



Trends in Perforated Peptic Ulcer: Incidence, Etiology, Treatment, and Prognosis

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Abstract. After increasing steeply at the beginning of the twentieth century, ulcer perforation incidence during the last decades has declined in the young and in men, and it has risen among the elderly and in women. These changes can be attributed to a cohort phenomenon: Ulcer perforation risk is particularly common in the cohorts born after the turn of the twentieth century and is less common in previous and succeeding birth cohorts. A decline in total incidence is expected with the death of the high risk cohorts. Most ulcer perforations among subjects < 75 years of age can be attributed to smoking. Subjects with a history of ulcer perforation therefore have poorer long-term survival than the general population, most pronounced for younger generations. About one of four ulcer perforations can be attributed to the use of nonsteroidal antiinflammatory drugs, a risk factor of particular importance in the elderly. Ulcer perforation was frequently treated by gastric resection in former days, whereas suture, being the first method introduced in 1887, is the method of choice today. The introduction of antibiotics improved the prognosis of ulcer perforation surgery greatly. Postoperative lethality decreased until 1950 but has remained stable since then. Lethality is higher in the elderly and is higher after gastric than after duodenal perforation. The delay before surgical treatment is a strong determinant for lethality, complication rates, and hospital costs. Treatment delay seems to have increased during the last few decades and is higher among women and the elderly. The prognosis of ulcer perforation is poorer in women owing to longer treatment delay.

Crisp's description of a perforated ulcer from 1843 [1] would fit into any modern textbook as far as the symptomatology is concerned. However, other features of the disease and of the patients affected have changed markedly since then. During the nineteenth century ulcer perforation was a rare disease that occurred mainly in young women, with the perforations located near the cardia of the stomach [1–3]. During the first decades of the twentieth century ulcer perforation incidence increased greatly, and there was an epidemic of ulcer perforations situated in the duodenum of middle-aged men [2–12]. Today ulcer perforation incidence is stable or tends to decline, and most patients with ulcer perforations are elderly men and women, with perforations in the prepyloric and pyloric areas as frequent as perforations in the duodenum [12–16].

Ulcer perforation was a lethal disease until surgical treatment was introduced at the turn of the century. Mikulicz sutured a perforated gastric ulcer for the first time in 1880 [17], and suture is still the most common treatment for ulcer perforation. The revolution in ulcer treatment that occurred with discovery of the role of *Helicobacter pylori* [18] has not yet led to any detectable changes in incidence or treatment of ulcer perforation. Thus ulcer

perforation is still a surgical disease for which the possibility for improvement in prognosis lies with the general advances of acute surgery. The potential for prevention lies in better understanding of causal factors, which have not been known until lately [19] but apparently differ somewhat from those of uncomplicated ulcer [20].

Incidence

A rare disease during the nineteenth century, ulcer perforation incidence increased greatly at the turn of the twentieth century. Since then the Western world has seen an epidemic of duodenal perforations among young men that now seems to be waning. Ulcer perforation incidence has been studied over an extended period in western Scotland (1924–1963) [7–10], the United Kingdom (1958–1983) [21, 22], and western Norway (1935–1990) (Fig. 1) [12]. These studies show fairly similar trends. In men, ulcer perforation incidence increased until about 1950 [7–10, 12] and declined thereafter [12, 21]. In women the incidence was low and fairly stable until about 1950 [7–9, 12], from which time it slowly increased [10, 12, 21]. Increasing age among ulcer perforation patients has been observed during this time span, with declining incidence among the young and increasing incidence among the elderly [10, 12, 22]. Most of this temporal variation could be attributed to changing rates of duodenal ulcer in men [10, 12], whereas rates of gastric ulcer perforation appear to have been fairly stable [12, 21]. Site-specific incidences during the period 1935–1990 in western Norway are presented in Figure 2.

