Epidemiology of Digestive Diseases

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W. Ahrens, I. Pigeot (eds.) *Handbook of Epidemiology, 2nd edition*,
DOI 10.1007/978-0-387-09834-0_49,

58.1 Introduction

The most obvious characteristic of digestive disease epidemiology is diversity. Most other clinical specialties deal with one or a limited number of organs each, and within these specialties, certain diseases feature much more prominently than others. In contrast, the digestive system comprises all parts of the alimentary canal from the esophagus to the anus, several solid organs (liver and pancreas), the biliary tree, and the intra-abdominal fascial structures (mesentery, peritoneum) (Fig. 58.1). As the organs are manifold, so are the ways in which they may be affected by disease – structural, inflammatory, cancerous, functional, psychosomatic, endocrine, toxic/drug induced – the list is non-exhaustive. None of the digestive diseases are so prevalent as to dominate the specialty. Rather, the most common 10 diseases taken together represent only 20% of the total prevalence of the digestive diseases (Everhart and Ruhl 2009a). The remaining 80% are spread out over a large number of less frequent diseases.

Similarly, in digestive disease epidemiology, most epidemiological methods may be applicable. Infection and vaccination, genetic epidemiology, cancer and screening, public health and prevention, nutrition, environment, clinical epidemiology including diagnosis, prognosis and therapy, health economics, pharmacoepidemiology all are relevant issues in gastroenterology. In short, digestive disease epidemiology offers a particularly wide scope of diseases and methods.

Conferences and textbooks of epidemiology rarely feature explicit sections on digestive disease epidemiology. More often, selected topics emerge in other contexts, such as risk factors for colorectal cancer in cancer epidemiology, *H. pylori* transmission in infectious disease epidemiology, and diarrhea prevention

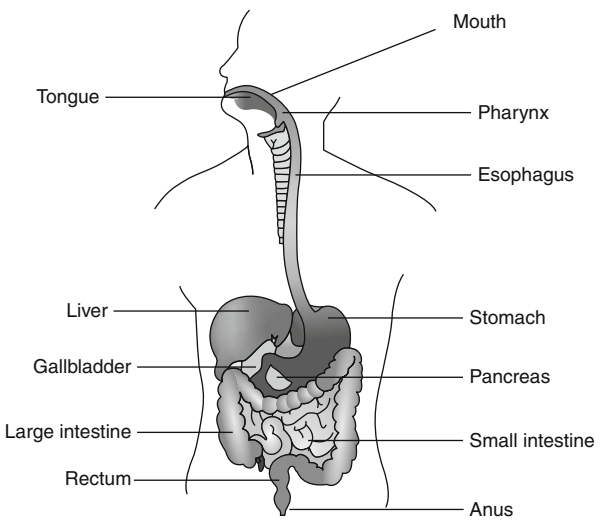

Fig. 58.1 Organs of the digestive system. Courtesy of David Darling, http://www.daviddarling.info/encyclopedia/D/digestive_system.html

and control in developing countries epidemiology. A substantial body of the digestive disease epidemiology literature is generated by clinical or bench-based researchers who have never attended an epidemiology course or conference. Putting this together in a comprehensive way is beyond the scope of a single chapter. Rather, we will highlight a few topics we feel are interesting or of prominent public health relevance. Others are chosen because they hide pitfalls which may evade the epidemiologist not familiar with the clinical aspects of these diseases. For a more comprehensive approach, we refer the interested reader to a book on gastrointestinal epidemiology (Talley et al. 2007).

Following an introduction into the scope and approaches used in digestive disease epidemiology, we will first discuss the relative frequency and burden of digestive diseases, including trends over time (Sect. 58.3). We will move from a global perspective to the descriptive epidemiology of several specific problems representing the main organ groups within the digestive tract. Care has been taken to focus on exemplary, common problems, such as viral Hepatitis and related liver disease, the more common gastrointestinal cancer sites, the inflamed bowel, and functional diseases.

In the fourth section, etiological aspects will be described, covering genetics, poverty-related factors, and behavioral risk factors. *H. pylori* infection will be discussed, as this is maybe the most important discovery in gastroenterology in the last century.

A special section will be devoted to clinical epidemiology, as this field features particularly strong in digestive disease epidemiology. All sections will be illustrated by a number of examples. We will start with an overview on the descriptive epidemiology of digestive diseases.

58.2 Scope and Approaches

Epidemiology of digestive diseases deals with the frequency, distribution, risk factors, clinical behavior, and management of diseases of the digestive tract. Internationally, concepts of what belongs to the corresponding clinical specialty of gastroenterology vary. The main categories as listed in ICD 10 (World Health Organization 2007; http://www.who.int/classifications/icd/en/) are shown in Table 58.1. For this chapter, we will include aspects of the epidemiology of the liver (hepatology) along with diseases of the upper gastrointestinal tract, bowel, and pancreas but exclude metabolic disease, in particular diabetes, and disorders of the oral cavity.

As there is no tradition of digestive disease epidemiology which might have driven specific methods, we will focus on the descriptive epidemiology of several of the more common disorders, risk factor associations, and some observations on the success of preventive measures. For more detailed methodological aspects, we refer the readers to other chapters of this handbook.

Table 58.1 Diseases of the digestive system

ICD 10	Disease
A00–A09	Intestinal infectious diseases
B15–B19	Viral Hepatitis
C15–C26	Malignant neoplasms of the digestive organs
D00, D01, D12, D13, D27	In situ neoplasms, benign neoplasms, unknown behavior of oral cavity and digestive organs
C15–C26	Malignant neoplasms of the digestive organs
K20–K31	Diseases of esophagus, stomach, and duodenum
K35–K38	Diseases of appendix
K40–K46	Hernia
K50–K52	Non-infective enteritis and colitis
K55–K63	Other diseases of intestines
K65–K67	Diseases of peritoneum
K70–K77	Diseases of liver
K80–K87	Disorders of gallbladder, biliary tract, and pancreas
K90–K93	Other diseases of the digestive system

58.3 Global Burden of Digestive Diseases

58.3.1 Overview

The burden of digestive diseases varies worldwide. In the developing world, infectious diseases, including diarrhea and viral Hepatitis, as well as cancer of the liver, are major problems. In the West, functional diseases are more prevalent. With the exception of infectious diseases and cancers of the digestive tract, there are few valid data on population prevalences. As many diseases are non-fatal, ranks based on mortality rates give another picture than figures derived from hospital discharge diagnoses, and the distribution in ambulatory care is again quite different, as are the health economical consequences (Table 58.2).

About one in three citizens attends a physician for digestive complaints each year in the Western world (Everhart and Ruhl 2009b). Gastrointestinal disease is the third most common cause of death, the leading cause of cancer death, and the most common cause of hospital admission in the UK (Williams et al. 2007).

The major causes of death from gastrointestinal disease in high-income countries, excluding cancer, are liver cirrhosis, peptic ulcer, ischemic bowel disease, diverticular disease, and gastrointestinal hemorrhage. Many other, non-fatal diseases of the digestive tract rank relatively low in vital statistics and hospital admission rates but impact substantially on the quality of life of those affected. Typical examples include gastroesophageal reflux disease, dyspepsia, irritable bowel syndrome, and

Table 58.2 Top ten prevalent digestive diseases (USA 2004; Everhart and Ruhl 2009b)

	Ambulatory care	Hospital discharges	Deaths	Total costs
1	Gastroesophageal reflux disease	Gastroesophageal reflux disease	Colorectal cancer	Chronic liver disease/cirrhosis
2	Chronic constipation	Diverticular disease	Liver disease/cirrhosis	Gastroesophageal reflux disease
3	Abdominal wall hernia	Chronic liver disease/cirrhosis	Pancreatic cancer	Colorectal cancer
4	Hemorrhoids	Chronic constipation	Esophageal cancer	Gallstones
5	Diverticular disease	Gallstones	Gastric cancer	Abdominal wall hernia
6	Irritable bowel syndrome	Peptic ulcer disease	Primary liver cancer	Pancreatic cancer
7	Hepatitis C	Pancreatitis	Bile duct cancer	Diverticular disease
8	Colorectal cancer	Gastrointestinal infections	Hepatitis C	Pancreatitis
9	Chronic liver disease/cirrhosis	Hepatitis C	Gastrointestinal infections	Peptic ulcer disease
10	Gastrointestinal infections	Abdominal wall hernia	Peptic ulcer disease	Hepatitis C

anorectal disorders (e.g., hemorrhoids or fecal incontinence). Symptoms of gastrointestinal disease tend to be unspecific, such as abdominal discomfort, loss of appetite, bloating, heartburn, fatigue, or constipation. Many patients never present to a physician, and in many instances, gastrointestinal conditions remain untreated or in patient self-management. There is an increasing body of research on the determinants of health-care-seeking behavior, in particular in functional diseases.

