Gastric cancer and Helicobacter pylori: the bug, the host or the environment?

Marjorie M Walker, Louise Teare, Cliodna McNulty

Worldwide, gastric cancer is still a leading cause of cancer deaths. The association of Helicobacter pylori and gastric cancer is well established, and the bacterium was declared a class one carcinogen by the International Agency for Research on Cancer and the World Health Organisation in 1994. H pylori infection is responsible for 5.5% of all global cancers, 75% of non-cardia gastric cancer and lymphoma, and 65% of gastric cancers worldwide.

In 2005, Marshall and Warren were awarded the Nobel Prize for Medicine for their pioneering work on H pylori (in 1984) showing the association between this bacterium and gastritis and that antibiotics could cure peptic ulcers. Parsonnet et al formally demonstrated the link to gastric cancer in 1991. However, although more than 50% of people worldwide are infected with H pylori, only a small percentage of those infected will have clinical complications, which include gastric and duodenal ulcers, precancerous lesions, atrophy and intestinal metaplasia, and progression to cancer or lymphoma. However, all those infected will have some degree of histological gastritis, likely to be present long term. It is the distribution and extent of gastritis that to some extent determines outcome: 10–15% of subjects will have antral-predominant gastritis, which is the duodenal ulcer phenotype, and 1% will have a body (corpus)-predominant phenotype, with the risk of gastric cancer. It has been estimated that 60–80% of gastric cancers would be preventable if H pylori was eradicated.

So what determines whether you live quietly with this potential carcinogen or whether it causes mayhem and havoc in your stomach? Conceptually, there are three contributing factors that determine your risk of cancer: the bug, the host and the environment. In this issue of the Postgraduate Medical Journal (see page 193), a study from India on the prognostic significance of genotyping H pylori infection in patients from younger age groups with gastric cancer explores the role of the bug. This study showed that young subjects with the H pylori genotype cagA+ve/rugA+ve/cagA+ve/cagEr+ve/vasA+ve have an increased risk of cancer. Other studies have shown that cagA is associated with a 20-fold risk of gastric cancer compared with controls. These studies demonstrate the importance of the bacterial strain in contributing to cancer risk. However, Tiwari et al did not evaluate the role of the host or environmental factors in these studies, as no genotyping of the host was performed. These may certainly have a bearing on outcome, functional polymorphisms in the host’s interleukin-1 gene cluster, and tumour necrosis-a (TNF-a-308) genes significantly increase the risk of gastric cancer in subjects, particularly if they are also infected with virulent strains of the bacterium.

What role does the environment play in infection and cancer? In Colombia, intervention studies with antioxidant supplements have shown that vitamin C and beta-carotene, in addition to H pylori eradication therapy, produced significant regression of gastric precancerous lesions, atrophy and intestinal metaplasia in the stomach. The Columbian study concluded that continual supplements are required to maintain protection, as the benefits of antioxidants were no longer evident after 6 years. The improving benefits of antioxidants were no longer evident after 6 years.1 The improving hygiene in developed countries has also contributed to the decline of infection and therefore H pylori-associated cancer. In the UK, H pylori infection has declined rapidly, to about 20%, and, in the USA, only 10% of the population is now infected, but in Asia and South America prevalence of infection still runs at 70–80% and rates of gastric cancer are also high.

Studies showing the importance of bacterial molecular markers, host genotypes and the environment in H pylori-related gastric cancer are unravelling the steps in carcinogenesis. These studies have characterised the complex pathway in which inflammation leads to cancer. An exciting breakthrough has been the establishment of the role of stem cells in gastric cancer: in inflammation there is local stem cell failure and recruitment of cells derived from bone marrow to damaged gastric mucosa. In this abnormal environment of cytokines and tissue dysregulation, these stem cells fail to differentiate correctly and progress to cancer. This shows that distant rather than local (gastric) factors may be important in determining response.

Therefore, the practical role of bacterial and genetic markers in routine clinical practice remains to be defined. The current policy in the UK for management of H pylori, as recommended by the HPA Helicobacter Working Group and NICE guidelines for treatment of dyspepsia in England, is test and treat. It is also recognised that even symptoms of different upper gastrointestinal diseases such as gastro-oesophageal reflux (not attributable to H pylori) and gastric cancer (attributable to H pylori) may overlap and it is therefore practical to offer test and treat to eradicate H pylori in the Asia Pacific region.

