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CAMPYLOBACTER PYLORI (CP-1) SESSION

Chairman's report

C.pylori clinical and therapeutic aspects

The number of papers submitted to this session reflects the rapid increase in interest in this organism since the last Workshop two years ago.

All workers have confirmed that *Campylobacter pylori* is commonly found in the gastric mucosa of patients attending for the investigation of upper gastrointestinal symptoms. The frequency of *C.pylori* varied, from 40% of 1,200 patients attending endoscopy in Gloucester U.K. (Abstract 251), and 58% of non ulcer dyspepsia patients in Leeds U.K., to 63% of patients attending endoscopy in Peru. The frequency of *C.pylori* increased with age, peaking at 60% in the 5th decade (Heatley *et al.*, abstract 63; Kist *et al.*, abstract 86; McNulty *et al.*, abstract 251) and thereafter decreased gradually. In several serological studies (Heatley *et al.*, abstract 63; Skoglund *et al.*, abstract 152) the frequency of *C.pylori* was higher in antacid users than asymptomatic blood donors, confirming the importance of *C.pylori* in these dyspeptic patients. In a small study from Chile (Figueroa *et al.*, abstract 248) 30 asymptomatic volunteers (mean age 32 years) were endoscoped and 20% were found to be *C.pylori* positive. These results concord with the frequency of *C.pylori* found by ELISA in blood donors of a similar age by Heatley *et al.* (abstract 63).

There was some disagreement about the effect of socioeconomic status on the frequency of *C.pylori*. In the Peru study (abstract 134) the frequency of *C.pylori* was the same in patients attending a State and Private hospital. In contrast, Kist *et al.* (abstract 86) found that the frequency of *C.pylori* was higher in their group of unemployed patients.

Several groups found that *C.pylori* infection was more common in men and smokers (Heatley *et al.*, abstract 63; Kist *et al.*, abstract 86; McNulty *et al.*, abstract 251). These risk factors probably need to be investigated further.

Several workers reported *C.pylori* in children with upper gastrointestinal symptoms. The largest study was by Cadranel *et al.* (abstract 32) who found *C.pylori* in 36 (31.5%) of 114 children. A characteristic micro nodular gastritis was seen at endoscopy in 19.

Lee and Berkowicz found that the frequency of *C.pylori* was much more common in a group of mentally retarded institutionalised patients than in a group of age matched blood donors. This suggests that infection is transmitted by close contact.

C.pylori only thrives in gastric type mucosa and is therefore only found in the duodenum or oesophogus if metaplasia is present. Wyatt *et al.* (ab-

stract 172) found that *C.pylori* colonization in the duodenum was associated with an inflammatory infiltrate. They suggest that in the presence of low gastric pH gastric metaplasia can develop in the duodenum. If *C.pylori* infection is also present in the stomach colonization of this duodenal, gastric type mucosa can occur resulting in duodenitis. With other cofactors this may lead to peptic ulceration.

In vitro antimicrobial work continues to be essential in the search for the most appropriate treatment. *In vitro C.pylori* is susceptible to a wide range of antimicrobial agents including bismuth salts, B lactams, quinolones and macrolides. Approximately 75% are sensitive to the imidazoles (Glupczinski *et al.*, abstract 32; Quintero *et al.*, abstract 133). However, this *in vitro* activity does not always correlate with *in vivo* success. Studies by Lambert *et al.* (abstract 92), Langenberg *et al.* (abstract 94), Gilligan *et al.* (abstract 235), and Goodwin *et al.* (abstract 60) found that *C.pylori* was cleared by bismuth salts in 50-70% of patients. However relapse was extremely common and long term clearance was achieved in only 30% of patients. Relapse is considered more likely than reinfection as BRENDA profiles of strains isolated before treatment and after relapse were identical (Langenberg *et al.*, abstract 94). Relapse usually occurred within three months. Patients free of infection at this time were not usually reinfected. Interestingly, isolates from a husband and wife with infection had the same BRENDA profiles.

Amoxycillin successfully clears *C.pylori* (Burette *et al.*, abstract 28; and Langenberg *et al.*, abstract 94). Although initial clearance is better than with the bismuth salts relapse is greater. Some other single agents that are active *in vitro* had no clinical benefit: ciprofloxacin and penicillin (Hirschl *et al.*, abstract 64), ofloxacin (Glupczynski *et al.*, abstract 58), josamycin (Lamouliatte *et al.*, abstract 190), and cephalexin (Bayerdörffer *et al.*, abstract 13), and tinidazole (Goodwin *et al.*, abstract 60). Acquired resistance was demonstrated after only three weeks treatment with ofloxacin or tinidazole (abstracts 58 and 60). The acquired resistance to tinidazole was prevented if the antimicrobial was given in combination with a bismuth salt.