For most diseases, there is no single test or key symptom to prove the diagnosis. This may pose problems in studying these diseases on a population level. Use of administrative data can also be a challenge as many gastrointestinal conditions occur in the presence of other morbidity. As an example, elderly patients on multiple drugs are of particularly high risk to suffer from gastrointestinal hemorrhage, for example, as a consequence of gastric ulcer related to the use of non-steroidal anti-inflammatory drugs (NSAID). Obviously, the accuracy of, for example, hospital discharge or mortality data depends on the number of diagnoses available for analysis per case.

58.3.2 Examples

58.3.2.1 Infectious Diseases: Hepatitis C Still on the Rise

Methodological approaches to infectious disease epidemiology are covered in chapter ▸Infectious Disease Epidemiology of this handbook. Three infectious entities seem particularly important and interesting from an epidemiological and public health view. Besides acute infectious diarrhea and *H. pylori*, which will be discussed below, these are viral hepatic infections, specifically chronic Hepatitis C.

Viral Hepatitis may be caused by a number of viruses, most prominently Hepatitis A, B, or C (HAV, HBV, and HCV). The main differences of these are described in Table 58.3. In summary, HAV infection is a food-borne and self-limiting acute infection. HBV and HCV are blood-borne and may run a chronic course. It is estimated that about one third of the world's population has been exposed to either HBV or HCV, although only about a third of those affected are aware of the infection (Lancet Editorial 2008).

HAV and HBV are, as so many infectious diseases, associated with poverty-related risks, namely poor sanitation (HAV, HBV), unsafe sex, and vertical transmission from infected mothers during delivery (HBV). Both HAV and HBV are endemic in certain low- and middle-income countries and currently on the decrease thanks to successful interventions, including vaccination programs and screening of pregnant women. In high-income countries, HAV and HBV are now mainly restricted to specific risk groups: HAV in international travelers and HBV in immigrants, inmates, and i.v. drug abusers.

Quite in contrast, the burden from HCV is still expected to rise. In most high-income countries, HCV is now the most common cause of chronic liver disease, in others, second only to alcohol. In the USA, the current prevalence of chronic HCV is 1.3% (RNA positive), as compared to 0.4% for chronic HBV (Liangpunsakul and

Table 58.3 Viral Hepatitis – differences A, B, C

Characteristics	HAV	HBV	HCV
Main mode of transmission	Feco-oral: Contaminated food and water Close personal contact	Blood-borne, mucosal: perinatal Sexual intercourse/unsafe sex i.v. drug abuse, needle sharing	Blood-borne: i.v. drug abuse, needle sharing blood products before 1992 Other iatrogenic (contaminated needles)
Other ways of transmission	Homosexual activity i.v. drug abuse	Hemodialysis Blood products in unsafe health care settings Household sharing	Hemodialysis Professional (needle stick injury) Controversial: sexual intercourse (multiple partners) Rare: tattooing, acupuncture, piercing, household sharing, perinatal
Diagnosis	Anti-HAV IgM/IgG – acute or past exposure; Immunity	HBs Ag = acute or chronic infection Anti-HBs = past exposure; immunity	Anti-HCV = past exposure or chronic infection HCV-RNA = confirmatory test (acute or chronic infection)
Vaccination	Available since 1995	Recommended since 1992	Not available
Acute infection	Mostly symptomatic in adults, often no symptoms in children	Mostly symptomatic (jaundice), Rare: fulminant (liver failure)	Rarely symptomatic
Proportion resulting in chronic infection	<1%	<10% (more if perinatally acquired)	55–90%, depending on age and sex
High-prevalence regions	Developing world (>90% exposed during childhood); occasional outbreaks in middle-/high-income countries	Far East, Southeast Asia (up to 16% chronic HBV), sub-Saharan Africa, Amazon area, Eastern Europe	More evenly distributed including North America and Europe (world wide 2.2%)
Number of persons currently infected (worldwide)	Incidence 1.4 million/year (acute)	Prevalence >350 million (chronic)	Prevalence 170 million (estimated) (chronic)
Preventive strategies	Vaccination (children, international travel, high-risk persons) Improve sanitation	Vaccinations (infants and high-risk persons) Screening of pregnant women Immunoprophylaxis to avoid perinatal transmission Screening of donors/inactivation of blood products Safer sex	Screening and testing of blood donors Risk reduction counseling of persons at risk, e.g., avoid needle sharing, safer sex

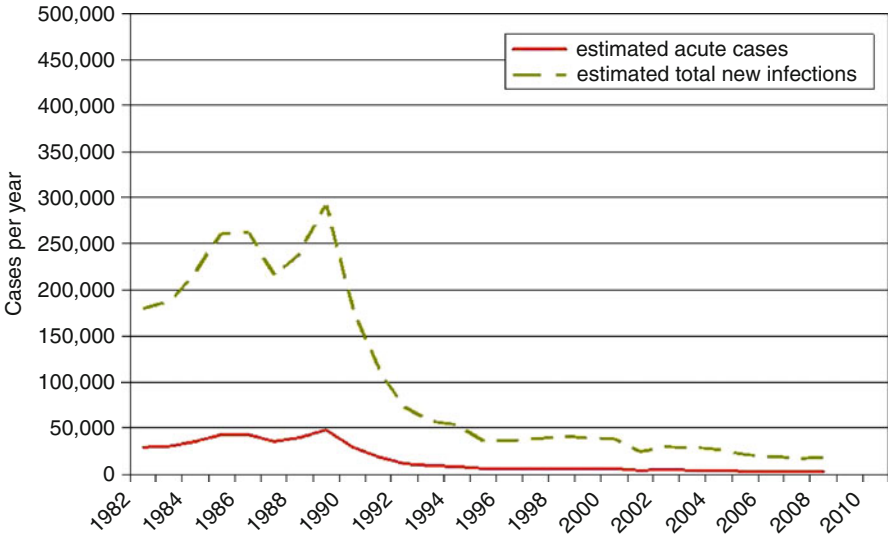

Fig. 58.2 HCV infection – number of cases per year (USA, CDC data). Source: http://www.cdc.gov/hepatitis/Statistics/index.htm (with kind permission)

Chalasani 2005). In Western Europe, HCV accounts for 70% of all cases of chronic Hepatitis, 40% of all liver cirrhosis, and 60% of hepatocellular carcinoma (Williams et al. 2007).

Acute HCV infection is rarely symptomatic and mostly goes unnoticed (World Health Organization 2007). Diagnosis is usually delayed until routine lab examinations unveil raised liver enzymes or until complications of liver disease manifest. In consequence, there are hardly any empirical data on the incidence of HCV. Estimations have been based on mathematical modeling (Davis et al. 2010). These indicate a steep fall in the incidence from the first description of the virus in 1989 to recent times. The decrease has been linked to the introduction of blood donor testing in 1989, improved diagnostic tests in 1992, and the promotion of safer needle using techniques in i.v. drug users (Fig. 58.2).

For the natural history of the disease, several natural experiments are available. In Germany, several thousand women were infected with HCV when immunoglobulin from donors with acute non-A and non-B Hepatitis (as this viral Hepatitis was known before the description of HCV) was used for rhesus incompatibility prophylaxis. Two thousand four hundred and sixty four affected women were acknowledged as vaccination victims and received compensation from the Eastern German Government from 1979 and later from the Federal Republic of Germany. In Ireland, a regional analysis of blood donors in 1991 discovered a strong association of chronic Hepatitis C with rhesus-negativity. In a subsequent national investigation, more than 62,000 of women were tested who had received anti-D immune globulin between 1970 and 1994, confirming that quantities used in 1977 and 1978 had been

contaminated. All infections could be traced back to a single donor, and 1,042 successful claims were made by infected women (Akehurst 1999). More diverse claimant cohorts are available for follow-up from other countries, such as the UK, Canada, and Japan (Harris et al. 2002; Pokorski 2001; Thein et al. 2009). Male sex, older age at infection, use of alcohol, and coinfection with HIV or HBV are the most important risk factors for HCV-related morbidity (Poynard et al. 1997).

A prognostic study using complex Markov modeling took into account the different prognosis by age and sex and arrived at the following estimations (Davis et al. 2010): Following acute infection in women under the age of 30, 55% will run a chronic course. Of these 4.2% will have end-stage liver disease (cirrhosis) after 30 years, 0.02% will have hepatocellular carcinoma (HCC), and 0.9% will have died from liver-related death. In contrast, infected male persons aged 31–50 have a risk of 80% for chronic HCV and, if chronic, will suffer from cirrhosis in 38.1%, HCC in 0.5%, and liver death in 11.1%.

