a viscous solution. This solution is now spray-dried to form the current CBS formulation called "swallowable tablets," which are undergoing evaluation in the United States.

Bismuth salts are poorly soluble in water, and in hydrochloric acid they convert to bismuth oxide [Bi_2O_3], bismuth hydroxide [$Bi(OH)_3$], and bismuth oxychloride [BiOCl], which are very insoluble. As a result, most bismuth salts form a precipitate of BiOCl in the stomach. In the upper small intestine they may be converted back to the subcarbonate; but this too is in-

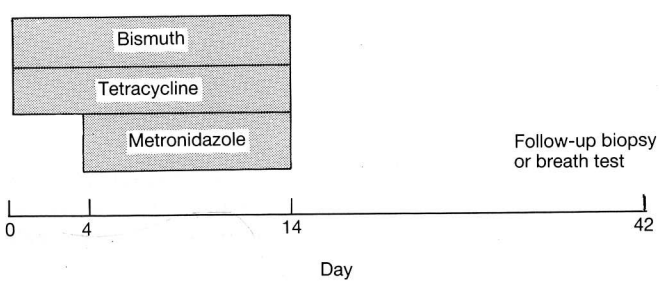

Fig. 13.2 Timeline of therapy for *H. pylori*.

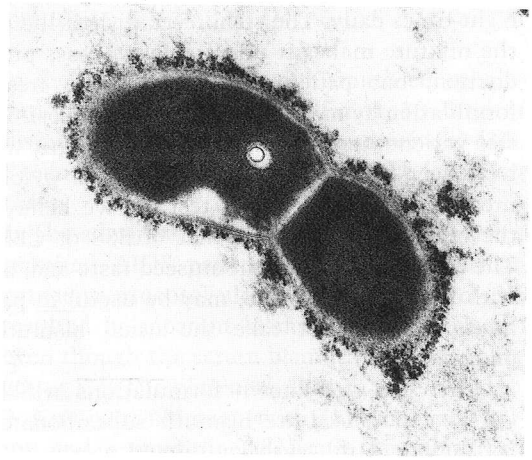

Fig. 13.3 *H. pylori* organism surrounded by dense bismuth granules. The bacterium has detached from the mucosa and is starting to lyse. (Electron micrograph taken 60 minutes after dosing with 120 mg bismuth subcitrate.)

soluble. Only trace amounts of bismuth (1–2% of an oral dose) are absorbed, probably via localization on the brush border glycocalyx of intestinal enterocytes and subsequent phagocytosis by the cells [19, 20].

Bismuth is excreted by the kidneys. The half-life of bismuth in blood is 5 days, but the half-life in cerebrospinal fluid (CSF), a more important factor in estimating toxicity, is 15 days. In the colon, bismuth salts are converted to black bismuth sulfide by the action of H_2S produced by bacteria. This causes the dark stools and tongue staining seen in patients regularly taking bismuth.

Action of bismuth on H. pylori

Bismuth salts probably work as topical antibacterial agents against *H. pylori* in the gastric mucosa. The exact mechanism of bacterial killing is unknown, but may be similar to that of the arsenical antibacterial agents, which are also trivalent cations which bind reversibly to sulfhydryl groups in proteins [21]. The most well-known example of such interaction is the inhibition of glycolytic enzymes by arsenic [22].

In electron microscope studies of gastric mucosa 60 minutes after dosing, bismuth granules are seen encircling non-viable, detached *H. pylori* organisms [7] (Fig. 13.3). The mechanism for this is unknown, but *in vitro*, bismuth salts inhibit *H. pylori* enzymes, particularly urease [23] and phospholipases [24].

Graham *et al.* [25] and Weil & Bell [26] have both noted disappearance of breath test urease activity soon after patients ingested bismuth, suggesting rapid killing of the organism or inactivation of its urease. Lanza *et al.* [27] observed that *in vivo*, clearance of *H. pylori* from gastric mucosa occurred in 80% of patients within 14 days, and that further therapy did not seem to increase the clearance rate. The half-life of bismuth in the gastric mucus may be too short to ensure inhibition of *H. pylori* for more than 4 hours after a dose (see Chapter 15), so more frequent dosing (e.g. 3-hourly) may be worthwhile.

The major advantage of bismuth salts for the treatment of *H. pylori* lies in their very low incidence of major side effects. In the absence of renal failure, there is virtually no toxicity of bismuth when given for 14 days in the doses recommended here.

Bismuth subsalicylate

In the United States, bismuth is readily available over the counter as "Pepto-Bismol" or similar generic formulations. "Pepto-Bismol" is a suspension of bismuth subsalicylate (BSS), 171 mg 10 ml^{-1}, in a vehicle containing magnesium aluminum silicate (montmorillonite clay), methylcellulose, methyl salicylate, and pink food coloring. The tablets contain 262 mg BSS plus 350 mg of calcium carbonate. The usual dose for diarrhea prophylaxis is 30 ml or two tablets, four to eight times daily. Each dose contains salicylate equivalent to 258 mg of salicylic acid [28]. Maximum strength "Pepto-Bismol" liquid contains double the above amount of BSS. Several other generic brands are also available in drug stores.

Early studies with BSS demonstrated that it healed gastritis and suppressed *H. pylori* infection [27, 29], but our observation is that suppression is only temporary. In a double-blind placebo-controlled study in which patients received 21 days' therapy with BSS [30], *H. pylori* was eradicated in only 6% (one in 17). For this reason, BSS is usually used in combination with another antibacterial agent. Only 14

days are required in such courses, so there is no concern about chronic toxicity.

Colloidal bismuth subcitrate

In Europe, Great Britain, and Australia, colloidal bismuth subcitrate (CBS, "DeNol"), is used for the treatment of gastric and duodenal ulcers. In its original form, called "liquid DeNol" or tripotassium dicitrato-bismuthate, it was noted to prevent duodenal ulcer relapse [5], but its antibacterial properties *in vivo* were never tested. It was superseded by a spray-dried tablet form called "chewable tablets," which was also proved to lower duodenal ulcer relapse [31], and which eradicated *H. pylori* in about 30% of patients [15, 32].

More recently, the chewable tablets were replaced by swallowable tablets. The new formulation is probably equivalent to BSS in its antibacterial properties, since it does not eradicate *H. pylori* by itself, but must be used in combination with another antibacterial agent [33]. The dose used is four tablets daily, equivalent to 480 mg of bismuth. Ulcer regimens have used this dose of CBS for up to 8 weeks with only minor elevation of serum bismuth levels [34]. Transient (1 hour) elevations of serum bismuth were noted with swallowable tablets by Nwokolo *et al.* [35].

Alternative formulations of bismuth

In the United States, two other bismuth products can be obtained. Bismuth subgallate is sold as a stool deodorizer for colostomy patients. The 200 mg tablets are available as "Devrom*". The efficacy of the formulation is unknown, but we have used 4–8 tablets per day in patients who say they are allergic to salicylate or "pink dye."

Bismuth subcitrate suspension may be obtained by mail order as "Bismagel**". The suspension comes as 120 mg per 5 ml in a 1 liter bottle. Patients take one teaspoonful four to eight times daily. The stability and shelf-life of the mixture makes it unsuitable for mass production, but patients can obtain the fresh formulation by mail order at reasonable cost. In two patients tested while on this medicine, we have seen complete suppression of *H. pylori* urease on ^{14}C-urea breath test, so we believe the efficacy is similar to that of BSS or CBS. The medicine has a slight aniseed taste and, as with bismuth subgallate, may be useful in patients who cannot take the usual bismuth preparations.

Other less-well-known formulations which we have not used are bismuth subcarbonate, 260 mg per 30 ml, with kaolin and pectin ("K-C†"), and bismuth subgallate, 300 mg per 30 ml, with kaolin ("Dia-Eze††").

In Germany, several bismuth salts were components of over-the-counter antacid medications, allowing them to be quickly revived as *H. pylori* therapy with the discovery of their antibacterial action. Small clinical studies with most of these have demonstrated an ability to suppress *H. pylori* infection, but not to eradicate the organism without the aid of supplementary antibiotics. The names and dosages of these salts are: bismuth subnitrate 350 mg, two tablets t.i.d. ("Ulkowis," Temmler Pharma); bismuth subnitrate 150 mg, and bismuth aluminate 50 mg, two tablets b.i.d. ("Angass," Medice-Iserlohn); bismuth subgallate 50 mg, and bismuth subnitrate 100 mg, two tablets t.i.d. ("Bismofalk," Falk); bismuth aluminate 200 mg, two tablets t.i.d. ("Campylotec," Pfizer; "Ultin," DrRentschler). In addition, the more-well-known bismuth salts are available, such as CBS ("Telen," Byk-Gulden) and BSS ("Jatrox," Rohm-Pharma).

In evaluating potential *H. pylori* therapeutic agents, shrewd pharmaceutical companies still prefer to measure efficacy as *H. pylori* "clearance" immediately after therapy. This allows publication of suppression results, rather than the exhibition of very much weaker cure data from biopsy samples taken 1 month later.

* The Parthenon Co Inc, 3311 West 2400 South, Salt Lake City, Utah 84119 (1-800-453-8898).
** Clark Pharmacy, 15615 Bel-Red Road, Bellevue, Washington, 98008 (206-881-0222).

† Century Pharmaceuticals, 10377 Hague Road, Indianapolis 46256 (317-849-4210).
†† Central Pharmaceuticals, 120 E. 3rd St., PO Box 328, Seymour, Indiana 47274-9985 (812-522-3915).

Safety of bismuth salts

In the French epidemic of bismuth encephalopathy, patients often consumed 10–20 g of bismuth subnitrate or subgallate per day [36]. Recent reports of toxicity include the following cases:

1 The administration of high doses of BSS to a terminal AIDS patient with diarrhea due to extensive mucosal ulceration of the bowel [37] resulted in apparent bismuth encephalopathy, even though the serum bismuth level was only 200 $\mu g l^{-1}$. The patient died from other causes.

