Ethical issues in the management of *Helicobacter pylori* infection

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Medical ethics are not absolute; they change according to social attitudes, technological advances and alterations in the doctor/patient relationship. The discovery of *Helicobacter pylori* highlighted entrenched attitudes in academia and the pharmaceutical industry that were not always appropriate. The explosion of research that followed was ethically controlled by local research ethics committees and the system of peer review and editorial responsibility. Now that effective treatments are available, the control arm in trials of new therapy should be either placebo (giving the option of effective treatment later) or a first-line treatment; mono and dual therapy should not be employed because of the risk of inducing bacterial resistance. Ethical issues that still remain include whether always to test patients for *H pylori* at endoscopy and what information should be given when they test positive. The most important issue is the approach of the medical profession to the high death rate carried by *H pylori* infection. Peptic ulcer and gastric cancer together account for a large number of deaths worldwide, and the medical profession and public health services have not yet grappled with this problem, neither advocating universal testing and treatment nor funding or research to determine whether this approach would be effective.

Key Words: Ethics; Gastric cancer; *Helicobacter pylori*; Peptic ulcer; Research

Medical ethics have changed enormously in recent years and continue to evolve. It is a common misconception that ethics are absolute and that it is a simple matter to distinguish what is right from what is wrong. In reality, many ethical issues are not black and white, but are a series of shades of grey. Prenatal screening, abortion, fertility treatment, choice of fetal sex, stem cell technology and cloning are all areas in which people, quite reasonably, may adopt a different stance according to their own beliefs, those of the community involved and those of the individual case being considered. Issues and beliefs have altered, not only because of social changes, but also as a result of advances in technology.

Neonatology is a particularly good example, but similar considerations relate to gastroenterology. The development of new drugs and the introduction of new endoscopic techniques (such as percutaneous endoscopic gastrostomy) into clinical practice, the advocacy of endoscopic screening for malignant

Questions d'éthique et traitement de l'infection à *Helicobacter pylori*

Les règles d'éthique en médecine ne sont pas immuables; elles changent selon les attitudes sociales, les progrès technologiques et l'évolution des relations médecin-patient. La découverte d'*Helicobacter pylori* a mis en évidence des attitudes bien ancrées dans les milieux universitaire et pharmaceutique, attitudes parfois douteuses. L'explosion de recherche qui a suivi la découverte de la bactérie était encadrée par les comités locaux d'éthique de la recherche ainsi que par le système d'examen par les pairs et la responsabilité des équipes de rédaction. Maintenant qu'il existe des traitements efficaces, les groupes témoins dans les essais de nouveaux traitements devraient recevoir un placebo, quitte à se voir offrir un traitement efficace plus tard, ou être soumis à un traitement de première intention; la mono- ou la bithérapie devraient être évitées en raison du risque de résistance bactérienne. Certaines questions d'éthique restent encore sans réponse, notamment la pertinence de procéder systématiquement à un examen de détection d'*H pylori* à l'endoscopie et le type d'information à donner aux patients lorsque les résultats sont positifs. La question la plus grave est l'attitude du monde médical devant le taux élevé de mortalité lié à l'infection à *H pylori*. L'ulcère gastro-duodénal et le cancer de l'estomac engendrent à eux seuls un nombre élevé de décès dans le monde, et la profession médicale tout comme les services de santé publique ne se sont pas encore attaqués au problème : ni promotion du dépistage systématique et du traitement ni financement ni recherche sur l'efficacité de l'approche.

gastrointestinal disease, the use of treatments that prolong the process of dying and the availability of drugs that the community is unable to afford all raise ethical issues that gastroenterologists have to address.

It is not just technological advances that have led to ethical changes, the role of the physician has altered, particularly in the developed world where paternalism has been replaced by patient empowerment, professional freedom by the development of clinical guidelines and individual responsibility by the development of multidisciplinary teams. There has also been a decline in professional confidence as a result of widespread litigation. Conversely, patient expectations have increased because medical care is now more effective and, therefore, more desirable. The rise in the standard of living and the provision of insurance or state coverage for medical care have led to greater demands. Patients are more knowledgeable, there is greater egalitarianism and a recognition that doctors are falli-

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ble. All these changes subtly, and sometimes not so subtly, influence the traditional doctor-patient relationship. How then do these developments affect the way in which we manage patients infected with *Helicobacter pylori*?

