

Strategies to improve the outcome of emergency surgery for perforated peptic ulcer

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Background: Perforated peptic ulcer (PPU) is a common surgical emergency that carries high mortality and morbidity rates. Globally, one-quarter of a million people die from peptic ulcer disease each year. Strategies to improve outcomes are needed.

Methods: PubMed was searched for evidence related to the surgical treatment of patients with PPU. The clinical registries of trials were examined for other available or ongoing studies. Randomized clinical trials (RCTs), systematic reviews and meta-analyses were preferred.

Results: Deaths from peptic ulcer disease eclipse those of several other common emergencies. The reported incidence of PPU is 3.8–14 per 100 000 and the mortality rate is 10–25 per cent. The possibility of non-operative management has been assessed in one small RCT of 83 patients, with success in 29 (73 per cent) of 40, and only in patients aged less than 70 years. Adherence to a perioperative sepsis protocol decreased mortality in a cohort study, with a relative risk (RR) reduction of 0.63 (95 per cent confidence interval (c.i.) 0.41 to 0.97). Based on meta-analysis of three RCTs (315 patients), laparoscopic and open surgery for PPU are equivalent, but patient selection remains a challenge. Eradication of *Helicobacter pylori* after surgical repair of PPI reduces both the short-term (RR 2.97, 95 per cent c.i. 1.06 to 8.29) and 1-year (RR 1.49, 1.10 to 2.03) risk of ulcer recurrence.

Conclusion: Mortality and morbidity from PPU can be reduced by adherence to perioperative strategies.



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Introduction

Perforation of a peptic (gastric or duodenal) ulcer is a potentially fatal surgical emergency that remains a formidable health burden worldwide¹. The global prevalence of peptic ulcer disease has decreased in recent decades (Fig. 1)^{2–5}, but this has not been followed by a similar reduction in complications from peptic ulcers^{4–7}. The reduction in peptic ulcer disease is in part explained by the introduction of antibacterial therapy to eradicate *Helicobacter pylori* and the widespread use of proton pump inhibitors (PPIs). Yet, despite the introduction of PPIs, the rate of peptic ulcer perforation has remained stable in several regions of the world^{4,7–10}. Improved medical management of peptic ulcer disease has virtually eradicated the need for acid-reducing surgery, such as proximal selective vagotomy, gastric resection and surgery performed for benign gastric outlet obstruction^{5,11}. The complications of peptic ulcer disease, however, in particular bleeding and perforation, continue to present as an emergency^{8,12}.

Bleeding ulcers are about five times more common than perforated ulcers². Non-operative management, including medication, endoscopy and interventional radiology, has decreased the role of emergency surgery to less than 2 per cent of patients; bleeding ulcer is now predominantly a medical emergency^{13,14}.

In contrast, the prevalence of perforated peptic ulcer (PPU) has remained fairly stable over the past decade⁸, and emergency surgery is the mainstay of treatment. As most patients with a PPU are elderly with considerable comorbidity¹⁵, a high mortality rate (up to 25 per cent) and a morbidity rate of up to 50 per cent have been reported, even in recent studies^{16–18}. Consequently, PPU remains a frequent challenge to surgeons^{15,19}, and optimal treatment strategies are needed²⁰.

This article reviews current knowledge on treatment of PPU, including optimal strategies and published evidence to support their use. Areas in need of improvement and further research are highlighted.

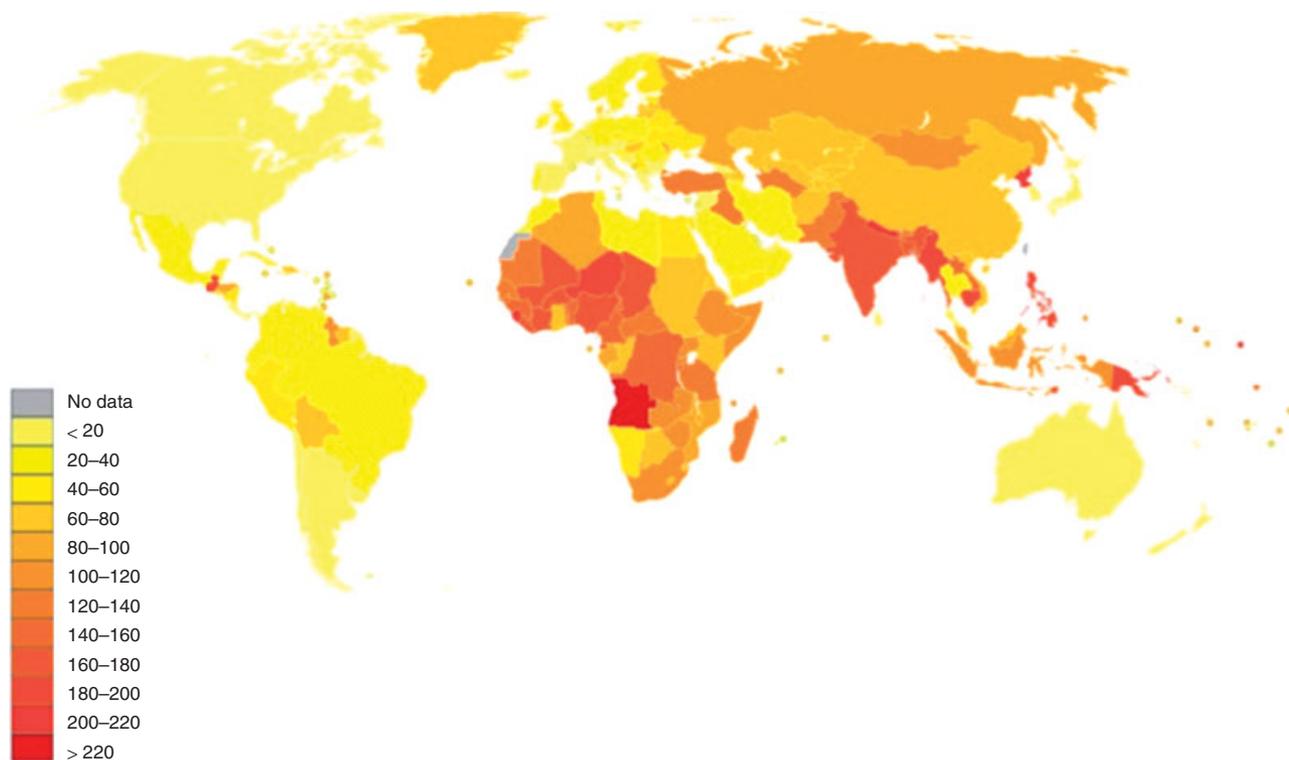


Fig. 1 Age-standardized disability-adjusted life-years from peptic ulcer disease by country (per 100 000 inhabitants). The data are based on a World Health Organization 2004 report, reproduced with permission from Wikimedia (http://commons.wikimedia.org/wiki/File:Peptic_ulcer_disease_world_map_-_DALY_-_WHO2004.svg)

Methods

The study included a systematic search of PubMed for research related to PPU using the search terms ‘peptic ulcer’, ‘gastroduodenal’, ‘gastric’, ‘duodenal’ with ‘ulcer’ and ‘perforation’ or ‘perforated’. The focus was on studies reported since 2000, with a particular emphasis on the past 5 years (search completed 31 August 2013). The search emphasized randomized clinical trials (RCTs), systematic reviews and meta-analyses covering themes on PPU. Papers using a collective review approach and recent narrative reviews were also included. Clinical trial registries (www.clinicaltrials.gov, www.controlled-trials.com) were searched for planned, ongoing or recently completed trials on PPU. Owing to the heterogeneous nature of the available data, formal meta-analyses were not planned.

Results

Papers covering specific topics, including systematic reviews with, or without meta-analyses were found for a few topics, including the epidemiology and mortality of PPU², the comparison of open and laparoscopic surgery^{21–25}, the

role of *H. pylori* eradication^{26–28}, and the role of scoring systems and prediction models^{29,30}.

Only one unpublished RCT was found in the clinical registries (ClinicalTrials.gov; registration number NCT01620671), which aimed to investigate fast-track surgery for PPU. The trial is recorded as completed in January 2013, with enrolment of 61 patients (all adults, perforations smaller than 5 mm, American Society of Anesthesiologists (ASA) grade I–II, no shock on admission), but no published results were found. One further registered trial³¹ (NCT01080326) investigated the feasibility of endoscopic omental patch repair in three patients, of whom two underwent natural orifice transluminal endoscopic surgery.

Global scope and health burden

Although there has been a substantial decrease, the estimated global number of deaths attributable to peptic ulcer disease in 2010 was 246 000 (95 per cent confidence interval (c.i.) 215 000 to 282 000). In context, this is seven times the death rate from appendicitis, considerably more than that for ruptured abdominal aortic aneurysm, and similar to the death rate from cancers such as those of

the prostate in men and ovarian and cervical cancer in women³². Almost 70 per cent of deaths from peptic ulcer disease are the result of perforation³³.

