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Perforated peptic ulcer

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Summary

Perforated peptic ulcer (PPU) is a frequent emergency condition worldwide with associated mortality up to 30%. A paucity of studies on PPU limits the knowledge base for clinical decision-making, but a few randomised trials are available. While *Helicobacter pylori* and use of non-steroidal anti-inflammatory drugs are frequent causes of PPU, demographic differences in age, gender, perforation location and aetiology exist between countries, as do mortality rates. Clinical prediction rules are used, but accuracy varies with study population. Early surgery, either by laparoscopic or open repair, and proper sepsis management are essential for good outcome.

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KS and planned the review and drafted the first manuscript version and panels. MHM drafted the section on prognostic factors and clinical risk scores. KS, EMH, KT, MYO searched literature and drafted the section on epidemiology. KS drafted the sections on pathogenesis and suggested the figure. KS drafted and KT and JAS revised the section on diagnosis and management. JB drafted the section on novel therapeutic approaches. EMH, KS and MHM made the suggestions/drafts for the figures 1, 2, and 3, respectively. All authors searched literature and made contributions to each of the sections. All authors contributed to several rounds of revisions of the manuscript sections towards the final version and approved the submitted manuscript.

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Selected patients can perhaps be managed non-operatively or with novel endoscopic approaches, but validation in trials is needed. Quality of care, sepsis care-bundles and postoperative monitoring need further evaluation. Adequate trials with low risk of bias are urgently needed for better evidence. Here we summarize the evidence for PPU management and identify directions for future clinical research.

Introduction

Perforated peptic ulcer (PPU) is a surgical emergency and is associated with short-term mortality and morbidity in up to 30 and 50% of patients, respectively.¹ Worldwide variation in demography, socioeconomic status, *Helicobacter pylori* prevalence and prescription drugs make investigation into risk factors for PPU difficult. PPU presents as an acute abdominal condition, with localized or generalized peritonitis and a high risk for developing sepsis and death. Early diagnosis is essential but clinical signs can be obscured in the elderly, or the immunocompromised and thus delay diagnosis. Imaging has an important role in diagnosis, as does early resuscitation including administration of antibiotics. Appropriate risk-assessment and selection of therapeutic alternatives becomes important to address the risk for morbidity and mortality. This review will present an update on the current understanding and management of perforated peptic ulcer.

Search strategy and selection criteria

We searched the PubMed/MEDLINE (January 2000–February 2015), and EMBASE (January 2000–February 2015) and the Cochrane Library (Issue 12, December 2014). We used the search terms “perforated peptic ulcer” and “gastric” or “duodenal” or “gastroduodenal ulcer” and “perforated” or “perforation”. Articles in all languages were considered for inclusion. The ClinicalTrials.gov, the ISRCTN Registry, PROSPERO and the WHO International Clinical Trials Registry Platform (ICTRP) databases for prospective trials were searched for any recruiting or closed studies (yet unpublished) on perforated peptic ulcer.

We focused on recently published research (past 5 years) where possible, and favoured studies/trials with low risk of bias (systematic reviews, randomized controlled trials, clinical trials, and well-conducted population-based observational studies), but did not exclude relevant commonly cited and highly regarded older publications. We also searched the reference lists of articles identified by the search strategy.

Epidemiology of peptic ulcer disease and its complications

Complications to peptic ulcer disease include perforation, bleeding and obstruction.^{2, 3} Although perforations are second to bleeding in frequency (about 1:6 ratio), they represent the most frequent indication for emergency surgery for PUD.^{4–6} Overall progress in medical management has made obstruction from recurrent ulcer scarring a rare event, and the addition of endoscopic techniques and transarterial embolization has reduced the need for emergency surgery for bleeding ulcers.³ In 2006,⁴ over 150,000 patients were hospitalized for complicated PUD in the US alone. Although the overall share of complications due to

perforations (n=14,500, 9%) was seven times lower than bleeding, PPU caused 37% of all ulcer-related deaths.⁴ Based on US data, more than one in every ten hospitalization for PPU leads to death. Indeed, PPU had a 5-fold higher mortality rate than bleeding ulcers, and was the single most important contributor to inpatient mortality with an odds ratio (OR) of 12.1 (95% confidence interval [c.i.], 9.8–14.9).⁴