2 A 68-year-old man with chronic renal failure and a creatinine clearance of only 15 ml $minute^{-1}$ consumed twice the recommended amount of liquid "DeNol" (CBS) for 8 weeks [38]. He developed encephalopathy with a serum bismuth level of 880 $\mu g l^{-1}$. The syndrome was completely reversible over 50 days, in which time the EEG returned to normal and serum bismuth fell to below 50 $\mu g l^{-1}$. This formulation of bismuth is no longer available.

3 Acute renal failure developed 10 days after a 27-year-old man took 100 "DeNol" tablets in a suicide attempt [39]. The colon was found to be still loaded with bismuth. Encephalopathy was not present, even though the serum bismuth level was only slightly elevated at 260 $\mu g l^{-1}$. With purgation and hemodialysis he completely recovered in 5 days.

4 A 76-year-old man took 80 "DeNol" tablets in a suicide attempt [40]. He died eventually from a perforated duodenal ulcer, but developed encephalopathy and renal failure with a serum bismuth level of 1600 $\mu g l^{-1}$.

In the doses recommended here I have never seen a side-effect related to bismuth accumulation. I do not keep patients on bismuth salts longer than 2 months and, if repeated courses are required, the patients take the drug for only 2 months in every 4 months. In patients who have taken more than 4 months' bismuth therapy in 1 year, I estimate the plasma bismuth level before prescribing more. Done by atomic absorption spectrometry at an experienced laboratory, levels less than 5 $\mu g l^{-1}$ can be detected. A bismuth concentration of 100 $\mu g l^{-1}$ (100 ppb or 480 $nmol l^{-1}$) is the upper limit of the safe range, although most patients with encephalopathy have blood levels in the 200–2000 $\mu g l^{-1}$ range.

In patients with renal failure, bismuth is best avoided since the potential for toxicity is high. On the other hand, absorption is unlikely to be a problem if a single 14-day course is used. If BSS is given, the chance of salicylate toxicity also needs to be considered.

Metronidazole and tinidazole

Nitroimidazoles are used mainly for the treatment of anaerobic infections and parasites such as *Giardia* and *Trichomonas*. They are secreted in saliva and differ from each other only in dosage and half-life. Tinidazole is usually given as a single daily dose of 1 g, whereas metronidazole is given as 250–500 mg t.i.d.

In developed countries, about 75% of *H. pylori* isolates are sensitive to nitroimidazoles [12]. Goodwin *et al.* observed that the bacterium immediately became resistant to nitroimidazoles if they were used as single antibacterial agents [41]. This phenomenon meant that eradication of *H. pylori* was seen in only one of 29 patients (4%) given a cimetidine/tinidazole combination.

Similarly, any person previously exposed to nitroimidazoles, whether for *H. pylori* therapy or for other reasons, is likely to have a resistant *H. pylori* organism. Since women are more commonly treated with these drugs, their carriage of resistant *H. pylori* is slightly greater than men. In areas where parasitic infections are commonly treated with metronidazole, resistant isolates are far more common, so much so that Glupczynski *et al.* [42] do not recommend the use of metronidazole in Africa.

Resistance to nitroimidazoles does not usually develop if a second antimicrobial drug is given concurrently. This was first observed with tinidazole/bismuth therapy, but appears to hold true if the bismuth is replaced with amoxicillin or tetracycline. The reason for this was studied by Goodwin *et al.* [41], who were able to select out resistant *H. pylori* isolates from broth cultures of organisms which on initial assessment appeared to be inhibited by nitroimidazoles. It is suspected that the large pool of gastric *H. pylori* present in infected persons ($\approx 10^{10}$ organisms) usually contains a few with inherent nitroimidazole resistance.

Exposure to the agent selects out the resistant organism, which becomes the predominant strain. After initial suppression of infection, gastritis redevelops in a week or so as the resistant isolate recolonizes the stomach.

If *H. pylori* is attacked initially with bismuth or amoxicillin, only a few organisms remain viable and the chances are that a nitroimidazole-resistant strain will not emerge. The bismuth salt or antibiotic used is not critical for this effect, as long as "sterilization" of the mucosa is achieved before the nitroimidazole reaches the gastric mucosa. Failure of sensitive organisms to be eradicated by bismuth/nitroimidazole combinations might be due to incomplete coating of the gastric mucosa with the bismuth drug. Both Lanza *et al.* [29] and McNulty *et al.* [28] found that 20% of patients still have detectable organisms while on bismuth. In such patients the bismuth therapy would not be expected to protect against development of resistance. Our own experience is that when *H. pylori* is sensitive, 90% of patients are cured during dual therapy with bismuth and metronidazole [43, 44]. Whenever failure occurs with this therapy, a resistant isolate has emerged.

The optimal duration of *H. pylori* therapy has not been decided. Several investigators have reported success using 5- or 7-day therapies, but no direct comparison with 14-day or 28-day therapy has been performed. At the World Congress of Gastroenterology, held in Sydney, Australia, in 1990, the working party on *H. pylori* recommended a 14-day therapy of bismuth (CBS), one tablet q.i.d., in combination with metronidazole 1 g day^{-1} and tetracycline 2 g day^{-1}. Presently, we continue to use a 14-day therapy, with 10 days of metronidazole commencing on the 4th day. The dose of metronidazole is 20 mg kg^{-1} day^{-1} (1–1.5 g day^{-1} as a t.i.d. dose). Doses less than 1 g day^{-1} may be less effective (C. O'Morain, personal communication).

Side-effects with nitroimidazoles are common, but usually of little consequence. The drugs are known to give a positive result with the "Ames Test," a sensitive bacteriologic indicator of genetic damage. Nitroimidazoles are therefore potentially teratogenic and carcinogenic, and should be avoided in women who might be pregnant. Chronic use can cause a reversible peripheral neuropathy, but has not been seen in any of our patients treated for only 10 days. The drugs also have a disulfiram-like effect, so alcohol should be avoided while taking them. High doses cause a metallic taste in the mouth and may alter the bacterial flora, causing a temporary (1–2 weeks) furry coat on the tongue. Diarrhea occurs in around 20%, but in our experience is limited to the duration of therapy. Since nitroimidazoles are always given in combination with other agents, the cause of the side-effects is often uncertain, and could equally be due to bismuth or the other agent.

Amoxicillin

Amoxicillin is the most widely reported penicillin used in the treatment of *H. pylori*. Amoxicillin and ampicillin are acid-stable and are absorbed from the stomach as well as the intestine. Although all isolates of *H. pylori* are sensitive to amoxicillin *in vitro*, treatment results *in vivo* have been disappointing. For example, Rauws *et al.* found only a 10–20% cure rate using the drug as monotherapy [16]. The failure of amoxicillin monotherapy to eradicate *H. pylori* has not been adequately explained. McNulty *et al.* [13] studied mucosal levels of pivampicillin (an ampicillin pro-drug) and amoxicillin. They observed levels 2–10 times the serum level of antibiotic, easily exceeding the *in vitro* MIC for *H. pylori*. In contrast, Cooreman *et al.* [45] reported levels of only 0.2 mg l^{-1} in the antrum, and levels were even lower than this in corpus mucosa.

Eradication rates for penicillins which are not soluble in gastric acid (e.g. phenoxymethyl penicillin) have not been published, but are believed to be negligible. This suggests that gastric absorption of penicillins is important and luminal activity is responsible for eradication.

After some initial success in individuals, Goodwin *et al.* [41] treated patients with 14 days of CBS plus amoxicillin 2 g day^{-1} for either 7 or 14 days. Cure rates were around 40% for both regimens. At the University of Virginia, we have achieved cure rates of only 30% using amoxicillin/BSS combinations, so we do not use

it as first-line therapy. In four of our patients, doses of amoxicillin up to 4 g daily for 14 days did not eradicate *H. pylori*, and in one patient pseudomembranous colitis developed.

Amoxicillin has been used as a supplementary antibiotic in combination with metronidazole or tinidazole. In this role it appears to act similarly to bismuth, perhaps sterilizing the gastric mucosa with a topical action and preventing the emergence of nitroimidazole resistance. In children, amoxicillin/tinidazole therapy eradicated 75% of infections during a 6-week course [18]. The dose of tinidazole was 20 mg kg^{-1} day^{-1} and of amoxicillin was 50 mg kg^{-1} day^{-1}.

Of interest is the observation that amoxicillin cure rates can be increased by adding omeprazole. In a controlled study, Unge *et al.* [46] observed eradication in 60–70% of patients given combination therapy with the two drugs. This suggests that *H. pylori* is protected by acid in the gastric lumen or in the parietal cell glands, and becomes adequately exposed to amoxicillin only when omeprazole is given. Lamouliatte *et al.* have had less success than the Swedish investigators, and only found a 40% cure rate using a dose of omeprazole 20 mg day^{-1} in combination with amoxicillin 2 g day^{-1} [47].

Triple therapy regimens have also benefited from the inclusion of amoxicillin. Coelho *et al.* [48] have reported 83% eradication of *H. pylori* in six patients treated with a regimen of furazolidone 100 mg, amoxicillin 500 mg, and metronidazole 250 mg, all given t.i.d. for 5 days. Note that the value of furazolidone remains unproved in this successful triple therapy regimen, since high cure rates are also obtained with amoxicillin and metronidazole dual therapy [18].

Since side-effects are related to duration of therapy, there are many advantages to using a short, rapidly-bactericidal therapy, but controlled trials comparing these short intensive therapies with bismuth combination therapies have not been performed.