Of those currently infected, most contracted the virus between 1970 and 1990 and are now entering the stages of complicated liver disease. According to the Markov model, the prevalence of cirrhosis within those currently infected will continue to increase from currently 25 to 45% in 2030, before, eventually, the burden will decrease. The most important message is: despite the major advances in reducing the incidence of this infection since it was first described, the peak of the HCV epidemic is still to come.

58.3.2.2 Cancer of the Gastrointestinal Tract: Subsite Matters

Cancer epidemiology is covered by chapter ▸Cancer Epidemiology of this handbook. A few aspects specific to gastrointestinal cancers seem worth noting in the context of digestive disease epidemiology. Digestive cancers account for about 18% of all cancers in the Western world. Most prominently, these are the primary malignancies of the esophagus, stomach, large bowel, liver, and pancreas. Less commonly, the biliary tract, the small bowel, or the peritoneal cavity is affected.

For most entities, men are affected more often than women. The average age at onset is relatively high as compared to cancers at other sites. Most malignancies in the gastrointestinal tract are solid, and of these, most are adenomas, although other entities, for example, lymphoma or neuroendocrine tumors, do occur. The majority of gastrointestinal cancers still have a very poor prognosis. For example, less than 5% of those diagnosed with cancer of the pancreas survive 5 years following the diagnosis; mortality rates still equal incidence. The decrease of both incidence and mortality in colorectal cancer (see chapter ▸Cancer Epidemiology of this handbook) is one of the rare successes in gastrointestinal cancer epidemiology and so far mainly restricted to Western countries, specifically those where screening takes place.

Quite in contrast to colorectal cancer, primary cancer of the liver (hepatocellular carcinoma, HCC) is endemic in Africa, where prevalence rates may be as high as 20% (Hainaut and Boyle 2008). This is a direct consequence of a high prevalence of chronic HBV. HCC almost exclusively develops in the presence of cirrhosis of the liver, and in low-income countries, chronic HBV infection is the most common cause of cirrhosis of the liver. Vertical transmission of HBV to newborns of infected

mothers carries the highest risk of both running a chronic course of HBV infection as well as of resulting in cancer. HBV is amenable to preventive measures, most importantly childhood vaccination programs, screening of pregnant women, and perinatal active-passive immunization of babies of infected mothers. Consequently, HCC may be expected to decrease in these countries, while it is currently on the rise in the Western world due to the epidemic of HCV-associated morbidity, as discussed above.

Divergent trends in incidence are observed in esophageal cancer. So far, the dominant histological type of cancer of the esophagus has been squamous, but adenomatous cancer is on the rise and is now more frequent in several Western European countries (Bosetti et al. 2008). Squamous carcinoma of the esophagus is closely associated with smoking and alcohol (see below). These risk factors are estimated to account for more than 80% of this highly fatal malignancy (Danaei et al. 2005). In contrast, adenocarcinoma of the esophagus, arising from the lower part of the esophagus, is related to acid reflux and obesity.

Cancer of the upper (cardiac) part of the stomach and the gastroesophageal junction is in its risk profile similar to lower esophageal cancer. The distinction may sometimes be difficult to make. Other than cancer of the lower (non-cardiac) part of the stomach, infection with *H. pylori* does not play a role in cancer of the cardiac region or may even be protective. Whereas the elimination of *H. pylori* will result in a decreased risk for non-cardiac gastric cancer, this is not the case for cancer of the cardiac region. There is even some controversy whether *H. pylori* might be protective for this type of cancer.

This may appear confusing. However, these examples underline the importance of thoroughly defining subtypes of a given cancer in terms of site and histology in order not to blur any risk associations or time trends.

58.3.2.3 The Inflamed Bowel: Inflammatory Bowel Disease, Appendicitis, and Diverticulitis

About every part of the digestive system may be affected by chronic inflammation and autoimmune reactions. Examples include autoimmune pancreatitis, pernicious anemia (arising from autoimmune gastritis), autoimmune Hepatitis, primary biliary cirrhosis, and celiac disease. With the exception of celiac disease (gluten-sensitive enteropathy, 1% of the population), these conditions are relatively rare, and few data are available from larger cohorts regarding risk factors and incidence. For some conditions, viral triggers are suspected. The epidemiological literature is scarce.

In contrast, innumerable descriptive and case-control studies have been published on the incidence and possible etiological factors of the inflammatory bowel diseases (IBD), Crohn's disease, and ulcerative colitis. Typically, these diseases manifest in early adulthood and run a chronic, relapsing course. Complications may include growth failure in the young, bowel obstruction, and fistulization in Crohn's disease frequently necessitating surgery and colorectal cancer in ulcerative colitis. Although life expectancy is now close to normal, morbidity is high. In consequence, these patients constitute a relevant fraction in the daily practice of a gastroenterologist. Inflammatory bowel diseases are also an attractive target for biological therapy,

as well as genetic studies, and feature highly in the clinical trial literature. The prevalence in the population is relatively low and is currently estimated to be about 0.4% in North America and Western Europe (Loftus Jr. 2004). These diseases have been linked to a Western lifestyle. They were very uncommon before World War II and have increased since.

Quite in contrast, other inflammatory bowel disorders are more common but receive less research attention. In particular, these are acute appendicitis, which may affect up to 10% of persons in the Western world during a lifetime, mostly at young age, and diverticulitis, a common condition in the elderly. While IBD is a disease of the second half of the twentieth century, appendicitis incidence peaked in the first half of the last century and has been declining since then. Not only do these diseases show divergent time trends in correlational studies, there is also a strong negative association between ulcerative colitis and appendicitis in individual level analyses: the odds ratio (OR) of getting ulcerative colitis in appendectomized persons is about one third of those not appendectomized (Frisch et al. 2009). This finding is so far unexplained. Overall, there has been remarkably little research on appendicitis, although it is such a common surgical condition. Most of the descriptive and etiological literature stems from the 1970s and 1980s (Heaton 1987).

Diverticular disease is another common but relatively understudied condition. Up to 70% of the elderly are estimated to have diverticulosis of the large bowel, little pouches in the colon wall arising from increased intraluminal pressure, associated with a sedentary lifestyle and low-fiber diets. Only a minority of these become symptomatic, but still so many as to make this one of the ten most common digestive diseases (Everhart and Ruhl 2009b). Diverticula of the large bowel are also the most frequent cause of lower gastrointestinal bleeding. In the case of inflammation (diverticulitis), if complicated by abscess, peritonitis, or recurring, the affected part of the bowel will be removed surgically. Thus, as appendicitis, diverticulitis can be cured by surgery. Other than IBD, it is usually not associated with lifelong morbidity.

58.3.2.4 Hepatobiliary and Pancreatic Diseases: Gall Stones, Pancreatitis, and Cirrhosis of the Liver

Gallstones are among the most common gastrointestinal conditions. They are easily diagnosed using ultrasonography, so valid cross-sectional evaluation of representative populations is possible. Ultrasonography-based prevalence data are very variable even within the same country (Kratzer et al. 1999). For example, figures within Germany ranged from 8% to 21% (Völzke et al. 2005; Walcher et al. 2005). This is not yet sufficiently explained.

Risk factors for gallstone disease include age, female sex (parity), obesity, fast weight loss, and some digestive diseases interfering with intestinal resorption, for example, inflammatory bowel disease. There is also a strong genetic component. Gallstones are particularly common in North American natives, where up to two thirds of the female population are affected.

The presence of gallstones does not indicate disease. Most gallstones are asymptomatic and not in need of therapy. It is estimated that only 1% to 2% of

persons with gallstones will develop complications per year. Most commonly, these are colics from biliary obstruction or inflammation of the gallbladder (cholecystitis). Usually, treatment is by cholecystectomy.

Gallstones are also the most common cause of acute pancreatitis, as obstruction of the biliary tract may lead to this condition. We will discuss this disease entity in the context of alcohol-related diseases.

Chronic liver disease, in particular cirrhosis of the liver, is among the most expensive disease groups in gastroenterology and among the most deadly (Everhart and Ruhl 2009c). This is the more tragic in that this condition is to a large extent preventable. We have touched on this before: in the developing world, cirrhosis is usually due to chronic HBV infection. In contrast, in high- and middle-income countries, cirrhosis of the liver is most commonly due to HCV infection, followed by alcoholic and non-alcoholic fatty liver disease. There are many other causes including autoimmune and metabolic disorders, but these non-preventable conditions taken together cause less than 20% of all cases of cirrhosis.