Many studies report a steady incidence of PPU, but studies from Sweden, Spain and the USA noted a decline in the incidence of both bleeding and perforations.^{7–9} Mortality rates for PPU in Europe have been fairly stable,¹⁰ despite progress in perioperative care, imaging techniques and surgical management.¹¹

The epidemiology of PUD overall has changed over the latter half century. First, following changes in socioeconomic development in high-income countries, then with the identification and medical therapy of *Helicobacter pylori* as a causative agent and, further, with the introduction of proton pump inhibitors (PPI) from 1989 and onwards. In low- and middle income countries (LMICs) during this period, the median age at diagnosis has increased by over 2 decades (from mid 30–40s to the 60s and above), gender-distribution has evened out (from a male:female ratio of 4–5:1, to an almost 1:1), and a previously predominant ulcer location in the duodenum has now shifted to more gastric ulcers.^{12–15}

There are geographical differences in aetiology and variation in risk factors for PPU. Regional differences exist even within Europe, such as for Turkey⁶ and Belarus¹⁶, reflecting variation in socioeconomic development, prevalence of *Helicobacter* and smoking habits that influence PPU rates. Notably, the presentation of PUD in LMICs, where PUD is several fold higher in incidence (figure 1), has a distribution similar to the patterns described in the western world during the middle half of the 20th century. For example, African cohorts from Nigeria, Kenya, Ethiopia, Tanzania and Ghana report of male rates from 6 to 13 times that of females, median age in the 40s, and a predominant duodenal location in up to 90%.^{17–21} Similar patterns are reported from the middle East and Arab countries and parts of southern Asia.^{22–25}

Pathogenesis, aetiology and risk factors for perforation

While an overall imbalance between the protective and the ulcerogenic factors is obvious in ulcer formation, it is unclear why some patients perforate and others do not. The ulcerogenesis involves infection (*H. pylori*), mucosal barrier injury (e.g. use of drugs) and increased acid-production (figure 2). However, the exact risk-estimates and contribution of each factor is still poorly understood.²⁶ Only about a third of patients with PPU have a previous history of or current known peptic ulcer at time of diagnosis. Further, some patients develop very small (<5 mm) perforations without large mucosal defects, which suggest ulcer size to be unrelated to perforation risk, while other patients may develop large mucosal defects with perforation of several centimetres.

The putative pathogenesis and role of *Helicobacter* virulence factors is reviewed extensively elsewhere.^{27, 28} About 50% of the global population is colonized by *H. pylori* in the gastric mucosa, yet it causes disease in only 10–20%. *H. pylori* shows a variable prevalence (0–90%) in perforated ulcers, and ulcers may also develop in the absence of *H. pylori* infection

and NSAIDs use.² Notably, cofactors such as smoking and alcohol are found across studies from different regions (figure 2).^{18, 29}

The perforation frequency follows in part the geographic distribution patterns of *H. pylori*, with duodenal perforations being more common in regions with a predominant *H. pylori* aetiology. One study suggested a higher density of *H. pylori* with perforations,³⁰ pointing to a potential ‘dose effect’ that leads to perforation. The virulence of *H. pylori* may also contribute, as different strains appear to have variable pathogenic influence.^{28, 31} Further, it is important to remember that PPU also may occur in children, where it is usually associated with *H. pylori* (90%).³² In parallel to the drop in the prevalence of *H. pylori* in many western countries (estimated at 20–30%), a change from predominantly duodenal ulcers to gastric ulcers seen in the elderly is attributed to increased NSAID use in this population.^{33, 34}

A diurnal peak of ulcer perforations has been observed with more perforations occurring in the morning, possibly related to circadian variation in acid-secretion. Perforation risk is increased by fasting, such as during Ramadan,³⁵ which may also be due to variation in acid release and exposure. Ulcer perforation is noted to occur after bariatric surgery,³⁶ after crack-cocaine or amphetamine use,^{37, 38} and after chemotherapy with angiogenesis inhibitors such as bevacizumab. Patients with acid-hypersecretion, including those with a gastrinoma (Zollinger-Ellison syndrome) are at risk for perforation³⁹ and a gastrinoma should be ruled out in patients with multiple or recurrent ulcers.