Combination treatment has achieved the best long term results. After a course of DeNol plus amoxycillin long term clearance was achieved in 50% of patients (Langenberg *et al.*, abstract 94). Large longitudinal studies will be essential to find the most effective treatment.

McNulty *et al.* (abstract 113) found that gastric mucosal concentrations of the macrolides and quinolones were greater than the MIC 90 for *C.pylori*. This suggests that stability and activity at a wide range of pHs and penetration into mucus will be important for any antimicrobial agent.

The role of *C.pylori* in duodenal ulcer relapse was investigated by Goodwin *et al.* (abstract 60) and Gilligan *et al.* (abstract 235). Both groups followed patients for at least one year and found that ulcer relapse was much more common in patients who had persistent *Campylobacter pylori* infection. These results are extremely important and provide tbe strongest evidence so far that *C.pylori* plays an important role in the aetiology of duodenal ulceration. Its detection and eradication may well prove essential

in the future management of patients with peptic ulceration. Larger studies in this field are urgently needed as this has great repercussions for the patient and the pharmaceutical industry.

Management of C.pylori infection: antibacterial regimens, bacteriologic and clinical response to therapy

At this meeting several investigators have described attempts ro eradicate *C.pylori* using antibiotics, bismuth subcitrate (CBS-DeNol), or a combination of the two. Before reviewing these studies three facts should be noted:

1. The clinical syndrome associated with CP did not appear to affect the bacteriologic outcome; i.e. eradication rates of the same order were achieved regardless of whether the patients had duodenal ulcer or gastritis without ulceration.

2. Whenever *C.pylori* was suppressed, histological gastritis also improved. In the past, suppression of *C.pylori* infection with bismuth was reported to heal gastritis but the improvement might have been attributed to a suspected "anti-inflammatory" action of bismuth rather than its antibacterial action.

3. Eradication of *C.pylori* is only proven when multiple biopsy specimens are still negative 28 days after completing therapy. For example, investigators who studied patients at time points less than 28 days after therapy, noted high clearance rates and were disappointed to find recrudescent infection in patients reassessed one month later. Clearance of the organism is defined as a negative biopsy in the first 28 days after therapy. Eradication is a negative biopsy at 28 days. Recrudescence has occurred when early biopsies are negative and biopsy at 28 days is infected. Recurrence is when biopsy is negative at 28 days but infected on a subsequent occasion. Recurrence and recrudescence can also be inferred if the histological appearance reverts to that of active chronic gastritis.

Hirschl (64) in a multidisciplinary study notes that in *C.pylori* negative patients, IgG antibody titer correlate with the patient's age, suggesting that "herd immunity" to the organism develops in man. They describe therapeutic failure with penicillin V, bacampillin, and ciprofloxacin.

Langenberg (94) reports a large consecutive study of patients treated with CBS (swallowing tablets), amoxycillin, or a combination of the two. CP clearance at the end of therapy was followed by recrudescence of the infection by one month in most cases. If the bacterium was not present one month after therapy however, long term eradication and healing of gastritis occurred, regardless of the therapy used. Amoxycillin was ineffective and CBS also gave a poor result with only 10% of infection cleared.

Lambert (92) studied the clinical response of patients with the non-ulcer dyspepsia syndrome, a common condition in which ulcer-like symptoms and vague upper gastrointestinal complaints are present but peptic ulcer is absent. He found that 66% of 53 such patients had CP, and that suppression of infection and bealing of the gastritis with bismuth resulted in a significant clinial improvement as judged by day pain, nigbt pain, nausea and vomiting. CBS gave long-term eradication in about 30% of patients in Lambert's study.

Goodwin (60) reports the effect of antibacterial regimens using bismuth and tinidazole initially. This combination gave the best eradication rate of all therapies, elimination of CP was achieved in 70% (20/29) which healed gastritis, improved duodenal ulcer healing, and resulted in a longer duodenal ulcer realspe rate than the control group treated with cimetidine (30% vs 80% in 12 months). Patients with persistent infection were later treated with CBS in combination with amoxycillin or erythromycin which gave clearance in 50% and 65% respectively. Tinidazole was useless when given by itself because nearly all CP isolates became resistant to the drug. The development of resistance was prevented when bismuth was given concurrently.