About 1% of the population is estimated to have histological evidence of cirrhosis, that is, scarring of the liver resulting from chronic liver injury. Hepatic tissue is replaced by connective tissue as part of the wound healing process; the liver slowly becomes fibrotic. The end stage is characterized, on the one hand, by loss of liver function and on the other hand by increased hepatic resistance resulting in hypertension within the portal vein and circulatory deregulation. Patients with end-stage liver disease may suffer from diverse life-threatening complications, including hepatic coma, bleeding from esophageal varicose veins, peritonitis, and kidney failure. These account for the substantial burden chronic liver diseases pose to society. Mortality is high, and liver transplantation is the only treatment option in advanced liver disease. The pattern of the global burden of liver disease and its causes is expected to change substantially over the coming decades.

58.3.2.5 Functional Diseases: Definitions Matter

Functional diseases of the digestive tract are among the most common disorders in the population, affecting about a third of the population in Western countries (Koloski et al. 2002). Irritable bowel syndrome alone is estimated to constitute up to 50% of the workload of a gastroenterologist working in ambulatory care (Williams et al. 2007). Prevalence rates are mostly unreliable and vary depending on the definitions used (Vandvik et al. 2004). Only a minority of those affected seeks medical care and ever gets a diagnosis, and of those who do see a general practitioner, many are never referred to a specialist.

In general, functional disease is assumed in the presence of symptoms without underlying organic disease. This is overly simplistic. Insufficiently understood gut motility abnormalities seem to arise from disordered interaction between the central nervous system and the gut nervous system (Cremonini and Talley 2004). Learned illness behavior and emotional factors may play a role in how the individual copes with these common symptoms and whether medical help is sought (Levy et al. 2000). Although not usually associated with increased mortality or

hospitalization, quality of life is known to be decreased, and substantial loss of work productivity has been shown.

Quite a few functional entities are defined in gastroenterology: globus pharyngis (feeling a lump in the throat), non-cardiac chest pain, functional (or non-ulcer) dyspepsia, functional abdominal pain, functional constipation, and irritable bowel syndrome. Of these, dyspepsia, constipation, and irritable bowel syndrome are the most common. Substantial overlap may exist in the symptoms reported, both between the different functional disorders, as between functional and organic disorders. This makes the definition of diagnostic criteria such a challenge. Dyspepsia, for example, refers to abdominal discomfort, which may or may not be associated with peptic ulcer, gastritis, or esophagitis. In about 50%, there is no structural correlate, and, thus, functional or non-ulcer dyspepsia is assumed (Vakil and Talley 2007). Clinical symptoms are not sufficient to differentiate between these entities (Moayyedi et al. 2006).

Chronic constipation is endemic in certain subpopulations, in particular the elderly. It may constitute a major management problem in nursing homes. In a minority of patients, slow bowel transit or defecatory dysfunction is identified. These patients form a specific subgroup. Constipation is also a side effect of many medications, most notably opioids. Furthermore, it is associated with a variety of neurological and psychiatric conditions such as Parkinson's disease, multiple sclerosis, or depression. The average prevalence in the normal population in North America is 15% if stringent diagnostic criteria are used but may be up to 27% when studies rely on self-reporting (Higgins and Johanson 2004).

Thus, functional disorders pose specific problems for epidemiological research. Not only do diagnosis and symptom severity require careful definitions, the choice of outcome criteria for clinical trials is also a challenge. Most commonly, the Rome criteria are used in research and practice, currently in their 2nd revision (Rome III) (Drossman 2006). The Rome group differentiates 28 adult and 17 pediatric functional gastrointestinal disorders and has developed consensus criteria for those more frequent. Symptom questionnaires are also available, although mostly not validated for use in epidemiological research. The key publications on the diagnostic criteria by disease as well as diagnostic questionnaires and scoring codes are available from the Rome Foundation website (www.romecriteria.org).

58.4 Risk Factors and Determinants, Prevention and Control

58.4.1 Overview

There is a high potential for public health interventions in digestive disease. Hand washing to prevent the spread of acute diarrhea is a prominent example. Many diseases of the alimentary tract are strongly associated with risk behavior, for example, alcohol and i.v. drug abuse in chronic liver disease. Some are amenable

to prevention by eradication of precursor conditions, such as adenomas in colorectal cancer or *H. pylori* infection in peptic ulcer disease and gastric cancer. Vaccination programs are also in place, apt to substantially changing the prevalence of several infectious diseases. Examples include Hepatitis B or rotavirus infection.

In this section, we describe some of the major risk factors in gastrointestinal disease by the example of selected entities. Besides poverty in the context of infant mortality, alcohol is probably the most important modifiable risk factor for digestive diseases. It contributes to the majority of cases of esophageal cancer, pancreatitis, and cirrhosis of the liver in affluent societies. A comprehensive analysis of published data calculated population attributable fractions for several common cancers due to nine common environmental and behavioral risk factors (Table 58.4) (Danaei et al. 2005).

Most of the current research in digestive disease etiology seems to focus on genetics.

58.4.2 Examples

58.4.2.1 Genetic Factors: Crohn's Disease as a Prominent Example of Complex Heritability

Several digestive diseases, or multiorgan diseases affecting the digestive system, display a monogenic heritability. Examples include hemochromatosis (affecting the liver, pancreas, and brain), cystic fibrosis (affecting the lung and pancreas), alpha-1-antitrypsin deficiency (affecting the lung and liver), several types of hereditary pancreatitis, hereditary non-polyposis cancer of the colon, and familial adenomatosis coli (FAP). These relatively rare conditions have, in the clinical context, important implications for surveillance programs, as some are precancerous, and others are associated with severe non-malignant, sometimes avoidable morbidity. Counseling of affected families is necessary.

More commonly, complex heritability is present, posing considerable challenges to the effective collaboration between epidemiologists and geneticists. For methodological issues, please refer to chapter ▸Statistical Methods in Genetic Epidemiology of this handbook. Crohn's disease may be taken to illustrate quite a few of the techniques presented there (Gaya et al. 2006; Cho 2008). Observations of increased prevalence in families of affected persons, higher concordance in monozygotics in several twin studies, segregational analysis pointing at an autosomal recessive gene, and mapping of a first susceptibility locus (IBD1) preceded the concurrent identification of the NOD2 gene using positional cloning on the one (Hugot et al. 2001) and candidate gene assessment on the other hand (Ogura et al. 2001) in 2001. This was just a start: as of today (July 2010), a PubMed search using the phrase "inflammatory bowel disease AND genetic" returns 3,268 hits – to go into detail is beyond the scope of this chapter. The many mutations discovered so far explain only a minority of cases.

Epigenetic approaches may help elucidate the pathogenesis not only of Crohn's disease but of gastrointestinal development in general (Waterland 2006). Differentiation of the colonic gut flora taking place in early infancy is suspected by some

Table 58.4 Risk factors for gastrointestinal cancer mortality with population attributable fractions (*PAF*), global (high-/low- and middle-income countries) (Danaei et al. 2005)

	High body mass index (BMI)	Low fruit/vegetable consumption	Physical inactivity	Smoking	Alcohol	Intravenous injection in health-care settings	Risk factors combined
Esophagus (combined)	–	18 (12/19)%	–	42 (71/37)%	26 (41/24)%	–	62 (85/58)%
Stomach (combined)	–	18 (17/19)%	–	13 (25/11)%	–	–	28 (34/27)%
Colorectum	11 (14/9)%	2 (1/2)%	15 (14/15)%	–	–	–	13 (15/11)%
Liver (HCC)	–	–	–	14 (29/11)%	25 (32/23)%	18 (3/21)%	47 (52/45)%
Pancreas	–	–	–	22 (30/15)%	–	–	22 (30/15)%

to play a major role in many diseases, including diabetes and obesity (Frank and Pace 2008; Peterson et al. 2009). Research in this has only just started and may bring the gut much more to the forefront of research, including epidemiology, than previously anticipated.

58.4.2.2 Poor Sanitation, Unsafe Water, and Contaminated Food: Acute Infectious Diarrhea

Several of the digestive diseases are poverty related and occur endemically in countries with crowded housing conditions as well as contaminated food and water supplies. Most of these are infectious (for methods, see chapter ▸Infectious Disease Epidemiology of this handbook). We have already mentioned viral Hepatitis, of which HBV and HAV are amenable to effective preventive measures, including vaccination and screening of pregnant women. *H. pylori* is another example, which we will discuss below. Here we would like to concentrate on an issue of primary importance in global public health: acute infectious diarrhea.