Clinical evaluation and diagnosis

Patients with PPU may present with severe, sudden-onset epigastric pain, which can become generalised. The peritonitis resulting from acid exposure may present as abdominal ‘board-like rigidity’. The clinical picture may be less clear in the obese, the immunocompromised, patients on steroids, patients with a reduced level of consciousness, in the elderly, and in children. In these situations, the clinical history and examination may be non-specific prompting additional imaging and laboratory studies to rule out differential diagnoses. Only two thirds of patients present with frank peritonitis,³⁹ which may in part explain the diagnostic delay in some patients.

During clinical evaluation, a number of differential diagnoses must be considered, but it is particularly important to exclude a ruptured abdominal aortic aneurysm or acute pancreatitis. The former, due to its high mortality if unrecognised and delayed in treatment, and; the latter, due to the primarily non-operative management.

Diagnostic imaging may have to be delayed pending resuscitation in critically ill patients. Those presenting with generalized peritonitis with or without signs of sepsis will usually be directed straight to the operating room. Notably, mortality increases with every hour surgery is delayed.^{25, 40}

Laboratory markers and radiological imaging

Laboratory markers are not diagnostic for perforated ulcers. However, they aid in the estimation of the inflammatory response and evaluation of organ function, as well as excluding relevant differential diagnoses, such as acute pancreatitis.

Blood cultures should be taken early, prior to starting broad-spectrum antibiotics, although it is important that antibiotic treatment is not be delayed.⁴¹ An arterial blood gas may serve as an adjunct to clinical evaluation of vital functions (e.g. pH, lactate, base excess, oxygen saturation) and measure the degree of metabolic compromise in septic patients.

Gastroduodenal perforation is the most frequent cause of pneumoperitoneum together with perforated diverticulitis (in developed countries)⁴² and typhoid/salmonella enteritis perforations (in LMICs).^{43, 44} Thus, demonstration of 'free air' on radiological examination is highly indicative of a perforated viscus organ. An erect chest x-ray or an upright abdominal x-ray is easy, cheap and quick to perform and may be diagnostic. However, sensitivity is only 75% and it may not reveal the exact cause of pneumoperitoneum.^{11, 42} Reports on the diagnostic use of ultrasonography exists, but has not gained widespread use and is investigator dependent. An abdominal computed tomography has become the imaging modality of choice because of superior sensitivity (reported at 98%) and additional value in evaluation for other differential diagnosis.^{11, 45, 46}

Prognostic factors and outcome prediction

No single factor can readily identify patients at high risk for a poor outcome, but older age, presence of comorbidity, and delay to surgery have consistently been associated with higher risk of death. Clearly, identification of modifiable risk factors with the potential to improve outcome are of greatest interest. In a systematic review⁴⁷ covering over 50 studies with 37 preoperative prognostic factors comprising a total of 29,782 patients, risk factors consistently associated with mortality were found (figure 3). Only two-thirds of the studies provided confounder-adjusted estimates.⁴⁷ Further, definitions and cut-offs (e.g. age-discriminator for 'old'; level of creatinine for defining 'acute renal failure', blood pressure to define 'shock' etc) were not consistent among studies. Thus, combining risk factors to predict disease outcome has been attempted.

Clinical prediction rules

The ideal clinical prediction rule should be easy to use, reliable, have a high generalizability, and be adequately validated both internally and externally. The PPU prediction rules evaluated to date are yet to be categorized as ideal.⁴⁷⁻⁴⁹ The difficulty in defining a uniform set of prognosticators is likely attributed to the overall complexity of the disease and the number of factors involved.⁵⁰ Some considered factors are fixed (e.g. age and gender) and others are amenable to intervention (e.g. time to treatment; resuscitative goals etc).⁵¹ Also, as geographical differences exist in age, gender and presentation patterns, a universal, reproducible and valid scoring system may be hard to develop.