Side-effects with amoxicillin are penicillin allergy, candidiasis, and diarrhea. We have not seen *C. difficile* colitis in patients given metronidazole/amoxicillin combinations, but two patients given amoxicillin/bismuth have developed it. We do not usually pursue the diagnosis if diarrhea is mild, proctoscopy is normal, stool is guaiac-negative and fecal leukocytes are absent.

Tetracyclines

H. pylori is always very sensitive *in vitro* to tetracyclines, and several have been studied as agents for *H. pylori* therapy. They vary in their half-life and acid stability, causing McNulty *et al.* [13] to suggest that tetracycline, which is active at low pH, would be the best agent to use. Tetracyclines chelate with bismuth salts, preventing absorption of the antibiotic [49]. This is not a problem in practice, since both bismuth and tetracycline may be acting topically in the stomach rather than depending on absorption for their action. Tetracycline, a less-well-absorbed drug than doxycycline, appears to be more effective for *H. pylori*, again pointing to a topical rather than a systemic antibacterial action. Minocycline, also poorly absorbed, may be an alternative. There are no data to suggest that spacing of tetracycline away from bismuth doses makes any difference to efficacy. Neither are there data to show that relationship to meals is important in *H. pylori* eradication.

Doxycycline has been studied by several investigators and found to be ineffective at eradicating *H. pylori*. At the University of Virginia, we did not see eradication in any of 15 patients treated with a doxycycline/BSS combination. Morris & Nicholson [50] and Unge & Gnarpe [51] have had similar experience. Unge found that doxycycline levels in mucosa were less than serum levels, perhaps explaining his poor results. Tetracyclines are concentrated in bile, so they may be useful in the post-gastrectomy stomach. Meshkinpour *et al.* [52] noted an excellent and reproducible clinical response in some individuals given doxycycline for "bile gastritis."

My own practice is to use doxycycline only as a "holding action" in patients who are acutely ill (with vomiting), who do not tolerate other medications. Suppression of *H. pylori* does occur, and the small once-daily dose (100–200 mg) is easy for nauseated patients to take. When the acute symptoms subside, more effective curative combinations can be started.

Erythromycin and other macrolides

Erythromycin

Erythromycin is available as erythromycin base, erythromycin stearate, erythromycin ethylsuccinate, and erythromycin estolate. The acid-stable forms of the drug were developed because erythromycin base, the active form, was quickly destroyed in gastric acid. Some of the gastric side-effects of erythromycin may be induced by acid metabolites [53] rather than erythromycin itself, so the acid-stable pro-drug forms are also better tolerated by patients. Erythromycin also increases gut motility by stimulating motilin receptors in the stomach. Abdominal cramping, gnawing, nausea, and diarrhea are all common with erythromycin therapy, often limiting its use. Erythromycin is secreted in bile, so may have more useful action in patients with free bile reflux.

Erythromycin stearate (ES), and erythromycin ethylsuccinate (EES), although acid-stable, are less active than erythromycin base and must be metabolized to the active drug after absorption. This may result in less activity for gastric infections. McNulty *et al.* [28] found that EES by itself eradicated less than 20% of *H. pylori* infections, suggesting that serum activity was ineffective at clearing the gastric mucosa. This poor *in vivo* effect is in striking contrast to the very low MIC seen for *H. pylori* with erythromycin *in vitro*. When mucosal levels of erythromycin were studied, McNulty *et al.* found 1–5 mg l^{-1}, about twice the serum level, to be present, but this still exceeded the MIC (0.1–1.0 mg l^{-1}).

Alternatives to locally inactive acid-stable formulations are enteric-coated erythromycin base delivered as small granules within a capsule ("Eryc," Park-Davis), and erythromycin base film-coated tablets ("Erythromycin base filmtabs," Abbott). The "Eryc" granules do not normally decompose until 90 minutes after they reach the neutral pH of the intestine, so they have fewer gastric side-effects and attain higher blood levels than the other forms of the drug. To achieve gastric dissolution and local action of the enteric-coated granules, the stomach should be rendered neutral with either high-dose H2 receptor antagonists or omeprazole, and the drug should be given with food.

Film-coated erythromycin base tablets can be expected to decompose in the stomach and supply active erythromycin to the mucosa, if the gastric pH can be kept neutral. I usually ask patients to take as much as they can tolerate of the 250 mg tablets by dosing every 3 hours. This ensures good absorption (a.c. doses) and prolonged gastric retention (p.c. doses). Therapy with high-dose H2 receptor antagonists (famotidine, 40 mg b.i.d.) or omeprazole, 40 mg day^{-1}, has given a cure rate of 70% in 30 patients we have treated with combination therapy B (see Fig. 13.4).

Erythromycin and bismuth appear to be synergistic *in vivo*. Goodwin *et al.* [41] observed that "DeNol" chewing tablets q.i.d., in combination with erythromycin ("Eryc"), achieved a 60% cure as assessed 14 days after treatment. These good results were in contrast to those reported by McNulty *et al.* [28] using EES alone. The improved clearance seen with combination therapy suggests that, whereas luminal and acid-exposed organisms are easily cleared by the bismuth, organisms in neutral pH areas such as antral mucus glands are attacked by erythromycin, either via the gastric lumen or systemically.

Our current practice at the University of Virginia is to use erythromycin combinations as second-line therapy for persons with metronidazole-resistant organisms. We always give the drug with acid reduction therapy (e.g. famotidine, 40 mg b.i.d., or omeprazole, 40 mg day^{-1}), to increase its gastric luminal activity and to decrease side-effects.

Other macrolides (clindamycin, azithromycin)

Clindamycin has been studied both as monotherapy, and in combination with BSS (U. Westblom, personal communication). Low eradication rates were achieved, suggesting that this is not a useful therapy. Theoretically, clindamycin should have been effective, since it is acid-stable and achieves very high intracellular levels in gastric mucosa and polymorphs, and is excreted in the bile [54].

Azithromycin, an acid-stable macrolide with a very long half-life, was also found to be

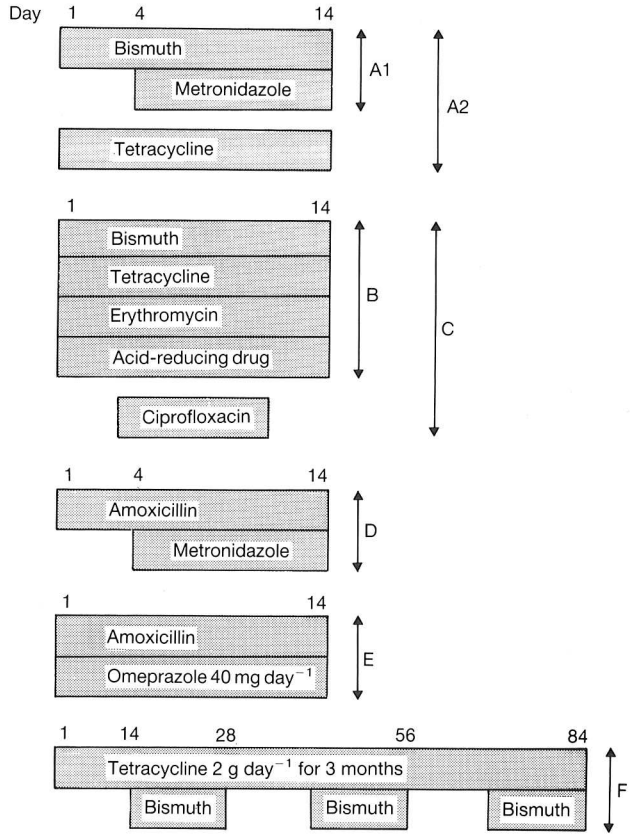

Fig. 13.4 Useful proven (A1, A2, B, D, E) and experimental (C, F) *H. pylori* therapies (see also Table 13.2).

ineffective for treating *H. pylori*. Glupczynski & Burette [55] found that 10 of 12 patients had persistent *H. pylori* during 7 days of azithromycin monotherapy, and that the infection relapsed in the remaining two. In most cases a resistant strain developed, tolerant also to erythromycin, clindamycin, and other macrolides. Similar poor results were seen with josamycin [56], which has been found to cause resistant *H. pylori* strains to emerge *in vitro* [57]. As with metronidazole and quinolones, a small proportion of *H. pylori* organisms seem to carry inherent macrolide resistance and emerge as the dominant strain when exposed to the drug. Thus, macrolides are best used in combination therapy rather than alone.

Rifampicin

Rifampicin has not been studied *in vivo* for the treatment of *H. pylori*, but may have some use. Experience with other organisms suggests that it should be used in combination therapy rather than alone, because resistant mutant bacteria usually emerge [54]. The MIC suggests that *H. pylori* is moderately sensitive to the drug and that mucosal levels will be adequate. The dose is 600–1000 mg day^{-1} (10–20 mg kg^{-1} day^{-1}), and the drug is available as 150 or 300 mg tablets. Absorption is not affected by food. Useful levels are found in saliva, and bile levels are 100 times those found in serum. Because of biliary excretion, lower doses are recommended in persons with liver disease.

Rifampicin is lipid-soluble and reaches high concentrations inside phagocytic cells, thus killing intracellular organisms. Mandell has shown it to be useful against *Staphylococcus aureus* in chronic granulomatous diseases caused by defective intracellular killing mechanisms [58]. A parallel exists in that *H. pylori* is chronic, phagocytosis occurs, immune mechanisms cannot eradicate the bacterium, and *H. pylori* is a strong catalase producer like *S.*

aureus. Catalase enzyme is known to protect phagocytosed bacteria from superoxide, the usual mechanism neutrophils use to kill ingested organisms [59].

Although I have no experience with rifampicin, I plan to try the drug in triple therapy regimens for patients with resistant organisms.

