



## Emergency surgery 2

# Perforated peptic ulcer

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Lancet 2015; 386: 1288–98

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This is the second in a Series of three papers about emergency surgery

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Perforated peptic ulcer is a common emergency condition worldwide, with associated mortality rates of up to 30%. A scarcity of high-quality studies about the condition limits the knowledge base for clinical decision making, but a few published randomised trials are available. Although *Helicobacter pylori* and use of non-steroidal anti-inflammatory drugs are common causes, demographic differences in age, sex, perforation location, and underlying causes exist between countries, and mortality rates also vary. 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. Selected patients can be managed non-operatively or with novel endoscopic approaches, but validation of such methods in trials is needed. Quality of care, sepsis care bundles, and postoperative monitoring need further assessment. Adequate trials with low risk of bias are urgently needed to provide better evidence. We summarise the evidence for perforated peptic ulcer management and identify directions for future clinical research.

### Introduction

Perforated peptic ulcer is a surgical emergency and is associated with short-term mortality in up to 30% of patients and morbidity in up to 50%.<sup>1</sup> Worldwide variations in demography, socioeconomic status, *Helicobacter pylori* prevalence, and prescription drugs make investigation into risk factors for perforated peptic ulcer difficult. Perforated peptic ulcer presents as an acute abdominal condition, with localised or generalised peritonitis and a high risk for development of sepsis and death. Early diagnosis is essential, but clinical signs can be obscured in elderly people or immunocompromised patients, thus delaying 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. In this review, we present an update on the present understanding and management of perforated peptic ulcer.

### Epidemiology of peptic ulcer disease and its complications

Complications to peptic ulcer disease include perforation, bleeding, and obstruction.<sup>2,3</sup> Although perforations are second to bleeding in frequency (about 1:6 ratio), they represent the most common indication for emergency surgery for peptic ulcer disease.<sup>4–6</sup> Overall progress in medical management has made obstruction from recurrent ulcer scarring a rare event, and the addition of

### Key messages

- Perforated peptic ulcer is associated with short-term mortality of up to 30% and is regarded as one of the most lethal surgical emergencies worldwide
- Incidence rates of perforated peptic ulcers have remained steady in developed countries in recent decades, but with substantial geographical differences in other regions such as Africa and Asia
- *Helicobacter pylori*, non-steroidal anti-inflammatory drugs, 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 the highest mortality rates
- Surgical repair should not be delayed in patients with general peritonitis because every hour of delay increases the mortality risk
- Laparoscopic surgical repair has similar morbidity and mortality rates as open surgery
- Patients with clinical signs of spontaneous resolution can be considered for non-operative management in selected cases
- Novel techniques, including endoscopy, might in the future reduce the surgical insult and improve outcomes
- Future improvements should be achieved through enhanced patient selection for surgery or alternative strategies and improved perioperative management of sepsis
- Long-term follow-up studies are needed, since mortality risk remains increased for several years after surgery

### Search strategy and selection criteria

We searched MEDLINE via PubMed and Embase for articles published between Jan 1, 2000, and Feb 28, 2015, and the Cochrane Library (issue 12, December, 2014), using the search terms “perforated peptic ulcer” and “gastric” or “duodenal” or “gastroduodenal ulcer” and “perforated” or “perforation”. Articles published in all languages were considered for inclusion. We also searched ClinicalTrials.gov, the ISRCTN Registry, PROSPERO, and the WHO International Clinical Trials Registry Platform databases for prospective trials for any recruiting or closed studies (as yet unpublished) on perforated peptic ulcer. We focused on recently published research (within the past 5 years) where possible, and favoured studies or trials with a low risk of bias (systematic reviews, randomised 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 our search.

endoscopic techniques and transarterial embolisation has reduced the need for emergency surgery for bleeding ulcers.<sup>3</sup> In 2006, more than 150 000 patients were admitted to hospital for complicated peptic ulcer disease in the USA alone. Although the overall share of complications caused by perforations (n=14 500 [9%]) was seven-times lower than that attributable to bleeding, perforated peptic ulcers caused 37% of all ulcer-related deaths.<sup>4</sup> According to US data,<sup>4</sup> more than one in every ten hospital admissions for perforated peptic ulcer leads to death. Indeed, perforated peptic ulcer had a fivefold higher mortality rate than bleeding ulcers, and was the single most important contributor to inpatient mortality in the USA between 1993 and 2006, with an odds ratio (OR) of 12·1 (95% CI 9·8–14·9).<sup>4</sup>

Many studies report a steady incidence of perforated peptic ulcer during the 1980s–90s, but studies from Sweden, Spain, and the USA in the 1990s and early 2000s noted a fall in the incidence of both bleeding and perforations.<sup>7–9</sup> Mortality rates for perforated peptic ulcer in Europe have been quite stable during the past three to four decades,<sup>10</sup> despite progress in perioperative care, imaging techniques, and surgical management.<sup>11</sup>

The epidemiology of peptic ulcer disease overall has changed in the past 50 years, initially following changes in socioeconomic development in high-income countries, then with the identification and medical treatment of *H pylori* as a causative agent, and finally with the introduction of proton-pump inhibitors from 1989 and onwards. In low-income and middle-income countries during this period, the median age at diagnosis has increased by more than two decades (from the mid-30s–40s to 60 years of age and older), sex distribution has evened out (from a male:female ratio of 4–5:1 to an almost 1:1 ratio), and a previously predominant ulcer location in the duodenum has now shifted to more gastric ulcers.<sup>12–15</sup>