Estimated annual incidence rates of peptic ulcer haemorrhage and perforation are 19.4–57.0 and 3.8–14 per 100 000 individuals respectively². Based on data from 11 European studies², there are between 4750 and 17 750 deaths from PPU every year. A study from 1993 to 2006, which captured 20 per cent of all hospital admissions in the USA, showed that the number of surgical procedures for perforation (defined as oversewing of peptic ulcer site) decreased by 21 per cent, from 15 000 to 12 000. The mortality rate from peptic ulcer disease was more than ten times higher than that from acute appendicitis and acute cholecystitis (index year 2006)⁵.

Cause of disease and risk factors

The aetiology of peptic ulceration has changed as *H. pylori* infections have decreased, and the use of

non-steroidal anti-inflammatory drugs (NSAIDs)^{34,35} and cyclo-oxygenase 2 inhibitors³⁶ has increased. Several risk factors remain strongly associated with perforation, including smoking^{37,38}, and the use of NSAIDs¹ and corticosteroids³⁹ (Fig. 2). A decrease in complicated peptic ulcer disease occurred after the introduction of PPIs^{6,40}. Other less common factors may contribute to PPU, such as the use of crack cocaine or amphetamine⁴¹, and prolonged fasting^{42–44}. The increase in bariatric surgery has resulted in marginal ulcer perforations following Roux-en-Y gastric bypass^{45–47}, replacing the stomal ulceration previously seen after gastric resection for malignant disease (such as Billroth II resection). In patients with recurrent or multiple peptic ulcers, the Zollinger–Ellison syndrome (gastrinoma) should not be forgotten⁴⁸.

Stress ulcers with perforation may occur in critically ill patients in intensive care, where the diagnosis may be obscured owing to lack of signs and symptoms in an unconscious or sedated patient. Evidence for the benefit

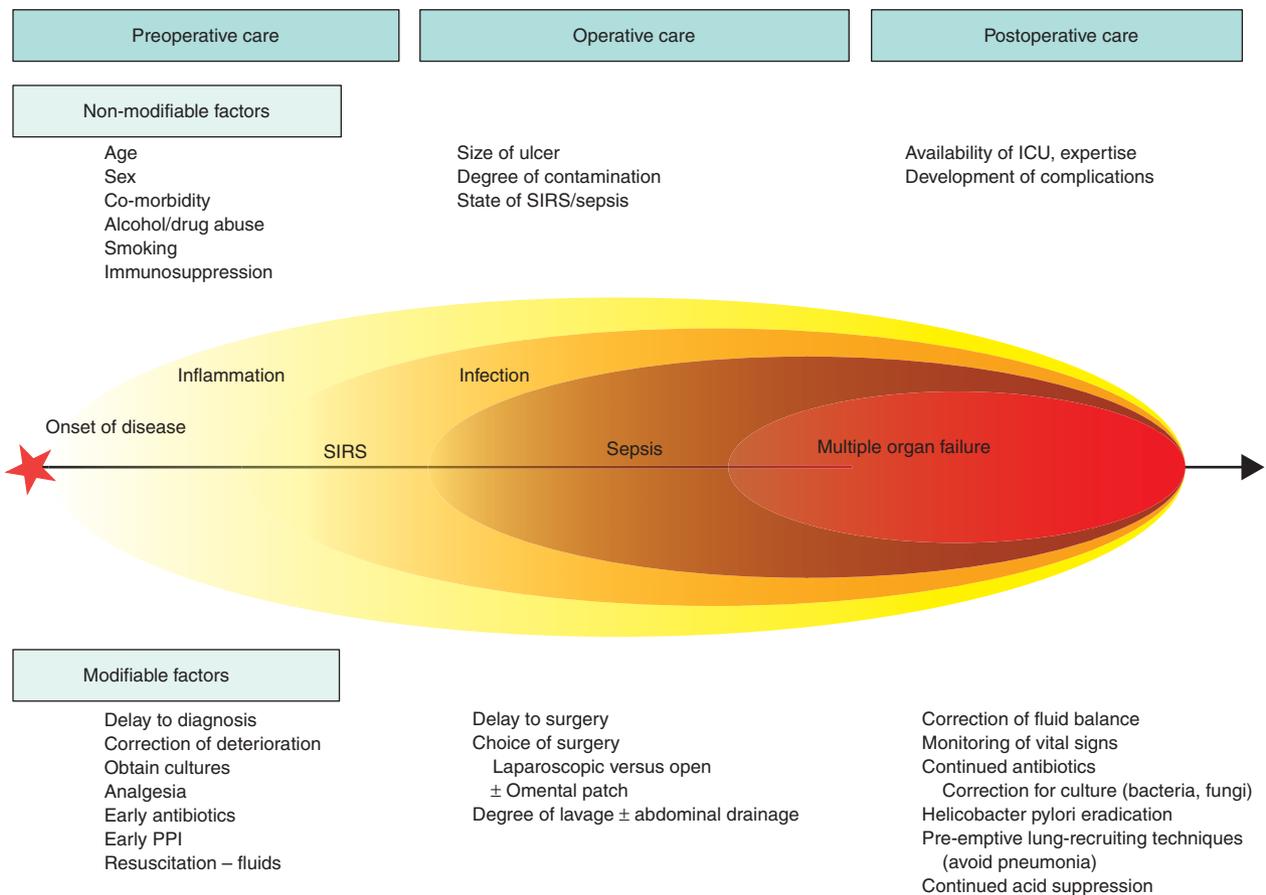


Fig. 2 Modifiable and non-modifiable risk factors in perforated ulcer disease. SIRS, systemic inflammatory response syndrome; ICU, intensive care unit; PPI, proton pump inhibitor

of prophylactic acid suppression against stress ulcer is sparse⁴⁹, and patients taking PPIs may still develop a perforated ulcer.

Perforated ulcer may also occur in children^{50–52}, sometimes associated with other conditions^{51,53}. Albeit rare, it should not be forgotten as a possible cause of acute-onset pain or otherwise unexplained abdominal symptoms.

Finally, although predominantly benign in nature, underlying gastric cancer can occasionally present with perforation, as reported in over 13 per cent in one series⁵⁴.

Risk scoring

Several investigators have tried to predict disease severity in patients with PPU. The first prediction model and the one most frequently used is the Boey score^{55,56}. It was developed and validated prospectively and uses three variables: major medical illness, preoperative shock and longstanding perforation (more than 24 h). The Boey score correctly predicted outcome in 93.8 per cent of patients with PPU⁵⁵. However, later evaluation in other cohorts demonstrated inconsistency^{57,58}, which led to alternative risk scores being developed^{59–62}, although none has yet been adopted universally. Most risk prediction models are limited in their ability to predict outcome for the individual³⁰.

Even though a number of risk factors for adverse outcome have been identified, many can be explained by the septic state of a patient with PPU. In a comprehensive literature search²⁹ of 50 studies comprising almost 30 000 patients, 37 prognostic factors were investigated. The strongest associations with mortality were older age, co-morbidity and use of NSAIDs or steroids. Shock, preoperative metabolic acidosis, tachycardia, acute renal failure, low serum albumin level, high ASA grade and preoperative delay exceeding 24 h were associated with poor prognosis. The authors suggested that early identification and treatment of sepsis is needed to improve the outcome of patients with PPU.

Another tool for predicting 30-day mortality is the Peptic Ulcer Perforation (PULP) score⁵⁹, which was developed on 2668 patients who had surgery for PPU across 35 hospitals in Denmark. The PULP score comprises eight variables associated with worse outcome including: age over 65 years, active malignant disease or acquired immunodeficiency syndrome, liver cirrhosis, steroid use, increasing time (more than 24 h) from perforation to admission, preoperative shock, raised serum creatinine level (over 130 mmol/l) and ASA grade over I⁵⁹. The score predicted mortality well, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.83. The

PULP score was better than the Boey score (AUC 0.70) and use of ASA grade alone (AUC 0.78)⁵⁹. However, the PULP score has yet to be validated outside this Danish cohort³⁰.

Diagnosis and imaging

The clinical presentation of acute pain in the upper abdomen, with signs of peritonitis, is typical for PPU, but is seen in only about two-thirds of patients^{63,64}. When present, peritonitis is an indication for immediate laparoscopy or laparotomy, taking into account the patient's condition and observations. Delay should not be introduced by additional imaging.

Fewer than one-third of patients have a history of peptic ulcer disease before perforation³³. Erect chest X-ray, seeking free air under the diaphragm, has been the imaging procedure of choice historically, but the diagnostic yield is suboptimal⁶⁵ and free air is reported to be visible at rates varying from 30 to 85 per cent^{33,63,66}. X-ray has now been replaced by abdominal computed tomography (CT), which has a higher diagnostic yield, reportedly around 70–98 per cent^{63,66–69}. In addition, CT can rule out other differential diagnoses of importance (such as acute pancreatitis) that would obviate the need for surgery.