The most used disease-specific prediction rule in PPU patients is the 'Boey score', based on the presence of major medical illness, pre-operative shock, and duration of perforation longer than 24 hours before surgery.⁵² However, the positive predictive value of 94% reported in early studies has not been replicated in subsequent studies.^{48, 49, 53} Other PPU-specific prediction rules have been proposed.⁴⁸ However, common to all is a lack of validation in external cohorts, which hampers generalizability. Also, a number of different generic surgical and intensive care unit (ICU) scores have been assessed in PPU patients.⁴⁸ Again, the scores do not perform uniform over time and in different cohorts, suggesting low external validity. Clearly, appropriate tools to evaluate and compare data across regions and studies are needed to identify high-risk patients, as well as to foster progress in research and trial development

Management strategies

The treatment of patients with PPU should follow early diagnosis and prompt initiation of resuscitative strategies.⁵¹ The associated high short-term mortality reported at 10–30% and morbidity and complications in up to 50–60% of patients require a careful and structured therapeutic approach to improve outcomes. Several strategies and options are available, and the patient's condition should be considered when planning management.

Perioperative management

Sepsis is frequently present and a leading cause of death in patients with PPU. An estimated 30–35% of patients with PPU have sepsis on arrival at the operating theatre, and sepsis is believed to account for 40–50% of fatalities. Within 30 days of surgery more than 25% of the patients develop septic shock,⁵⁴ which carries a mortality rate of 50–60%. Accordingly, investigation and interventions aimed at preventing, detecting, and treating sepsis in PPU patients may reduce mortality and morbidity. This can be accomplished by systematically assessing for signs of sepsis and treating according to the principles of the Surviving Sepsis Campaign, including fluid resuscitation, cultures, empirical broad-spectrum antibiotics, and source control.⁵⁵ A multidisciplinary perioperative approach based on such principles has been evaluated in a non-randomized clinical trial for PPU, with a statistically significant reduction in mortality shown (number-needed-to-treat of 10).⁵⁴

Non-operative treatment

In patients with minimal or localized symptoms and in good clinical condition, the choice to operate may be deliberately delayed in favour of a period of observation. The choice to forego a direct surgical approach for an initial attempt at primary non-operative strategy not new and was propagated over half a century ago.⁵⁶ In selected consecutive series, up to half of all patients with a PPU sealed spontaneously and underwent a successful non-operative strategy.^{57, 58} The strategy should include intravenous antibiotics, nil per os and a nasogastric tube, anti-secretory and anti-acid medication (PPIs) and a water-soluble contrast imaging study to confirm a sealed leak. The only RCT ever performed (prior to the introduction of PPIs) showed success with a non-operative strategy in the majority of patients, but a high failure-rate in the elderly (>70 years).⁵⁹ The non-operative approach

must be considered in view of the reported mortality increase that occurs with every hour of delay to surgery.^{25, 40}

Surgical management

Delay to surgery has been a consistent factor related to mortality.^{25, 40, 52} Laparotomy with closure of the perforation using interrupted sutures with or without an omental pedicle on top of the closure has been the main approach for decades. Laparoscopic repair of perforated ulcers is increasingly used, reaching 30–45% in recent series.^{11, 60} However, the uptake of laparoscopy is variable worldwide. A recent US study reported <3% of PPU patients treated by laparoscopy.⁶¹

Two recent systematic reviews,^{62, 63} including three RCTs, reported no difference in mortality or any clinically relevant postoperative complications between open and laparoscopic surgery. A literature review⁶⁴ of collected case series suggested a slight advantage of laparoscopy towards less postoperative pain and length of stay (and some even reduced mortality), but these reports are biased towards selection of younger patients, favourable ASA risk scores I–II, smaller perforations (<10 mm) and a shorter history duration before surgery.

Currently, no evidence suggests laparoscopy is better than open surgery, but there is also no evidence that laparoscopy is harmful in patients with sepsis or generalized peritonitis. However, as no difference in mortality has been shown for open versus the laparoscopic technique, the local surgeons' experience and patient evaluation must be considered robust evidence can be obtained.