Gilligan (235) treated duodenal ulcer patients with CBS and examined the outcome of patients rendered CP negative. He achieved CP clearance in 30% and in these patients ulcer relapse usually coincided with CP reinfection. The relapse rate for CP negative ulcers was less than 20% verses >70% for those who remained CP+.

Anderson (7) studied the activity of *in vitro* of some anti uleer agents. He notes slight inhibition of CP sucralfate which could explain tbe marginal improvement in the duodenal ulcer relapse rate which has been noted with this drug. Inhibition of CP was not noted *in vivo* however.

Bayerdörffer (13) reports a study of 90 patients, mostly with duodenal ulcer, who were given a H2 receptor antagonist with ofloxacin or placebo. Suppression of *C.pylori* was achieved in 92% of patients and the corresponded with faster ulcer healing in the antibiotic treated group. They also noted that supplimentary antibiotic gave good healing of "refractory" ulcers. This latter finding could explain why duodenal ulcers resistant to cimetidine heal very well on CBS therapy. Unfortunately, recrudescent infection occurred in most patients and CP became resistant to quinolones after ofloxacin therapy.

Blanco (21) studied the *in vitro* effect of several ulcer drugs on *C.pylori*. Patients were followed for 8 weeks and infection persisted in every case. This paper, when combined with data from Goodwin, Gilligan and Langenberg, demonstrates that spontaneous eradication of *C.pylori* is very rare when treated with the usual ulcer therapies (except bismuth). In future trials which study only the efficacy of an antibiotic, there will be no need to have an untreated control group because any eradication of CP can be assumed to be due to the therapeutic agent, not natural causes.

Burette (28) used amoxycillin suspension to treat CP. As with capsules, suppression of the infection was followed by recrudescence in almost every case. Nevertheless, at the end of 8 days therapy, noticable improvement in

gastritis had occurred. Although the daily dose was than Langenberg's (2 mg vs 1125 mg), results were worse suggesting that the duration of therapy (8 days) was insufficient.

Kalenic (75) studied a small group of patients treated with ofloxacin or metronidazole. Although suppression of CP occurred, 2 of 4 ofloxacin treated patients had recurrent infection six months later. Interestingly, one other had active gastritis suggesting the CP was also present, but undetected. In this study, recurrent infection also occurred with metronidazole (2/2 patients), probably as a result of the development of resistance as occurred with timidazole in Goodwin's study.

Lambert (91) reports a very low relapse rate (none!) for duodenal ulcer patients rendered CP negative with CBS. Using CBS he apparently eradicated the organism in 30% of 42 patients, the same percentage reported by Goodwin and O'Morain. The numbers reported are small but the difference in relapse is significant at $p < 0.001$.

Lastovica (95) describes a new disease association with CP, that of protein losing enteropathy, presumably from the gastric mucosa. In three children suppression of the infection with erythromycin was effective in releiving symptoms. Bacteriologic cure was not achieved so an alternative therapy may be necessary to prevent relapse.

Lamoulliatte (190) reports failure of josamycin in the treatment of CP.

The data concerning therapy for CP can be summarized in the following table:

DRUG	% CLEAR	AUTHORS (abstract No)
amoxicillin	0-25	Langenberg (94) Burette (28)
erythromycin	0-25	Lastovica (95) McNulty (BMJ 1986)
josamycin	0	Burette (28)
metronidazole	0	Kalenic (75)
tinidazole	4	Goodwin (60)
ciprofloxacin	0	Hirschl (64)
ofloxacin	0-30	Kalenic (75) Bayerdörffer (13)
coll.bism.subc	10-30	Langenberg (94) Goodwin (60) Lambert (92) Gilligan (235)
CBS+amox	50	Langenberg (94) Goodwin (60)
CBS+erythrom	65	Goodwin (60)
CBS+tinidaz	70	Goodwin (60)

Previously reported studies mention that doxycycline is also relatively ineffective *in vivo* (Lancet 1987 letters).

The present lack of hard double-blind data on the response of clinical symptoms to eradication of CP is partly due to the inadequacy of treatment methods. It appears that CBS is synergistic with antibiotic drugs. perhaps by preventing the emergence of antibiotic resistant strains. When designing clinical trials, it would be useful to put most patients into an active therapy group because eradication would only occur in around 70%, even with the best therapy.

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