Geographical differences exist in cause and variation in risk factors for perforated peptic ulcer. Regional differences exist even within Europe, such as for Turkey<sup>6</sup> and Belarus,<sup>16</sup> which represent variations in socioeconomic development, the prevalence of *H pylori*, and smoking habits that affect perforated peptic ulcer rates. Notably, the presentation of peptic ulcer disease in low-income and middle-income countries, where the incidence of peptic ulcer disease is several fold higher than in high-income countries (figure 1) has a distribution similar to the patterns described in the developed countries during the middle half of the 20th century. For example, African cohorts from Nigeria, Kenya, Ethiopia, Tanzania, and Ghana report rates of peptic ulcer disease in male patients between six and 13-times higher than that in female patients, median age around 40 years, and a predominant duodenal location in up to 90% of patients.<sup>17–21</sup> Similar patterns are reported from the Middle East and Arab countries and parts of southern Asia.<sup>22–25</sup>

## Pathogenesis, causes, and risk factors for perforation

Although an overall imbalance between the protective and the ulcerogenic factors is obvious in ulcer formation, the reasons why some patients' ulcers perforate and others do not remain unclear. The ulcerogenesis involves infection (*H pylori*), mucosal barrier injury (eg, use of drugs), and increased hydrochloric acid production (panel; figure 2). However, the precise risk estimates and contribution of each factor are still poorly understood.<sup>26</sup> Only about a third of patients with perforated peptic ulcer have a previous history of or current known peptic ulcer at the time of diagnosis. Furthermore, some patients develop very small (<5 mm) perforations without large mucosal defects, which suggests that ulcer size is unrelated to perforation risk, whereas others might develop large mucosal defects with perforation several centimetres in size.

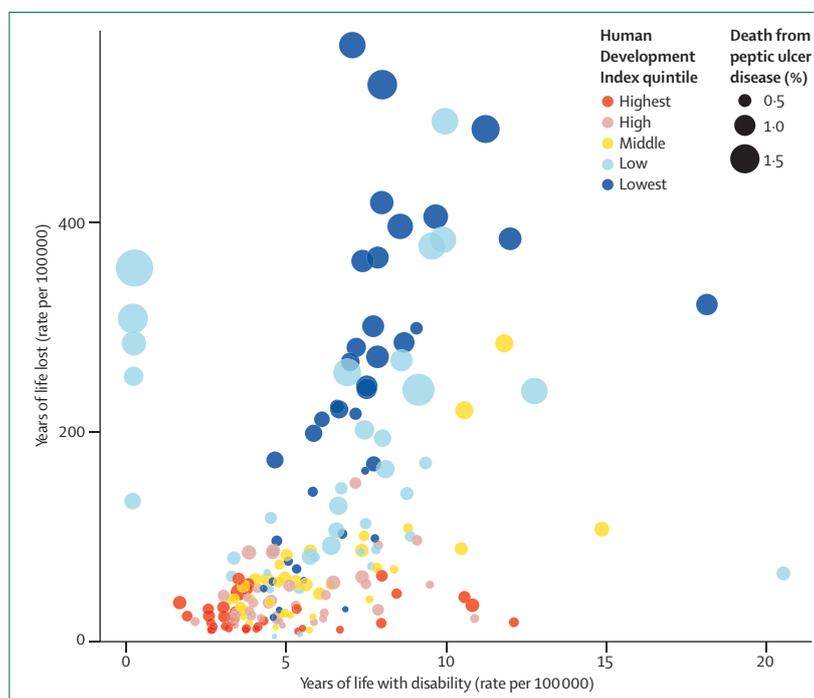
The putative pathogenesis and role of *Helicobacter* virulence factors is reviewed extensively elsewhere.<sup>27,28</sup> About 50% of the global population is colonised by *H pylori* in the gastric mucosa, yet it causes disease in only 10–20% of people. *H pylori* shows a variable prevalence (0–90%) in perforated ulcers, and ulcers can also develop in the absence of *H pylori* infection and non-steroidal anti-inflammatory drug use.<sup>2</sup> Notably, co-factors such as smoking and alcohol are recorded across studies from different regions (figure 2).<sup>18,29</sup>

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For the Global Burden of  
Disease Study 2010 see <http://ghdx.healthdata.org/record/global-burden-disease-study-2010-gbd-2010-results-cause-1990-2010-country-level>

For the United Nations  
Development Programme  
Human Development Index see  
<http://hdr.undp.org/en/content/human-development-index-hdi>



**Figure 1: Global peptic ulcer disease burden, by country Human Development Index**  
Years of life lost and years of life with disability for quintiles of the Human Development Index. Age-standardised estimates for peptic ulcer disease were retrieved from the Global Burden of Disease Study 2010 repository. Proportion of deaths (circle size), rate of years of life lost, and rate of years of life with disability for both sexes in 2010 were analysed. Data are presented by United Nations Development Programme Human Development Index quintiles.