Birth Cohort Patterns

The temporal changes in ulcer perforation incidence can be explained by a cohort phenomenon where disease risk follows particular birth cohorts. This has been shown in studies from Norway covering the period 1935–1990 and including subjects born between 1870 and 1970 [12] and from Iceland during the period 1962–1990 with subjects born during 1890–1960 [23]. Subjects born after the turn of the twentieth century carried a high risk for ulcer perforation throughout their lives, whereas subjects born before the turn of the twentieth century and more recent birth cohorts showed a lower incidence during the studied age spans (Fig. 3) [12]. A similar pattern was indicated for both men and women and for all ulcer locations. The age pattern of ulcer

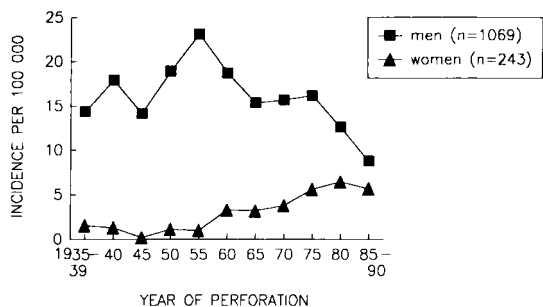


Fig. 1. Incidence of ulcer perforation among men and women in western Norway between 1935 and 1990.

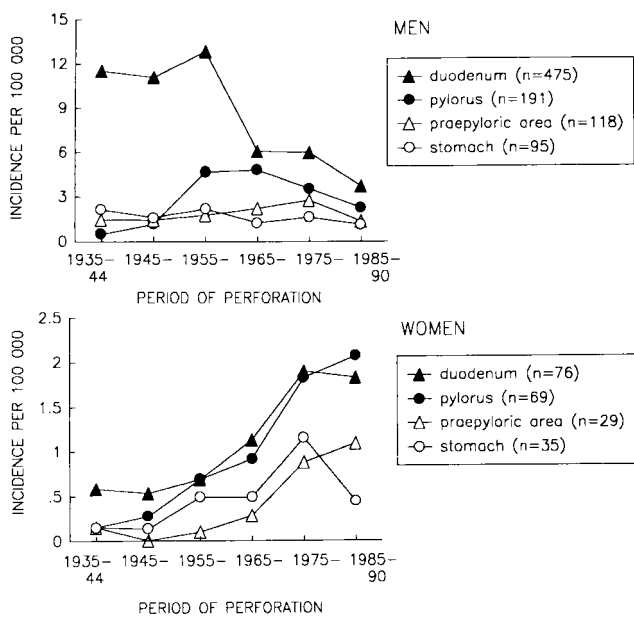


Fig. 2. Incidence of ulcer perforation in western Norway by ulcer site from 1935 to 1990. (From Svanes et al. [12], with permission.)

perforation during the life-span, however, seemed to differ between men and women. In men the incidence was highest during middle-age and old age, whereas women tended to have ulcer perforation after the age of menopause [12]. Women thus seem to be protected from ulcer perforation during their reproductive period.

Aging of the high risk cohorts can explain the increase in age observed for ulcer perforation patients over the last few decades. The incidence in men seemed to decline concurrently with the death of the high risk birth cohorts. The women of the high risk birth cohorts are now getting old and reaching the age of maximum risk, explaining the current increase in incidence among elderly women. We can possibly expect declining rates of ulcer perforation when the high risk female generations die as well, although the decrease in risk for the more recent female cohorts is not entirely convincing owing to the low incidence among women of the ages these cohorts have reached.

Time trends of ulcer perforation has been attempted compared with time trends in the use of nonsteroidal antiinflammatory drugs (NSAIDs) and smoking in the population. In Norway, use of

NSAIDs was not related to time trends in ulcer perforation [12], consistent with similar studies of other ulcer manifestations [24, 25] probably because this causal factor is not common enough to influence population rates. The cohort pattern of smoking, however, could partly explain the time trends in ulcer perforation, even though ulcer perforation followed a more consistent cohort pattern than did smoking rates [12].

Birth cohort patterns have also been shown for peptic ulcer mortality. Susser and Stein showed in 1962 that peptic ulcer mortality in the United Kingdom followed birth cohorts [26], a finding that later was supported by other studies [27, 28]. All these studies show that ulcer mortality increased for successive generations until a turning point, after which mortality declined. Ulcer mortality is, however, somewhat less suitable for such analysis than incidence data, as lethality has changed over time [13].