Ultrasonography may be useful in experienced hands and can locate the site of ulcer perforation^{70,71}. The role of ultrasonography is limited and it should not delay surgery if other diagnostic procedures have confirmed the presence of free air, or the patient is ill.

Surgical treatment

Since gastric resections and truncal vagotomy for acid reduction became obsolete with the advent of PPIs, the main surgical treatment for PPU has become simple suture of the perforation site with, or without the addition of an omental patch (*Fig. 3*). The surgical trend has shifted towards minimally invasive laparoscopic surgery in selected patients^{63,72–74}.

Laparoscopic repair (*Fig. 4*) was first used for a perforated duodenal ulcer in 1990⁷⁵. The first RCT that compared open and laparoscopic surgery for PPU was done in Hong Kong and included 103 procedures⁷⁶; there were no differences in the outcomes between the two procedures (*Table 1*). Similarly, a second small randomized trial⁸⁰ of 20 patients, which examined possible effects on the acute-phase response and the presence of endotoxaemia, found no difference between laparoscopy and open repair; a subsequent similar investigation⁸¹ confirmed this finding. A further RCT⁷⁸, also from Hong Kong, that included

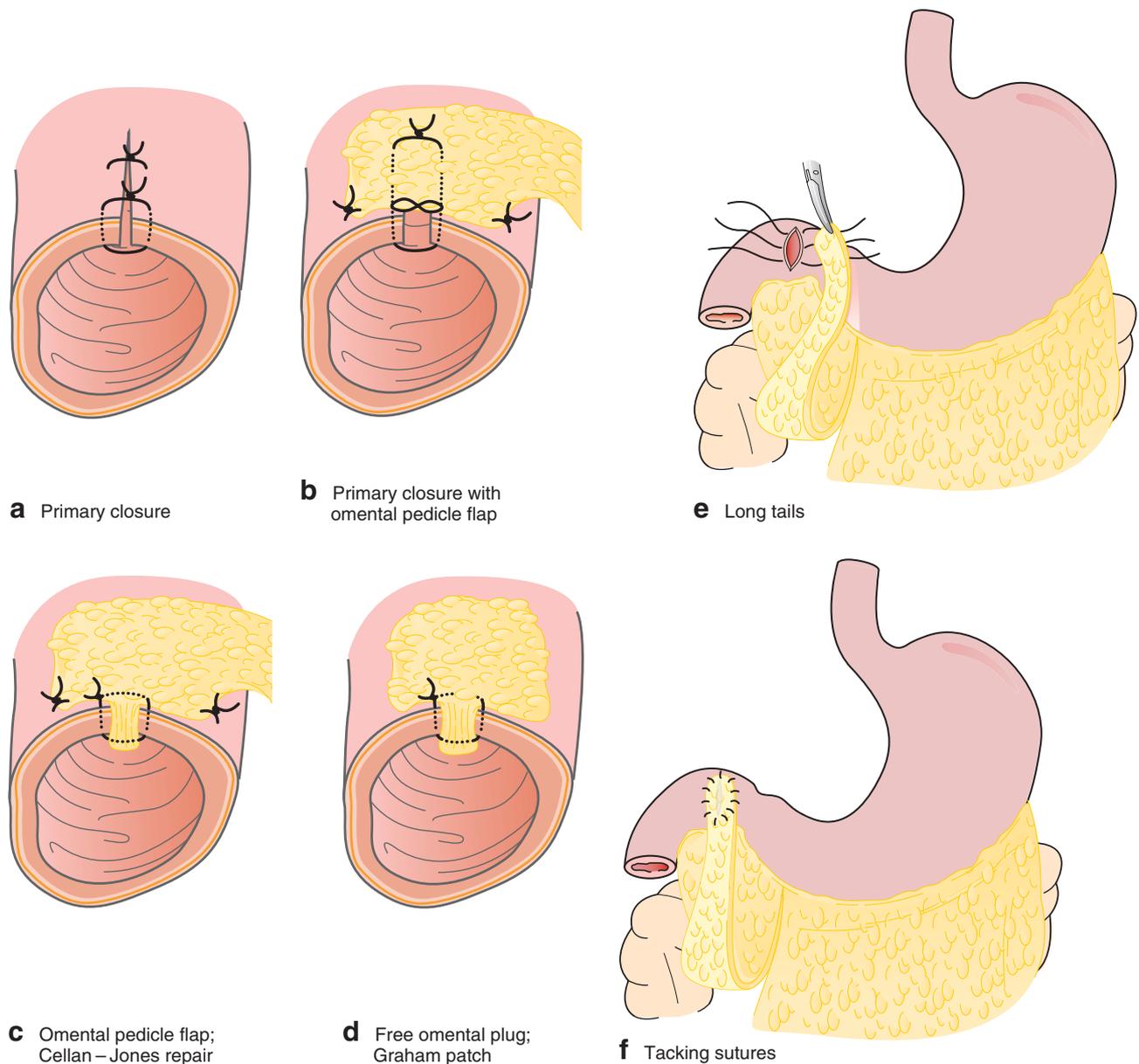


Fig. 3 Alternative techniques for suture of a perforated ulcer: **a** primary suture; **b** primary suture with pedicled omental flap; **c** pedicled omental flap sutured into the perforation (Cellan–Jones repair); **d** free omental plug sutured into the perforation (Graham patch); **e** use of three long-tailed sutures to close the perforation and buttress with a pedicled omental flap; **f** use of tacking sutures around the perforation (for example when friable edges or a large perforation may not allow approximation of wound edges)

130 patients reported in 2002, and the only European study (the Dutch LAMA trial)⁷⁹ reported in 2009. All three RCTs favoured laparoscopic repair, as being at least not inferior to open surgery for PPU; however, a subsequent meta-analysis²² has provided inconclusive results owing to the small sample sizes for each outcome measured (*Table 1*).

As increasing numbers of retrospective and cohort studies of laparoscopic surgery for PPU have been reported, the combined meta-analyses of RCTs, prospective observations and retrospective cohorts have yielded more favourable advantages for laparoscopy²¹. Collective reviews⁷⁴ also favour a laparoscopic approach, but most of these were conducted before the advent of guidelines