**Panel: Risk factors predisposing for perforated peptic ulcer disease****Non-steroidal anti-inflammatory drugs (including aspirin)**

Inhibitors of synthesis of prostaglandins. Leads to increased production of gastric acids and reduced mucus secretion.

**Smoking**

Smoking inhibits secretion of bicarbonate. Nicotine stimulates secretion of acid. Strongly linked to perforated peptic ulcer in people younger than 75 years of age.

***Helicobacter pylori***

Most common in cohorts of young men (usually <40 years) with perforated duodenal ulcers in low-income and middle-income countries. Different virulence strains might be of relevance in genesis.

**Marginal ulcer after bariatric surgery**

Probably due to ischaemia of the anastomosis.

**Fasting**

Several reports of perforated peptic ulcers during Ramadan. Fasting leads to increased acid production on an empty stomach.

**Crack cocaine, cocaine, and metamphetamine use**

Can lead to intense vasoconstriction followed by ischaemia. Can also cause thrombus formation and necrosis of mucosa.

**Zollinger-Ellison syndrome (gastrinoma)**

Rare; risk for recurrent and multiple ulcers. Increased secretion of gastrin causes increased and persistent hydrochloric acid secretion in the stomach and duodenum, with ulceration and potential perforation of the gastrointestinal wall.

**Stress ulcers**

Ulcers in critically ill patients (burns, trauma, etc) in intensive care; most often complicated by bleeding but occasionally perforation occurs. Difficult diagnosis in patients who are sedated or those on artificial ventilation.

**Steroids**

Affects inflammatory cascade, including prostaglandin synthesis. Can blunt signs of peritonitis.

**Salt**

High consumption increases acidity in the stomach.

**Alcohol**

High consumption is especially linked to risk of bleeding ulcers, but also to increased risk of perforation.

**Chemotherapy with bevacizumab**

VEGF inhibition has increased risk of gastrointestinal perforations; can increase with more widespread use.

The perforation frequency partly follows the geographical distribution patterns of *H pylori*, with duodenal perforations being more common in regions where *H pylori* is the main cause. One study showed an increased density of *H pylori* with perforations,<sup>30</sup> suggesting a potential dose effect that leads to perforation. The virulence of *H pylori* might also contribute, since different strains seem to have variable pathogenic effects.<sup>28,31</sup> Furthermore, perforated peptic ulcer can also occur in children, in whom it is usually associated with *H pylori* (in 90% of cases).<sup>32</sup> In parallel to the drop in the prevalence of *H pylori* in many

high-income countries (estimated at 20–30%), a change from mainly duodenal ulcers to gastric ulcers reported in elderly patients is attributed to increased non-steroidal anti-inflammatory drug use in this population.<sup>33,34</sup>

A diurnal peak of ulcer perforations has been reported, with more perforations occurring in the morning, which is possibly related to circadian variation in acid secretion. Perforation risk is increased by fasting, such as during Ramadan,<sup>35</sup> which might also be caused by variation in acid release and exposure. Ulcer perforation is reported to occur after bariatric surgery,<sup>36</sup> after crack cocaine or amphetamine use,<sup>37,38</sup> 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 perforation<sup>39</sup> and a gastrinoma should be ruled out in patients with several or recurrent ulcers.