Biorhythms of Ulcer Perforation

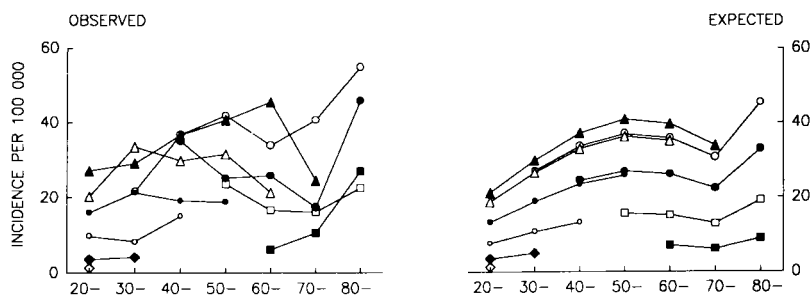
Owing to the typical acute and dramatic onset of ulcer perforation, the hour of the day when the ulcer perforation occurred can be assessed. Through decades with major epidemiologic changes in ulcer perforation, a consistent daily variation in the acute onset of ulcer perforation has been reported from various countries and periods of time [4-10, 13, 29-32]. A pronounced circadian variation of ulcer perforation with greater incidence during the day and lower incidence during late night was described as early as 1903 [29]; it does not seem to have changed since this first report [30]. The circadian pattern seemed to differ between gastric and duodenal perforations [30, 31], with duodenal perforations showing peak incidence during the afternoon and evening, and gastric perforations showing a primary peak around midday and a secondary peak around midnight (Fig. 4). These differences possibly relate to the differences in acid secretion by patients with gastric and duodenal ulcers [30].

Etiology of Ulcer Perforation

Smoking seem to be a risk factor of major importance for ulcer perforation [19-20, 33, 34]. A study from Norway showed a strong association between ulcer perforation and smoking [19]. The risk was increased by a factor of 10 in smokers among both men and women. It was estimated that smoking might account for 77% of all ulcer perforations in the age group younger than 75 years. In the older population, however, smoking seemed to be of much less importance. A major role of smoking in the etiology of ulcer perforation is also supported by studies reporting smoking prevalences of 84% and 86% among ulcer perforation patients [20, 33]. Furthermore, Doll et al. [34] showed that smokers had a threefold higher mortality due to peptic ulcer than nonsmokers, and excess mortality in ulcer perforation survivors can be attributed to smoking-related diseases (C. Svanes, unpublished data).

Use of NSAIDs is another well documented, important risk factor for ulcer perforation. Five to eight times increased ulcer perforation risk has been reported for NSAID users [35-37]. However, use of NSAIDs is not as common in the population as is smoking and thus accounts for a smaller number of perforations. One can estimate that NSAIDs may contribute to one-fifth to one third of ulcer perforations, the proportion increasing with increasing age [38].

MEN



WOMEN

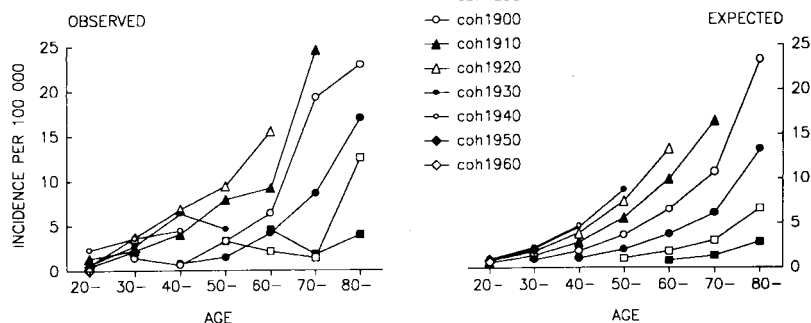


Fig. 3. Incidence of ulcer perforation in western Norway by age and year of birth for men and women born between 1870 and 1969. (From Svanes et al. [12], with permission.)