Until molecular markers are cost effective, should we not adopt the screen and treat approach to eradicate all H pylori identified as being more carcinogenic? Although this is recognised as a potential answer to this problem in countries with a high rate of gastric cancer such as in Asia, there is a growing problem of antibiotic resistance. In Europe, resistance to clarithromycin and metronidazole is increasing, and some patients may harbour resistant strains. It is in this setting that host and bug profiling may be of value in patient reassurance or determining antibiotic sensitivity. Although the aim should be to develop a vaccine, which has proved effective in reducing the incidence of other infection-related cancers such as hepatitis B, the development of either a protective or prophylactic vaccine for H pylori infection is as yet an elusive goal. Currently, enhancing host immunity to generate a protective response holds promise, but translation from animal to human studies remains ethereal. As always in medicine, it seems
Prescribing errors by family practice residents

Anthony J Avery

Prescribing errors are an important cause of morbidity and mortality worldwide. Recently there has been particular concern about prescribing errors among doctors in training. For example, in the UK a number of influential clinicians have raised serious concerns about undergraduate training in pharmacology and therapeutics. As a result, the General Medical Council has recently commissioned research to try to determine how common prescribing errors are among junior doctors and to try to assess the extent to which errors are related to deficiencies in training.

Given the lack of studies of prescribing errors among doctors in training, the paper by Al Khaja et al. in this edition of the Journal (see page 198) provides an important contribution to the literature. Focusing on the Family Practice Residency Programme in Bahrain, the authors judged that, from nearly 2700 dispensed prescriptions, there were major errors in 58% of these. Interestingly, there were no differences in total numbers of errors between doctors who had been through a problem-based learning undergraduate medical degree in Bahrain and doctors who were trained on other types of course in other countries.

The findings of Al Khaja et al. are clearly worrying, but it is important to put them in context and consider a number of issues. (1) Does this study raise particular concerns about family practice residents in Bahrain? (2) Did the methods used in this study lead to error rates that are particularly high compared with other studies? (3) How do these findings compare with prescription error rates among fully qualified family practitioners? (4) What are the implications of the findings in terms of training for family practitioners? (5) What might be the impact of computerisation on error rates?

Although it is tempting to attribute the high error rates found in this study to the quality of the family practice residents in Bahrain, I have first-hand experience of the Family Practice Residency Programme in Bahrain and found residents’ baseline knowledge of therapeutics to be reasonably good. Nevertheless, there is clearly a need for greater emphasis on prescription writing skills during the residency programme.

There have been many studies, across the world, of prescription error rates in primary and secondary care. In previous studies, error rates in primary care varied from less than 1% to over 40% of prescriptions, the latter being a Scandinavian study where failure to report the indication for a drug was considered an error. It is clear on reviewing the studies that error rates are very strongly associated with the definitions of error used and the rigour with which detection of error is undertaken. The study by Al Khaja et al. is at the far end of the spectrum, both in terms of error rates reported and the range of issues that fell within their definition of error. Nevertheless, the problems most commonly reported are those that one would expect to be avoided by most competent doctors when issuing prescriptions. For example, lack of dosage form and lack of information on length of treatment made up 39% and 19% of errors, respectively, and incorrect dosing frequency made up 20% of errors. In relation to the latter point, the main problem was a lack of qualifying information in relation to prescriptions to be taken “as required”, a problem reported in previous studies but not with anything like this frequency. Although this study shows a particularly high prescription error rate for a group of doctors in training, it is important to know whether rates are appreciably lower for qualified doctors. According to another paper by Al Khaja et al., this would appear to be the case. In a study of family doctors and general practitioners in Bahrain in 2003, using similar methodology, only 7.7% of prescriptions were identified to contain errors. Thus, there appears to be a more than tenfold difference in rates of prescribing errors between residents and qualified family doctors/general practitioners in Bahrain. This is a surprising finding which suggests that, once qualified, family doctors/general practitioners in Bahrain greatly improve their prescription-writing behaviour.

It clearly makes sense, however, for family practice residents to be provided with help in developing their prescription writing skills before they are let loose on patients. In a small study of family practice residents in the USA, prescription rates were reduced from 14% to 6% as a result of continuous evaluation of prescription writing and feedback about any problems. It would seem reasonable to try out similar schemes in other residency programmes, particularly where high
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doi: 10.1136/pgmj.2008.068346

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