**Clinical assessment and diagnosis**

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

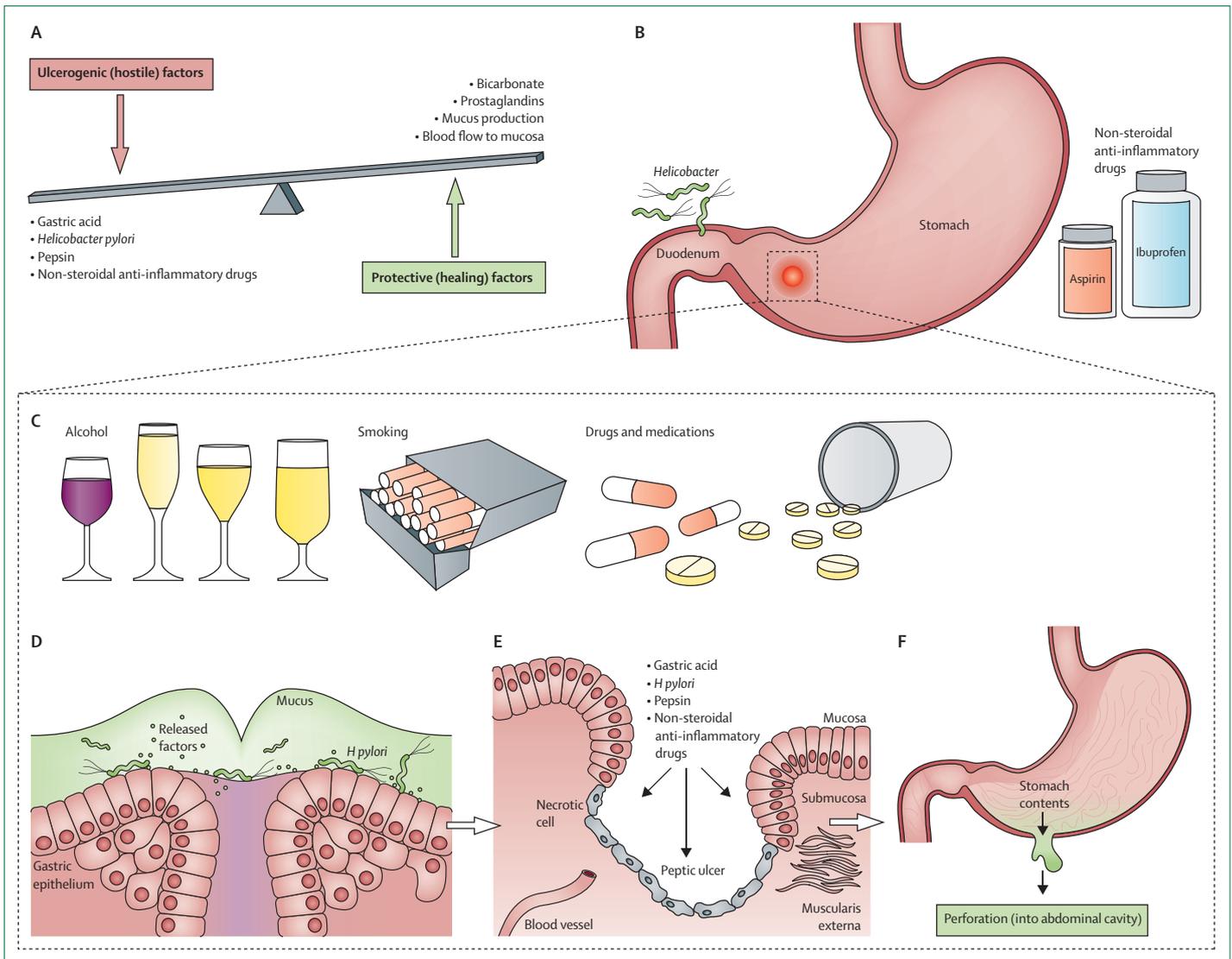
During clinical assessment, several differential diagnoses should be considered, but, most importantly, a ruptured abdominal aortic aneurysm or acute pancreatitis must be excluded—the former because of its high mortality rate if unrecognised and treatment is delayed, and the latter because its management is mainly non-operative.

Diagnostic imaging might have to be delayed pending resuscitation in critically ill patients. Those presenting with generalised peritonitis with or without signs of sepsis will usually be directed straight to the operating theatre. Notably, mortality increases with every hour by which surgery is delayed.<sup>25,40</sup>

**Laboratory markers and radiological imaging**

Laboratory markers are not diagnostic for perforated ulcers. However, they do help doctors to estimate the inflammatory response and assess organ function, and to exclude relevant differential diagnoses, such as acute pancreatitis.

Blood cultures should be taken early, before broad-spectrum antibiotics are started, although antibiotic treatment must not be delayed.<sup>41</sup> An arterial blood gas can serve as an adjunct to clinical assessment of vital functions (eg, pH, lactate, base excess, and oxygen saturation) and can measure the degree of metabolic compromise in patients with sepsis.



**Figure 2: Mechanisms and factors in pathogenesis of perforated peptic ulcer**

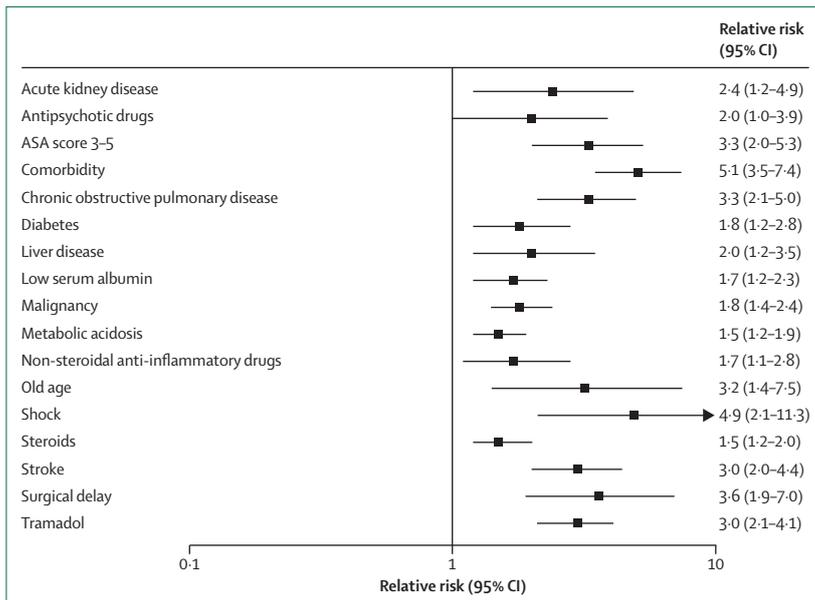
(A) An imbalance between between hostile and protective factors start the ulcerogenic process, and (B) although many contributors are known, *Helicobacter pylori* infection (mainly duodenal ulcers) and use of non-steroidal anti-inflammatory drugs (mainly gastric ulcers) seem to be of importance in disturbing the protective mucosal layer and exposing the gastric epithelium to acid. (C) Several additional factors (eg, smoking, alcohol, and several drugs) can augment the ulcerogenic process (D) that leads to erosion (E). Eventually, the serosal lining is breached (F) and, when perforated, the stomach content, including acidic fluid, will enter the abdominal cavity, causing intense pain, local peritonitis that can become generalised and eventually lead to a systemic inflammatory response syndrome, and sepsis with the risk of multi-organ failure and death.