A major role of *Helicobacter pylori* infection in ulcer perforation cannot be confirmed. Reinbach et al. showed similar frequencies of *H. pylori* (HP) in patients with acute duodenal perforations and in hospital controls [20]. A study from the Arab Emirates showed that 24 of 29 patients with ulcer perforation were HP-positive (¹³C urea breath test) 8 days after operation, but population data were not available [39]. In an ongoing study in Bergen, Norway, 67% of ulcer perforation patients were HP-positive (serology) at the time of perforation and 37% were HP-positive (¹³C urea breath test) 8 weeks after ulcer perforation surgery [40]. Thus ulcer perforation seem to differ from uncomplicated ulcer with regard to the importance of *H. pylorii* infection.

Treatment

The surgical treatment of perforated ulcer dates from the year 1880, when Mikulicz sutured a perforated gastric ulcer for the first time [17]. Suture is still the method of choice for surgical treatment of ulcer perforation [13]. The first two cases of primary gastric resection for ulcer perforation was described by von Haberer as early in 1919 [41]. The method was used extensively for several decades [13] but is now rarely used for treatment of ulcer perforation. During the 1970s and 1980s suture supplemented with vagotomy was an alternative surgical procedure [42, 43]. Conservative management of ulcer perforation as an alternative to surgery in selected patients was first advocated by Taylor in 1946 [44]. Series practicing such treatment have reported amazingly good results, with lethality rates of 5% to 11% [44–46]. This treatment strategy, however, has never been accepted generally.

When antibiotics came into general use around 1950, markedly reduced rates of postoperative complications and deaths after

ulcer perforation were observed (Fig. 5) [13, 47]. Use of antibiotics is today standard treatment with ulcer perforation surgery.

As recognized from the first years of surgical treatment, the duration of perforation is an important treatment aspect [48]. In older studies (1939–1953) the time from perforation to operation was short (median values up to 6 hours), reported by Yudine [4], DeBakey [5, 6], and Noordijk [11]. Far longer treatment delays are reported in more recent studies (1980–1990) (median values ranging from 12 to > 24 hours); reported by Mattingly et al. [49], Boey et al. [50], Irvin [51], Bodner et al. [14], and Gunshefski et al. [15]. A study from Norway showed a steady increase in treatment delay during the period 1935–1990, reflecting an increase in in-hospital delay whereas preadmission delay was stable [52]. This increase could be partly attributed to more extensive preoperative diagnostic effort [53], aging of the patients, and a larger proportion of female patients. Delay was longer during regular working hours than at other times of the day, and treatment delay was particularly long among women and elderly patients [52].

Prognosis

Ulcer perforation was a lethal disease until the turn of the twentieth century when surgical treatment was introduced [2, 3]. The first patients treated by Mikulicz died [17], but in 1896 Barker reported a series where three of seven patients operated on for ulcer perforation recovered [48]. For patients treated during the years 1920–1950, lethality rates around 20% were reported [4–8, 11, 47]. In reports of patients treated after 1950, lethality ranges from 5% to 24% [14–16, 43, 47, 51, 54–57]. A study from western