Quinolones (ciprofloxacin, norfloxacin, ofloxacin)

Quinolones inhibit *H. pylori in vitro* but have had limited success when used *in vivo*. Bayerdorffer *et al.* [60] reported that ofloxacin enhanced duodenal ulcer healing when used in addition to ranitidine. This effect was noted even though *H. pylori* could not be eradicated by the combination. When persistent *H. pylori* isolates were examined *in vitro* after therapy, they were found to be resistant to all quinolone drugs. Thus, quinolones cannot be used as monotherapy.

The failure of quinolones to eradicate *H. pylori* is paradoxical, because they achieve very high levels (2–10 × serum concentration) in the gastric mucosa [13]. Their use in combination regimens has not been evaluated, but they may have an adjuvant role in patients with resistant infections. Ciprofloxacin (which is less effective for *H. pylori*) is secreted in bile at 5–10 times the serum concentration [54]. Ofloxacin is secreted in saliva at concentrations equal to that in serum. We have used ciprofloxacin 1–1.5 g day^{-1} as a supplementary agent to triple therapy in a few patients (see Table 13.1), but it is very expensive and currently unproved. I recommend that, if it is available, ofloxacin, 300 mg day^{-1} be used instead of ciprofloxacin, since it has been proved to have some action *in vivo* against *H. pylori* [60].

Nitrofurantoin and furazolidone

The first reports suggesting activity for these drugs came from China, where Zheng *et al.* reported gastric and duodenal ulcer healing with low relapse after treatment with furazolidone [61]. The ulcer-healing action of the drug had been observed in China even before the discovery of *H. pylori*. Later reports by Morgan *et al.* [62] and by Borsch *et al.* [63] have shown that both furazolidone and nitrofurantoin are relatively ineffective as single agents in doses as high as 400 mg day^{-1}. In addition, gastric side-effects made clinical response difficult to assess. Morgan *et al.* found that *H. pylori* was usually suppressed, but eradicated in only 20–40% of the patients they could follow up [62].

Furazolidone is poorly absorbed and has been used in the United States as therapy for traveler's diarrhea. It is available as a 25 mg ml^{-1} suspension ("Furoxone," Norwich-Eaton) and as 100 mg tablets. The adult dose is 400 mg day^{-1} [60]. The drug has many gastrointestinal side-effects and sometimes causes a disulfiram-type reaction with alcohol. Nitrofurantoin has similar activity against *H. pylori*, although it is well absorbed and is usually used for urinary tract infections. The drug is available in a suspension (25 mg per 5 ml) and in 50 mg tablets ("Macrodantin," Norwich-Eaton). The daily dose is 200–400 mg. If used for *H. pylori*, frequent small doses may be most effective (see below).

Nitrofurans retain their *in vitro* activity towards *H. pylori* and may have some use as topical agents for the gastric mucosa. Graham *et al.* [25] have demonstrated that frequent low-dose furazolidone suspension (7 mg, seven times daily) suppresses *H. pylori* in most patients as assessed by ^{13}C-urea breath test. This suggests that it may be used as a gastric luminal antibacterial agent, supplementing the actions of bismuth, tetracycline, and amoxicillin. Against this are data from Borsch *et al.* [63], who did not observe any extra benefit if furazolidone was combined with BSS.

Triple therapy

Triple therapy (antibiotic/metronidazole/bismuth) gives far better *H. pylori* eradication than single drug therapy, but direct comparisons with dual therapy (metronidazole/bismuth) have not been performed. Borody *et al.* [64, 65] achieved 90–95% eradication using DeNol chewing tablets q.i.d. (28 days), tetracycline, 500 mg q.i.d. (28 days) and metronidazole, 200 mg q.i.d. (10 days). Most of the patients were suffering from duodenal ulcer in Borody *et al.*'s study. McNulty *et al.* [66] used this regimen in patients with non-ulcer dyspepsia, but only achieved a 65% eradication. Our experience is that triple therapy does not

eradicate metronidazole-resistant organisms present in 10–25% of patients. Direct comparison studies have not been performed.

Triple therapies have the advantage of luminal activity and systemic activity. Luminally-active agents are bismuth, tetracycline, amoxicillin/ampicillin, and perhaps furazolidone [67]. Combining two luminally-active agents causes marked suppression of *H. pylori* and may have an inherent cure rate of 10–40%. In addition, these agents do not appear to cause resistance, so they may be used in repeated courses and in various combinations.

The luminally-active component of triple therapy usually includes bismuth because it is cheap and has very few side-effects. Tetracycline/bismuth, amoxicillin/bismuth, and tetracycline/amoxicillin are all effective, but the last two combinations may give more side-effects due to the broad-spectrum antibacterial suppression they produce. It is our experience that bismuth is very well tolerated except for patients allergic to the salicylate in BSS. With multiple antibiotic therapies, many patients develop vaginal or oral candidiasis or diarrhea. Usually we provide a prescription for topical antifungal therapy to be taken if needed.

Systemic action is achieved primarily with metronidazole or tinidazole. The dose of metronidazole is $20\,mg\,kg^{-1}\,day^{-1}$, which results in 1–1.5 g total daily dose. Borody *et al.* have achieved success using $800\,mg\,day^{-1}$ [64], although O'Morain has had less success with this lower dose, and now uses at least $1\,g\,day^{-1}$ (personal communication). If *H. pylori* is known to be resistant to nitroimidazoles, or if the patient has previously failed therapy with metronidazole, then metronidazole should be replaced with erythromycin, 500 mg q.i.d. Whenever erythromycin is used, omeprazole, $40\,mg\,day^{-1}$, or famotidine, 40 mg b.i.d., should be given to reduce gastric acidity.

Several regimens used successfully at the University of Virginia are described in Fig. 13.4 and Table 13.2.

Patients with severe gastric symptoms

In patients who are very unwell, and intolerant of high-dose antibiotic therapy (for example, with nausea and vomiting), triple therapy should be introduced cautiously. Commence treatment with bismuth (usually BSS, "Pepto-Bismol") as one tablet every 3 hours, supplemented with antiemetic and H2 blocker medication if necessary. When symptoms have settled somewhat, add tetracycline 250 mg every 3 hours, and finally metronidazole, 500 mg b.i.d. or t.i.d., can be commenced. If triple therapy can be continued at full dose for 5 days, cure should be expected. Patients in whom *H. pylori* is the only identifiable pathologic process will usually settle over 2–4 weeks. Continued symptoms may reflect delayed gastric emptying and should be treated concurrently with prokinetic agents (e.g. metoclopramide, or cisapride).

If a culture is available and the organism is found to be sentitive to metronidazole, therapy can be started with bismuth and supplemented with a quick course of metronidazole (oral or by suppository). This will result in the lowest possible incidence of side-effects and will give a very high cure rate. After therapy, symptomatic treatment is all that is necessary and symptoms settle over 2–4 weeks.

Duration of therapy

The optimal duration of therapy for *H. pylori* eradication is not known, but treatment courses as short as 5 days have been successful. Shorter therapy may have better compliance and fewer side-effects, as well as being less expensive. Since comparative studies have not been performed, we still recommend 14 days' treatment as routine. Longer therapy is not necessary, except when long-term suppression of a resistant *H. pylori* organism is planned (e.g. with bismuth or tetracycline).

There is a theoretical advantage to starting bismuth/tetracycline therapy 1–4 days prior to metronidazole. The broad-spectrum combination should cause marked suppression of *H. pylori* in this time, preventing the emergence of a resistant strain of *H. pylori* once the patient is exposed to metronidazole. In practice this may be of marginal benefit, since sensitive isolates had an 85% cure rate with dual therapy in the study reported by Marshall *et al.* [68], and the excellent results achieved by Borody *et al.* [64] reflect contemporaneous institution of triple therapy.

Table 13.2 Examples of triple therapy treatment of *H. pylori*

A1 90% cure in metronidazole-sensitive isolates, 70% cure if given blind (United States), depending on level of metronidazole resistance in the population	BSS ("Pepto-Bismol"), 1 tablet every 3 hours for 14 days (preferred); *or* 2 tablets q.i.d. for 14 days; *or* CBS ("DeNol"), 1 tablet q.i.d. (120 mg) for 14 days *AND* Metronidazole, 250 mg four to six times daily (20 mg kg^{-1} day^{-1}) for 10 days; *or* tinidazole 1 g day^{-1} for 10 days
A2 75–90% cure if given blind, depending on level of metronidazole resistance in the population. Good results in Sydney and Houston (duodenal ulcer patients), only 65% cure in United Kingdom (non-ulcer dyspepsia patients)	To A1, add tetracycline, 2 g day^{-1} for 14 days
B 60–80% cure in metronidazole-resistant organisms at University of Virginia. Side-effects of erythromycin limit its use in some patients.	BSS ("Pepto-Bismol"), 1 tablet every 3 hours for 14 days (preferred); *or* 2 tablets q.i.d. for 14 days; *or* CBS ("DeNol"), 1 tablet q.i.d. for 14 days *AND* Tetracycline, 250 mg eight times daily for 14 days *AND* Erythromycin, 250 mg eight times daily for 14 days *AND* Famotidine, 80 mg; *or* ranitidine, 600 mg; *or* omeprazole, 40 mg, daily for 14 days
C 40% of patients who fail therapy B obtain cure with regimen C ($n = 5$). The quinolones can only be used once because of antibiotic resistance. Instead of ciprofloxacin, try ofloxacin if it is available	Supplement B with ciprofloxacin, 500 mg b.i.d. or t.i.d. for 7 days. Use omeprazole as acid-reducing agent if possible
D 70% cure in several studies	In A1, bismuth and/or tetracycline can be replaced with amoxicillin, 1500–2000 mg day^{-1}
E ? 50% cure. Small numbers of patients treated but a very simple therapy	Amoxicillin, 250 mg every 3 hours for 14 days *AND* Omeprazole, 40 mg day^{-1} for 14 days
F ? 40–50% cure. Small numbers treated. A cheap regimen suitable for patients who have failed many other therapies and require suppression	Tetracycline, 500 mg q.i.d. for 3 months *AND* Any bismuth salt every 3 hours in 14-day pulses every month
G ? 40–50% cure. A modification of F incorporating breath test monitoring	Start bismuth salt as in A1, check breath test after 1 week. If breath test is still positive, increase the dose and add tetracycline, 250 mg every 3 hours. Repeat breath test. Escalate therapy with further suppressive agents (furazolidone, nitrofurantoin, amoxicillin) until breath test is negative, then add bactericidal drug(s) (erythromycin, amoxicillin, ?ciprofloxacin, rifampicin) for 14 days

Management of patients with *H. pylori*

Screening for *H. pylori*: is culture necessary?