Acute diarrhea is still, besides pneumonia, the leading cause of death in children under the age of five. It accounts for 17% of the infant deaths worldwide (World Health Organization 2007). Diarrhea is common all over the world, in particular in children. Fatality from diarrhea is closely related to the traditional risk factors associated with poverty – the combined risks of underweight, insufficient breastfeeding, and vitamin deficiencies are estimated to account for 73% of infant mortality from diarrhea, and 99% of deaths from diarrhea occur in low-income countries (World Health Organization 2007).

A short summary (not comprehensive) of common causative organisms is presented in Table 58.5 (O'Brian and Halder 2007). Good advances have been made in the prevention and treatment of bacterial and parasitic organisms. Previously common enteric infections such as typhoid fever, cholera, and amoebic colitis are on the decline. Today, most intestinal infections are viral. Of these, norovirus is ubiquitous and regularly causes outbreaks all around the world, affecting persons of any age. In children under the age of five, rotavirus is more common. Besides watery diarrhea, fever and vomiting are also typical, aggravating the risks for the underprivileged. In high-income countries, the disease will subside within a few days. In low-income countries, many children die from dehydration. The relative contribution of rotavirus infection to infant deaths from diarrhea has been increasing and may currently be as high as 40% (Parashar et al. 2009).

The high mortality from acute diarrhea including rotavirus infection is the more tragic as cheap and effective measures are available for treating this condition. WHO oral rehydration solution (ORS) works via the sodium channel glucose transport system in the bowel mucosa. It is superior to i.v. fluids or any other therapy in watery diarrhea (Hartling et al. 2006; Gregorio et al. 2009). Diarrhea prevention programs have been in place from 1978 and have led to dramatic falls in the infant death rate from diarrhea in the following years (Santosham et al. 2010). Unfortunately, in the 1990s, the specific diarrhea programs were merged into integrated health programs. Diarrhea as a distinct entity lost priority, as did the promotion of ORS, formerly named the major medical advance of the twentieth century (Santosham et al. 2010).

Table 58.5 Common risk factors for specific antigens causing infectious diarrhea (Modified from O'Brian and Halder (2007))

Antigens	Risk factors
E. coli O157:H7	Undercooked beef, unpasteurized milk, apple cider, visits to animal farms, petting zoos
Shigella	Contaminated water and vegetables, day-care centers, custodial institutions
Clostridium difficile	Antibiotics, hospitalized patients
Campylobacter	Undercooked poultry, contaminated milk, tuna salad
Salmonella	Raw eggs, undercooked poultry, unrefrigerated dressing, reptiles as a pet, family members with Salmonella
Non-cholera vibrio	Raw/undercooked seafood
Giardia	Contaminated water, recreational exposure in lakes, rivers, or swimming pools, day-care centers
Cryptosporidium	International travel, contact with cattle, freshwater swimming
Rotavirus	Cold season, infancy
Norovirus	Cold season, raw oyster consumption, cruise ships, health institutions

Since 1995, there has not been much progress in the acceptance of this easy and effective therapy. Currently, only about a third of children with watery diarrhea receive ORS; many health workers still prefer antibiotics for watery diarrhea. If the millennium goal of reducing infant mortality worldwide by two thirds by 2015 is to be met, the prevention and treatment of acute diarrhea need to get back in focus.

A seven-point plan set up for comprehensive diarrhea control includes rotavirus vaccination, promotion of early and exclusive breastfeeding, vitamin A supplementation, promotion of hand washing with soap, improvement of water quantity and quality, promotion of community-wide sanitation, and, for treatment, fluid replacement and zinc supplements (Wardlaw et al. 2010). Two vaccines against rotavirus are now available in developed countries but need to be evaluated in endemic countries as soon as possible. Introduction to low-income countries will depend on priority setting by governments and WHO (Rose et al. 2009).

58.4.2.3 Peptic Ulcer Disease and *H. Pylori*: A Success Story?

One of the most exciting milestones in gastroenterology in the twentieth century was the discovery that peptic ulcer disease was caused by a bacterial agent, *Helicobacter pylori* – rightly awarded the Nobel Prize in Medicine in 2005 (Lang 2005). This major success story of clinical medicine was, quite in contrast, prominently discussed as one famous example where epidemiology failed (Davey-Smith and Ebrahim 2001).

For most of the twentieth century, peptic ulcer disease was a common problem with high morbidity and mortality. Severe complications occurred frequently, such as life-threatening bleeding or perforation into the abdominal cavity. If not fatal, recurrence was almost inevitable. Many patients ended up having major surgery,

such as total or, more often, subtotal gastrectomy or vagotomy. These procedures are themselves associated with high perioperative morbidity and subsequent decreased quality of life.

There have been numerous epidemiological studies into the etiology of peptic ulcer disease (Davey-Smith and Ebrahim 2001). This was sparkled, among other things, by so far unparalleled patterns in the incidence and prevalence of these diseases, similar as, more than 50 years later, the inflammatory bowel diseases. Comparable to coronary heart disease, lung cancer, and appendicitis, the incidence of both gastric and duodenal ulcer increased during the first half of the twentieth century. From the 1950s on, however, the incidence of peptic ulcer decreased for unknown reasons. Strong birth cohort effects were discovered as early as 40 years ago, pointing at the relevance of events occurring early in life (Susser 1982; Sonnenberg 2007). Persons born between 1870 and 1920 had the highest risk. For each subsequent generation, the risk for peptic ulcer incidence and mortality successively decreased.

Similar observations for, for example, tuberculosis incidence could have raised the suspicion of an infectious etiology in peptic ulcer disease. It did not. Up until the 1970s, diet, alcohol, emotional stress, and personality had been identified as risk factors for peptic ulcer disease – none of them would have explained the birth cohort effect. Davey-Smith in his critical essay on our discipline points out that the epidemiological transition from infectious to non-infectious diseases may have had, in this case, clouded the view of epidemiologists in favor of non-infectious factors (Davey-Smith and Ebrahim 2001). Improved sanitary conditions and less domestic crowding resulting in lower infection rates would have been a plausible explanation of the birth cohort phenomenon. Still, etiological hypotheses focused on nutrition and psychosomatics.

Epidemiology was not the only discipline led astray in this case. The notion that peptic ulcer disease was caused by microbes colonizing the gastric mucosa was revolutionary in clinical medicine, pathology, and microbiology as well. Until then, the stomach had been assumed to be sterile, due to its high acidity.

It was a junior gastroenterology fellow who performed a simple cross-sectional study in 100 patients referred to endoscopy after a pathologist had described a curved bacterium, later called *Helicobacter pylori*, in the gastric mucosa of patients with gastritis (Marshall and Warren 1984). He found a strong association between the presence of the microbe and active chronic gastritis, duodenal ulcer, or gastric ulcer. Later, he demonstrated acute gastritis in himself after ingestion of *H. pylori*.

H. pylori gastritis is a chronic inflammation as a reaction to *H. pylori* colonization, playing a pivotal role in the development of several gastric disorders. Carriers of *H. pylori* have a 10% to 20% lifetime risk of peptic ulcer disease and a 1% to 2% life time risk of gastric cancer. Taking another perspective, more than 70% of all gastric cancer is attributable to *H. pylori* (Goodwin et al. 1997). Eradication of *H. pylori* with combination of antibiotic therapy effectively cures peptic ulcer disease. It is also expected to decrease the risk for gastric cancer.

Naturally, the question now arises whether screening for and treatment of *H. pylori* are useful from a public health perspective. Several issues play a role

in this ongoing discussion – the prevalence of the infection in a population, the availability of tests and their performance, costs, acceptance, and rates of microbial resistance to antibiotic agents.

On average, about 50% of a population carries *H. pylori*. This varies by age and region. In developing countries, prevalence rates may be as high as 80%. In industrial countries, the rate is, on average, 40%, but with a marked generational gradient. Infection seems to occur in the first years of life, primarily from close family contacts. In adults, new infection is very rare, as is spontaneous seroconversion. This means that the observed differences by age group are almost completely caused by generation (birth cohort) effects. Crowding during industrialization and decreasing hygiene has been suggested to explain the effect (Sonnenberg 1995). The prevalence in children is a good indicator for the future burden. German school children now have prevalence rates as low as around 10% (Rothenbacher et al. 1999).

58.4.2.4 Behavioral Risk Factors: Alcohol and Smoking

Four entities in particular are strongly associated with high alcohol intake: esophageal cancer, acute and chronic pancreatitis, and cirrhosis of the liver.

As pointed out above, in esophageal cancer, the type of cancer needs to be defined in order to correctly interpret risk data. For example, in a recent prospective cohort study, the relative risk for squamous esophageal cancer in persons with high alcohol intake ($\geq$30 g/d) was 4.6 (95% confidence interval (CI) 2.2–9.5) as compared to abstainers, but no association was found for adenocarcinoma of the esophagus (Steevens et al. 2010).