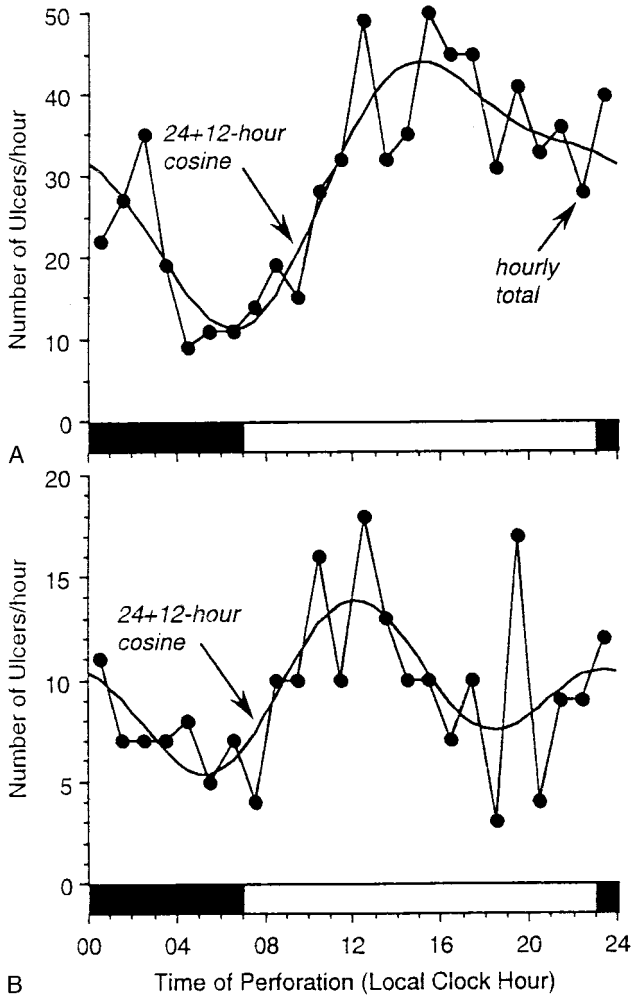


Fig. 4. Numbers of duodenal ulcer ($n = 707$) (A) and gastric ulcer ($n = 224$) (B) perforations in western Norway by hour of the day. (Reprinted from Svanes et al. [30], with permission, by courtesy of Marcel Dekker, Inc.)

Norway, covering the period 1935–1990, reported a decrease in lethality from 1935 to 1950 after which time lethality was stable until it increased slightly during the last decade (Fig. 5) [47]. Thus surgical treatment and treatment with antibiotics revolutionized the prognosis of ulcer perforation.

The prognosis of ulcer perforation today, given surgical treatment accompanied by use of antibiotics, is determined by the patient's age, the site of the perforation, and the delay in treatment [47, 58]. The last factor is the only one that can be modulated by good clinical practice and is thus of particular interest. Risk for postoperative death and complications is closely related to duration of perforation, as demonstrated in several studies [4–6, 11, 58, 59]. Adverse effects seem to increase particularly when the delay exceeds 12 hours [58]. Delay of more than 24 hours increased lethality seven- to eightfold, the complication rate threefold, and the length of hospital stay twofold in a study from western Norway (Fig. 6) [58]. The prognosis after ulcer perforation is reported to be poorer in women than in men [54, 60] owing