At all endoscopies, the presence or absence of *H. pylori* should be ascertained by biopsy of the antrum. If the endoscopist is merely screening for the presence of the organism and the endoscopy is normal, then a rapid urease test such as the CLOtest is sufficient. If culture and sensitivity can be done, a second biopsy should be taken for microbiological studies because this extra information is a useful guide to therapy. It is our practice to discard this biopsy if the CLOtest is negative. If the CLOtest indicates presence of *H. pylori*, then the extra expense of culture is justified and the refrigerated culture specimen is processed. At the University of Virginia our endoscopy population has an *H. pylori* prevalence of 35%. Allowing a sensitivity of 95% for the CLOtest, we correctly determine the *H. pylori* status in 98 out of every 100 patients we screen, and HP− patients do not bear the expense of culture.

In CLOtest-positive patients, culture and antibiotic sensitivity testing of *H. pylori* takes about 10 days. While waiting for results, the patient should be treated with conventional ulcer therapy. If antibiotic sensitivity cannot be performed, then "blind" triple therapy for *H. pylori* may be commenced immediately, concurrently with acid-reducing ulcer therapy if indicated.

If the patient is very unwell, commence H2 receptor antagonists (H2RAs) and other appropriate symptomatic therapy, add bismuth as tolerated, then add the other antibiotics when the patient can tolerate them. Any treatment which suppresses *H. pylori* will provide maximal clinical improvement, so the drug used initially for this purpose is not critical. In this scenario it is my practice to use BSS ("Pepto-Bismol"), one tablet four to eight times daily, because it has the lowest potential for side-effects. *H. pylori* gastritis and associated ulcers should heal very quickly on any antibiotic/H2RA regimen and related symptoms should improve in 3–7 days.

When antibiotic sensitivity results are available, our usual practice is to mail the patient a prescription for the optimal combination. For organisms sensitive to metronidazole, we prescribe a 14-day course of BSS, one tablet eight times daily for 14 days, with the addition of metronidazole, 250 mg four to six times daily, from day 4 to day 14. At the end of therapy, patients who are well may take ulcer medication on a p.r.n. basis (as necessary), since nearly all ulcers will have healed after 1 month of *H. pylori*/H2RA therapy [59].

Metronidazole failure and persistence

In patients with metronidazole-resistant organisms, metronidazole or tinidazole add nothing to the efficacy of triple therapy [42]. After treating the acute ulcer and its symptoms as described above, second-line triple therapy may be commenced using bismuth–tetracycline–erythromycin. The duration of therapy should be 14 days, with erythromycin being given from day 1 to day 14. As described above, erythromycin in the required dose (2 g daily) has many side-effects which may benefit from acid-reducing therapy. Omeprazole, 40 mg daily, ranitidine, 300 mg b.i.d., or famotidine, 40 mg b.i.d., is usually added. Before starting second-line therapy, patients should be warned that they have a resistant organism which will be hard to treat, and that the cure rate for each course of therapy may be no more than 50%.

After therapy, patients should avoid all antibacterial drugs until follow-up study 1 month later. This may be endoscopy with biopsy, or breath test. If these tests indicate continuing infection, therapy should be repeated with an alternative antibiotic combination.

Treatment failures

Antibacterial therapy for *H. pylori* is ultimately limited by the occurrence of side-effects. Although these are rarely serious, patients in clinical remission with a persistent *H. pylori* infection will eventually decide to return to maintenance therapy of some kind, rather than continue with antibacterial regimens which have a progressively lower cure rate. Some patients experience marked improvement in their symptoms each time a suppressive therapy is given, and thus may request continued antibacterial therapy of some sort. Options at this

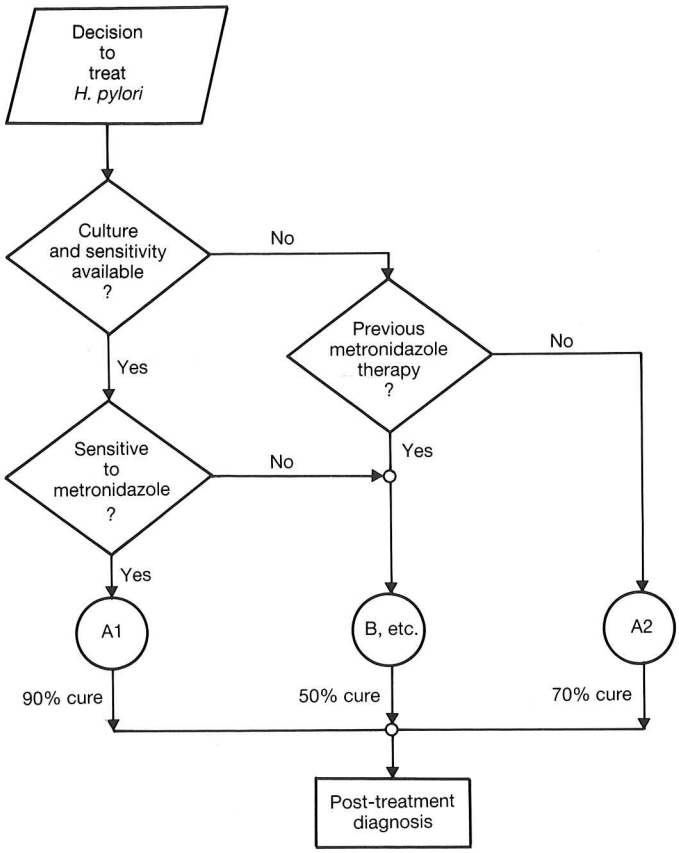

Fig. 13.5 Flow chart for antibiotic treatment of *H. pylori*.

stage include intermittent bismuth therapy (BSS, CBS), or antibiotics such as tetracycline, doxycycline, or amoxicillin. Since a topical suppressive effect is needed, I recommend that patients disperse the drug in water and take it morning and night on an empty stomach.

In patients who fail the usual therapy, an increased dose or different bismuth formulation may be successful. In occasional patients we have commenced treatment with BSS and monitored its efficacy 1 week later with a ^{14}C-urea breath test. If urease is still present, the dose is doubled for a further week and the breath test repeated. In this fashion, antibacterial agents can be added in a stepwise fashion until suppression of *H. pylori* has been achieved. Once the breath test is negative, the combination can either be continued for 4–6 weeks, or an additional agent can be added for a short burst of intensive therapy. An example would be the addition of erythromycin/omeprazole, amoxicillin/omeprazole, or ciprofloxacin/erythromycin/omeprazole. No doubt all these combinations are likely to cause side-effects, but they will be requested by well-motivated patients whose symptoms obviously respond to antibacterial therapy.

Using the flow chart in Fig. 13.5, 80–90% of patients will respond to an initial course of triple therapy or metronidazole/bismuth dual therapy. Of the remaining 10–20%, half will be cured with one of the alternative regimens, given as either the initial therapy (if sensitivities were obtained) or as a second therapy. Thus, after one or two treatments, 90% of all patients will have been cured of *H. pylori*. The remaining 10% will have the option of continuing therapy, trying long-term suppression, or abandoning attempts to eradicate *H. pylori*. At the University of Virginia, where all gastritis clinic patients are offered *H. pylori* therapy, we have eradicated the organism from 100 patients,

15 patients decided not to be treated, and in 15 patients treatment was abandoned after several unsuccessful attempts. Poor compliance is a factor in some of these treatment failures. They commonly occur in patients with limited financial resources who cannot afford the expense of therapy.

Reinfection

Reinfection is uncommon in Western countries. At the University of Virginia we have seen apparent reinfection in three patients (3%) followed for 1 year. In Australia the reinfection rate is similar, about 5% [15, 65]. In most reinfected patients a family source can be identified. Langenberg *et al.* report that in 0.1–1.0% of patients, reinfection occurs during endoscopy [69]. For this reason, I recommend that a dose of bismuth subsalicylate be given after follow-up endoscopy of HP− patients.

Should infected spouses be treated?

It is our practice to screen patients' spouses with the ^{14}C-urea breath test. Infected symptomatic spouses will usually request therapy, and so no dilemma exists in this group. Infected asymptomatic spouses need not be treated, because reinfection of the patient is the exception rather than the rule. If the patient's first course of therapy was effective, then it is simple enough to treat the spouse with the same thing and follow up with a breath test. If infection persists in the spouse, I do not usually attempt further therapy unless a clinical indication develops or the patient becomes reinfected.

Duodenal ulcer

As shown in the accompanying flow chart (Fig. 13.6), therapy for duodenal ulcer disease should be a two-pronged attack aiming both at the ulcer and the underlying gastritis. H2RAs do not appear to impair *H. pylori* eradication attempts, so may be used prior to, or concurrently with, antibacterial regimens. The patient should be given a proven ulcer-healing agent for at least 4 weeks. In the United States this will be H2RA, sucralfate, or perhaps omeprazole. In Europe and Britain, CBS ("DeNol") may be used for the ulcer-healing agent, and also as a component of the antibacterial therapy.