Sometimes a perforation may be too large (i.e. >2 cm) or the inflamed tissues too friable to allow for a safe primary suture. Also, if a leak follows an attempt at primary repair, a second repair may not be feasible. In these instances, resection may be a safer option. Notably, large gastric ulcers or persistent leaks should raise the suspicion of malignancy, which may be encountered in up to 30% in this situation.^{65, 66} The surgical strategy may then involve resection (distal gastrectomy for gastric ulcer or, formal gastric resections if malignancy is suspected), gastric partition with a diverting gastrojejunostomy (if located in the pyloric region), or placement of a T-drain if located in duodenum.⁶⁷ In Japan, some report a higher number (up to 60%) of PPU patients treated by gastric resections rather than primary suture,⁶⁸ possibly based on tradition and the much higher incidence of gastric neoplasia in Japan.

Novel treatment strategies for perforation closure—Novel management and in particular endoscopic techniques have been employed over recent years (Supplement/online: Videoclip). Some applications represent an alternative between non-operative and operative treatment, such as endoscopic clips or stents, but based on small case series only (Panel 3). Other innovations, such as biodegradable material to cover the ulcer site or use of mesenchymal stem cells to enhance wound healing have only been evaluated experimentally and are not yet in clinical testing.⁶⁹

Postoperative care

The postoperative level of care is dependent on the patient's frailty, physiological status and the degree of inflammatory insult preceding and following the surgical repair. Obviously, younger patients with no or limited systemic insult may have a faster recovery than elderly patient with several co-morbidities. Also, patients developing severe sepsis and associated organ failure have increased need for supportive care, a longer length of stay and higher risk for mortality. Thus, a standardized post-operative care regimen for the whole group, as done for elective surgery, is not feasible. However, individualized postoperative care based on risk stratification may improve outcome.

Intensive care and continued sepsis management

Postoperative care should follow the recommended bundles by the Surviving sepsis campaign in order to reduce mortality.⁷⁰ In a non-randomised study, PPU patients were managed according to a protocol from hospital admission to 3 days postoperatively.⁵⁴ The protocol aimed at preventing, detecting and treating sepsis, including risk stratification, sepsis screening, minimization of surgical delay, fluid resuscitation, broad-spectrum antibiotics, adequate monitoring, and administration of nutrition and fluids postoperatively. Compared to historical and concurrent national controls, the 30-day mortality was reduced from 27% to 17%, corresponding to a relative risk of 0.63 (95% CI 0.41 to 0.97). In a nationwide quality of care initiative, the compliance to several of the same factors was noted although no effect on mortality could be demonstrated.⁷¹ While a Scottish audit of consultant input and increased use of high-dependency units appeared to improve outcomes in peptic ulcer,⁷² this study did not discriminate between ulcer bleeding and perforations.

Early administration of broad-spectrum intravenous antibiotics is important, but the effect of additional antifungal therapy is not clear. More intra-abdominal infections, longer stay and higher mortality are associated with positive fungal cultures in PPU patients^{73, 74}, but data to support routine antifungal therapy is scarce and has not demonstrated an effect on mortality.

Enhanced recovery

A small, RCT⁷⁵ from Turkey included young (mean age about 38 years), predominantly male patients with minor perforations (<10 mm) who underwent laparoscopic repair. The enhanced recovery protocol consisted of early removal of nasogastric tube and early start of oral intake. The mean length of stay was significantly shorter by about 3 days for enhanced recovery patients and a quicker start of oral uptake of food (4.82 days \pm 1.28 (3–8) vs 1.55 days \pm 1.27 (1–8); $P < 0.001$) found in the enhanced recovery group. These results lack generalizability beyond patients with a good performance status and no or little comorbidity (ASA I or II). In patients with limited disease, early uptake of food, early removal of drains and tubes and aim of early discharge seems possible.

Helicobacter eradication

A meta-analysis⁷⁶ of 5 RCTs (n=401 patients) has confirmed that eradication of *H. pylori* significantly reduces the incidence of ulcer recurrence at 8 weeks (relative risk=RR 2.97;

95% CI 1.06–8.29) and at 1-year (RR 1.49; 95% CI 1.10–2.03) after surgery. Of note, the included studies only comprised patients with duodenal ulcer perforations.