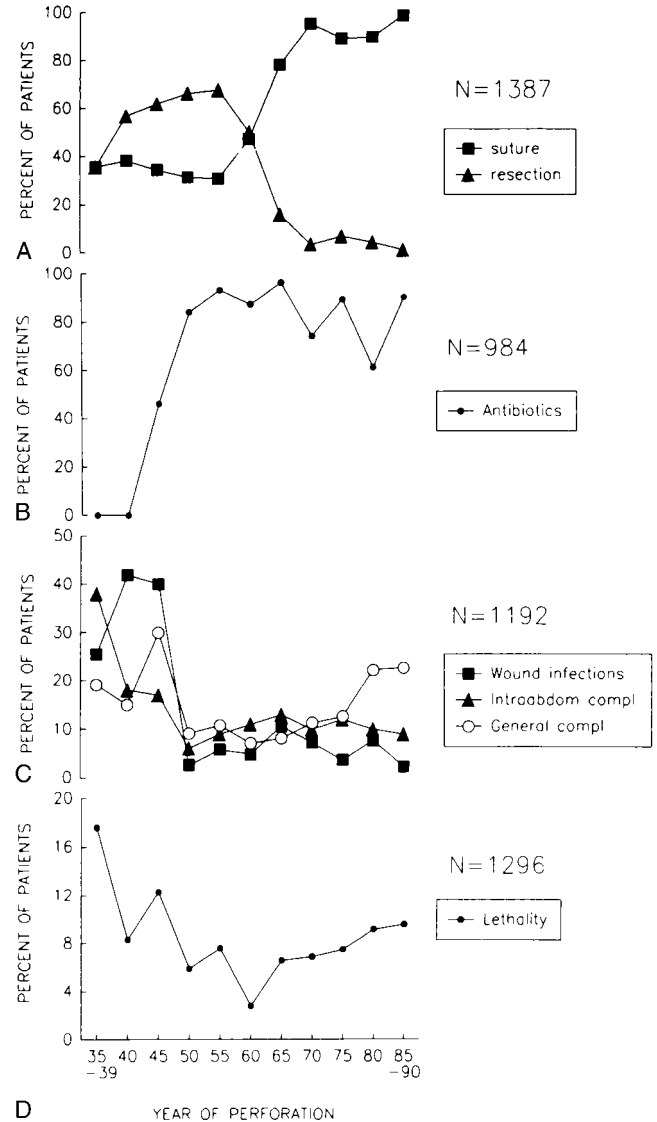


Fig. 5. Surgical procedure (A), use of antibiotics (B), postoperative complications (C), and lethality (D) after ulcer perforation during the period 1935–1990 in western Norway.

to a longer delay in treatment [60]. The increase in treatment delay that appear to take place in the Western world is thus of great concern. Surgical emergencies other than ulcer perforation may be affected as well, and the efficiency of modern emergency care needs attention.

In the long run, subjects with a history of ulcer perforation have a lower survival rate than the general population [60]. Long-term survival in ulcer perforation patients compared to the general population was poorer in recent birth cohorts than in earlier birth cohorts [60]. Lower survival is not due to excess ulcer mortality, as peptic ulcer is a rare cause of death in ulcer patients. However, poorer survival in ulcer perforation survivors seem to be related to excess mortality due to smoking-related disorders (C. Svanes, unpublished data). Similar findings have been reported for subjects who survived a bleeding ulcer [61] and for patients treated with elective ulcer surgery [62–64].

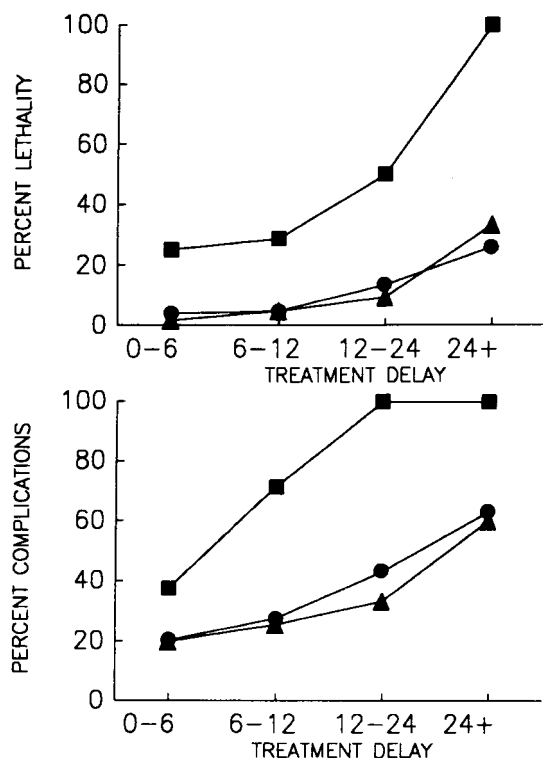


Fig. 6. Lethality and complication rates after ulcer perforation according to the treatment delay during the periods 1935–1950 (squares), 1951–1970 (triangles), and 1971–1990 (circles) in western Norway. (From Svanes et al. [58], with permission.)

Conclusions

Ulcer perforation epidemiology has changed greatly throughout this century, largely owing to an epidemic of ulcer perforation in specific birth cohorts. Subjects born after the turn of the century have carried a high risk for ulcer perforation throughout their lives. The increasing ulcer perforation risk among the elderly today is related to aging of these high risk cohorts; in younger generations the incidence is decreasing. Thus ulcer perforation appears to be a slowly vanishing disease in our society.

The distinct cohort phenomenon suggests that factors during early life contribute to determining susceptibility to ulcer perforation throughout adult life. Age-related vulnerability to *H. pylori* infection has been suggested as a possible early life factor of importance. Smoking seems to be a causal factor of major importance for ulcer perforation today, and a smaller proportion of ulcer perforations seem to be related to the use of NSAIDs.