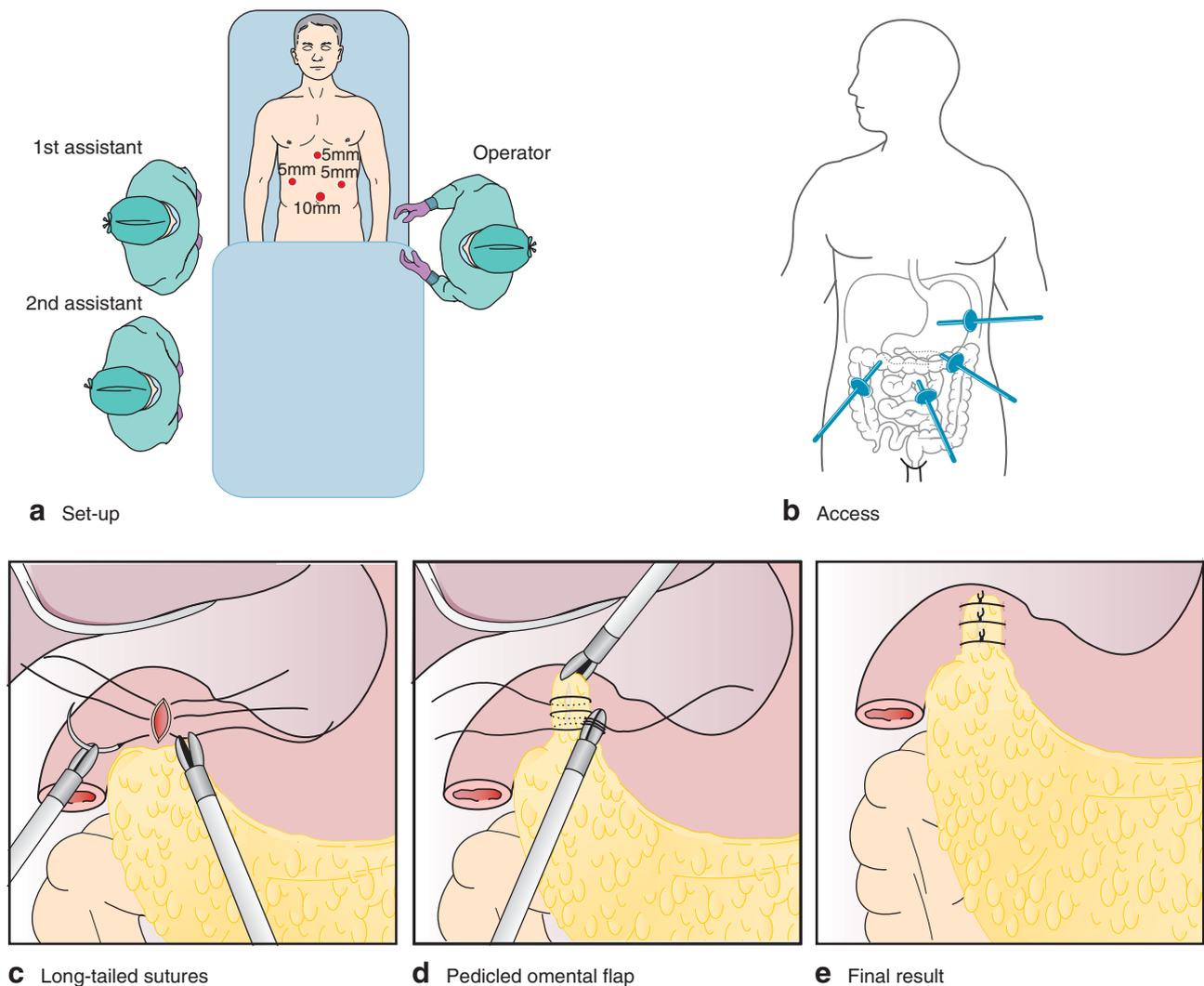


Fig. 4 Laparoscopic set-up for suture of perforated peptic ulcer: **a** suggested arrangement of patient, surgeon and assistants; **b** triangulation of equipment and camera access through umbilicus, with one additional port for the assistant to retract the liver; **c** use of long-tailed sutures to form **d** pedicled omental flap; **e** final result

for systematic reviews, such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations⁸², and have the inherent risk of publication bias. Thus, the current state of evidence remains poor for choosing laparoscopy over laparotomy for PPU. Yet laparoscopic surgery for PPU has been taken up enthusiastically in many hospitals and reports from population-based series have shown no adverse effects on outcomes^{63,83}. Specialist society guidelines^{84,85} suggest that a laparoscopic approach is warranted in selected patients. Laparoscopic repair of PPU has also been done by trainee surgeons, with acceptable results^{63,86}, probably because of the increased exposure to laparoscopy by current young

surgical trainees^{73,87}. Guidelines on which patients with PPU are best suited to a laparoscopic approach have not yet been established, but shock on admission (blood pressure below 90 mmHg), delayed presentation (over 24 h) after perforation, age over 70 years, ASA fitness grade III–IV and a high Boey score should be considered adverse risk factors, and should guide towards laparotomy rather than laparoscopy⁸⁸. Inadequate ulcer localization, large perforation (defined by some as larger than 6 mm diameter, and by others as over 10 mm) and ulcers with friable edges are also likely to result in failure of laparoscopic surgery, with conversion to open repair⁸⁸. Patient selection for laparoscopic repair remains a challenge, but considerable

Table 1 Available evidence for treatment decisions regarding perforated peptic ulcer management

Intervention	Evidence-based data	Study information and results	Country of origin*	Comment on results, limitations
Perioperative protocol	Multicentre prospective study ¹⁶ , <i>n</i> = 2619	Reduced 30-day mortality rate in hospitals applying protocol (17% versus 27% for others; <i>P</i> = 0.005); RR 0.63 (95% c.i. 0.41 to 0.97)	Denmark	Strong role of preoperative, perioperative and postoperative optimal care with focus on sepsis, fluid management and systematic monitoring Only 117 patients in intervention group
Non-operative management	RCT ⁷⁷ , <i>n</i> = 83 43 had immediate surgery; 40 had resuscitation with i.v. fluids, nasogastric suction, and i.v. antibiotics and ranitidine	Similar mortality (5% in each group) 11 (27%) in conservative group required surgery after 12 h Non-operative management failed in patients aged > 70 years	Hong Kong, China	Success rate > 70%, but based on small study sample Not repeated/validated Performed before PPI era
Laparoscopic versus open surgery	Meta-analyses ^{21–25} based on 3 RCTs ^{76,78,79} , <i>n</i> = 315	No difference between open and laparoscopic approach for most outcomes investigated in meta-analysis	The Netherlands (1) Hong Kong, China (2)	First trial in 1996, last in 2009 Small numbers, two single-centre studies Early laparoscopic experience; may include learning curve effect
<i>Helicobacter pylori</i> eradication after surgery to reduce ulcer recurrence	Meta-analyses ^{27,28} of 5 RCTs, <i>n</i> = 401	Reduced incidence of ulcer recurrence at 8 weeks (RR 2.97, 95% c.i. 1.06 to 8.29) and at 1 year (RR 1.49, 1.10 to 2.03) after surgery	Egypt (1) India (2) Hong Kong (1) Turkey (1)	Reduces risk of ulcer recurrence Published between 2000 and 2011 Sample size 40–124 patients Only simple duodenal ulcers included Long-term effects not reported

*Country of primary studies. RR, relative risk; c.i., confidence interval; RCT, randomized clinical trial; i.v., intravenous; PPI, proton pump inhibitor.

laparoscopic expertise of the surgeon is mandatory⁸⁹. In addition, the optimal laparoscopic surgical technique for closure of the perforation remains unknown; the decision rests on whether or not to use an omental patch^{74,89–91}. Finally, the latest options for PPU include endoscopic closure⁹² and natural orifice transluminal treatment, which has been reported in a few small series^{31,93,94}; these remain experimental and beyond the scope of this review.

Supportive treatment

As soon as the diagnosis of PPU has been made, antibiotic treatment should commence (after obtaining blood cultures). No specific antibiotics are recommended⁹⁵, and antibiotic regimens should be based on institutional, national or society guidelines, drug availability and any

known local patterns of microbial resistance^{96–98}. It is important not to stop antibiotics too soon after surgery, particularly if there is significant contamination, as intra-abdominal abscess may complicate subsequent recovery. For patients who do not improve on broad-spectrum antibiotics, fungal cultures should be obtained, as fungal superinfection is a known late complication of PPU^{99,100}. Routine use of prophylactic antifungal therapy in high-risk patients was well tolerated but did not reduce mortality in critical care¹⁰¹, although it did decrease the rate of fungal infection¹⁰².

As vagotomy is seldom performed during surgery for PPU¹⁰³, it is important to eradicate *H. pylori* after surgery, and to give long-term antacid treatment, as perforation may recur in about 12 per cent of patients. This is particularly true for duodenal ulcers, and also in endemic

areas^{104–107}. Two recent systematic reviews^{27,28} support *Helicobacter* eradication to prevent ulcer recurrence (Table 1). Wong and colleagues²⁸ included five RCTs with a total of 401 patients treated surgically for PPU. Eradication of *H. pylori* significantly reduced the rate of ulcer recurrence after 8 weeks (relative risk 2.97, 95 per cent c.i. 1.06 to 8.29) and 1 year (1.49, 1.10 to 2.03). A second report²⁷ concluded that patients who completed eradication therapy had a 1-year recurrent ulcer rate of 5 per cent, compared with 35 per cent in those without eradication. The choice of eradication therapy and outcomes are reviewed elsewhere¹⁰⁸. The role of H₂-receptor blockers has largely decreased with the more widespread availability and use of PPIs. Overall, PPIs reduce the risk of complications after the diagnosis of peptic ulcer¹⁰⁹, and should be used particularly for patients taking NSAIDs.

Non-operative management

In high-risk patients, those who would not tolerate or cannot undergo general anaesthesia, or for patients with a sealed retroperitoneal perforation, a non-operative approach may be considered (Table 1). This includes PPI and antibiotic treatment, a nasogastric tube and percutaneous drainage of any collections, as required^{110–112}. For the elderly and very sick patients with PPU, the mortality rate is over 50 per cent for both operative and conservative approaches¹¹³.

One report suggested that patients with PPU and a short duration of symptoms, few signs and no generalized peritonitis, with only minor amounts of free air visible on imaging, may be most suitable for conservative treatment¹¹⁴. However, the amount of visible free air is not always a reliable guide to disease severity. A small RCT of 83 patients, of whom 40 were randomized to primary conservative treatment and 43 to immediate surgery, reported that conservative management was successful in 73 per cent, with a mortality rate similar to that of surgery; it was less likely to work in patients aged over 70 years⁷⁷. Conservative treatment for PPU is seldom reported¹¹⁵, and restricted mostly to case reports, so its role remains uncertain and best based on individual evaluation. Notably, for gastric ulcer perforations, it is crucial to perform an upper gastroendoscopy to rule out gastric cancer if the patient has not undergone surgery, or biopsies have not been obtained during surgery.

