PART ONE

Gastrointestinal Diseases and Disorders: The Public Health Perspective

1 The burden of gastrointestinal and liver disease around the world

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Key points

- Gastrointestinal and liver diseases are among the most common diseases worldwide, with diarrheal disease, malignancies, and liver disease having a substantial toll on worldwide mortality.
- Many of these diseases are preventable and possibly curable.
- There is wide variability in the incidence, management, and mortality associated with these disease states throughout the world.
- Understanding trends in GI illness and the factors responsible for variability in incidence and outcomes will allow clinicians, public health professionals, policy makers, and healthcare organizations to intervene in a more logical way and allocate resources to meet the needs of afflicted patients and decrease the burden of gastrointestinal and liver diseases.

Introduction

Gastrointestinal and liver diseases represent a significant global health problem, and cause approximately 8 million deaths per year worldwide [1]. In developed countries, GI malignancies are among the leading causes of death. In developing countries, diarrheal disease and viral liver infections are highly prevalent and are responsible for significant mortality. These and other diseases are tracked by international and regional health organizations. These tracking measures allow for some assessment of the global burden of GI disease, and may allow identification of important temporal trends.

Below we highlight sources of burden of GI illness internationally. Using international databases, we will highlight some important trends in diarrheal disease and childhood mortality, explore the burden of gastrointestinal malignancies, and discuss the toll of several selected liver diseases. Because valid international estimates are not available for some gastrointestinal conditions, we report regional data with respect to the toll of other selected GI diseases.

Much of the data demonstrated below has been collected as part of various projects conducted by the World Health Organization (WHO). Geographical regions that are discussed throughout this chapter are based on the six officially delineated WHO regions: Africa, the Americas, Eastern Mediterranean, Europe, Southeast Asia, and Western Pacific. A map delineating each region can be found at: http://www.who.int/about/regions/en/index.html.

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Diarrheal disease

Global burden

An estimated 2.5 billion cases of diarrhea occur annually in children under five years of age [2], with an estimated frequency of 2–3 episodes per child per year in developing countries [3]. Diarrheal disease is the second leading cause of mortality in this age group worldwide, after pneumonia. Responsible for over 15 % of deaths of children less than five years of age, diarrheal disease accounts for more than 1.3 million deaths each year. It is also responsible for more deaths than HIV/AIDS, malaria, and measles combined [1].

Figure 1.1 displays the number of under-5 deaths secondary to diarrheal disease by WHO region. Diarrheal death is much more common in the developing world, with over 56 % of deaths occurring in Africa. Africa and Southeast Asia combined account for nearly 80 % of all under-5 diarrhea-related deaths. Furthermore, 75 % of childhood deaths attributable to diarrheal disease can be found in just 14 developing countries, led by India, Nigeria, and the Democratic Republic of the Congo [4]. This is largely due to contamination of drinking water and compromised sanitation in these countries. Children in these countries develop nutritional deficiencies, and are more susceptible to repeated episodes of diarrhea and severe dehydration, also contributing to the high incidence of mortality due to diarrhea in developing nations [2].

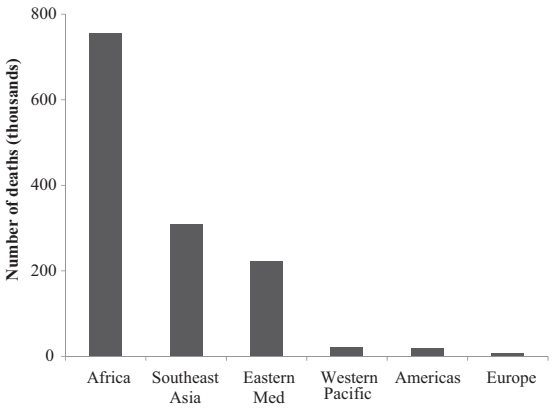

Figure 1.1 Deaths secondary to diarrheal disease among children aged <5 years by WHO region, 2008. Source: WHO Health statistics and health information systems – child mortality by cause.

Efforts to reduce the number of childhood deaths secondary to diarrheal disease in the 1970s and 1980s have favorably impacted the burden of diarrheal disease. These efforts included increasing oral rehydration therapy and the implementation of programs to educate caregivers on proper treatment. While the overall incidence rates of diarrheal disease have remained stable throughout the past three decades, there has been a decrease in diarrhea-associated deaths [3]. Estimates have shown a steady decline with 4.6 million deaths per year in the 1960s and 1970s, 3.3 million deaths per year in the 1980s, 2.5 million deaths per year in the 1990s, and 1.5 million deaths in 2004 [2, 5–7]. Despite this improvement, diarrhea continues to be an unacceptably common cause of childhood death, especially in developing countries.

Gastrointestinal malignancies

Global burden

Cancer is the leading cause of death in developed nations and is the second leading cause of death in developing nations [8]. GLOBOCAN is a WHO project which estimates the international burden of cancer using population-based cancer registries [9]. Gastrointestinal cancers were responsible for nearly one-third of new cancer cases in 2008. Table 1.1 displays incidence of, and mortality from, gastrointestinal cancers worldwide, as well as their rank among all major cancer sites. Colorectal cancer continues to have the highest incidence rate among gastrointestinal malignancies and is the third most commonly occurring cancer worldwide, with over 1.2 million new cases estimated in 2008. Hepatocellular, esophageal, and pancreatic cancers are of particular importance because of their high mortality; in fact, mortality-to-incidence ratios approach one internationally. Colorectal cancer is associated with a much better prognosis, with a mortality-to-incidence ratio of approximately 0.5. Assessment of the three most commonly occurring gastrointestinal malignancies worldwide demonstrates marked variation in incidence and mortality. Colorectal and gastric cancers will be discussed in the following two sections and liver cancer will be discussed in a later section.