Gastroduodenal perforation is the most common cause of pneumoperitoneum, together with perforated diverticulitis (in high-income countries)<sup>42</sup> and typhoid or salmonella enteritis perforations (in low-income and middle-income countries).<sup>43,44</sup> Thus, demonstration of so-called free air on radiological examination is highly indicative of a perforated viscus organ. An erect chest radiograph or an upright abdominal radiograph is easy, cheap, and quick to do and can be diagnostic. However, its sensitivity is only 75% and it might not show the exact cause of pneumoperitoneum.<sup>11,42</sup> Reports on the diagnostic use of ultrasonography exist, but the approach has not gained widespread use and is investigator

dependent. An abdominal CT scan has become the imaging modality of choice because of its superior sensitivity (reportedly 98%) and its additional value in assessment for other differential diagnoses.<sup>11,45,46</sup>

### 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 an increased risk of death. Clearly, the identification of modifiable risk factors with the potential to improve outcome is of great interest. In a systematic review<sup>47</sup> covering more than 50 studies with 37 preoperative



**Figure 3: Preoperative adverse prognostic factors for mortality in perforated peptic ulcer**  
Adjusted preoperative prognostic factors for mortality. Data derived and developed from Møller et al.<sup>47</sup>  
ASA=American Society of Anesthesiologists risk score.

prognostic factors comprising a total of 29782 patients, several risk factors were consistently associated with mortality (figure 3). Only two-thirds of the studies provided confounder-adjusted estimates.<sup>47</sup> Furthermore, definitions and cutoffs (eg, age discriminator for “old” patients, level of creatinine to define “acute renal failure”, and blood pressure to define “shock”) were not consistent across studies. Thus, physicians have attempted to combine risk factors to predict disease outcome.<sup>48–51</sup>

### Clinical prediction rules

The ideal clinical prediction rule should be easy to use, reliable, have a high generalisability, and be validated adequately both internally and externally. However, the perforated peptic ulcer prediction rules assessed so far are yet to be categorised as ideal.<sup>47–49</sup> The difficulty in defining a uniform set of prognosticators is probably attributed to the overall complexity of the disease and the number of factors involved.<sup>52</sup> Some considered factors are fixed (eg, age and sex) whereas others are amenable to intervention (eg, time to treatment and resuscitative goals).<sup>53</sup> Additionally, in view of geographical differences in age, sex, and presentation patterns, a universal, reproducible, and valid scoring system might be difficult to develop.

The most widely used disease-specific prediction rule in patients with perforated peptic ulcer is the Boey score, which is based on the presence of major medical illness, preoperative shock, and duration of perforation longer than 24 h before surgery.<sup>50</sup> However, the positive predictive value of 94% reported in early studies<sup>50</sup> has not been replicated in subsequent studies.<sup>48,49,51</sup> Other perforated peptic ulcer-specific prediction rules have been proposed.<sup>48</sup> However, none of these sets of rules have been validated

in external cohorts, which hampers generalisability. Additionally, several different generic surgical and intensive care unit scores have been assessed in patients with perforated peptic ulcer.<sup>48</sup> Again, the scores do not perform uniformly over time and in different cohorts, which suggests low external validity. Clearly, appropriate devices to analyse and compare data across regions and studies are needed to identify high-risk patients, and to foster progress in research and trial development.

### Management strategies

The treatment of patients with perforated peptic ulcers should follow early diagnosis and prompt initiation of resuscitative strategies.<sup>53</sup> The associated high short-term mortality reported at 10–30% and morbidity and complications in up to 50–60% of patients mean that a careful and structured therapeutic approach is needed to improve outcomes. Several strategies and options are available (table 1), and the patient’s condition should be considered when their management is planned.

### Perioperative management

Sepsis is often present in patients with perforated peptic ulcer, with an estimated 30–35% of patients having sepsis on arrival at the operating theatre, and is a leading cause of death, accounting for 40–50% of fatalities.<sup>47</sup> Within 30 days of surgery, more than 25% of patients develop septic shock,<sup>1</sup> which carries a mortality rate of 50–60%. Accordingly, investigation and interventions aimed at the prevention, detection, and treatment of sepsis in patients with perforated peptic ulcer could reduce mortality and morbidity. This goal can be achieved by systematically assessing for signs of sepsis and treating patients according to the principles of the Surviving Sepsis Campaign, including fluid resuscitation, cultures, empirical broad-spectrum antibiotics, and source control.<sup>56</sup> A multidisciplinary perioperative approach based on such principles has been assessed in a non-randomised clinical trial for perforated peptic ulcer, with a statistically significant reduction in mortality shown (number-needed-to-treat of ten patients).<sup>1</sup>