THE DISCOVERY OF *H PYLORI*

When Marshall and Warren (1) first drew attention to *H pylori* 20 years ago, their discovery was treated with incredulity by the medical establishment. Those who had devoted their professional lifetime to the study of gastric acid secretion were academically challenged. As the evidence supporting the *H pylori* hypothesis began to accumulate, certain sections of the pharmaceutical industry perceived the discovery to be a threat to their products and some campaigned against it, while others with a different portfolio were prepared to provide generous support. The period between 1985 and 1995 provided an interesting insight into the psychology of gastroenterological academia, market forces and the ethical issues that relate to each.

RESEARCH IN *H PYLORI*

Following the discovery and isolation of *H pylori*, there was an exponential explosion of research to a degree not experienced before in gastroenterology. Fortunately, the accepted policy that all research projects should be reviewed and approved by ethics research committees meant that few patients were disadvantaged as a result of this research, much of which was clinical in nature. Today, it is recognized that *Helicobacter* species infection is a potentially serious disease and certain ethical principles should be adhered to when planning clinical trials. In the past, a number of studies were designed using treatments in a control arm that were known to be relatively ineffective. There is no ethical reason why a placebo controlled trial should not be undertaken in patients infected with *H pylori* provided that, at the end of the study, they are offered appropriate effective treatment. What is unacceptable is that some of the control regimens used have not only been relatively ineffective, but have led to the development of microbial resistance in those recruited. In other words, the opportunity for long term cure in these patients may have been impaired. In future studies, if a placebo is not to be used, an effective first line medication should be employed in the control arm, not a monotherapy or dual therapy known to be ineffective.

Another area where ethical problems in research may arise is the use of invasive testing for the infection in children. Unfortunately, to type organisms it is necessary to obtain a culture of *Helicobacter* species and this can only be obtained by invasive testing (usually endoscopy). The investigation of children is an attractive scientific objective when studying the epidemiology of infection; however, small children are not capable of giving informed consent and studies of this nature are to be avoided. Editors of journals and those who are involved in reviewing manuscripts or grant applications should bear in mind ethical considerations such as this when assessing research for publication or for presentation in scientific meetings. If there does appear to be an ethical issue the authors should be approached to justify on ethical grounds the scientific method that has been used.

WHO TO TEST OR TREAT?

Some of the main debating points in *Helicobacter* species management are who should be tested and which patients should be treated? One American set of guidelines has stated that if a

doctor does not intend to treat *Helicobacter* species infections, he or she should not test for it at endoscopy. Few would argue that a patient with an ulcer should be tested and treated if positive. The situation, however, is different in patients who present with dyspepsia and in whom no macroscopic gastric pathology can be identified. Not all gastroenterologists believe that patients with nonulcer dyspepsia who are infected with *H pylori* should be treated. To test for the organism at endoscopy, therefore, can lead to an ethical dilemma. If the patient is negative he or she can be reassured, but, if positive, the information will either have to be suppressed or fully discussed with the patient. If the patient, having been informed that they are infected, wishes to receive treatment, then the doctor is put in a difficult position. He or she has either to accede to the request of the patient, which ethically he or she should not do, because the physician should not provide treatment for a patient if he or she believes that it is not in the patient's interest, or alternatively he or she has to refuse treatment, thus injuring the patient-doctor relationship, possibly causing the patient to seek advice elsewhere. If the endoscopist follows the guidelines and does not test for *H pylori* infection, then he or she can be accused of paternalism and failure to empower patients to make their own decisions as to how they should be treated. Increasingly, most physicians do test for *Helicobacter* species at endoscopy and do fully discuss with their patients the pros and cons of treatment.

WHAT INFORMATION SHOULD BE PROVIDED TO THE PATIENT?