Multimodal approach to assessment and resuscitation

A multidisciplinary approach to patients with PPU should be initiated at the time of diagnosis. Because the risk

of sepsis is considerable, resuscitation should commence before surgery, as recommended in guidelines from the Surviving Sepsis Campaign¹¹⁶. The PULP project¹⁶ in Denmark demonstrated a decrease in the overall mortality rate from 27 to 17 per cent by instituting a care bundle. A Danish nationwide quality-of-care (QoC) initiative has since been launched to improve outcome in patients with PPU. During the study, an increasing number of hospitals fulfilled four preset QoC indicators. These included preoperative delay no more than 6 h, and daily monitoring of bodyweight, fluid balance and vital signs. After introduction of the care bundle, fewer patients had early discontinuation of routine prophylactic antibiotics. The adjusted 30-day mortality rate decreased, albeit non-significantly, and the rate of reoperation remained unchanged; a further RCT is planned¹¹⁷.

Other outcomes

The 30-day mortality rate varies considerably in reported studies and is related to patient selection, as well as geographical differences^{2,8,83,118–120}. There is consistent evidence of adverse effects of delay in diagnosis and delay before surgery^{118,121,122}, as well as higher mortality among the elderly^{7,8,123–125}. Postoperative complications are frequent^{120,126,127}, and include common diagnoses such as wound and other abdominal infections, thromboembolic events and organ failure. Rarer complications include omental patch leakage requiring reoperation in about 4 per cent of patients¹²⁶ and persistent duodenal fistula¹²⁸.

Long-term outcomes

Data on long-term survival after treatment for PPU are based on just a few studies. One from the Mayo Clinic¹²⁹ followed all patients residing in Rochester, Minnesota from treatment until death. Death rates were high, in particular from heart disease and cancer; excess mortality was highest in older patients, men and smokers. Another study from Norway¹³⁰ found similar results, with most deaths due to smoking-related diseases. A national cohort from Denmark¹³¹ showed no difference in survival up to 2 years after surgery between patients who had the PULP trial bundle of care compared with those who did not. Whether changes in national smoking habits (many countries currently report a significant reduction) will coincide with improvements in long-term survival after surgery for PPU is currently unknown.

Future strategies to improve outcomes

The evidence of an optimal strategy for patients with PPU is currently based on a few small RCTs (Table 1).

There is also information from a limited number of prospective studies, but most published research derives from retrospective single-institution studies. For a common disease with a high mortality rate and considerable morbidity after surgery, there is ample scope for improvement. The worldwide prevalence of PPU suggests that large trials of various aspects of care could be conducted through international collaboration¹³².

Investigation into the value of protocol-driven care bundles that focus on sepsis and sepsis syndrome in patients with PPU could inform QoC outcomes. A 'before and after' approach could be explored, in order to demonstrate any potential effect on mortality, which is the most obvious hard endpoint. As PPU is a worldwide disease, simple agreement to adhere to a specified protocol is an affordable intervention that could be applied across several regions; this is the most likely action to reduce mortality from PPU.

Current controversies include the role of non-operative management, both in frail patients, and also in the healthy patient with minimal disease. Patient selection for conservative treatment is currently poorly understood, and better data could be provided by large-scale studies. Optimal management strategies remain to be defined in relation to the range of disease severity.

There also remains uncertainty about the optimal role of laparoscopic repair for PPU. Future comparison of open and laparoscopic surgery for PPU could focus on softer endpoints than death, such as: need for reoperation, time to recovery and rate of intra-abdominal infection/abscess. Laparoscopic experience has increased since the previous RCTs, which were not powered to examine the secondary endpoints reliably. Other operative variables that could be studied include whether or not an omental patch is beneficial, type and duration of antibiotics, and antifungal therapy. Long-term follow-up studies would be valuable, particularly for young patients treated for PPU.

Finally, life expectancy is increasing in many highly populated regions of the world, including Europe¹³³, the USA¹³⁴ and China¹³⁵. A study of the increasing burden of gastrointestinal disorders requiring admission to hospital in Ireland estimated that admission of patients aged over 65 years will increase by 128 per cent by 2031¹³⁶, with an equal increase in the need for surgical procedures. Surgeons should be prepared for an increasing number elderly, frail patients needing emergency treatment for PPU^{137–139}.

Disclosure

The authors declare no conflict of interest.

References

- 1 Svanes C. Trends in perforated peptic ulcer: incidence, etiology, treatment, and prognosis. *World J Surg* 2000; **24**: 277–283.
- 2 Lau JY, Sung J, Hill C, Henderson C, Howden CW, Metz DC. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality. *Digestion* 2011; **84**: 102–113.
- 3 Dutta AK, Chacko A, Balekuduru A, Sahu MK, Gangadharan SK. Time trends in epidemiology of peptic ulcer disease in India over two decades. *Indian J Gastroenterol* 2012; **31**: 111–115.
- 4 Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Complicated and uncomplicated peptic ulcers in a Danish county 1993–2002: a population-based cohort study. *Am J Gastroenterol* 2006; **101**: 945–953.
- 5 Wang YR, Richter JE, Dempsey DT. Trends and outcomes of hospitalizations for peptic ulcer disease in the United States, 1993 to 2006. *Ann Surg* 2010; **251**: 51–58.
- 6 Hermansson M, Ekedahl A, Ranstam J, Zilling T. Decreasing incidence of peptic ulcer complications after the introduction of the proton pump inhibitors, a study of the Swedish population from 1974–2002. *BMC Gastroenterol* 2009; **9**: 25.
- 7 Wysocki A, Budzynski P, Kulawik J, Drożdż W. Changes in the localization of perforated peptic ulcer and its relation to gender and age of the patients throughout the last 45 years. *World J Surg* 2011; **35**: 811–816.
- 8 Thorsen K, Søreide JA, Kvaløy JT, Glomsaker T, Søreide K. Epidemiology of perforated peptic ulcer: age- and gender-adjusted analysis of incidence and mortality. *World J Gastroenterol* 2013; **19**: 347–354.
- 9 Arveen S, Jagdish S, Kadambari D. Perforated peptic ulcer in South India: an institutional perspective. *World J Surg* 2009; **33**: 1600–1604.
- 10 Canoy DS, Hart AR, Todd CJ. Epidemiology of duodenal ulcer perforation: a study on hospital admissions in Norfolk, United Kingdom. *Dig Liver Dis* 2002; **34**: 322–327.
- 11 Søreide K, Sarr MG, Søreide JA. Pyloroplasty for benign gastric outlet obstruction – indications and techniques. *Scand J Surg* 2006; **95**: 11–16.
- 12 Youn YH, Park YJ, Kim JH, Jeon TJ, Cho JH, Park H. Weekend and nighttime effect on the prognosis of peptic ulcer bleeding. *World J Gastroenterol* 2012; **18**: 3578–3584.
- 13 Lau JY, Barkun A, Fan DM, Kuipers EJ, Yang YS, Chan FK *et al*. Challenges in the management of acute peptic ulcer bleeding. *Lancet* 2013; **381**: 2033–2043.
- 14 Rudler M, Cluzel P, Massard J, Menegaux F, Vaillant JC, Martin-Dupray A *et al*. Optimal nonsurgical management of peptic ulcer bleeding, including arterial embolization is associated with a mortality below 1%. *Clin Res Hepatol Gastroenterol* 2013; **37**: 64–71.
- 15 Sarosi GA Jr, Jaiswal KR, Nwariaku FE, Asolati M, Fleming JB, Anthony T. Surgical therapy of peptic ulcers

