Ministry of Defence

Synopsis of Causation

Peptic Ulcer

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September 2008

Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1 A peptic ulcer is a defect in the mucosa of the stomach or the duodenum that extends at least through the muscularis mucosae; it may involve all layers of the gut wall.

1.2 A gastric ulcer is a peptic ulcer in the stomach. A duodenal ulcer is a peptic ulcer in the duodenum.

2. Clinical Features

2.1 Peptic ulcer is more common in men than women, with lifetime prevalence for men estimated at 11–20% and for women at 8–11%.[1]

2.2 About 4% of general practice consultations in the UK are for symptoms of dyspepsia, and about 10% of these consultations lead to referral for further investigations. Of these patients who are investigated further, about 10–15% are found to have duodenal ulcer and about 5–10% are found to have gastric ulcer.[2]

2.3 This ratio of the relative frequency of duodenal and gastric ulcers is typical of most of the developed world, where duodenal ulcers are generally about 1.5 times more common than gastric ulcers. However, these findings contrast with data from Japan, where the ratio is reversed.[1]

2.4 The risk of peptic ulcer is related to date of birth and has been declining in the developed world for all generations born since the turn of the 20th century.[3]

2.5 The symptoms most commonly associated with peptic ulcer are epigastric pain (which is sometimes described as burning or gnawing in nature), nausea and vomiting. The symptoms may be relieved by food or antacids.

2.6 However, the relationship between symptoms and peptic ulcer is not always helpful, in that some 80% of people with symptoms suggestive of peptic ulcer do not in fact have ulcers and about half of all peptic ulcers cause no symptoms.

2.7 Complicated peptic ulcer may cause gastrointestinal bleeding, gastric outlet obstruction, penetration into an adjacent organ, or perforation.

2.8 Gastric cancer may develop in a gastric peptic ulcer.

3. Aetiology

3.1 Peptic ulcers result from a breakdown in the normal mechanisms that protect the gastric and duodenal mucosa from the acidic gastric juices. The mucosa is constantly subject to the caustic effects of the gastric juices, and it is normally protected by a number of defence mechanisms.[4] There are three levels of defence, and disruptions to these defence mechanisms increase the risk of peptic ulceration.

3.1.1 The epithelial cells in the stomach and duodenum are protected from the gastric juices by the layer of mucus and by a layer of fluid rich in bicarbonate, which acts to neutralise the acidic gastric juices.[4]

3.1.2 Tight junctions between the epithelial cells limit the diffusion of hydrogen ions into the mucosa. When the apical cell membranes are exposed to dilute acid, the resistance to the diffusion of hydrogen ions through the tight junctions is enhanced. However, when the apical cell membranes are exposed to more concentrated acid (pH <2.5), they are injured and hydrogen ions are able to leak through the tight junctions more readily.[4]

3.1.3 Mucosal blood flow adds another layer of defence by providing much of the energy and substrates that are needed by the epithelial cells for protection against the gastric juices.

3.2 There are a number of factors, both exogenous and endogenous, that increase the risk of developing peptic ulcer. The mechanism by which these factors promote peptic ulceration is not known in every case.

3.3 **Endogenous risk factors: hypersecretory disorders.** Peptic ulcer may rarely result from one of several well-defined medical conditions that cause increased secretion of gastric acid sufficient to overwhelm the usual defence mechanisms of the mucosa. Gastrinoma, systemic mastocytosis, antral G-cell hyperfunction and sometimes myeloproliferative disorders (e.g. polycythaemia vera, basophilic chronic myelogenous leukaemia) are associated with peptic ulcer by this mechanism.

3.4 **Other endogenous risk factors.** A number of other endogenous risk factors for the development of peptic ulcer have been identified, the best known of which is blood group O, which has been repeatedly shown to be associated with duodenal ulcer, although no causative link has been established.

3.5 Duodenal ulcer is associated with a number of apparently unrelated medical conditions: it has been noted to occur more commonly in people with chronic obstructive pulmonary disease, cystic fibrosis, alpha-1-antitrypsin deficiency, chronic renal disease and cirrhosis. The mechanisms of these associations are mostly unknown or uncertain,[1] and no causative link is known.

3.5.1 Because of the strong relationship between chronic obstructive pulmonary disease and smoking, which is known to be independently associated with peptic ulcer, it is difficult to establish the exact relationship between these two disorders.

3.5.2 Cystic fibrosis and cirrhosis may be associated with decreased bicarbonate concentrations in the gastric and duodenal contents, which may account at least in part for the relationship between these diseases and peptic ulcer.

3.6 **Exogenous risk factors** The two main exogenous risk factors for peptic ulcer are infection with the bacterium *Helicobacter pylori* and the use of non-steroidal anti-inflammatory drugs (NSAIDs). These two risk factors are considered to be overwhelmingly the most important factors in the aetiology of peptic ulcer.

3.7 **Infection with *Helicobacter pylori*.** The identification of *Helicobacter pylori* (originally classified as *Camplyobacter pylori*) in the 1980s[5] led rapidly to the recognition that it is a cause of gastric inflammation and peptic ulceration.