### Non-operative treatment

In patients with very few or localised symptoms who are in good clinical condition, the choice to operate might be delayed deliberately in favour of an observation period. The decision to forego a direct surgical approach for an initial attempt at a primary non-operative strategy is not new and was first propagated more than half a century ago.<sup>71</sup> In selected consecutive series, up to half of all patients with a perforated peptic ulcer sealed spontaneously and underwent a successful non-operative treatment strategy.<sup>58,59</sup> The strategy should include intravenous antibiotics, nil per mouth and a nasogastric tube, anti-secretory and antacid medication (proton-pump inhibitors), and a water-soluble contrast imaging study to confirm a sealed leak. The only randomised

	Comments	Evidence*
<b>Prehospital, primary care</b>		
Recognise symptoms, high index of suspicion	No peritonitis in a third of patients. No peptic ulcer disease history in up to half of patients. Note that symptoms may be different or subtle in elderly patients, obese individuals, immunocompromised people, and children	Observational studies <sup>54,55</sup>
Monitor vital signs	Detect early signs of systemic inflammatory response syndrome or sepsis by blood pressure, heart rate, respiratory rate, and temperature	Surviving Sepsis Campaign <sup>56</sup>
Rapid referral	Make rapid contact with emergency department or hospital. Every hour of delay increases mortality risk	Observational studies <sup>40</sup>
<b>Emergency department</b>		
Diagnose	Clinical alone if general peritonitis. Otherwise, CT scan>radiograph>ultrasound. Serum lipase to rule out pancreatitis as a differential diagnosis	Observational studies <sup>11</sup>
Prepare	Stabilise according to sepsis guidelines, but be aware to minimise delay to surgery	Surviving Sepsis Campaign <sup>56</sup>
Screen for sepsis	Extrapolated data for sepsis	Surviving Sepsis Campaign <sup>56</sup>
Early resuscitation	Administer fluids, monitor vital signs	Surviving Sepsis Campaign <sup>56</sup>
Early antibiotics	Blood cultures (x2); broad-spectrum intravenous antibiotics	Surviving Sepsis Campaign <sup>56</sup>
<b>Decision making</b>		
Indication for surgery	Consent	Common sense
Non-operative management	Non-operative if: very limited disease/symptoms; patient unfit for surgery (eg, American Society of Anesthesiologists risk score of 5); or patient unwilling to have surgery. Consider risk for and if suitable for postoperative intensive care; dialysis; ventilator support	One randomised controlled trial for non-operative management; <sup>57</sup> case series; observational data with high risk of bias <sup>58,59</sup>
Surgery	Open or laparoscopic (plan for conversion) (endoscopic alternatives†)	3 randomised controlled trials, <sup>60</sup> no difference in outcome; experimental; anecdotal
Palliative care	If patient's condition indicates an end-stage terminal disease	Best supportive care, expert opinion, no specific data, observational <sup>61</sup>
<b>Perioperative</b>		
Obtain cultures and biopsy	Abdominal swabs, with or without tissue biopsy	Surviving Sepsis Campaign <sup>56</sup>
Abbreviated laparotomy	If patient in severe shock	Case series <sup>62</sup>
Intra-abdominal drains	No data to support routine use	Observational <sup>63</sup>
<b>Postoperative</b>		
Enhanced recovery	Fast recovery possible if limited disease; food at will, early removal of drains, early discharge	One small randomised controlled trial with high risk of bias <sup>64</sup>
Eradication of <i>Helicobacter pylori</i>	Esomeprazole 20 mg twice daily, or omeprazole 20 mg twice daily; amoxicillin 1 g twice daily; clarithromycin 500 mg twice daily	Randomised controlled trials and meta-analyses <sup>65</sup>
Follow-up (after discharge from hospital)	Increased long-term mortality, possibly because of shared risk factors, such as smoking and comorbidity	Few observational series <sup>66-68</sup>
Upper endoscopy	Rule out malignancy in gastric ulcers if no perioperative biopsy, or if location not certain (duodenal ulcers very unlikely to be malignant)	Expert opinion, observational studies <sup>69,70</sup>

\*The references cited in this column are suggested references, not an exhaustive list. †See table 2, experimental.

**Table 1: Overview of peptic ulcer disease management**

controlled trial ever done (before the introduction of proton-pump inhibitors) showed success with a non-operative strategy in most patients, but a high failure rate in elderly patients (aged >70 years).<sup>57</sup> However, the non-operative approach should be considered in view of the reported mortality increase that occurs with every hour of delay to surgery.<sup>25,40</sup>

### Surgical management

Delay to surgery has been a consistent factor related to mortality.<sup>25,40,50</sup> Laparotomy with closure of the perforation through the use of interrupted sutures with or without an omental pedicle on top of the closure has been the main approach for several decades.

Laparoscopic repair of perforated ulcers is increasingly being used, reaching rates of 30–45% in recent series.<sup>11,72</sup> However, the uptake of laparoscopy varies worldwide. A recent US study reported that less than 3% of patients with perforated peptic ulcer were treated by laparoscopy.<sup>73</sup>

Two recent systematic reviews,<sup>58,74</sup> which included three randomised controlled trials, showed no difference in mortality or any clinically relevant postoperative complications between open and laparoscopic surgery. A literature review<sup>75</sup> of collected case series suggested a slight advantage of laparoscopy towards less postoperative pain and length of hospital stay (and some even reduced mortality), but these reports are biased towards selection of younger patients, favourable

American Society of Anesthesiologists risk scores I–II, small perforations (<10 mm), and a short history since onset of disease before surgery.