- in the 21st century: more common than you think. *Am J Surg* 2005; **190**: 775–779.
- 16 Møller MH, Adamsen S, Thomsen RW, Møller AM; Peptic Ulcer Perforation (PULP) trial group. Multicentre trial of a perioperative protocol to reduce mortality in patients with peptic ulcer perforation. *Br J Surg* 2011; **98**: 802–810.
 - 17 Nakano A, Bendix J, Adamsen S, Buck D, Mainz J, Bartels P *et al.* 30-days mortality in patients with perforated peptic ulcer: a national audit. *Risk Manag Healthc Policy* 2008; **1**: 31–38.
 - 18 Towfigh S, Chandler C, Hines OJ, McFadden DW. Outcomes from peptic ulcer surgery have not benefited from advances in medical therapy. *Am Surg* 2002; **68**: 385–389.
 - 19 Lee CW, Sarosi GA Jr. Emergency ulcer surgery. *Surg Clin North Am* 2011; **91**: 1001–1013.
 - 20 Møller MH, Adamsen S, Wøjdemann M, Møller AM. Perforated peptic ulcer: how to improve outcome? *Scand J Gastroenterol* 2009; **44**: 15–22.
 - 21 Lunevicius R, Morkevicius M. Systematic review comparing laparoscopic and open repair for perforated peptic ulcer. *Br J Surg* 2005; **92**: 1195–1207.
 - 22 Sanabria A, Villegas MI, Morales Uribe CH. Laparoscopic repair for perforated peptic ulcer disease. *Cochrane Database Syst Rev* 2013; (2)CD004778.
 - 23 Sanabria AE, Morales CH, Villegas MI. Laparoscopic repair for perforated peptic ulcer disease. *Cochrane Database Syst Rev* 2005; (4)CD004778.
 - 24 Antoniou SA, Antoniou GA, Koch OO, Pointner R, Granderath FA. Meta-analysis of laparoscopic *versus* open repair of perforated peptic ulcer. *JLS* 2013; **17**: 15–22.
 - 25 Lau H. Laparoscopic repair of perforated peptic ulcer: a meta-analysis. *Surg Endosc* 2004; **18**: 1013–1021.
 - 26 Danesh J, Appleby P, Peto R. How often does surgery for peptic ulceration eradicate *Helicobacter pylori*? Systematic review of 36 studies. *BMJ* 1998; **316**: 746–747.
 - 27 Tomtitchong P, Siribumrungwong B, Vilaichone RK, Kasetsuwan P, Matsukura N, Chaikyapunpruk N. Systematic review and meta-analysis: *Helicobacter pylori* eradication therapy after simple closure of perforated duodenal ulcer. *Helicobacter* 2012; **17**: 148–152.
 - 28 Wong CS, Chia CF, Lee HC, Wei PL, Ma HP, Tsai SH *et al.* Eradication of *Helicobacter pylori* for prevention of ulcer recurrence after simple closure of perforated peptic ulcer: a meta-analysis of randomized controlled trials. *J Surg Res* 2013; **182**: 219–226.
 - 29 Møller MH, Adamsen S, Thomsen RW, Møller AM. Preoperative prognostic factors for mortality in peptic ulcer perforation: a systematic review. *Scand J Gastroenterol* 2010; **45**: 785–805.
 - 30 Thorsen K, Søreide JA, Søreide K. Scoring systems for outcome prediction in patients with perforated peptic ulcer. *Scand J Trauma Resusc Emerg Med* 2013; **21**: 25.
 - 31 Bingener J, Loomis EA, Gostout CJ, Zielinski MD, Buttar NS, Song LM *et al.* Feasibility of NOTES omental plug repair of perforated peptic ulcers: results from a clinical pilot trial. *Surg Endosc* 2013; **27**: 2201–2208.
 - 32 Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095–2128.
 - 33 Bertleff MJ, Lange JF. Perforated peptic ulcer disease: a review of history and treatment. *Dig Surg* 2010; **27**: 161–169.
 - 34 Musumba C, Jorgensen A, Sutton L, Van Eker D, Moorcroft J, Hopkins M *et al.* The relative contribution of NSAIDs and *Helicobacter pylori* to the aetiology of endoscopically-diagnosed peptic ulcer disease: observations from a tertiary referral hospital in the UK between 2005 and 2010. *Aliment Pharmacol Ther* 2012; **36**: 48–56.
 - 35 Gisbert JP, Legido J, García-Sanz I, Pajares JM. *Helicobacter pylori* and perforated peptic ulcer prevalence of the infection and role of non-steroidal anti-inflammatory drugs. *Dig Liver Dis* 2004; **36**: 116–120.
 - 36 Christensen S, Riis A, Nørgaard M, Thomsen RW, Sørensen HT. Introduction of newer selective cyclo-oxygenase-2 inhibitors and rates of hospitalization with bleeding and perforated peptic ulcer. *Aliment Pharmacol Ther* 2007; **25**: 907–912.
 - 37 Svanes C, Søreide JA, Skarstein A, Fevang BT, Bakke P, Vollset SE *et al.* Smoking and ulcer perforation. *Gut* 1997; **41**: 177–180.
 - 38 Andersen IB, Jørgensen T, Bonnevie O, Grønbaek M, Sørensen TI. Smoking and alcohol intake as risk factors for bleeding and perforated peptic ulcers: a population-based cohort study. *Epidemiology* 2000; **11**: 434–439.
 - 39 Christensen S, Riis A, Nørgaard M, Thomsen RW, Tønnesen EM, Larsson A *et al.* Perforated peptic ulcer: use of pre-admission oral glucocorticoids and 30-day mortality. *Aliment Pharmacol Ther* 2006; **23**: 45–52.
 - 40 Vonkeman HE, Fernandes RW, van der Palen J, van Roon EN, van de Laar MA. Proton-pump inhibitors are associated with a reduced risk for bleeding and perforated gastroduodenal ulcers attributable to non-steroidal anti-inflammatory drugs: a nested case-control study. *Arthritis Res Ther* 2007; **9**: R52.
 - 41 Jones HG, Hopkins L, Clayton A, McKain E. A perforated duodenal ulcer presenting as inferior lead ST elevation following amphetamine use. *Ann R Coll Surg Engl* 2012; **94**: e144–e145.
 - 42 Gali BM, Ibrahim AG, Chama CM, Mshelia HB, Abubakar A, Takai IU *et al.* Perforated peptic ulcer (PPU) in pregnancy during Ramadan fasting. *Niger J Med* 2011; **20**: 292–293.
 - 43 Torab FC, Amer M, Abu-Zidan FM, Branicki FJ. Perforated peptic ulcer: different ethnic, climatic and fasting risk factors for morbidity in Al-ain medical district, United Arab Emirates. *Asian J Surg* 2009; **32**: 95–101.

- 44 Ohene-Yeboah M, Togbe B. Perforated gastric and duodenal ulcers in an urban African population. *West Afr J Med* 2006; **25**: 205–211.
- 45 Wheeler AA, de la Torre RA, Fearing NM. Laparoscopic repair of perforated marginal ulcer following Roux-en-Y gastric bypass: a case series. *J Laparoendosc Adv Surg Tech A* 2011; **21**: 57–60.
- 46 Gypen BJ, Hubens GJ, Hartman V, Balliu L, Chapelle TC, Vaneerdeweg W. Perforated duodenal ulcer after laparoscopic gastric bypass. *Obes Surg* 2008; **18**: 1644–1646.
- 47 Felix EL, Kettelle J, Mobley E, Swartz D. Perforated marginal ulcers after laparoscopic gastric bypass. *Surg Endosc* 2008; **22**: 2128–2132.
- 48 Singh MH, Fraker DL, Metz DC. Importance of surveillance for multiple endocrine neoplasia-1 and surgery in patients with sporadic Zollinger–Ellison syndrome. *Clin Gastroenterol Hepatol* 2012; **10**: 1262–1269.
- 49 Krag M, Perner A, Wetterslev J, Møller MH. Stress ulcer prophylaxis in the intensive care unit: is it indicated? A topical systematic review. *Acta Anaesthesiol Scand* 2013; **57**: 835–847.
- 50 Schwartz S, Edden Y, Orkin B, Erlichman M. Perforated peptic ulcer in an adolescent girl. *Pediatr Emerg Care* 2012; **28**: 709–711.
- 51 Goldman N, Punguyire D, Osei-Kwakye K, Baiden F. Duodenal perforation in a 12-month old child with severe malaria. *Pan Afr Med J* 2012; **12**: 1.
- 52 Hua MC, Kong MS, Lai MW, Luo CC. Perforated peptic ulcer in children: a 20-year experience. *J Pediatr Gastroenterol Nutr* 2007; **45**: 71–74.
- 53 Van Wagoner ZD, Evans DC, Askegard-Giesmann JR, Kenney BD. Perforated peptic ulcer in a child with a vagus nerve stimulator for seizure control. *Brain Stimul* 2013; [Epub ahead of print].
- 54 Ergul E, Gozetlik EO. Emergency spontaneous gastric perforations: ulcer *versus* cancer. *Langenbecks Arch Surg* 2009; **394**: 643–646.
- 55 Boey J, Choi SK, Poon A, Alagaratnam TT. Risk stratification in perforated duodenal ulcers. A prospective validation of predictive factors. *Ann Surg* 1987; **205**: 22–26.
- 56 Boey J, Wong J, Ong GB. A prospective study of operative risk factors in perforated duodenal ulcers. *Ann Surg* 1982; **195**: 265–269.
- 57 Lee FY, Leung KL, Lai BS, Ng SS, Dexter S, Lau WY. Predicting mortality and morbidity of patients operated on for perforated peptic ulcers. *Arch Surg* 2001; **136**: 90–94.
- 58 Buck DL, Vester-Andersen M, Møller MH. Accuracy of clinical prediction rules in peptic ulcer perforation: an observational study. *Scand J Gastroenterol* 2012; **47**: 28–35.
- 59 Møller MH, Engebjerg MC, Adamsen S, Bendix J, Thomsen RW. The Peptic Ulcer Perforation (PULP) score: a predictor of mortality following peptic ulcer perforation. A cohort study. *Acta Anaesthesiol Scand* 2012; **56**: 655–662.
- 60 Suriya C, Kasatpibal N, Kunaviktikul W, Kayee T. Development of a simplified diagnostic indicators scoring system and validation for peptic ulcer perforation in a developing country. *Clin Exp Gastroenterol* 2012; **5**: 187–194.
- 61 Mishra A, Sharma D, Raina VK. A simplified prognostic scoring system for peptic ulcer perforation in developing countries. *Indian J Gastroenterol* 2003; **22**: 49–53.
- 62 Koç M, Yoldaş O, Kiliç YA, Göçmen E, Ertan T, Dizen H *et al.* Comparison and validation of scoring systems in a cohort of patients treated for perforated peptic ulcer. *Langenbecks Arch Surg* 2007; **392**: 581–585.
- 63 Thorsen K, Glomsaker TB, von Meer A, Søreide K, Søreide JA. Trends in diagnosis and surgical management of patients with perforated peptic ulcer. *J Gastrointest Surg* 2011; **15**: 1329–1335.
- 64 Suriya C, Kasatpibal N, Kunaviktikul W, Kayee T. Diagnostic indicators for peptic ulcer perforation at a tertiary care hospital in Thailand. *Clin Exp Gastroenterol* 2011; **4**: 283–289.
- 65 Chen CH, Yang CC, Yeh YH. Role of upright chest radiography and ultrasonography in demonstrating free air of perforated peptic ulcers. *Hepatogastroenterology* 2001; **48**: 1082–1084.
- 66 Grassi R, Romano S, Pinto A, Romano L. Gastro-duodenal perforations: conventional plain film, US and CT findings in 166 consecutive patients. *Eur J Radiol* 2004; **50**: 30–36.
- 67 Hainaux B, Agneessens E, Bertinotti R, De Maertelaer V, Rubesova E, Capelluto E *et al.* Accuracy of MDCT in predicting site of gastrointestinal tract perforation. *AJR Am J Roentgenol* 2006; **187**: 1179–1183.
- 68 Furukawa A, Sakoda M, Yamasaki M, Kono N, Tanaka T, Nitta N *et al.* Gastrointestinal tract perforation: CT diagnosis of presence, site, and cause. *Abdom Imaging* 2005; **30**: 524–534.
- 69 Yeung KW, Chang MS, Hsiao CP, Huang JF. CT evaluation of gastrointestinal tract perforation. *Clin Imaging* 2004; **28**: 329–333.
- 70 Kuzmich S, Harvey CJ, Fascia DT, Kuzmich T, Neriman D, Basit R *et al.* Perforated pyloroduodenal peptic ulcer and sonography. *AJR Am J Roentgenol* 2012; **199**: W587–W594.
- 71 Minardos I, Ziogana D, Hristopoulos H, Dermitzakis I. Peptic ulcer perforation: sonographic imaging of active fluid leakage. *J Clin Ultrasound* 2006; **34**: 38–41.
- 72 Varcuş F, Lazăr F, Beuran M, Lica I, Turculeţ C, Nicolau E *et al.* Laparoscopic treatment of perforated duodenal ulcer – a multicenter study. *Chirurgia (Bucur)* 2013; **108**: 172–176.
- 73 Sneider EB, Cahan MA, Litwin DE. Laparoscopic repair of acute surgical diseases in the 21st century. *Minerva Chir* 2010; **65**: 275–296.
- 74 Bertleff MJ, Lange JF. Laparoscopic correction of perforated peptic ulcer: first choice? A review of literature. *Surg Endosc* 2010; **24**: 1231–1239.