When it comes to treatment of ulcer perforation, modern times have allowed treatment of elderly patients with associated severe diseases—the ulcer perforation patients we usually meet today. However, lethality after ulcer perforation is still relatively high, representing a potential for improvement. There are indications that modern health care, with many professional groups involved and extensive possibilities for preoperative diagnostic measures available, is hampered by time-consuming routines. With ulcer perforation the prognosis is clearly related to efficiency of treatment; limiting the treatment delay to within 12 hours is likely to improve life expectancy after ulcer perforation.

Prevention of ulcer perforation can only be obtained through

smoking prevention. This is an area that may be of greater importance for ulcer surgery than *H. pylori* eradication.

Résumé

Après une augmentation au début de ce siècle, l'incidence de la perforation d'ulcère a diminué chez le sujet jeune et masculin, alors qu'elle a continué d'augmenter chez les plus âgés et chez la femme. On peut attribuer ces changements à un phénomène de cohorte. Le risque de perforation d'ulcère étant particulièrement élevé dans les cohortes nées après le début du siècle, il est moins élevé dans les cohortes nées avant ou après cette période. On peut s'attendre à une diminution de l'incidence globale lorsque les cohortes à haut risque disparaîtront. La plupart des perforations d'ulcère parmi les sujets de <75 peuvent être attribuées au tabac. Les sujets ayant une histoire de perforation ont une survie à long terme moins bonne que celle de la population en générale, surtout chez les sujets jeunes. Environ 25% de ces ulcères sont en rapport avec l'utilisation des AINS, un facteur de risque particulièrement élevé chez le sujet âgé. Autrefois, la perforation d'ulcère a été traitée le plus souvent par la résection gastrique, alors que la suture, méthode introduite en 1887, est la méthode de choix aujourd'hui. L'introduction des antibiotiques a beaucoup amélioré le pronostic de la perforation d'ulcère. La mortalité postopératoire a diminué jusqu'en 1950, mais, depuis, elle est restée stable. La mortalité est plus élevée chez le sujet âgé; elle est plus élevée également pour les perforations d'ulcères gastriques par rapport aux perforations duodénales. Le délai entre la perforation et le traitement chirurgical est un facteur primordial pour la mortalité, les taux de complications et les coûts hospitaliers. Il semble que le délai entre le diagnostic et le traitement ait augmenté depuis quelques décennies, et qu'il soit plus important chez la femme et dans la population plus âgée. Le pronostic de perforation d'ulcère est plus mauvais chez la femme en raison de ce délai dans le traitement.

Resumen

Tras un abrupto crecimiento a principios de siglo de la frecuencia de las úlceras perforadas, durante las últimas décadas se ha producido una disminución de esta complicación en jóvenes y en hombres, aumentándose la incidencia en los viejos y en mujeres. Estos cambios pueden atribuirse a un conjunto de fenómenos. El riesgo de perforación es más frecuente en cohortes de pacientes nacidos a principios de siglo y menos frecuente en las series de pacientes nacidos antes o después. Se espera una disminución de la incidencia total de esta complicación con la desaparición por muerte de estas series de alto riesgo. Muchas de las úlceras perforadas en sujetos menores de 75 años pueden referirse al tabaco (fumadores). Individuos con historia de úlcera perforada tienen una menor supervivencia a largo plazo, que la población general, siendo este hecho más pronunciado para las generaciones jóvenes. Una de cada cuatro úlceras perforadas se debe al consumo de NSAIDs, medicación que constituye un factor de riesgo muy importante, sobre todo en el viejo. Hace unos cuantos años, la úlcera perforada se trataba casi siempre mediante resección gástrica; en la actualidad, la sutura simple de la perforación introducida en la Técnica quirúrgica en 1887, constituye el tratamiento de elección. La utilización de antibióticos ha mejorado extraordinariamente el pronóstico de la

perforación de la úlcera péptica. La mortalidad postoperatoria decreció hasta el año 1950, permaneciendo estable desde esta fecha. La mortalidad es mayor en el viejo y en los casos de perforación gástrica que en las perforaciones duodenales. Todo retraso en el tratamiento quirúrgico implica una mayor morbimortalidad y aumento de los costos hospitalarios. El retraso en la intervención quirúrgica parece haber aumentado en las últimas décadas, sobre todo en los viejos y en las mujeres, en estas últimas por diferirse más el tratamiento quirúrgico.

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