As *H. pylori* eradication is standard, outstanding questions relate to the choice of eradication regimen. Resistance development and patterns, as well as efficacy and compliance issues must be considered. A 2013 Cochrane review showed that eradication rates using a standard triple regimen (PPI + clarithromycin + amoxicillin) increased with longer duration of treatment (e.g. 14 days compared to 7 or 10 days).⁷⁷

Outcomes, follow-up and quality of life

Short-term mortality

Mortality rates for ulcer have been stable over time in Europe,¹⁰ and reported at 10–30% in a systematic review.⁵ However, mortality numbers differ considerably between reports, mainly influenced by geographic variations (ranging between 3% and 30%), aetiology, patient inclusion, but also by mode of data capture. Administrative data sources, such as the US National Inpatient Sample⁶¹ and Health Insurance Claims Registry in Korea⁷⁸, report low mortality rates (around 3%). For the US, such low mortality in administrative data captures contrasts other reports (mortality at 15%) from the same country.⁴ In prospective, nationwide data collection, such as the Danish Clinical Register of Emergency Surgery, mortality is reported as high as 28%.⁷⁹ Thus, in addition to geographic variation (Figure 1), mode of data capture must carefully be considered when comparing mortality rates.

Endoscopic follow-up after surgery

After surgery for gastric ulcers, routine post-operative endoscopy is often performed to rule out malignancy as the primary cause for perforation, as up to 13% of gastric perforations may be due to a gastric cancer.⁶⁶ This is usually scheduled some 6 weeks after recovery from the procedure and after completion of *H. pylori* eradication. The available evidence for this is scarce and based on clinical acumen. Endoscopic follow-up is usually not recommended in duodenal ulcers, as the risk for malignancy is very low. However, distinction between duodenal and gastric location can be difficult in the juxtapyloric region and in very inflamed and contaminated settings. Endoscopy should be considered if exact location is uncertain and no perioperative biopsy done.

Long-term outcomes

Survival in the long-term after surgery for PPU has been poorly evaluated and data only exists from three observational cohorts.^{80–82} All three studies reported excessive long-term mortality and were reported in elderly European cohorts. As none of the studies were comparative in design, further studies into relative survival and causes of death is needed. In younger populations, quality of life is reported to be good in most patients 6 months after surgery.⁸³

Conclusions and future directions

The paucity in clinical progress and basic understanding of perforated peptic ulcers begs for increased attention in order to reduce morbidity and mortality. Compared to the toll on

human health worldwide, there is poor understanding of the pathophysiology underlying perforation, the ability to self-heal and the development of the sepsis syndrome in these patients.

Identification of prognostic factors and pathways of care that may enhance recovery, reduce morbidity and potentially also reduce mortality should be further investigated. Novel techniques may be further explored to seek alternatives to invasive surgical repair. Similarly, some patients with minimal symptoms may also benefit from less invasive therapeutic approaches. However, groups should be investigated in prospective protocols and trials dedicated to find the safest and most efficacious management strategies and the appropriate criteria for selection. Long-term follow up studies with evaluation of quality of life are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel take home messages

- Perforated peptic ulcer is associated with short-term mortality up to 30% and is considered one of the most lethal surgical emergencies globally
- Incidence rates of perforated peptic ulcers have remained steady over the past decades, but with considerable geographic differences
- *Helicobacter pylori*, NSAIDs and smoking are confirmed risk factors for ulcers, but the pathogenesis that leads to perforation is not well understood
- Clinical prediction rules can identify patients at high-risk of death, but with variable accuracy
- Elderly patients with sepsis, presenting with delay to surgery have highest mortality
- Surgical repair should not be delayed as every hour of delay increases mortality
- Laparoscopic surgical repair is performed with comparable morbidity or mortality rates to open surgery
- Patients with clinical signs of spontaneous resolution can be considered for non-operative management in selected cases
- Novel techniques, including endoscopy, may in the future reduce the surgical insult and improve outcome
- Future improvements should come through enhanced patient selection for surgery or alternative strategies and improved perioperative management of sepsis
- Long-term follow-up studies are needed, as mortality remains increased for several years after surgery