Alcohol plays the major role in the pathogenesis of acute pancreatitis, ahead of biliary causes (obstruction by gall stones). The exact mechanism by which alcohol exerts this effect is unclear. Several hypotheses have been discussed, including direct toxic effects of acetaldehyde on acinar cells, sensitization of the pancreas to injury, or mediation via alcohol-induced duodenitis (Chowdhury and Gupta 2006). A genetic predisposition to pancreatic injury from alcohol seems to be essential. Only a minority of heavy drinkers develops pancreatitis.

In acute pancreatitis of any etiology, systemic reactions are common, including multiorgan failure. Case fatality is now about 10%. Acute pancreatitis is also a relevant side effect of some drugs (e.g., occurs in about 3% of those on the immunosuppressive azathioprine) or diagnostic procedures involving the pancreatic duct (endoscopic retrograde cholangiopancreatoscopy (ERCP), occurs in up to 5% of procedures), but these account for only a small part of the overall burden. Other rare causes are viral, traumatic, autoimmune, or hereditary. What makes some people's pancreas susceptible to damage by alcohol is still subject of research. Both genetic and environmental factors seem to play a role (Haber et al. 1995; Yadav and Whitcomb 2010).

Chronic pancreatitis is probably not a consequence of recurrent or intractable acute pancreatitis but due to different yet unclear mechanisms. Up to 80% of cases are estimated to be due to chronic abuse of alcohol. Pancreatic tissue is replaced by scarring; characteristic features are chronic pain and loss of weight, in advanced cases diabetes due to destruction of islet cells (endocrine function) and maldigestion

due to loss of exocrine function. Chronic pancreatitis is a major risk factor for pancreatic carcinoma making the latter another mediate, potential consequence of alcoholism.

In the liver, different pathologies may occur following alcoholic injury. Alcoholic fatty liver is the earliest stage, in which lipids are deposited in hepatic cells, and is found in 90% to 100% of liver biopsies in heavy drinkers (Dufour 2007). Alcoholic Hepatitis affects about 10% to 35% of drinkers at some time. It may present very acutely and may result in acute liver failure. Recurrent hepatitic episodes and progression of fatty deposits will result in fibrosis and eventually cirrhosis, in up to 20% of heavy drinkers or 70% of drinkers who have had alcoholic Hepatitis (Mandayam et al. 2004). Alcohol is also an important cofactor for liver damage from other causes, such as chronic viral Hepatitis, where it exerts synergistic effects. Ultimately, cancer may occur in the cirrhotic liver, as in cirrhosis of other etiologies.

As compared to alcohol, smoking is less important in gastrointestinal disease. Several disorders show elevated risks, but for most, the associations are moderate (Steevens et al. 2010). Smoking is, however, an important cofactor of alcohol in several entities – both in esophageal squamous carcinoma as well as in acute pancreatitis, smoking increases the deleterious effect of alcohol.

In inflammatory bowel disease, contrasting roles for smoking have been demonstrated by type of disease. Smoking is the only established external risk factor for Crohn's disease and is, in addition, associated with a poor prognosis (Calkins 1989; Birrenbach and Bocker 2004). In contrast, in ulcerative colitis, smoking seems to be protective. Typically, the disease begins in former smokers, following smoking cessation (Corrao et al. 1998). Attempts to use nicotine (gums, patches) in the treatment of ulcerative colitis have been unsuccessful, partly due to incompliance as side effects are common with nicotine. Although these divergent associations have been known since the 1980s, the underlying mechanisms remain obscure.

58.4.2.5 Risk Factors in Affluent Societies: Sedentary Lifestyle, Nutrition, and a Sheltered Childhood

Colorectal cancer is commonly perceived as a malignant disorder particularly closely associated with the sedentary Western lifestyle. High-calorie food intake low in fruits, vegetables, and fibers and high in processed meats has been confirmed as risk factors (Bingham et al. 2003; Norat et al. 2005; Friedenreich et al. 2006; van Duijnhoven et al. 2009). However, the joint behavioral risk factor attributable fraction is relatively low in colorectal cancer as compared to the other common digestive tract cancers (Table 58.4). It constituted only 13% in a cumulative analysis based on published data and results from the WHO Comparative Risk Assessment Project (http://www.who.int/whr/2002/en/) (Danaei et al. 2005).

In contrast, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis are increasingly recognized as sequelae of overnutrition in affluent societies. They are now considered the digestive disease manifestation of the metabolic syndrome. Exact mechanisms are still unclear. On biopsy, features resemble those of alcoholic liver disease. Prevalence data depend on the method used for detection

(ultrasonography, magnetic resonance imaging (MRI), or liver biopsy). Prevalence has been reported as up to 30% of the US population (Browning et al. 2004). NAFLD may progress and is expected to become the most common cause of cirrhosis and HCC in Western societies once HCV-related complications have peaked and started to regress (Davis et al. 2010). Currently, a lot of research, bench based, as well as clinical, is addressing this relatively newly discovered phenomenon. New diagnostic tools, in particular the elasticity liver scan, may make this disease easier to examine in large-scale population-based studies.

For data on the importance of nutrition on digestive cancers, we refer to chapter ▸Cancer Epidemiology of this handbook and Table 58.4.

In inflammatory bowel disease, a lot of effort has been devoted to the identification of nutritional risk factors, compromised by recall bias and problems of reverse causation. Due to the relative scarcity of the diseases, most investigators relied on retrospective studies. Since long time periods may elapse between the onset of symptoms and first diagnosis, eating patterns are usually already altered once patients become available for interview. There are now a few prospective studies looking into risk factors for IBD as secondary research aims, in particular EPIC (Hart et al. 2008). Unfortunately, as this cohort is conceptionalized for the investigation of causes of cancer, the population is rather old, and only an atypical subgroup of IBD patients presenting late is available.

More interestingly, in analogy to findings for atopic diseases, IBD seem to be associated with a "sheltered childhood," that is, improved hygienic conditions in infancy (Timmer 2003). Most likely, in genetically predisposed persons, insufficient priming results in an inappropriate immunological response to antigens, probably within the normal gut flora later in life (Baumgart and Carding 2007).

58.5 Clinical Epidemiology of Digestive Diseases

58.5.1 Overview

Clinical epidemiology and, as its application in clinical medicine, evidence-based medicine have a relatively long and successful history in the treatment of digestive diseases. This is reflected by a growing number of clinical practice guidelines taking into account the results of clinical research. Mega-trials, as encountered in cardiovascular diseases, are uncommon, making meta-analyses more important. Quality of life issues are particularly important in functional disorders, and there has been substantial work to develop validated instruments to measure patient-related outcomes of health interventions. However, there are still many underdeveloped areas in clinical epidemiology research.

Diagnostic and therapeutic options available to highly skilled endoscopists and ultrasonographers advance rapidly, and so must be the rigor in assessing the benefit of these procedures. Prognosis and surveillance in high-risk populations are prominent issues, in particular the prevention or early detection of complications

in chronic diseases. The clinical strategies to deal with these risks are often insufficiently corroborated by epidemiological data.

Lastly, pharmacoepidemiology in clinical digestive disease epidemiology is very important. Side effects on the digestive tract are the most common side effects of drugs, ranging from slight nausea to life-threatening gastrointestinal bleeding.

58.5.2 Examples

58.5.2.1 Therapy: Randomized Controlled Trials and the Cochrane Collaboration

The evidence base for therapy in digestive diseases varies substantially by entity. There is extensive clinical trial activity for IBD, HCV, and cancer. In contrast, for some of the more common conditions, the evidence base is surprisingly small. As an example, a PubMed search for randomized clinical trials (publication type) renders 1,104 trials for inflammatory bowel disease, but only 55 for diverticulitis (July 2010). For the latter, potential treatment options are relatively cheap. For example, a diet rich in fiber is commonly recommended to prevent recurrence despite absence of evidence of efficacy. In contrast, immunomodulating drugs as applicable in IBD, the duration of interferon therapy in viral Hepatitis, or individualized (antibody) therapy in colorectal cancer have severe commercial as well as health economical consequences.

For the treatment of HCV, combination therapy with interferon and ribavirin is effective (Brok et al. 2010). The virus can now be eliminated in about 50%, depending on viral genotype, age, sex, and coinfections, for example, with HBV or HIV. Very complex treatment recommendations tailor length of treatment to the various clinical situations (Mangia and Andriulli 2010), mostly supported by evidence from clinical trials and observational prognostic studies. Stepping back from the clinical context to a population perspective, the situation is sobering. In the Markow model cited above, treatment of Hepatitis C by combination of antiviral therapy was estimated to reduce the future risk of late complications (cirrhosis, death, HCC) in those infected today by just 1% (World Health Organization 2007). The problem is that an estimated 70% of infections remain undetected and only 25% of all detected cases are offered treatment. The effect of antiviral therapy on the prevalence on HCV-related morbidity will remain small unless awareness both of the infection and of the treatment options is improved along with the advances in efficacy.