3.7.1 Excluding ulcers that are thought to be due to NSAIDs, *Helicobacter pylori* infection has been identified by some studies in more than 95% of people with peptic ulcers,[6] although such estimates may be overstated. More recent studies suggest that it is associated with about 80% of duodenal ulcers and 60% of gastric ulcers.[4]

3.7.2 The epidemiology of *Helicobacter pylori* infection or colonisation varies geographically. In developed countries, the rate of infection in children and young adults is low, with rates increasing to approximately 50% by the age of 60, after which the infection rate flattens out.[7] This increase in infection rate with age is probably attributable to a cohort effect, meaning that infection was more common 20–30 years ago and earlier than it is now, so that an age-related increase is observed as the cohort ages.

3.7.3 Conversely, outside developed countries, infection is very common in children.[8]

3.7.4 There is an association between social class and infection, with low income, low educational level, and crowded living conditions having a strong positive correlation with infection.[9] There is a positive correlation between the number of children in a family and the risk of *Helicobacter pylori* infection, and children seem to promote the spread of infection within a family.[10]

3.7.5 Infancy in a developing country is also a risk factors.[11]

3.7.6 Infection, once established, is chronic and will persist throughout life if it is not treated.

3.7.7 Reservoirs of the organism and the routes of its transmission are under investigation, but direct spread from person to person by the faecal–oral or the oral–oral route is probably the most likely form of transmission. The organism can also be transmitted via contaminated invasive medical equipment such as endoscopes if these are not completely sterilised after use.[12]

3.7.8 Contaminated water may be a source of infection in some areas, and there are some data suggesting that animal vectors may play a part.[8]

3.7.9 The exact mechanisms by which *Helicobacter pylori* promotes gastritis and peptic ulceration are not known.

3.7.10 It is thought that *Helicobacter pylori* infection that involves predominantly the antrum of the stomach may predispose to duodenal ulcer, whereas infection that involves the more proximal parts of the stomach may predispose to gastric ulcer.[4]

3.8 **NSAIDs.** The use of NSAIDs, which is increasing in the UK largely as a result of the ageing population, is the second major cause of peptic ulcer.

3.8.1 The point prevalence of peptic ulcer in patients taking NSAIDs has been

estimated at 15–25%,[13,14] and about 2% per year of patients on long-term NSAID therapy develop a serious complication that requires hospitalisation.[15]

3.8.2 Most NSAIDs, including all the older agents, inhibit the enzyme cyclo-oxygenase-1 (COX-1), which is intimately involved in the synthesis of prostaglandins.

3.8.3 NSAIDs, which are weakly acidic, remain undissociated in the strongly acidic environment of the stomach and can easily penetrate the gastric lining and inhibit prostaglandin synthesis there. This inhibition leads to decreases in mucus production, bicarbonate secretion by the gastroduodenal mucosa and mucosal blood flow.[1,14]

3.8.4 Toxicity of an NSAID to the gastroduodenal mucosa may be increased if the drug is excreted in the bile. This, if combined with reflux of the duodenal contents into the stomach, can result in repeated exposure of both the gastric and the duodenal mucosa to the drug, rendering it toxic even if the actual ingested dose was small or the drug was not given orally.

3.8.5 Patients with a previous history of peptic ulcer and those who have gastritis secondary to infection with *Helicobacter pylori* are more prone than other people to develop peptic ulcer if they take NSAIDs. It is possible that the higher rates of complications and death secondary to peptic ulcer in the elderly may be in part a reflection of the increased rates of *Helicobacter pylori* infection with age.[14]

3.8.6 The risk of peptic ulcer is probably reduced with the newer class of NSAIDs, which inhibit cyclo-oxygenase-2 (COX-2) rather than COX-1. These COX-2 inhibitors have less effect on prostaglandin synthesis. However, the COX-2 inhibitors, while useful in many conditions in which older-style NSAIDs are employed, cannot replace them in every indication.[1] Examples of COX-1 inhibitors are diclofenac, fenbrufen, fenoprofen, ibuprofen, ketoprofen, naproxen and piroxicam. Ibuprofen appears to carry the least risk of upper gastrointestinal side effects. Examples of COX-2 inhibitors are celecoxib, etodolac, etoricoxib, meloxicam, rofecoxib and valdecoxib.