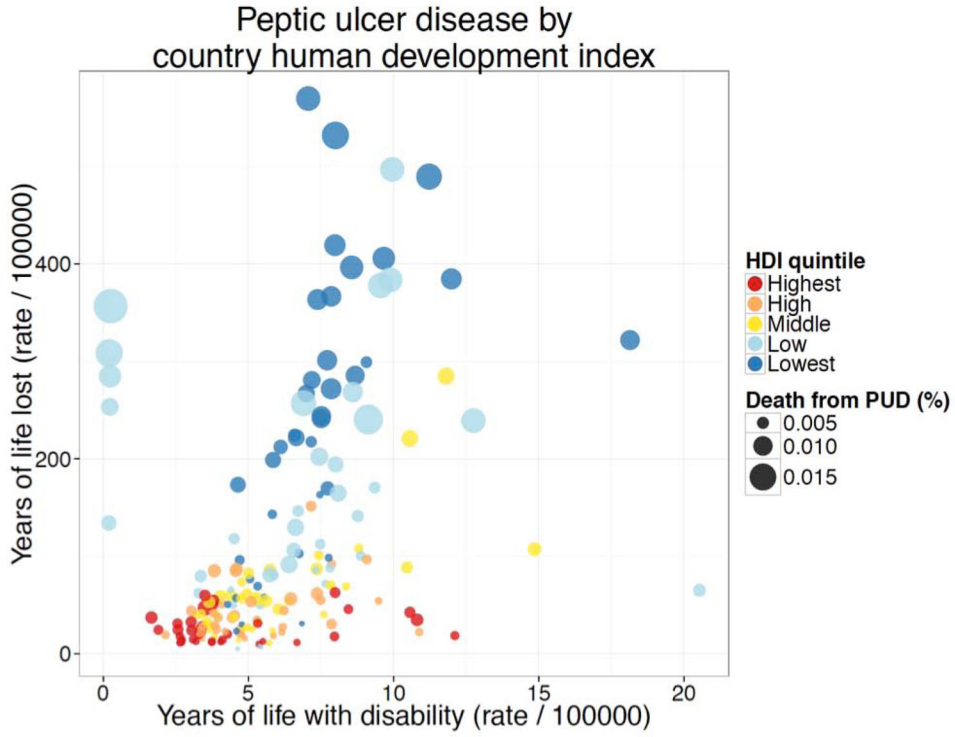


Figure 1. Peptic ulcer disease burden globally
Years of life lost (YLL) and years of life with disability (YLD) presented for quintiles of the Human Development Index (HDI). Age-standardised estimates for peptic ulcer disease were retrieved from the Global Burden of Disease Study 2010 repository (<http://ghdx.healthdata.org/record/global-burden-disease-study-2010-gbd-2010-results-cause-1990-2010-country-level>). Proportion of deaths (bubble size), rate of years of life lost (YLL) and rate of years of life with disability (YLD) for both sexes and year 2010 were analysed. Data are presented by United Nations Development Programme Human Development Index quintiles (<http://hdr.undp.org/en/content/human-development-index-hdi>)