When discussing with patients the advantages and disadvantages of therapy, doctors should focus not on the responsibilities that they have to the general population, but on the specific needs of the patient. Will the patient worry about the risk of cancer and go away to read about it on the Internet? Is the patient an elderly person who has lived with his or her *Helicobacter* species infection for many years and whose symptoms are unlikely to be related to it? Is the patient the 'one in 10' who may be cured of their nonulcer dyspepsia as a result of *Helicobacter* species eradication or is he or she a patient who, given treatment, will have side effects that may cause him or her to complain about the therapy for many years after? Decision-making under these circumstances is clinical rather than ethical. The ethical responsibility, however, is for the doctor to discuss the issues clearly and objectively, pointing out the advantages and disadvantages and ending with personal advice along the lines that he or she feels is most appropriate for the individual patient in question.

DEATH FROM *H PYLORI*

An important ongoing issue is whether *H pylori* infection is responsible for gastric cancer and, if so, what should be done about it. Scientific data provide strong circumstantial evidence that infection with *H pylori* is the main factor responsible for the development of gastric cancer, which is the second most common cause of death from malignancy in the world. Infection with the organism probably increases the risk by a factor of six. No prospective studies of treatment versus non-treatment for the prevention of cancer have been undertaken, so proof of cause and effect is lacking. Nevertheless, apart from the epidemiological data, *Helicobacter* species infection has been shown to cause cancer in an animal model, and there is a wealth of data showing how the infection, in association with

other factors, provides a credible pathogenetic mechanism for carcinogenesis. It is difficult, therefore, to understand why the medical establishment is so reluctant to support the concept of a test-and-treat policy in the general population. The arguments against this include the overuse of antibiotics, the fact that no study has shown that eradication of the infection prevents cancer, that infection with the organism may have some, as yet, undetermined benefit to mankind, that treatment may be expensive and that it may give rise to adverse events. Against these arguments, it may be said that the use of antibiotics would be small in relation to those used already (in the United Kingdom more than one course of antibiotic therapy for each man, woman and child every year). Society has introduced screening for cervical cancer, breast cancer and now colonic cancer without prospective evidence that these interventions are effective. There is no convincing evidence that *H pylori* infection does anything but harm to the human race and treatment is remarkably free from significant side effects compared with, for example, cone biopsy and colonoscopy.

The burden of disease from *H pylori* infection is perhaps best expressed by comparing *Helicobacter* species infection with other infectious diseases. Figure 1 shows mortality rates in England and Wales for a variety of infections during 2001. These data, were obtained from the Office for National Statistics (2), show that roughly twice as many people died from peptic ulcer and gastric cancer than from all the diseases designated as infectious combined. While accepting that not all peptic ulcers and gastric cancers are caused by *Helicobacter* species, a conservative estimate suggests that this infection is by far the most serious cause of death compared with other infections in most developed countries. The argument put forward that *Helicobacter* species infection is declining and will not remain a problem in the future is wildly optimistic, particularly when considering the infection rate in the developing world and the potential impact that it will have on their populations as the standard of living increases and populations live long enough to reach an age where complications of *H pylori* infection become more serious. The cost of introducing a test-and-treat policy in a developed country is relatively small and it is possible that it would pay for itself within a decade (3).

H PYLORI MANAGEMENT: AN ETHICAL, SCIENTIFIC, POLITICAL OR ECONOMIC ISSUE?

It is difficult to disentangle the morality of medical decision making from science and economics. Doctors have an ethical duty to ensure that the money provided for health care is spent appropriately. Priorities will vary from country to country. At

Figure 1) 2001 mortality statistics for England and Wales. HIV Human immunodeficiency virus. Data from reference 2

present, the problem of *Helicobacter* species infection in the developing world, though serious, does not compare, for example, with that of human immunodeficiency virus infection in Africa, with malaria worldwide or with enteric diseases associated with polluted water supplies. Nevertheless, in eastern Europe and the far East, where gastric cancer is rampant, public health intervention could make a significant impact, and taking peptic ulcer into consideration would be worthwhile in western Europe. At present, little money or enthusiasm is forthcoming for research into the epidemiology of this serious infection or for investigation of public health measures to control it. Doctors, and, in particular, gastroenterologists, do not seem to be prepared to take a lead in this area, and there is not sufficient funding available for research to explore the effect of a test-and-treat policy. Perhaps it is time that the medical profession took a higher profile in advising where health care money should be spent, rather than leaving it to government and the biomedical industry, both of whom have agendas that are not wholly altruistic.

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