3.9 **Other exogenous risk factors.** Once the close association between *Helicobacter pylori* infection and peptic ulcer had been uncovered – and, moreover, once it became apparent that eradication of the infection was curative in most cases, even if other exogenous risk factors (other than NSAID use) were present – the influences of these other exogenous factors ceased to have the clinical relevance that they once had.[14]

3.9.1 **Smoking** Smokers are twice as likely as non-smokers to develop peptic ulcer, with the effect of smoking on duodenal ulcer being greater than that on gastric ulcer. The mechanism by which smoking has this effect is not well understood, but its influence is very much less in patients who are not infected with *Helicobacter pylori* or in whom infection has been eradicated.[14]

3.9.2 **Alcohol** The consumption of alcohol is not of itself a risk factor.[14]

3.9.3 **Salt** Very high salt consumption has been associated with the development of gastric ulcer, although the levels of consumption needed were more likely to be encountered in developed countries in the days before universal refrigeration obviated the need for the use of salt as a preservative.[14]

3.9.4 **Trauma** Physiological stress (e.g. from injury or surgery) is not generally

considered to be a risk factor of itself. However, it may promote haemorrhagic erosions of the gastroduodenal mucosa or bleeding from pre-existing ulcers.[14]

3.9.5 **Systemic corticosteroids** The link between peptic ulceration and steroids is tenuous, but they do predispose to perforation of existing ulcers.

3.9.6 **Psychological stress** Psychological stress may contribute to the development of peptic ulcers, possibly by increasing the secretion of gastric acid and pepsin. It is not known, however, whether this mechanism is applicable to everyone or only to certain susceptible people.[1] It is also possible that this association is accounted for, at least in part, by the increased likelihood of *Helicobacter pylori* infection in people with lower socioeconomic backgrounds,[14] which is in turn related to the number of children living in the family – children seem to promote the spread of the infection within the household.[10] Conversely, living with an infected spouse is not a risk factor if there are no children in the household.[16] Despite a number of negative case-control studies, further investigation of the relationship between psychological stress and peptic ulcer is warranted.[17]

3.9.7 **Diet** There is little evidence that diet per se is a contributory factor in peptic ulceration.

3.9.8 **Military service** Few studies have been conducted into the effects of military service on the rate of *Helicobacter pylori* infection, and the findings are not consistent.[18,19] There is no strong evidence that military service is a risk factor for *Helicobacter pylori* infection.

4. Prognosis

4.1 The natural history of peptic ulcer disease is typically one of spontaneous healing of an ulcer, over 4–8 weeks, followed by recurrent ulcerations, sometimes at the rate of several per year.

4.2 *Helicobacter pylori* infection, once established, is chronic and will persist throughout life if it is not treated.

4.3 Complications of peptic ulcer include perforation, haemorrhage, penetration into an adjacent organ, and gastric outlet obstruction. Up to 5% of peptic ulcers per year result in such complications.

4.4 The aims of treatment are to promote healing, reduce symptoms and avoid complications.

4.5 Eradication of *Helicobacter pylori* infection with appropriate antibiotic therapy is usually successful and speeds ulcer healing and avoids complications. Re-infection after successful eradication is unusual in developed countries.

4.6 The mainstays of treatment of peptic ulcer are eradication of *Helicobacter pylori* infection, when present, with appropriate antibiotic therapy, and suppression of gastric acid secretion with proton pump inhibitors. COX-2 inhibitors can replace the older COX-1 inhibitors in some patients. With the success of modern pharmacological treatments, surgery now plays a limited role in the management of peptic ulcer.

5. Summary

5.1 A peptic ulcer is a defect in the mucosa of the stomach or duodenum that extends through the muscularis mucosae.

5.2 Peptic ulcers result from a breakdown in the normal mechanisms that protect the gastric and duodenal mucosa from the acidic gastric juices.

5.3 Overwhelmingly the two main exogenous risk factors for peptic ulcer are infection with the bacterium *Helicobacter pylori* and the use of non-steroidal anti-inflammatory drugs (NSAIDs).

5.4 Peptic ulcer may rarely result from one of several well-defined medical conditions that cause increased secretion of gastric acid sufficient to overwhelm the usual defence mechanisms of the mucosa.

6. Related synopses

Cancer of the Stomach

7. Glossary

antrum (of the stomach)	The distal, wide part of the stomach before it narrows down at the pyloric sphincter (pylorus), which leads into the duodenum. Hence *antral*.
duodenum	The proximal portion of the small intestine, which extends from the pylorus to the jejunum, so called because it is about 12 fingerbreadths in length. Hence *duodenal*.
dyspepsia	A group of symptoms, the principal of which is pain or discomfort located centrally in the upper abdomen. Other symptoms may include a feeling of bloating, retrosternal pain, and nausea.
epigastrium	The upper region of the abdomen, in the middle. Hence *epigastric*.
epithelium	Cellular lining.
gastritis	Inflammation of the stomach.
mucosa	Also known as mucous membrane; a membrane that lines a body cavity and that is covered in mucus, a smooth, slimy fluid composed of secretions, white blood cells, desquamated cells, and various salts.
muscularis mucosae	Smooth muscle layer of the mucosa.
non-steroidal anti-inflammatory drug (NSAID)	One of a class of drugs used for their anti-inflammatory and analgesic properties.
prostaglandin	One of a group of naturally occurring substances; as a group, prostaglandins have multiple pharmacological effects, including a role in the regulation of inflammation and the regulation of acid secretion by the stomach.
substrate	a substance that an enzyme acts on and that is necessary for an enzymatic chemical reaction to occur.

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