Inflammatory bowel diseases are a good example for difficulties encountered when choosing appropriate endpoints for clinical trials in non-fatal diseases. There is considerable interindividual diversity of symptoms and signs which may indicate relapse or a severe disease course. No single phenomenon has been identified which might function as a useful outcome criterion in clinical trials on inflammatory bowel disease, in particular in Crohn's disease. Instead, a number of composite

indices have been developed to allow for standard assessment across patients with varying symptoms. The combination of time in or to remission, based on predefined thresholds of well-validated composite clinical activity scores, and the additional assessment of quality of life have been recommended for use in clinical trials (Sandborn et al. 2002; D'Haens et al. 2007). Unfortunately, at this time, there seems to be some falling back on a preference for surrogate measures of (so far) unproven prognostic relevance. They are not even easily assessable nor without risk for the patient. We allude to "mucosal healing," which requires endoscopy for visualization and is poorly correlated with patient symptoms (Rutgeerts et al. 2007).

Clinical trials are even more challenging in the functional diseases. In these disorders, not just the outcome criteria but also diagnosis and inclusion criteria require thoughtful definitions in order to avoid misclassification and advance generalizability.

Of specific concern are the new invasive procedures, such as endoscopic mucosal resection for early cancers of the esophagus and stomach or natural orifice transluminal endoscopic surgery (NOTES) for intra-abdominal operations. These emerging techniques require highly skilled interventional gastroenterologists or abdominal surgeons proficient in endoscopic techniques. Slow learning curves and restriction to highly specialized centers make these techniques difficult to evaluate, even more so than was previously the case for laparoscopic techniques (Sauerland et al. 2004; Keus et al. 2006).

As mega-trials are rare in digestive disease due to the relative rarity of most conditions, meta-analysis strongly features in gastroenterology and hepatology. Inflammatory bowel diseases were the first digestive diseases to be represented by a Cochrane review group. A Cochrane review group is a team within the Cochrane Collaboration which serves as an editorial basis for systematic reviews prepared for a specific group of diseases (see chapter ▸Clinical Epidemiology and Evidence-Based Health Care of this handbook). Currently, there are 52 of these groups worldwide. Four of them are devoted to digestive tract diseases (Table 58.6). Some disorders may be covered by other groups, such as acute diarrhea by the Infectious Diseases Group and fecal incontinence and rectal prolapse by the Incontinence Group. All groups keep specialized registries of clinical trials in the respective area, including hand search activities, screening conference abstracts, and journals not currently indexed in Medline, representing a useful resource for clinical researchers.

58.5.2.2 Diagnosis: Endoscopy and Symptom Scores

Many gastrointestinal diseases depend on invasive procedures for a definite diagnosis, making these diseases difficult to study in epidemiology. For example, in gastroesophageal reflux disease (GERD), there are structural correlates (esophagitis, acid reflux) to define the diagnosis, but these require upper endoscopy and, possibly, pH-metry.

In functional disease, such as non-ulcer dyspepsia and irritable bowel syndrome, there are no diagnostic signs. These are rather syndromes, requiring thoughtful definitions as discussed above. Even where internationally agreed on definitions are

Table 58.6 Cochrane groups covering digestive disease therapy and diagnosis

Name (year founded)	Location, web address	Scope
Inflammatory Bowel Diseases (1995) and Functional Bowel Disorders Group (renamed 2005)	London, Ontario, Canada http://www.cochrane.uottawa.ca/ibd/	Ulcerative colitis Crohn's disease Since 2005: other intestinal disorders including microscopic colitis, collagenous colitis, lymphocytic colitis, irritable bowel syndrome, chronic constipation, and diarrhea
Hepatobiliary Diseases Group (1996)	Copenhagen, Denmark http://ctu.rh.dk/chbg	Hepatic diseases, including alcoholic liver disease, Hepatitis B and C, cirrhosis of the liver, hepatic malignancies Biliary diseases, including gallstone diseases, infections, malignancies
Colorectal Cancer Group (1998)	Copenhagen, Denmark http://cccg.cochrane.org/	Colorectal, anal, and small bowel cancer Benign proctologic diseases Benign peritoneal diseases Surgical treatment for inflammatory bowel diseases Surgical anal diseases Abdominal hernias Appendiceal diseases Diverticulitis Peritonitis
Upper Gastrointestinal and Pancreatic Diseases Group (1998)	Hamilton, Ontario, Canada http://fhs.mcmaster.ca/ugpd/index.html	Disorders of the esophagus, stomach, duodenum, and pancreas

in place such as the Rome III criteria, these have a tendency to undergo frequent revisions and are subject to severe interrater disagreement (Vandvik et al. 2004).

Advanced diagnostic techniques develop rapidly in gastroenterology at this time. More and more new modifications become available, posing new challenges both with respect to the manual skills of the investigators, as to the technical equipment. Examples include contrast-enforced ultrasonography, the endoscopic capsule, virtual colonoscopy, endoscopic ultrasonography, chromo-endoscopy, virtual chromo-endoscopy, magnetic resonance imaging (MRI) of the small bowel or biliary-pancreatic ducts, and so forth. There is some risk that the technical and manual advances are not accompanied by thoughtful evaluation of diagnostic test accuracy, not to speak of the critical assessment of whether the procedure has an effect on outcome. At times, the ultimate goal of diagnosis (or any clinical maneuver) – make the patient better! – gets out of focus when enthused clinicians formulate clinical guidelines. More input from clinical epidemiologists would be desirable to help researchers adhere to good standards as set out in chapter ▸Clinical Epidemiology and Evidence-Based Health Care of this handbook.

58.5.2.3 Prognosis: Early Detection of Long-Term Complications of Gastrointestinal Disease

Gastroenterology and hepatology comprise many conditions associated with severe, potentially avoidable long-term consequences, some of them malignant. Generally in these conditions, the question arises if and how surveillance is appropriate to prevent or alleviate these complications.

Few conditions will inevitably result in cancer if untreated. An example is familial adenomatous polyposis (FAP) – all affected will develop colorectal cancer at an early age, and total proctocolectomy is recommended in the teenage years. More often, the risks are less well defined.

Long-standing extensive ulcerative colitis is associated with an increased risk of colon cancer. Data are conflicting, but cancer rates of up to 30% after 20 years have been reported (Eaden et al. 2001). Most clinical guidelines recommend regular surveillance colonoscopy from about 10 years after the diagnosis, depending on the extent of the inflammation in the bowel. More recent data have given rise to some controversy whether the risk is really that high.

There is a biliary condition associated with ulcerative colitis, primary sclerosing cholangitis, which is itself strongly associated with cholangiocarcinoma, but surveillance is more difficult. Visualization of the biliary system by endoscopic retrograde cholangiography (ERC) or the MRI equivalent (magnetic resonance cholangiography (MRC)) is required, with unproven, maybe improvable, effectiveness.

As pointed out before, cirrhosis of the liver may result in hepatocellular carcinoma (HCC); in fact, very few HCC develop in a non-cirrhotic liver. Tumor markers (alpha-fetoprotein, AFP) and ultrasonography used to be recommended for follow-up. More recently, AFP has been found of insufficient specificity and sensitivity and has been replaced by imaging techniques only (once yearly). The effectiveness of these schemes is still unclear.

Other examples include Barrett's esophagus, which corresponds to displaced gastric mucosa in the low esophagus. From Barrett's metaplasia, adenocarcinoma of the gastroesophageal junction or lower esophagus may develop. Most endoscopists would probably recommend regular follow-up of patients with Barrett's esophagus diagnosed via upper endoscopy, in particular if a longer segment is involved. However, this has, so far, not been shown to be effective. Most cases of Barrett's are undetected, as this condition, as GERD, correlates poorly with symptoms. As Barrett's metaplastic areas can now be removed by endoscopic resection, the role of screening by upper endoscopy might be reconsidered. So far, population screening for upper gastrointestinal disease is not recommended, and individual surveillance is only contemplated when Barrett's mucosa was detected by endoscopy performed for symptoms.