H2RAs are usually continued in full dose for 1 month, but in patients who are asymptomatic at the end of antibacterial therapy I allow p.r.n. therapy. Breath test or biopsy is repeated 4 weeks after completing antibacterial therapy. If HP−, patients may be reassured that ulcer relapse is unlikely. Depending on the age of the patient and the presence of other associated lesions, symptoms may persist after eradication of *H. pylori*. It is worthwhile to repeat endoscopy in these cases.

In most patients, symptoms will totally resolve after eradication of *H. pylori*, in which case patients should be provided with p.r.n. H2RAs and reviewed 3 months later. At the 3-month visit a non-invasive test such as a breath test should be performed to confirm long-term eradication of *H. pylori*. Patients who are HP− at 3 months, and who are asymptomatic, will benefit from a further endoscopy at this time. The absence of any identifiable lesion indicates a very good long-term prognosis and probable cure of the disease.

In a proportion of patients, symptoms continue to some degree. These are commonly related to persisting erosive duodenitis, particularly in older persons with very long-standing ulcer disease. Therapy with H2RAs or sucralfate should be given, but need only be continued while symptoms persist. Endoscopic lesions do not usually progress to frank ulceration once *H. pylori* has been eradicated, but patients with persisting gastroduodenal erythema and/or erosive changes remain very susceptible to non-steroidal antiinflammatory drug (NSAID)-induced damage.

Scarring and pyloric stenosis

The duodenal mucosa usually appears normal after eradication of *H. pylori*, but scarring and duodenal deformity may still worry the endoscopist. According to George *et al.* [65], these changes also gradually resolve over 1–4 years. While they persist, however, patients may have symptoms of bloating and post-prandial discomfort, particularly with undigestible dietary fiber and salads. Metoclopramide may help these symptoms.

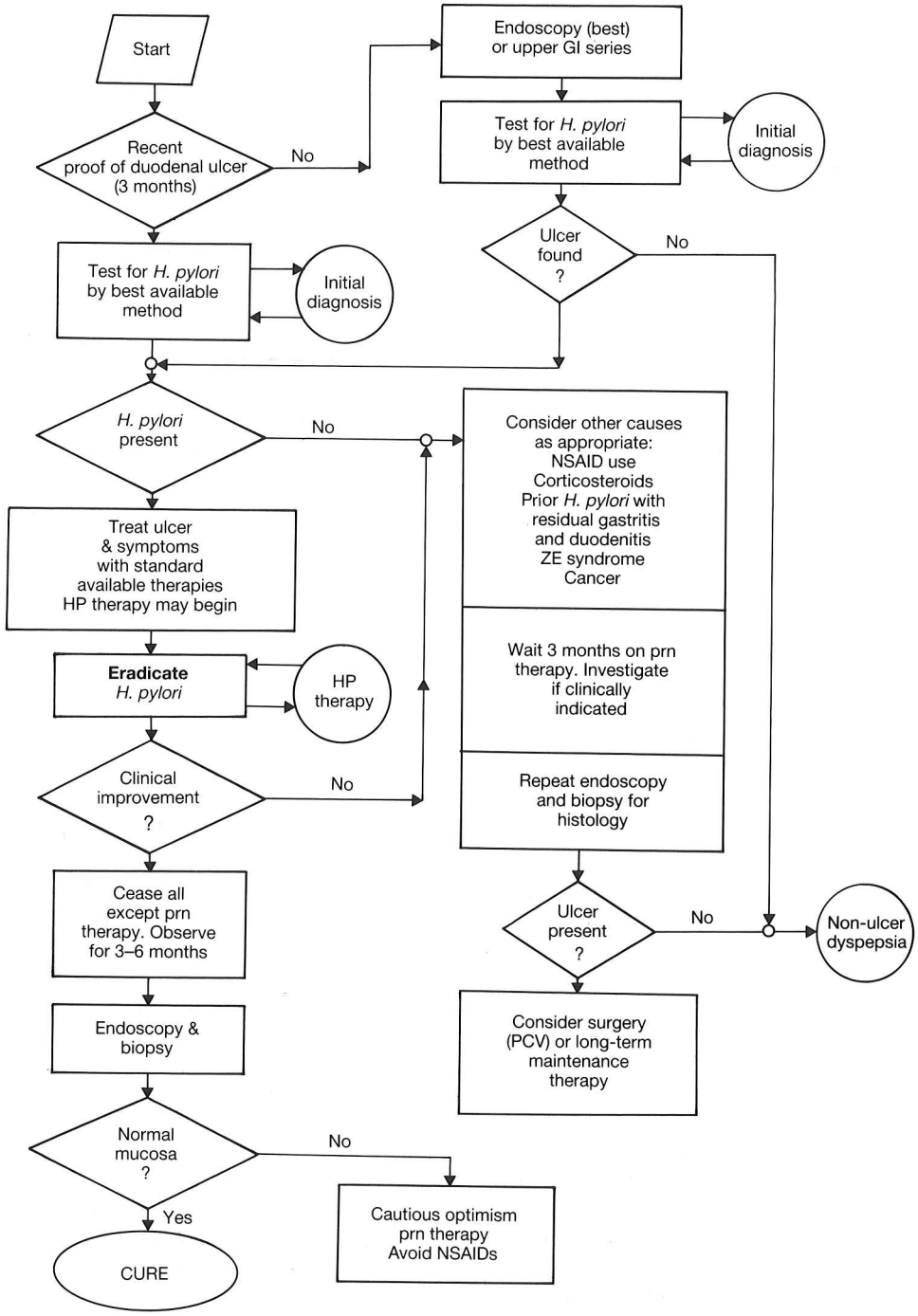

Fig. 13.6 Flow chart for the management of duodenal ulcer. PCV, parietal cell vagotomy; ZE, Zollinger–Ellison (syndrome).

Pyloric stenosis subsequent to duodenal ulcer may be a troublesome persistent component of the disease. Often, the high acid secretory state and delay in gastric emptying combine to cause erosive changes in the esophagus, which may be the major cause of persisting symptoms. When the esophagus is involved, treatment of gastric hyperacidity should be more intensive, and high-dose H2RAs or omeprazole should be given during and after antibacterial regimens. Breath tests may give weak false-positive results in patients rendered achlorhydric, so follow-up is best performed with endoscopy and biopsy.

At initial and subsequent endoscopies, balloon dilatation of any stricture should be performed. If the endoscope (9 mm) can pass the stricture, then the patient should be able to tolerate a low-residue soft diet. Once *H. pylori* has been eradicated, gradual improvement will occur except in patients with very hard pyloric fibrosis. These patients will still benefit from eradication of *H. pylori*, since at least the lesion will not progress. If they require surgical correction of the problem, a post-gastrectomy syndrome will be less likely if *H. pylori* and gastritis are no longer present. At this stage the surgeon may not have to address a continuing ulcer diathesis, and so should be encouraged to perform a conservative operation. Parietal cell vagotomy with pyloroplasty may suffice, rather than the usual Billroth II. Patients with large dilated stomachs should be assessed thoroughly prior to surgical intervention, since they may have hypomotility which would be worsened by vagotomy.

Gastric ulcer

In general, the management of gastric ulcer is similar to that of duodenal ulcer (Fig. 13.6), although gastric ulcer tends to be harder to treat and is more often related to factors other than *H. pylori*. The two main causes of gastric ulcer are *H. pylori* (~70%) and NSAIDs (~30%). As some ulcers are malignant, all gastric ulcers should be biopsied. Extra biopsies for *H. pylori* diagnosis should be taken away from the gastric ulcer, on the antral greater curve. If intestinal metaplasia is widespread, false-negative biopsies may occur, so when *H. pylori* is not detected on such a biopsy, idiopathic gastric ulcer should be investigated further with either serology or breath test to ensure that *H. pylori* has not been missed.

NSAID ingestion is the cause of ulcers which occur in histologically normal gastric mucosa. If the patient is known to be taking NSAID, *H. pylori* should still be excluded. Normal histology implies that the NSAID is the sole cause of the ulcer and that the patient will heal quickly once the offending agent is withdrawn. When the mucosa shows active and/or chronic gastritis (with or without intestinal metaplasia), *H. pylori* is equally likely to be the primary cause [70].

For patients in whom the NSAID is an essential medication, it makes sense to eradicate *H. pylori* in the hope that the mucosal defect will diminish and the NSAID will be able to be continued. It is my experience that about 50% of patients will be able to resume taking NSAID after the ulcer has healed and the *H. pylori* has been eradicated. Asymptomatic ulcer relapses are common in NSAID users, so endoscopic follow-up is advised for 3–6 months after *H. pylori* eradication.

Uncomplicated *H. pylori*-associated gastric ulcer should be treated similarly to duodenal ulcer, but with different expectations. Gastric ulcer patients usually have severe widespread histologic gastritis, and acid secretion may be normal or even decreased. In addition, gastric ulcer patients are usually older and may have had lifelong *H. pylori*. Thus the mucosal lesion is more severe than in duodenal ulcer, and may not revert to normal after treatment.

There are no clinical trials confirming the benefit of *H. pylori* therapy in gastric ulcer, but my own experience is that most patients are cured after the organism has been eradicated. Young patients with prepyloric ulceration, which has a natural history similar to that of duodenal ulcer, do very well. In older persons, the gastric mucosa often appears abnormal for many months after ulcer healing. If these endoscopic lesions, for example patchy erosive gastritis, are asymptomatic, I do not treat them. Nevertheless, it is my practice to follow them endoscopically for 1–2 years. Major ulceration sometimes occurs in patients who subsequently take NSAID.