At present, no evidence suggests that laparoscopy is better than open surgery, but equally no evidence suggests that laparoscopy is harmful in patients with sepsis or generalised peritonitis. However, since no difference in mortality has been shown for open surgery versus the laparoscopic technique, the local surgeons' experience and patient assessment must be considered until robust evidence can be obtained.

Sometimes a perforation can be too large (ie, >2 cm) or the inflamed tissues too friable to allow for a safe primary suture. Furthermore, if a leak follows an attempt at primary repair, a second repair might not be feasible. In these circumstances, resection can be a safer option. Notably, large gastric ulcers or persistent leaks should raise the suspicion of malignancy, which can be encountered in up to 30% of patients in this situation.<sup>70,76</sup> The surgical strategy might 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 the duodenum.<sup>77</sup> In Japan, some investigators report a higher proportion (up to 60%) of patients with perforated peptic ulcer treated by gastric resections rather than primary suture,<sup>78</sup> which is possibly based on tradition and the much higher incidence of gastric neoplasia in Japan than in North America and Europe.

#### New treatment strategies for perforation closure

Novel management and in particular endoscopic techniques have been used in recent years (video). Some applications represent an alternative between non-operative and operative treatment, such as endoscopic clips or stents, but are based on small case series only (table 2). Other innovations, such as the use of biodegradable material to cover the ulcer site or mesenchymal stem cells to enhance wound healing have only been assessed experimentally and are not yet in clinical trials.<sup>90</sup>

#### Postoperative care

The level of postoperative care depends on the patient's frailty, physiological status, and the degree of inflammatory insult preceding and following the surgical repair. Clearly, young patients with no or limited systemic insult are likely to have a faster recovery than are elderly patients with several comorbidities. Furthermore, patients developing severe sepsis and associated organ failure have increased need for supportive care, a longer length of hospital stay, and raised mortality risk. Thus, a standardised postoperative care regimen for the whole group, as done for elective surgery, is not feasible. However, individualised postoperative care based on risk stratification might improve outcomes.

#### Intensive care and continued sepsis management

Postoperative care should follow the recommended guidelines by the Surviving Sepsis Campaign to reduce mortality.<sup>91</sup> In a non-randomised study, patients with postoperative peptic ulcer were managed according to a protocol from hospital admission to 3 days postoperatively.<sup>1</sup> The protocol aimed to prevent, detect, and treat sepsis, including by risk stratification, sepsis screening, minimisation of surgical delay, fluid resuscitation, broad-spectrum antibiotics, adequate monitoring, and postoperative administration of nutrition and fluids. Compared with historical and concurrent national controls, the 30-day mortality rate was reduced from 27% to 17%, corresponding to a relative risk of 0.63 (95% CI 0.41–0.97). In a nationwide quality-of-care initiative, increased compliance to several of the same factors related to sepsis management was noted, although no effect on mortality could be shown.<sup>92</sup> Although a Scottish audit of consultant input and increased use of high-dependency units seemed to improve outcomes in patients with peptic ulcer,<sup>93</sup> 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 hospital stay, and increased mortality are associated with positive fungal cultures in patients with perforated peptic ulcer,<sup>94,95</sup> but data to support routine antifungal therapy are scarce and have not shown an effect on mortality.

#### Enhanced recovery

A small randomised controlled trial from Turkey<sup>64</sup> included young (mean age about 38 years), mostly male patients with minor perforations (<10 mm) who underwent laparoscopic repair. The enhanced recovery protocol consisted of early removal of nasogastric tube and early initiation of oral intake of food. Compared with individuals in the control group, patients in the enhanced recovery group had a significantly shorter mean length of hospital stay (by about 3 days) and also had a quicker start of oral uptake of food (mean length of stay 4.82 days [SD 1.28, range 3–8] in the control group vs 1.55 days [SD 1.27, range 1–8] in the enhanced recovery group;  $p < 0.001$ ). These results cannot be generalised beyond patients with a good performance status and no or little comorbidity (American Society of Anesthesiologists risk score I or II). In patients with mild disease severity, early uptake of food, early removal of drains and tubes, and aim of early discharge from hospital seem possible.

#### *H pylori* eradication

A meta-analysis<sup>65</sup> of five randomised controlled trials (401 patients) has confirmed that eradication of *H pylori* significantly reduces the incidence of ulcer recurrence at 8 weeks (relative risk 2.97; 95% CI 1.06–8.29) and at