- 75 Mouret P, François Y, Vignal J, Barth X, Lombard-Platet R. Laparoscopic treatment of perforated peptic ulcer. *Br J Surg* 1990; **77**: 1006.
- 76 Lau WY, Leung KL, Kwong KH, Davey IC, Robertson C, Dawson JJ *et al.* A randomized study comparing laparoscopic *versus* open repair of perforated peptic ulcer using suture or sutureless technique. *Ann Surg* 1996; **224**: 131–138.
- 77 Crofts TJ, Park KG, Steele RJ, Chung SS, Li AK. A randomized trial of nonoperative treatment for perforated peptic ulcer. *N Engl J Med* 1989; **320**: 970–973.
- 78 Siu WT, Leong HT, Law BK, Chau CH, Li AC, Fung KH *et al.* Laparoscopic repair for perforated peptic ulcer: a randomized controlled trial. *Ann Surg* 2002; **235**: 313–319.
- 79 Bertleff MJ, Halm JA, Bemelman WA, van der Ham AC, van der Harst E, Oei HI. Randomized clinical trial of laparoscopic *versus* open repair of the perforated peptic ulcer: the LAMA Trial. *World J Surg* 2009; **33**: 1368–1373.
- 80 Lau JY, Lo SY, Ng EK, Lee DW, Lam YH, Chung SC. A randomized comparison of acute phase response and endotoxemia in patients with perforated peptic ulcers receiving laparoscopic or open patch repair. *Am J Surg* 1998; **175**: 325–327.
- 81 Schietroma M, Piccione F, Carlei F, Sista F, Cecilia EM, Amicucci G. Peritonitis from perforated peptic ulcer and immune response. *J Invest Surg* 2013; **26**: 294–304.
- 82 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535.
- 83 Kuwabara K, Matsuda S, Fushimi K, Ishikawa KB, Horiguchi H, Fujimori K. Community-based evaluation of laparoscopic *versus* open simple closure of perforated peptic ulcers. *World J Surg* 2011; **35**: 2485–2492.
- 84 Sauerland S, Agresta F, Bergamaschi R, Borzellino G, Budzynski A, Champault G *et al.* Laparoscopy for abdominal emergencies: evidence-based guidelines of the European Association for Endoscopic Surgery. *Surg Endosc* 2006; **20**: 14–29.
- 85 Agresta F, Ansaloni L, Baiocchi GL, Bergamini C, Campanile FC, Carlucci M. Laparoscopic approach to acute abdomen from the Consensus Development Conference of the Societa Italiana di Chirurgia Endoscopica e nuove tecnologie (SICE), Associazione Chirurghi Ospedalieri Italiani (ACOI), Societa Italiana di Chirurgia (SIC), Societa Italiana di Chirurgia d'Urgenza e del Trauma (SICUT), Societa Italiana di Chirurgia nell'Ospedality Privata (SICOP), and the European Association for Endoscopic Surgery (EAES). *Surg Endosc* 2012; **26**: 2134–2164.
- 86 Critchley AC, Phillips AW, Bawa SM, Gallagher PV. Management of perforated peptic ulcer in a district general hospital. *Ann R Coll Surg Engl* 2011; **93**: 615–619.
- 87 Karamanakos SN, Sdralis E, Panagiotopoulos S, Kehagias I. Laparoscopy in the emergency setting: a retrospective review of 540 patients with acute abdominal pain. *Surg Laparosc Endosc Percutan Tech* 2010; **20**: 119–124.
- 88 Lunevicius R, Morkevicius M. Management strategies, early results, benefits, and risk factors of laparoscopic repair of perforated peptic ulcer. *World J Surg* 2005; **29**: 1299–1310.
- 89 Lee FY, Leung KL, Lai PB, Lau JW. Selection of patients for laparoscopic repair of perforated peptic ulcer. *Br J Surg* 2001; **88**: 133–136.
- 90 Bertleff MJ, Liem RS, Bartels HL, Robinson PH, Van der Werff JF, Bonjer HJ. The 'stamp method': a new treatment for perforated peptic ulcer? *Surg Endosc* 2006; **20**: 791–793.
- 91 Lam PW, Lam MC, Hui EK, Sun YW, Mok FP. Laparoscopic repair of perforated duodenal ulcers: the 'three-stitch' Graham patch technique. *Surg Endosc* 2005; **19**: 1627–1630.
- 92 Swahn F, Arnelo U, Enochsson L, Löhr M, Agustsson T, Gustavsson K *et al.* Endoscopic closure of a perforated peptic ulcer. *Endoscopy* 2011; **43**(Suppl 2 UCTN): E28–E29.
- 93 Moran EA, Gostout CJ, McConico AL, Michalek J, Huebner M, Bingener J *et al.* Assessing the invasiveness of NOTES perforated viscus repair: a comparative study of NOTES and laparoscopy. *Surg Endosc* 2012; **26**: 103–109.
- 94 Bonin EA, Moran E, Gostout CJ, McConico AL, Zielinski M, Bingener J. Natural orifice transluminal endoscopic surgery for patients with perforated peptic ulcer. *Surg Endosc* 2012; **26**: 1534–1538.
- 95 Wong PF, Gilliam AD, Kumar S, Shenfine J, O'Dair GN, Leaper DJ. Antibiotic regimens for secondary peritonitis of gastrointestinal origin in adults. *Cochrane Database Syst Rev* 2005; (2)CD004539.
- 96 Sartelli M, Catena F, Coccolini F, Pinna AD. Antimicrobial management of intra-abdominal infections: literature's guidelines. *World J Gastroenterol* 2012; **18**: 865–871.
- 97 Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ *et al.* Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010; **11**: 79–109.
- 98 Augustin P, Kermarrec N, Muller-Serieys C, Lasocki S, Chosidow D, Marmuse JP *et al.* Risk factors for multidrug resistant bacteria and optimization of empirical antibiotic therapy in postoperative peritonitis. *Crit Care* 2010; **14**: R20.
- 99 Shan YS, Hsu HP, Hsieh YH, Sy ED, Lee JC, Lin PW *et al.* Significance of intraoperative peritoneal culture of fungus in perforated peptic ulcer. *Br J Surg* 2003; **90**: 1215–1219.
- 100 Prakash A, Sharma D, Saxena A, Somashekar U, Khare N, Mishra A *et al.* Effect of *Candida* infection on outcome in patients with perforation peritonitis. *Indian J Gastroenterol* 2008; **27**: 107–109.
- 101 Eggimann P, Francioli P, Bille J, Schneider R, Wu MM, Chapuis G *et al.* Fluconazole prophylaxis prevents

