Treatment failures and secondary resistance to antibiotics. A growing concern in *Helicobacter pylori* therapy

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Increasing numbers of patients are being treated for *Helicobacter pylori* (*H. pylori*) infection. Treatment of this infection has shifted from secondary to primary care medicine. A test-and-treat strategy is increasingly popular in the approach to dyspepsia. Patients with ulcer diathesis are less frequently encountered and those being treated today are mostly patients with functional or non-ulcer dyspepsia (NUD). It has been a consistent finding that *H. pylori* infection associated with NUD is more difficult to cure. Cure rates of proton pump inhibitor (PPI)-triple therapy in patients with NUD appear to be 5-15% lower than cure rates in patients with ulcer diathesis [1-5]. This cannot be explained by a difference in compliance. We have shown it can be explained by a difference in infecting strains [1]. The virulent strains, more often found in ulcer patients, are easier to cure than the non-virulent strains which are more often found in NUD patients [1].

The shift from treating ulcer patients to treating patients with NUD leads to lower cure rates of *H. pylori* infection. Furthermore, in day-to-day clinical experience, *H. pylori* cure rates are typically lower than the cure rates seen in clinical trials. Fewer and fewer studies, today, seem to reach the required efficacy level of >80% cure by intention-to-treat (ITT) and >90% cure by per protocol (PP) analysis [6] and some results are really worrying. In the very large Leeds HELP study a PPI-triple therapy at population level cured a mere 74% [7]. The results reported by Pilotto et al. in this issue of **Digest Liver Dis (2000;32:667-72)** [8], in a highly selected group of patients with sensitive strains, must also be regarded as disappointing and inadequate. The ITT cure rate only touches the lower level of the required efficacy standard. These results, partly explained by the inclusion of patients with NUD, demonstrate once more that results of recent eradication studies are getting worse. There is also an increasing awareness of the problem of eradication failure (EF). With more persons being treated and lower over-all cure rates, the number of EF's is on the rise. More and more dyspeptics with EF are referred by general practitioners. What then are we to do with the eradication failures?

Most treatment studies deal with previously untreated new patients. As a result, EF has not been widely studied. When an attempt to eradicate *H. pylori* fails, secondary resistance may occur. In those who used clarithromycin, clarithromycin resistance may develop [9], whereas in patients who used metronidazole, metronidazole resistance may develop [10]. We can address this issue to a degree by using basic bacteriological rules. That is to use metronidazole for retreating those who have failed a clarithromycin containing regimen and to use clarithromycin for retreating those who have failed a metronidazole containing regimen [11]. This logical approach, where different antibiotics are applied in primary and secondary treatment is usually successful. It is also probably advisable to prolong the regimen used for retreatment from 7 to either 10 or 14 days [12].

However, if the initial regimen already contains a combination of clarithromycin and metronidazole either single – or even worse – double re-

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Invited Commentary received October 23, 2000.

sistance to both metronidazole and clarithromycin can develop. Buckley et al. showed that double resistance occurs mainly in patients with primary metronidazole resistance and warn against the use of this regimen in areas with a high prevalence of primary metronidazole resistance [13]. However induction of double resistance may also occur in sensitive strains. Pilotto et al. show that this is not rare [8]; it occurred in 5 of the 9 failures of his pantoprazole-metronidazole-clarithromycin regimen. A German survey also reported alarmingly high rates of double resistance [14]. Overall 71% of patients with EF in Pilotto et al.'s paper [8] were found to develop secondary resistance to one or two antibiotics. A rate similar to that previously reported in Europe [15 16] and Japan [17]. Pilotto et al's paper [8] then is timely in that the question of EF, secondary resistance and re-treatment is encountered daily by gastroenterologists around the world.

At present, we have no clear direction as to how to treat patients with double resistance [11 12]. Culture and susceptibility testing could be helpful to identify those with absent or single resistance and therapy could be based on the outcome. If this is not available, empiric treatment should be based on the assumption that all have double resistance. Quadruple therapy is the most investigated rescue therapy and seems to be the best option. It can overcome primary metronidazole resistance, but is less successful in secondary metronidazole resistance. Seppala et al. reported a cure rate of 97% with quadruple therapy as initial treatment, but 79% after failure of a metronidazole-based treatment [18]. Published results of quadruple therapy after a PPI-triple therapy with clarithromycin and metronidazole have not given a consistent picture: 16/32 (50%) [19], 25/36 (69%) [20], 13/18 (72%) [21] and 21/21 (100%) [22]. Alternative options to treat patients who have, or must be assumed to have, double resistance inlude high dose PPI-amoxycillin dual therapy [12 23] and a triple therapy of a PPI, amoxycillin and rifabutin [12].

The clinical consequences of secondary resistance requires more focused attention and perhaps formation of therapeutic committees to propose regional guide-lines as resistance and EF appear to behave differently in different cultural settings. Research on EF cannot be performed in a single centre and failures of multiple centres should be combined and treated similarly to provide us with data on how best to manage EF. Surveys show that most treated patients in primary, as well as in secondary, care are not being followed up [24 25]. This means that the secondary resistance that is induced is allowed to remain and potentially to spread. This is an important argument against the continued use of triple therapies that combine clarithromycin and metronidazole because these are, as shown in Pilotto et al.'s paper [8], the main cause of inducing double resistance. A call should also be made for a more widespread use of culture and susceptibility testing. This will not only allow for more rational use of antibiotics but also for data collection so that we can understand more clearly how *H. pylori* is evading our efforts at its eradication.

Perhaps the main issue, today, is to decrease the number of EF's as much as possible. In everyday care, only regimens that achieve a 90% cure-rate are cost-effective [26]. Today, partly due also to a rising prevalence of primary resistance, in many geographic areas the 7-day PPI-triple therapy does not seem to reach this goal. If we assess that our own cure rates are sub-optimal, we ought to reassess the local prevalence of primary resistance and maybe change the choice of antibiotics [27]. But we should also consider prolonging the duration of our primary treatment. Increasing PPI-triple therapy from 7 to 14 days increases the cure rates by 5 to 10% [28]. This is especially important in patients with NUD who may need longer treatment [1-5 29]. Patients with duodenal ulcer disease can usually still be managed with a 7-day regimen [29]. Furthermore, we need an all-embracing therapeutic strategy based on fundamental bacteriological principles.

A true treatment strategy consists of a combination of two therapies, which, if used consecutively, come close to 100% cure [11]. It is also important to select a primary regimen that does not compromise future therapeutic possibilities. PPI-amoxycillin-clarithromycin and PPI-clarithromycin-metronidazole were equally effective in two seperate meta-analyses [30 31]. The Maastricht 2000 Consensus Meeting decided to adopt our proposal [11] and it advised a fixed combination of two therapies; a "package" which considers first- and second-line therapy together. As first-line therapy, a PPI-amoxycillin-clarithromycin triple therapy was advised for at least 7 days. This should always be followed by a diagnostic test for cure and quadruple therapy of a PPI-bismuth-tetracycline and metronidazole for at least 7 days as empirical back-up for those who failed the first attempt. It was decided that subsequent failures should be handled on a case by case basis. This package of two complimentary regimens used one after the other has already been tested in well over 800 patients and a 98% PP and 95% ITT pooled cure rate could be calculated for this fixed combination of therapies [12]. It is hoped that the adoption of this package-approach will decrease EF, decrease the spread of (double) secondary resistance and provide physicians, in primary and secondary care, with similar tools to treat this important infection.

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