In a minority of patients, ulceration redevelops at the original ulcer site, even when the histology shows that the gastritis has healed. After eradication of *H. pylori*, there is no further need for antibacterial therapy, and even the use of cytoprotective bismuth salts such as CBS is of doubtful benefit. Recurrence of an idiopathic gastric ulcer after eradication of *H. pylori* should be treated conventionally with H2RAs and/or sucralfate. It is reasonable to hope for improvement in the tendency to relapse for 12 months after treating *H. pylori*, but subsequent problems imply a permanent mucosal defect and indicate the need for long-term maintenance ulcer therapy. In such patients surgery may be an attractive option. Once the main component of the ulcer diathesis has been treated, however, more conservative surgical procedures may be possible, rather than the usual Billroth II. Since the mucosal defect may be localized to the area of recurrent ulceration, the surgeon should consider a local ulcer resection with parietal cell vagotomy.

Gastroesophageal reflux disease (GERD)

No link has been demonstrated between GERD and *H. pylori*-associated gastritis. Nevertheless, in one small study of therapy for esophagitis, the combination of bismuth–cimetidine was superior to cimetidine alone [71].

Many investigators have reported a 30% prevalence of reflux esophagitis in patients with duodenal ulcer [72, 73]. The reason for this is not clear. Duodenal ulcer patients may secrete more acid, or the gastric juice may be more toxic to the esophageal mucosa due to ammonia and other *H. pylori* toxins. Alternatively, long-standing pyloroduodenal disease, nausea and vomiting, belching, and associated alterations of motility, might compromise the esophageal sphincter.

It is my current practice to treat *H. pylori* gastritis when it is present in association with GERD. When taking the history, the presence of nausea indicates that the lesion is not solely due to esophageal acid reflux. In many patients, symptoms of reflux and of gastritis cannot be separated and, whereas GERD requires long-term acid suppression therapy, gastritis symptoms might be cured with a short course of triple therapy. Remember that patients with *H. pylori* gastritis sometimes have relative hypochlorhydria due to ammonia and toxin production. In a few patients, acidic dyspepsia worsens immediately after commencing antibacterial therapy. This responds well to acid reduction and is usually only a temporary phenomenon.

Antireflux surgery, a less frequent occurrence since the advent of H2RAs and omeprazole, is often complicated by the "gas bloat syndrome." In some patients this is aggravated by continuing *H. pylori* gastritis and/or a motility disturbance. The cause of the syndrome is in doubt, but appears to be secondary to both air trapping and gastric generation of gas. Since *H. pylori* may produce CO_2 by hydrolysis of urea in the stomach, the potential exists for the organism to aggravate this syndrome.

In two patients, both with *H. pylori*, I have seen gastric ulcers develop high on the lesser curve immediately adjacent to or beneath the esophageal wrap. I therefore attempt to eradicate *H. pylori* before referring patients for antireflux surgery. After such surgery patients cannot easily vomit, so they fare badly if nausea from *H. pylori* goes untreated.

Non-ulcer dyspepsia

What is non-ulcer dyspepsia?

Non-ulcer dyspepsia (NUD) exists in those patients with symptoms suggestive of ulcer disease who do not have an ulcer found at endoscopy. The proportion of these who have *H. pylori*-associated disease is between 40% and 70%, depending on geographic location, ethnic and socioeconomic factors. Italian series have a high prevalence of *H. pylori*, whereas only 38% of patients at the University of Virginia have it [74]. In general, the amount of *H. pylori*-associated NUD is at least equal to the amount of ulcer disease.

Can H. pylori gastritis cause NUD?

Gastritis is common in asymptomatic persons and the prevalence of gastritis in age-matched endoscopy patients is often very similar to this background prevalence. At the University of

Virginia, where *H. pylori* is uncommon (8% rising to 25% in elderly patients), the overall prevalence of dyspepsia in the population is 20% in normal persons and 55% in those persons with serologic evidence of *H. pylori* [75]. Thus the presence of *H. pylori* is associated with a 2.5 times increased risk of dyspepsia.

Logic dictates that NUD must be more common in patients with *H. pylori*. Non-ulcer dyspepsia includes many persons who have had ulcer disease in the past, and some others who will develop peptic ulcer disease if observed for long enough. Patients with new ulcer disease often give a long history of dyspepsia, in which various searches for an ulcer crater were negative. In between ulcer episodes, patients with duodenal ulcers often have continuing low-grade ulcer-type symptoms. In patients with well-documented ulcer disease, recurrence of severe ulcer symptoms often occurs in the absence of an ulcer crater. These patients have etiologies other than an ulcer crater for their pain, and in most cases only duodenitis or gastritis will be found.

Current thought is that factors such as gastric metaplasia in the duodenal bulb, level of acid secretion, and toxin production by *H. pylori*, will determine the expression of ulcer disease (see Chapter 11). Many believe that lesser degrees of ulcerogenesis result in symptoms but no macroscopic ulcer crater. This disease state is equal to the "Moynihan's disease" (chronic gastroduodenitis) referred to by Spiro [76]. These patients have minimal or no endoscopic abnormality, but may have severe histologic damage with subsequent ingress of hydrogen ion into the mucosa.

There are several controlled studies showing improvement of clinical symptoms with bismuth therapy for *H. pylori* in NUD patients. With the old formulation CBS ("DeNol") chewable tablets, Rokkas *et al.* [77] noted benefit after 3–5 weeks, as did Lambert *et al.* [78], Borody *et al.* [9], and Kang *et al.* [79]. More recently, Loffeld *et al.* [80] reported only marginal clinical benefit (nausea improved) using a q.i.d. dosage of the new formulation CBS 'swallowable' "DeNol" tablets, although the gastritis did improve histologically during therapy. Our observation [81], and data reported by McNulty *et al.* [28], indicate that short-term (3-weeks') suppression of *H. pylori* with BSS does greatly affect symptoms of NUD.

The discordant results of the above studies may have been due to the different formulations of bismuth they used, the variable degree of *H. pylori* suppression achieved, the inability of the medication to eradicate *H. pylori* when used as a single agent, the short time allowed to show improvement, and the very wide variety of possible etiologies present in any group of patients with NUD. To settle the issue, a 100-patient study is needed in which *H. pylori* is eradicated by therapy and 3-month follow-up is available. There is hardly any need to include HP− patients in such a study, because all the above investigators have failed to notice any difference between HP− NUD patients treated with bismuth, and those treated with placebo.

At the University of Virginia we have preliminary results from a follow-up survey of all patients seen at my clinic between 1987 and 1990 [82]. In patients with *H. pylori*, there was no change in symptoms if the bacterium remained and only conventional therapies were used (H2RAs, etc.). If the bacterium was eradicated, however, 50% of patients were markedly improved or cured, 25% were somewhat improved, and only 25% were unchanged. In patients who did not have *H. pylori* (HP− dyspepsia), a less remarkable but definite improvement also occurred, so that 25% were markedly improved, 50% were somewhat improved, and about 25% were unchanged during a 2-year follow-up. Of interest was the observation that the HP− group still required medication for their symptoms, whereas many of the treated *H. pylori* patients no longer required medication.

Symptoms which were improved after eradication of *H. pylori* were: bloating, burping, gnawing sensations, vomiting, intolerance to spicy food, bad taste in the mouth, acid reflux, heartburn, swelling, nausea, loss of appetite, flatulence, and constipation.

Approach to the patient with NUD

When first seeing patients with apparent NUD, the physician should be aware that a real diagnosis will be made in less than half, and that

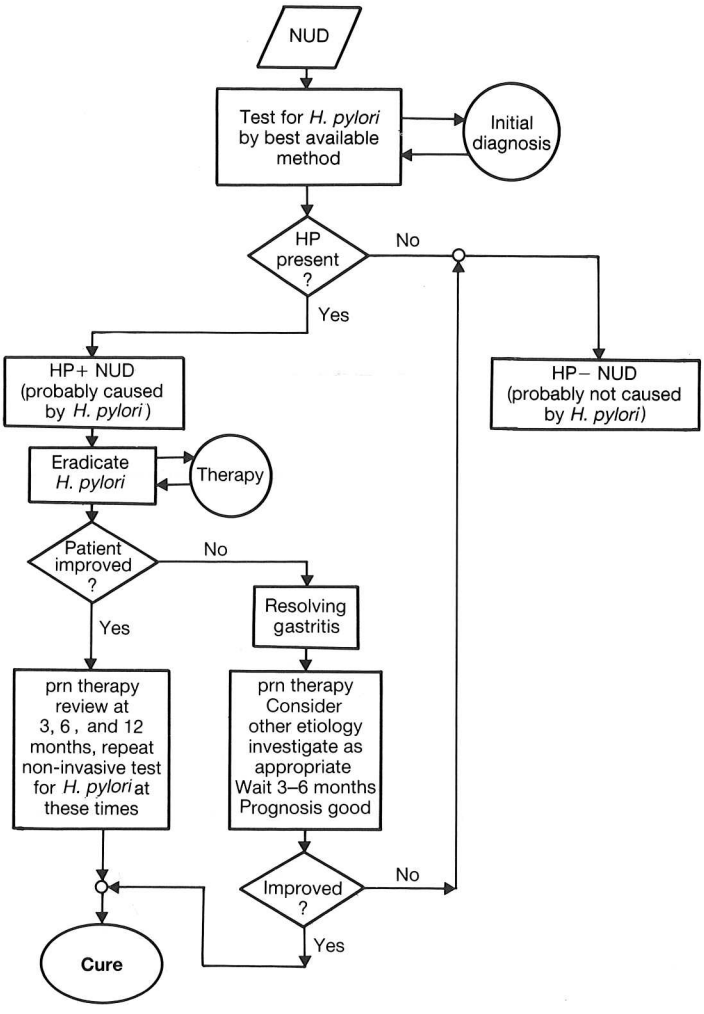

Fig. 13.7 Flow chart of management for non-ulcer dyspepsia (NUD) (see also Table 13.3).

curative therapy will be possible in very few. By the time a patient reaches a specialist gastroenterologist, he or she has usually already been investigated and common causes of dyspepsia have been ruled out. Often, asymptomatic gallstones will have been removed! Since *H. pylori* does not feature in most texts as a cause of abdominal symptoms, some patients with gastritis may have slipped through a diagnostic screen.