See Online for video

	Description of technique	Comments	Studies/documentation
Natural orifice transluminal endoscopic surgery (NOTES)	Endoluminal full-thickness closure of gastroduodenal wall; intraperitoneal inspection	Inflammation of gastrointestinal wall and large size of perforation might limit use	Experimental; animal studies, <sup>79,80</sup> used for iatrogenic perforations in clinical practice
Transluminal omental patch closure	Endoscopic placement of a vascularised omental pedicle through the perforation that is clipped in place	Insufflation of CO <sub>2</sub> , monitor pneumoperitoneum; needs viable tissue (not friable wound edges)	Clinical review suggests that up to 50% of patients could be eligible for technique; <sup>81</sup> small pilot trial <sup>82</sup>
Over-the-scope-clip (OTSC)	Endoluminal grasping of wound edges and deployment of a large clip with transmural grasp across the perforation	Indurated ulcer edges might be difficult to manoeuvre because of insufficient pliability; no vascularised immune-competent tissue (omental pedicle) added	Often used to treat anastomotic leaks or gastrocutaneous fistulae, such as after a temporary percutaneous gastrostomy tube <sup>83,84</sup>
The OverStitch Endoscopic Suturing System	Commercially available (Apollo Endosurgery (Austin, TX, USA) endoscopic suturing device that uses an endoscopic cap and catheter-based suturing mechanism; used for interrupted or running sutures and to bridge gaps of varying sizes	Needs a dual channel upper endoscope, which restricts manoeuvrability in the duodenum and at the cardia. An omental patch can be sewn into place	Currently used for endoscopic gastric sleeve formation, anastomotic leaks, or gastrocutaneous fistulae <sup>85</sup>
Self-expanding metal stents (SEMS)	Covered self-expandable metal stents	Needs endoscopic skills; uncertain long-term results	Case series <sup>86</sup>
Nitinol U-clips	Laparoscopic suturing device without knot-tying	Only for perforations <10 mm	Only case series; <sup>87</sup> used in other medical areas
Plug with acellular matrix	Material is approved by the US Food and Drug Administration for other uses (eg, anal fistulae)	Needs the development of an endoscopic delivery mechanism (eg, plunger extrusion)	Not in clinical use; animal studies
A biodegradable patch	Closure of the perforation by gluing a biodegradable patch made of lactide-glycolide-caprolacton (LGC, Polyganics, B.V. Groningen, Netherlands) on the outside of the stomach	No clinical data	Animal studies, <sup>88</sup> anecdotal human data with similar materials not successful
A patch coated with fibrinogen and thrombin	Suture of the gastric wall, followed by patch application covered by the omental patch	Add-on to regular omental pedicle	2 case reports <sup>89</sup>
Mesenchymal stem cells	Injection of adipose tissue-derived mesenchymal stem cells into the experimental wound in the stomach wall provided faster growth with improved strength	Improved wound healing, question of future carcinogenesis	Animal study; <sup>79</sup> procedure has not been done in contaminated environment, nor in human beings

**Table 2: Novel techniques or translational innovations for the treatment of perforated peptic ulcer**

1 year (1.49; 1.10–2.03) after surgery. Notably, the included studies only included patients with duodenal ulcer perforations.

Since *H pylori* eradication is a standard approach, outstanding questions relate to the choice of eradication regimen. Resistance development and patterns, in addition to efficacy and compliance issues, should be considered. A 2013 Cochrane review showed that eradication rates using a standard triple regimen (proton pump inhibitor plus clarithromycin plus amoxicillin) increased with longer duration of treatment (eg, 14 days vs 7 or 10 days).<sup>96</sup>

## Outcomes, follow-up, and quality of life

### Short-term mortality

Mortality rates for peptic ulcers have remained stable over time in Europe,<sup>10</sup> and were reported to be 10–30% in a 2011 systematic review.<sup>5</sup> However, mortality rates differ substantially between reports (ranging from 3% to 30%), mainly because of geographical variations in causes and patient inclusion, but also differences in method of data

collection. Administrative data sources, such as the US National Inpatient Sample<sup>72</sup> and Health Insurance Claims Registry in Korea,<sup>97</sup> report low mortality rates (around 3%). For the USA, such low mortality in administrative datasets contrasts with rates in other reports (mortality of 15%) from the same country.<sup>4</sup> In prospective, nationwide data collection, such as the Danish Clinical Register of Emergency Surgery, mortality is reported to be as high as 28%.<sup>98</sup> Thus, in addition to geographical variation (figure 1), method of data capture must be considered carefully when mortality rates are compared.

### Endoscopic follow-up after surgery

After surgery for gastric ulcers, routine postoperative endoscopy is often done to rule out malignancy as the primary cause of perforation, since up to 13% of gastric perforations can be due to a gastric cancer.<sup>76</sup> This endoscopy is usually scheduled around 6 weeks after recovery from the procedure and after completion of *H pylori* eradication. The available evidence for this approach is scarce and is

based on clinical acumen. Endoscopic follow-up is usually not recommended in duodenal ulcers because 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 to rule out malignancy if the exact location of the ulcer is uncertain and no perioperative biopsy was done.

### Long-term outcomes

Survival in the long term after surgery for perforated peptic ulcer has been poorly assessed and data are only available from three observational cohort studies.<sup>66–68</sup> All three studies reported excessive long-term mortality and were reported in European cohorts of elderly patients. Since none of the studies were comparative in design, further studies into relative survival and causes of death are needed. In younger patient populations, quality of life is reported to be good in most patients 6 months after surgery.<sup>99</sup>

### Conclusions and future directions

The paucity in clinical progress and basic understanding of perforated peptic ulcers calls for increased attention to reduce morbidity and mortality. Compared with its toll on human health worldwide, we have a poor understanding of the pathophysiology underlying perforation, the ability of these ulcers to self-heal, and the development of the sepsis syndrome in affected patients.

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

### Contributors

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

### Declaration of interests

We declare no competing interests.

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