There are several conditions with markedly raised incidence ratios but low absolute risks of lymphoma or other malignancies. These include small bowel malignancy in celiac disease or Crohn's disease. Surveillance is not recommended in these cases. Similarly, screening for pancreatic cancer in chronic pancreatitis (which is a risk factor for pancreatic cancer) or new onset diabetes (which may be a symptom of advanced pancreatic cancer) is not helpful to improve survival in pancreatic cancer. And lastly, there is the unanswered question on how to

proceed following a diagnosis of an *H. pylori* infection in asymptomatic patients, as discussed above. So far, most gastroenterology societies do not recommend eradication to prevent gastric cancer, but the issue is still controversial.

In short, many conditions await critical assessment to help decide on the usefulness of surveillance programs. At this moment, for most cases, patients and clinicians are left with considerable uncertainty.

58.5.2.4 Assessment of Quality of Life in Persons with Digestive Diseases

Several of the more prevalent chronic gastrointestinal diseases have mortality rates close to those of the normal population but impact heavily on persons' daily functioning and life satisfaction. Quality of life research aims at assessing this impact, preferably from the patient's view (chapter ▸Health Services Research of this handbook). Health-related quality of life (HRQL) assessment is now firmly established in gastroenterological research (Glise and Wiklund 2002). In functional diseases, the impact of symptoms on HRQL may be the only measure that defines disease status. In chronic inflammatory disease and cancer, HRQL is now routinely used as an adjunct outcome measure in therapeutic trials. A good example is the inflammatory bowel disease questionnaire (IBDQ), developed by Guyatt et al. (1989). HRQL assessment is also important for health economical analyses and pharmacoeconomical evaluations.

Many instruments are available for use in digestive disease epidemiology, some of them well validated and translated to various languages (Borgaonkar and Irvine 2000). Most are multi-item instruments, appreciating aspects of physical well-being and functioning as well as emotional and social consequences of health. Generally, they can be classified as generic or disease specific, symptom or function oriented, and treatment specific (Wiklund 2007).

Generic instruments help to compare quality of life across various diseases or to the general population (Coons et al. 2000). With respect to physical symptoms, generic instruments tend to focus on issues of self-care and mobility – aspects that may be particularly important in joint disease or cancer, but would be expected of limited relevance in most gastrointestinal diseases. Even so, several of these instruments have been shown to work remarkably well in gastroenterology. Most often, the SF-36 and various modifications of this score have been used (Ware Jr. and Sherbourne 1992; Ware Jr. et al. 1996; Bernklev et al. 2005; Billingsley et al. 2007). Also, the 5-item EuroQol has been successfully validated in patients with various bowel and liver diseases (König et al. 2002; Spiegel et al. 2009). This instrument is particularly helpful in that it facilitates the calculation of health utilities (Stark et al. 2010).

Disease-specific quality of life instruments in gastroenterology are numerous. The Patient-Reported Outcome and Quality of Life Instruments Database (ProQolid, http://www.proqolid.org/) currently lists 30 different instruments for digestive diseases excluding cancer. A detailed overview on available instruments has been published a few years ago and is recommended for reference (Borgaonkar and Irvine 2000). The European Organization for Treatment of Cancer (EORTC) promotes a

modular approach to assessing quality of life in clinical trials. The core instrument QLQ-C30 assesses quality of life in cancer patients in general and is available in 81 languages (Aaronson et al. 1993). Additional modules have been developed for specific cancer entities, including many gastrointestinal sites (Sprangers et al. 1993). These can be found at the official EORTC website (http://groups.eortc.be/qol/index.htm).

58.5.2.5 Adverse Events, Pharmacoepidemiology, and Health Economics

Some of the most frequent side effects of drugs relate to the digestive system: nausea and vomiting, diarrhea, and constipation. All of these may have grave consequences for the management of patients, in particular in the elderly and in patients with cancer. Here we would like to focus on two other problems: NSAID-induced gastrointestinal bleeding and the various forms of hepatotoxicity.

Following the introduction of successful treatment schemes for *H. pylori*-associated associated peptic ulcer disease, drug related gastric lesions are now the most frequent reason for ulcer bleeding. The risk is particularly high with aspirin, followed by conventional NSAID's (Hawkey 2009). As often the elderly and the multimorbid are affected, mortality from gastrointestinal hemorrhage is substantial. The prevention of cardiovascular events by antiplatelet therapy on the one hand and the risk of gastrointestinal bleeding on the other hand need thoughtfully balanced consideration. The issue is further complicated by suspected interactions between antiplatelet (clopidogrel) and antiulcer treatment (proton pump inhibitors).

The short history of selective COX-2 inhibitors is an interesting example on how perspectives differ by clinical specialty. These drugs were expected to alleviate the substantial problem of severe gastrointestinal bleeding in patients depending on NSAID therapy. Most of these are patients with joint disease, often elderly. The drugs decreased ulcer bleeding but increased cardiac events.

Critics have noted the paradoxon that

> "COX-2 inhibitors and NSAIDs were found to increase risks of myocardial infarction and liver failure, while NSAIDs additionally caused hundreds of thousands of deaths from ulcer complications worldwide, (but) it were COX-2 inhibitors rather than NSAIDs that fell from favour" (Steinfeld and Bjorke 2002; Hawkey 2009).

As a side note, there are interesting methodological issues relating to these associations. For example, pharmacovigilance studies came to different conclusions as compared to randomized clinical trials with respect to the bleeding potential of selective COX-2 inhibitors due to insufficient control for confounding. This clinical problem has been used to illustrate the usefulness of propensity scores (Schneeweiss et al. 2006).

Drug-related liver toxicity is an interesting field in pharmacoepidemiology and a somewhat complex one. Different mechanisms apply: cell injury, cholestatic patterns or enzyme induction, and hypersensitivity. The clinical relevance may range from asymptomatic, transient liver enzyme elevation to acute life-threatening situations requiring urgent liver transplantation. Most cases are not reported, so the

true incidence is unknown. In the USA, hepatotoxicity is the most frequent reason for the Food and Drug Administration to take regulatory action (Navarro and Senior 2006). A recent example is troglitazone used for glycemic control in patients with diabetes, which was withdrawn in 2000 because of an increased risk of acute liver failure.

With respect to costs of medication, proton pump inhibitors are high up the list. Indications include heartburn and GERD, peptic ulcer disease, gastritis, and ulcer protection with antiplatelet therapy. Many patients use this medication lifelong.

There are quite a few situations where cost-oriented decision analyses have the potential to guide treatment recommendations. Besides lifelong drug treatment of GERD as opposed to surgical interventions (fundoplicatio), these concern, for example, screening and treating of *H. pylori*-positive persons in the absence of symptoms or inflammation, the treatment of viral Hepatitis in subgroups of patients with low chances of virus elimination, and the introduction of vaccines. Most of these issues have not been resolved.

58.6 Conclusions

In this chapter, we have highlighted the burden of various digestive diseases and some of the most important risk factors. Some previously important disorders are currently on the decline, some for unknown reasons, some due to improved living conditions, and some due to successful public health interventions. The retreat of peptic ulcer disease is most likely to fall in the category of hygiene-related diseases; the infectious agent has been identified (*H. pylori*). For appendicitis, the etiology is still unclear, and remarkably little research has been published although this is such a common condition. Good examples for successful public health interventions include screening for colorectal cancer and vaccination to prevent Hepatitis B virus infection. Squamous esophageal cancer is also on the decline, due to the decreasing prevalence of smoking and alcohol abuse in Western populations.

For other diseases, the burden is still expected to increase. These are, for example, the long-term sequelae of chronic Hepatitis C infection, non-alcoholic fatty liver disease as a previously undescribed manifestation of the metabolic syndrome, adenocarcinoma of the esophagus and gastroesophageal junction, and, possibly, functional disorders as well as those conditions associated with old age – NSAID-induced gastrointestinal hemorrhage, diverticulitis, and constipation, to name just a few.

A large proportion of the presented problems are preventable. There are strong associations with modifiable risk factors. Specifically, these include alcohol and i.v. drug abuse in the economically advanced societies and infections for which vaccinations and simple sanitary measures are available (Hepatitis B, rotavirus) in the developing world.

Digestive disease epidemiology seems to be difficult to grasp as an entity, as the conditions are so diverse. Also, there are no epidemiological methods specific to gastroenterology. However, we hope that the gastroenterologists' perspective is

helpful to bring some issues back into focus that may have run the risk of losing priority. Most urgently, this refers to acute diarrhea in low-income countries.

With the gut flora as the major part of the human microbiom increasingly acknowledged as potentially crucial in the pathogenesis of various disorders, both gastrointestinal as well as others, the digestive system may become more prominent in the study of health in the future. More input from methodologically advanced epidemiology would certainly be of help in many clinical decisions, such as surveillance of clinical populations at high risk for malignancy.

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