The physician should take a careful history, including a family history with enquiries about children and also the spouse's family. Travel may be important, especially to Third World countries and Latin America. Occupation is relevant, since *H. pylori* may be transmitted by the fecal–oral route and persons such as plumbers and sewerage engineers could acquire *H. pylori* in their occupation. Doctors (particularly senior gastroenterologists) are likely to pick up *H. pylori* from patients, as are nurses in medical and surgical wards and geriatric units, and perhaps persons in institutions for the mentally retarded.

Psychosomatic factors have been overemphasized in the past as causes for NUD. Talley *et al.* have published several studies in which major life events and/or abnormal personality traits were no more common in NUD patients than in any other group with chronic gastrointestinal diseases [83, 84]. Whereas "stress' can certainly aggravate an

underlying medical condition, it rarely causes abdominal pain *de novo*. Most patients recognize that the diagnosis of "stress-induced" disease really means that the physician has been unable to find any organic cause for their symptoms. I prefer not to raise their hopes of an organic diagnosis in the first place, and to admit that there are many patients in whom the cause of abdominal pain cannot be determined with the current technology.

Usually the physical examination will be normal. Follow this with a set of laboratory tests to screen for overt organic disease (blood count, differential, erythrocyte sedimentation rate, urea and electrolytes, metabolic screen, amylase, and liver function tests). Have stool examined for leukocytes, ova, and parasites if diarrhea is present. Obtain a plain abdominal X-ray film if bowel sounds seem abnormal or abdominal distension is present.

If the above process fails to identify any abnormality, perform a test to exclude *H. pylori*. Usually this is a breath test (result immediately available in my clinic) or an antibody titer. If an endoscopy is indicated (see flow chart, Fig. 13.7), then accurate biopsy diagnosis is possible, followed by culture and sensitivity result if positive (see Chapter 12). If *H. pylori* is not detected, then the diagnosis of HP− dyspepsia is made. At this stage a positive serologic test may indicate recent *H. pylori*, and therefore a tendency to improve with time (residual gastritis). Otherwise, the investigation and treatment are quite conventional. Numerous articles have been written on the subject, but none really pretends to give a diagnosis or effective therapy in more than 50% of patients with HP− NUD [85, 86]. A detailed review of non-ulcer dyspepsia is available as a working party report chaired by Colin–Jones [86, 87]. The subject is also discussed in Chapter 3.

As shown in Table 13.3, the best approach is an attempt to pigeon-hole patients into one of five categories. These are briefly discussed below.

Esophageal-type. Atypical cardiac symptoms can mimic esophageal disease, so a cardiology opinion is often indicated before proceeding. Radiology, endoscopy, and motility studies have a role, depending on their availability. The Bernstein test may reproduce the pain, and can be done at the same time as the motility study. Twenty-four hour ambulatory pH monitoring may prove that acid reflux exists, although a therapeutic trial of omeprazole (see below) may replace this nowadays. After such a work-up, the treatment will usually be H2RAs or omeprazole, or calcium channel blockers. In general, esophageal disease requires much higher doses of acid-reduction therapy than does peptic ulcer disease.

Ulcer-like. Ulcer- and acidic-type symptoms centered in the epigastrium usually respond to acid-reduction therapy, and may be treated the same as peptic ulcer disease. In a gastroenterology practice, however, patients referred with these symptoms will have already tried H2RAs and responded poorly. Investigation should include endoscopy and biopsy of the gastric mucosa. In some patients with burning epigastric pain, I have seen widespread intestinal metaplasia of the gastric body with few parietal cells present. These persons, even if peak gastric acid secretion is quite low, may respond to omeprazole. Pancreatic and biliary disease need to be ruled out and endoscopic retrograde cholangiopancreatographic (ERCP) examination performed if any related investigations are abnormal. There may be a role for biliary manometry in persons with post-cholecystectomy syndromes.

Patients who do not respond to empiric trials of therapy should be investigated further, often coming to computed tomography (CT) scan and colonoscopy or barium enema. At least at the end of the work-up the physician should be able to confidently assure the patient that a malignancy is not present.

Dysmotility/hypomotility-type. Dysmotility-type dyspepsia includes a group with organic disease (scleroderma, diabetic neuropathy, previous peptic ulcer, or partial gastrectomy) which has caused hypomotility of the stomach. The symptoms are related to poor gastric emptying, which can be detected by a solid phase gastric emptying study. Results of gastric emptying studies vary in patients from day to day, and so a normal study does not absolutely exclude hypomotility. If the gastric anatomy

Table 13.3 Diagnosis of *H. pylori*-negative non-ulcer dyspepsia

Symptoms	Investigations
Type 1: esophageal-type dyspepsia Chest pain, dysphagia, heartburn, belching, reflux, bad taste in the mouth, worse after food and bedtime	Exclude cardiac causes; endoscopy, esophageal biopsy, barium swallow/upper GI series (fluoroscopy), esophageal motility study, 24-hour esophageal pH monitoring, Bernstein test, gastric analysis, trial of therapy with Ca^{2+} antagonists or nitroglycerin (esophageal spasm), omeprazole or H2RAs (reflux)
Type 2: ulcer-like (acidic) dyspepsia Burning epigastric pain, gnawing sensations, nausea, aching pain, epigastric tenderness, usually relieved by food or antacids	Endoscopy and biopsy of duodenum, antrum and body mucosa; upper GI series, ultrasound, computed tomography (CT) scan, gastric analysis, serum gastrin. Usually responds to H2RAs and/or omeprazole. Common in persons with a recent past history of *H. pylori*. *H. pylori* serology may be borderline-positive, and mild chronic gastritis may be present
Type 3: dysmotility/hypomotility-type dyspepsia Belching and bloating, gnawing/hunger, early satiety during meals, distension, nausea and vomiting (± undigested food), intolerance to salads and fiber, foul eructations, halitosis, ± reflux symptoms	Exclude *Giardia*; endoscopy and biopsy of duodenum, antrum and body mucosa; gastric emptying study, plus electrogastrogram (if available), upper GI series, ultrasound, CT scan. Trial of metoclopramide or other prokinetic agents (cisapride, clebopride, domperidone, ?erythromycin)
Type 4: irritable bowel-type dyspepsia Subsets of the above syndromes, associated with intermittent altered bowel habit (usually diarrhea) and lower GI pains associated with meals and upper GI symptoms	Upper GI endoscopy, biopsies, upper GI series, lactose tolerance test, small bowel series (?terminal ileal disease), lower GI series, colonoscopy and biopsy
Type 5: abdominal pain syndromes Right upper quadrant pains (usually after cholecystectomy), liver pain, colonic pain; left upper quadrant pain, splenic flexure pain, gastric/esophageal pain, diaphragmatic pain; central and other sharp pains, usually in post-surgical abdomen	Plain abdominal film during exacerbations, ESR, upper and lower GI series, upper GI endoscopy and biopsy, ultrasound, colonoscopy, CT scan, laparoscopy

and histology are normal, and there is no known predisposing condition, then gastric stasis is idiopathic and has an unpredictable course. If *H. pylori* has been recently treated, eradication of the bacterium will result in improvement of the patient's nausea over several months, although the actual motor disturbance may remain. Often such patients undergo apparent relapses, but these are usually short-lived and become less common with time. If *H. pylori* has not recurred then reassurance and symptomatic therapy are all that is required.

Often patients with past gastric disease, pyloric scarring, etc. cannot tolerate a high fiber diet, and improve if fiber is removed from the diet for a few weeks, after which various vegetables and fiber sources are selectively reintroduced. In many cases these patients have been deliberately increasing their dietary fiber to treat an "irritable bowel" syndrome. Prokinetic agents have a role in NUD, and in Europe, cisapride is already an accepted therapy. Gastric stasis and vomiting are reviewed in Chapter 14.

Irritable bowel-type. Irritable bowel syndromes are often part of an "irritable gut" and consist of a combination of upper and lower gastrointestinal symptoms. Women seem prone to a syndrome of colicky upper gastrointestinal discomfort, coming on unpredictably after meals, relieved by vomiting and associated with diarrhea. Sometimes these respond very well to anticholinergic drugs such as IV or sublingual scopolamine. Dicyclomine hydrochloride is standard therapy (20–40 mg q.i.d.) if attacks occur frequently. An alternative is hyoscyamine sulfate, available in oral or sublingual formulations. If all else fails, antidepressant drugs with their anticholinergic effect are useful, especially in patients with severe pain, anxiety, and sleep disturbance.

Abdominal pain syndromes. A few patients, usually middle-aged women, have undiagnosed abdominal pains. Associated findings may be fatty liver, cholecystectomy, previous multiple surgeries, or previous peptic ulcer disease, but no proven organic cause for the pain can be found. Often these patients have been diagnosed as "irritable bowel" for want of a better diagnosis. I categorize pain syndromes by their location, and direct investigations at the possible underlying organs. My experience with left and right upper quadrant pains is that they do not resolve. Occasional patients report improvement with antibiotics, but this is inconsistent. Laparoscopy may be a useful new avenue of investigation by a surgeon or gastroenterologist. I usually see these undiagnosed patients every 3–6 months, and reinvestigate them during acute exacerbations if it seems indicated. Any laboratory or radiologic abnormality is a signal that the disorder is not merely functional and that further work-up should be performed.

Non-ulcer dyspepsia patients with a completely negative diagnostic evaluation should be reassured that they do not have a serious organic disease, and that they will almost certainly improve with time (1–2 years). They should be reviewed at 3–6-month intervals after that, and examined carefully whenever exacerbations occur. Patients will accept this approach if they have received a careful and thorough initial consultation, appropriate investigations have excluded treatable diseases, and malignancy has been ruled out.

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