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# Causes of failure of eradication of *Helicobacter pylori*

## Antibiotic resistance is the major cause, and susceptibility testing may help

Peter J Jenks, honorary consultant microbiologist

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Eradication of *Helicobacter pylori* from the gastric and duodenal mucosa of infected patients is the most important goal in the management of peptic ulcer disease and other conditions associated with *H pylori*.[1] The survival capabilities of *H pylori* in the stomach make it difficult to eradicate, and effective treatment requires multidrug regimens consisting of two antibiotics (usually selected from clarithromycin, metronidazole, amoxicillin, and tetracycline), combined with acid suppressants and bismuth compounds.[2] A significant proportion of patients do not respond to treatment, and adverse treatment outcome is associated with advanced age, smoking, high intragastric bacterial load before treatment, bacterial genotype, and host genetic polymorphisms of the cytochrome-P450 isoenzymes that are specifically involved in the metabolism of proton pump inhibitors.[3] Adherence to the drug regimen is particularly important for successful eradication of infection and can be improved by education of patients and programmes to improve compliance.[4] But as in many other infectious diseases,

antibiotic resistance is the major cause of treatment failure. Meta-analyses have established beyond doubt that resistance to either the macrolide or 5-nitroimidazole component of the regimen is an important predictor of eradication failure.[5–7] The extent to which resistance compromises efficacy is related to the other components of the drug regimen and is less pronounced for metronidazole than clarithromycin.

Widespread use of antimicrobial drugs has resulted in a worldwide increase in the prevalence of antibiotic resistance in *H pylori*; 11-70% of clinical strains isolated in western Europe are resistant to metronidazole, and up to 15% are resistant to clarithromycin. Although tetracycline resistance seems rare, resistance to amoxicillin is an emerging and possibly under-recognised problem. Although basing therapy on susceptibility data obtained from the laboratory before treatment improve the eradication rate,[8] cost implications and ease of access to alternative, non-culture-based diagnostic tests mean that susceptibility testing in the laboratory is rarely performed before empirical treatment is started. In many centres such testing is practical and cost effective only for patients whose treatment has failed repeatedly. Consequently, selection of the most appropriate first line eradication regimen is critical for preventing primary failure and the subsequent emergence of resistant strains as a result of suboptimal treatment.[9] Although it is recommended that this choice is based on local susceptibility patterns, which vary geographically and in specific treatment groups, few countries have regional surveillance programmes.

A recent survey in the United Kingdom showed that only seven of 49 laboratories of the Public Health Laboratory Service undertook routine culture and susceptibility testing of *H pylori*, confirming that few laboratories are equipped or experienced to provide such a service.[10] This is likely to reflect the methodological problems of testing an organism that is slow growing and requires specific growth conditions, as well as the difficulty of interpreting susceptibility data that do not necessarily correlate with in vivo efficacy.

Until recently, methods of susceptibility testing of *H pylori* suffered from a lack of consistency, and conflicting results were often found when different techniques were compared. In an attempt to improve agreement in reporting and encourage centres to reassess the importance of routine susceptibility testing, a recent trend towards standardisation of testing has been noted.[10–12] These methods are relatively straightforward and should mean that culture and susceptibility testing of *H pylori* can now be done in most

hospital laboratories. Refinement of protocols and participation in quality control schemes will improve reproducibility of testing and allow national and international surveillance of antibiotic resistance, both to monitor the prevalence of resistant strains and to guide empirical treatment on the basis of local resistance patterns.

A clear consensus regarding what defines resistance is also needed before it will be possible to predict accurately individual responses to treatment. Although the presence of resistance to clarithromycin is highly predictive of treatment failure, the relation between susceptibility determined in vitro and clinical outcome for other antibiotics is less clear. In particular, methods for assessing resistance to metronidazole and amoxicillin are often not predictive of clinical outcome. This is largely because current breakpoints, which are the in vitro concentrations that define the cut off between sensitive and resistant strains, do not correlate with levels required for eradication of infection from the gastric mucosa. It is essential that future interpretative criteria are established on the basis of trials where the in vitro susceptibility of a large population of isolates is correlated with the pharmacokinetic profile of the drug and, most importantly, the clinical efficacy of a regimen.

Although at present susceptibility testing is not a prerequisite for successful eradication of *H pylori* from individual patients, this is likely to change as the proportion of patients colonised with resistant strains continues to rise. This change in the epidemiology of *H pylori* infection will eventually mean that the savings that can be made by avoiding follow up of patients, and costs for repeated treatment, will outweigh the expense of acquiring specimens by endoscopy. In certain regions, it may soon become cost effective to obtain antibiotic susceptibility testing before treatment, especially if minimally invasive and less expensive procedures to reliably obtain specimens for culture become widely available. Reproducible laboratory methods for ascertaining resistance and the establishment of clinically relevant interpretative guidelines will be increasingly important in allowing a more rational approach to the use of currently available drug regimens.

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