- intra-abdominal candidiasis in high-risk surgical patients. *Crit Care Med* 1999; **27**: 1066–1072.
- 102 Lipsett PA. Surgical critical care: fungal infections in surgical patients. *Crit Care Med* 2006; **34**(Suppl): S215–S224.
- 103 Gilliam AD, Speake WJ, Lobo DN, Beckingham IJ. Current practice of emergency vagotomy and *Helicobacter pylori* eradication for complicated peptic ulcer in the United Kingdom. *Br J Surg* 2003; **90**: 88–90.
- 104 Nuhu A, Madziga AG, Gali BM. Acute perforated duodenal ulcer in Maiduguri: experience with simple closure and *Helicobacter pylori* eradication. *West Afr J Med* 2009; **28**: 384–387.
- 105 Ugochukwu AI, Amu OC, Nzegwu MA, Dilibe UC. Acute perforated peptic ulcer: on clinical experience in an urban tertiary hospital in south east Nigeria. *Int J Surg* 2013; **11**: 223–227.
- 106 Chalya PL, Mabula JB, Koy M, McHembe MD, Jaka HM, Kabangila R *et al.* Clinical profile and outcome of surgical treatment of perforated peptic ulcers in northwestern Tanzania: a tertiary hospital experience. *World J Emerg Surg* 2011; **6**: 31.
- 107 El-Nakeeb A, Fikry A, Abd El-Hamed TM, Fouda el Y, El Awady S, Youssef T *et al.* Effect of *Helicobacter pylori* eradication on ulcer recurrence after simple closure of perforated duodenal ulcer. *Int J Surg* 2009; **7**: 126–129.
- 108 Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. *Lancet* 2009; **374**: 1449–1461.
- 109 Hernández-Díaz S, Martín-Merino E, García Rodríguez LA. Risk of complications after a peptic ulcer diagnosis: effectiveness of proton pump inhibitors. *Dig Dis Sci* 2013; **58**: 1653–1662.
- 110 Saber A, Gad MA, Ellabban GM. Perforated duodenal ulcer in high risk patients: is percutaneous drainage justified? *N Am J Med Sci* 2012; **4**: 35–39.
- 111 Bucher P, Oulhaci W, Morel P, Ris F, Huber O. Results of conservative treatment for perforated gastroduodenal ulcers in patients not eligible for surgical repair. *Swiss Med Wkly* 2007; **137**: 337–340.
- 112 Oida T, Kano H, Mimatsu K, Kawasaki A, Kuboi Y, Fukino N *et al.* Percutaneous drainage in conservative therapy for perforated gastroduodenal ulcers. *Hepatogastroenterology* 2012; **59**: 168–170.
- 113 Larkin JO, Bourke MG, Muhammed A, Waldron R, Barry K, Eustace PW. Mortality in perforated duodenal ulcer depends upon pre-operative risk: a retrospective 10-year study. *Ir J Med Sci* 2010; **179**: 545–549.
- 114 Dascalescu C, Andriescu L, Bulat C, Danila R, Dodu L, Acornicesei M *et al.* Taylor's method: a therapeutic alternative for perforated gastroduodenal ulcer. *Hepatogastroenterology* 2006; **53**: 543–546.
- 115 Berne TV, Donovan AJ. Nonoperative treatment of perforated duodenal ulcer. *Arch Surg* 1989; **124**: 830–832.
- 116 Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; **41**: 580–637.
- 117 Vester-Andersen M, Waldau T, Wetterslev J, Møller MH, Rosenberg J, Jørgensen LN *et al.* Effect of intermediate care on mortality following emergency abdominal surgery. The InCare trial: study protocol, rationale and feasibility of a randomised multicentre trial. *Trials* 2013; **14**: 37.
- 118 Surapaneni S, Rajkumar S, Reddy AVB. The perforation–operation time interval; an important mortality indicator in peptic ulcer perforation. *J Clin Diagn Res* 2013; **7**: 880–882.
- 119 Ben-Ishay O, Bahouth H, Kluger Y. Perforated peptic ulcer: determinants of outcome and mortality. *J Emerg Trauma Shock* 2013; **6**: 61.
- 120 Montalvo-Javé EE, Corres-Sillas O, Athié-Gutiérrez C. Factors associated with postoperative complications and mortality in perforated peptic ulcer. *Cir Cir* 2011; **79**: 141–148.
- 121 Buck DL, Vester-Andersen M, Møller MH; Danish Clinical Register of Emergency Surgery. Surgical delay is a critical determinant of survival in perforated peptic ulcer. *Br J Surg* 2013; **100**: 1045–1049.
- 122 Chan WH, Wong WK, Khin LW, Soo KC. Adverse operative risk factors for perforated peptic ulcer. *Ann Acad Med Singapore* 2000; **29**: 164–167.
- 123 Bae S, Shim KN, Kim N, Kang JM, Kim DS, Kim KM *et al.* Incidence and short-term mortality from perforated peptic ulcer in Korea: a population-based study. *J Epidemiol* 2012; **22**: 508–516.
- 124 Su YH, Yeh CC, Lee CY, Lin MW, Kuan CH, Lai IR *et al.* Acute surgical treatment of perforated peptic ulcer in the elderly patients. *Hepatogastroenterology* 2010; **57**: 1608–1613.
- 125 Sweeney KJ, Faolain MO, Gannon D, Gorey TF, Kerin MJ. Surgical management of perforated peptic ulcer disease. *Ir J Med Sci* 2006; **175**: 50–54.
- 126 Maghsoudi H, Ghaffari A. Generalized peritonitis requiring re-operation after leakage of omental patch repair of perforated peptic ulcer. *Saudi J Gastroenterol* 2011; **17**: 124–128.
- 127 Lynn JJ, Weng YM, Weng CS. Perforated peptic ulcer associated with abdominal compartment syndrome. *Am J Emerg Med* 2008; **26**: 1071.e3–e5.
- 128 Gupta V, Singh SP, Pandey A, Verma R. Study on the use of T-tube for patients with persistent duodenal fistula: is it useful? *World J Surg* 2013; **37**: 2542–2545.
- 129 Duggan JM, Zinsmeister AR, Kelly KA, Melton LJ III. Long-term survival among patients operated upon for peptic ulcer disease. *J Gastroenterol Hepatol* 1999; **14**: 1074–1082.
- 130 Svanes C, Lie SA, Lie RT, Sørdeide O, Svanes K. Causes of death in patients with peptic ulcer perforation: a long-term follow-up study. *Scand J Gastroenterol* 1999; **34**: 18–24.
- 131 Møller MH, Vester-Andersen M, Thomsen RW. Long-term mortality following peptic ulcer perforation in

- the PULP trial. A nationwide follow-up study. *Scand J Gastroenterol* 2013; **48**: 168–175.
- 132 Søreide K, Alderson D, Bergenfelz A, Beynon J, Connor S, Deckelbaum DL *et al.* Strategies to improve clinical research in surgery through international collaboration. *Lancet* 2013; **382**: 1140–1151.
- 133 Mackenbach JP, Karanikolos M, McKee M. The unequal health of Europeans: successes and failures of policies. *Lancet* 2013; **381**: 1125–1134.
- 134 US Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA* 2013; **310**: 591–608.
- 135 Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M *et al.* Rapid health transition in China, 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **381**: 1987–2015.
- 136 Alonge V, Codd MB. Gastrointestinal diseases: projected burden of care on acute public hospitals. *Ir Med J* 2013; **106**: 47–50.
- 137 Al-Temimi MH, Griffée M, Enniss TM, Preston R, Vargo D, Overton S *et al.* When is death inevitable after emergency laparotomy? Analysis of the American College of Surgeons National Surgical Quality Improvement Program database. *J Am Coll Surg* 2012; **215**: 503–511.
- 138 Yaghoubian A, Ge P, Tolan A, Saltmarsh G, Kaji AH, Neville AL *et al.* Renal insufficiency predicts mortality in geriatric patients undergoing emergent general surgery. *Am Surg* 2011; **77**: 1322–1325.
- 139 Duron JJ, Duron E, Dugue T, Pujol J, Muscari F, Collet D *et al.* Risk factors for mortality in major digestive surgery in the elderly: a multicenter prospective study. *Ann Surg* 2011; **254**: 375–382.