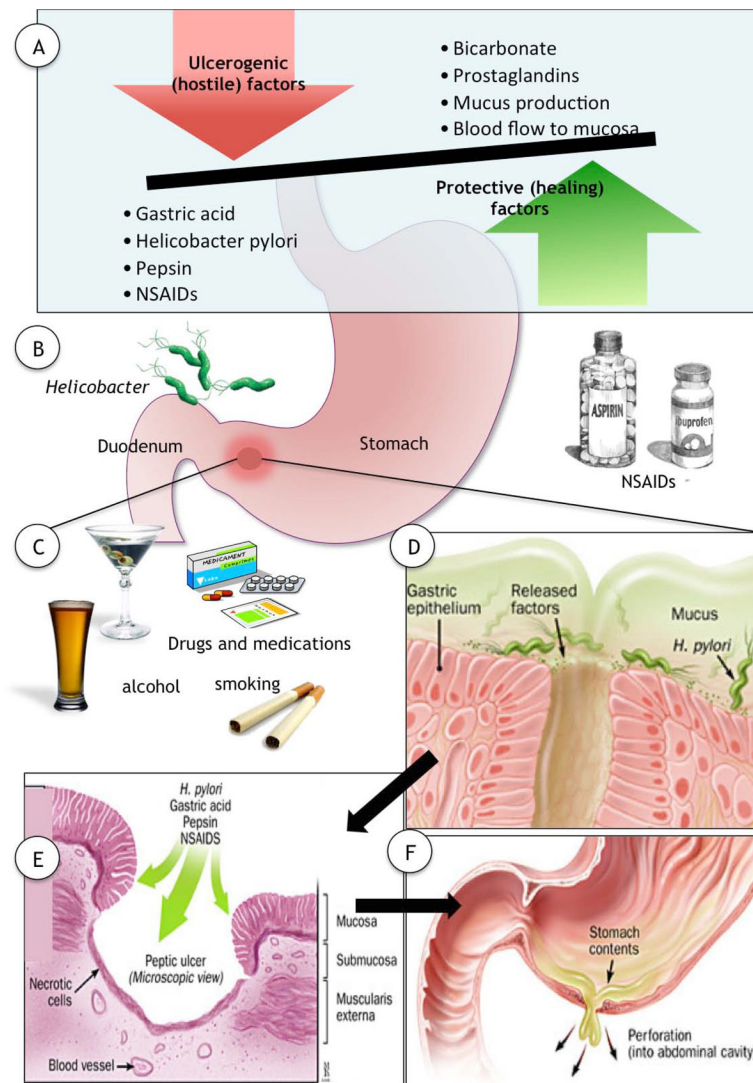


Figure 2. Mechanisms and factors in pathogenesis of perforated peptic ulcer [sketch, to be redrawn]

(A) an imbalance between between hostile and protective factors start the ulcerogenic process, and (B) although many cotributors are known, *helicobacter* infection and use of non-steroidal anti-inflammatory drugs appear of importance in disturbing the protective mucosal layer and (C) expose the gastric epithelium to acid. Several additional factors (D) may augment the ulcerogenic process (such as smoking, alcohol and several drugs) that lead to erosion (E). Eventually, the serosal lining is breached (F), and when perforated, the stomach content, including acidic fluid, will enter the abdominal cavity giving rise to intense pain, local peritonitis that may become generalized and eventually lead to a systemic inflammatory response syndrome and sepsis with the risk of multiorgan failure and mortality.

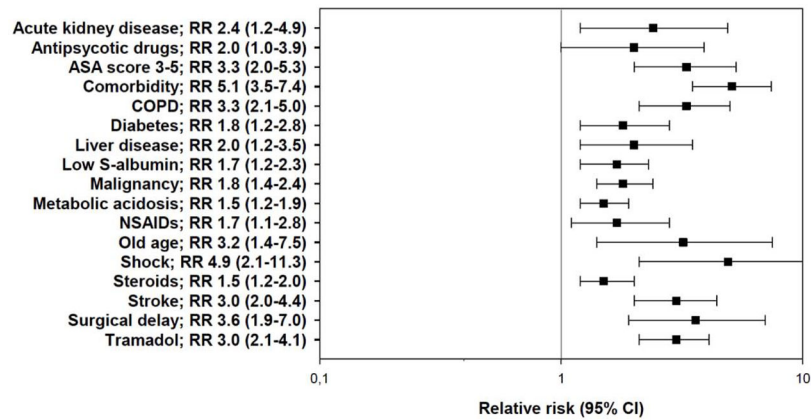


Figure 3. Preoperative adverse prognostic factors for mortality in PPU disease

Adjusted preoperative prognostic factors for mortality. Data derived and developed from Møller et al ^[47].

ASA, denotes American Society of Anesthesiologist risk score

COPD, denotes chronic obstructive pulmonary disease

S-albumin, denotes serum albumin

NSAIDs, denotes non-steroidal antiinflammatory drugs

RR, denotes relative risk

CI, denotes confidence interval