Table 1.1 Incidence and mortality of gastrointestinal cancers worldwide, 2008

				Incidence			Mortality		
Rank among GI sites	Rank among all sites	Cancer site	ICD-10 code	Numbers	Crude rate†	ASR§	Numbers	Crude rate†	ASR§
1	3	Colorectum*	C18-21	1,235,108	18.3	17.3	609,051	9.0	8.2
2	4	Stomach	C16	988,602	14.6	14.1	737,419	10.9	10.3
3	6	Liver	C22	749,744	11.1	10.8	695,726	10.3	10.0
4	8	Esophagus	C15	481,645	7.1	7.0	406,533	6.0	5.8
5	13	Pancreas	C25	278,684	4.1	3.9	266,669	4.0	3.7
6	15	Lip, oral cavity	C00-08	263,020	3.9	3.8	127,654	1.9	1.9
7	21	Gallbladder	C23-24	145,203	2.2	2.0	109,587	1.6	1.5

Source: GLOBOCAN 2008.
*Includes anal cancer.
†Crude rates are per 100,000.
§ASR, age-standardized rates per 100,000.

Colorectal cancer

Colorectal cancer is the third highest incident cancer, and fourth most common cause of death from cancer worldwide, with over 609,000 deaths estimated in 2008. Approximately 60 % of colorectal cancer cases are found in developed regions; however, only approximately 53 % of deaths attributable to colorectal cancer are found in these same regions. Of note, the incidence rate of colorectal cancer in Africa is a small fraction of that in Europe, but is associated with cancer-related mortality in nearly all cases.

In the last three decades, the United States has witnessed a decrease in the incidence rate of colorectal cancer and an even greater decrease in the mortality rate. The extent to which decreasing colorectal cancer mortality can be attributed to earlier detection of colorectal cancer and improved methods of treatment is debated [10]. Unfortunately, those in less developed regions, where proper resources are lacking, suffer poorer prognoses.

Gastric cancer

Gastric cancer is the second most common gastrointestinal cancer and the fourth most common cancer worldwide. It was responsible for nearly 1 million new cancer cases and approximately 737,000 cancer deaths in 2008, making it the number one GI-related cancer killer worldwide. More than 70 % of the new cases and more than 75 % of deaths occurred in less developed regions. The incidence rate of gastric cancer is greatest in the Western Pacific, with nearly half of all cases being found in China (463,000 cases) and with highest incidence rates among the Republic of Korea and Japan. The lowest rates of gastric cancer can be found in Africa, Southeast Asia, and the Eastern Mediterranean regions. Regional variation may be partially attributed to differences in dietary patterns and the prevalence of *Helicobacter pylori* infection [8]. While gastric cancer is one of the leading causes of cancer death, individuals with gastric cancer in the Western Pacific tend to have better prognoses than those in other regions, possibly due to the increased use of screening methods and earlier detection of cancer [11].

Selected diseases of the liver

Hepatitis B

An estimated 2 billion people worldwide have been infected with the hepatitis B virus (HBV). More than 350 million people have chronic liver infections, and approximately 600,000 persons die annually due to acute or chronic consequences of the virus. Hepatitis B is estimated to be the cause of 30 % of cirrhosis and 53 % of hepatocellular carcinoma [12]. Hepatitis B is endemic in China and other parts of Asia, with most infections occurring during childhood, and 8–10 %

of the adult population being chronically infected. In contrast, less than 1 % of the population in Western Europe and North America is chronically infected [13].

In developing countries, HBV is largely transmitted during childbirth and early childhood infections. In developed countries, transmission is primarily through high-risk sexual behavior and IV drug use, as well as from migration of infected individuals from high prevalence areas [14]. Those infected at a young age are most likely to develop chronic infections. Whereas about 90 % of infants <1 year infected with HBV will develop chronic infections, about 90 % of healthy adults who are infected will completely recover within six months. Approximately 25 % of adults who become chronically infected during childhood die from HBV-related liver cancer or cirrhosis [15].

Hepatitis C

An estimated 3–4 million people are infected with hepatitis C virus (HCV) each year with a total of 130–170 million people chronically infected internationally. Additionally, more than 350,000 people die from hepatitis C-related liver diseases annually. Hepatitis C is estimated to be the cause of 27 % of cirrhosis and 25 % of hepatocellular carcinoma worldwide [12]. Although HCV infection is found worldwide, high rates of infection are found in Egypt (22 %), Pakistan (4.8 %), and China (3.2 %) [16]. The main mode of transmission in these countries is secondary to injections using contaminated needles. Other modes of transmission include contaminated blood transfusions, organ transplants, IV drug use with contaminated needles, and pre- or perinatal transmission from an HCV-infected mother.

Viral hepatitis in the United States

It is clear that the toll of hepatitis B and hepatitis C infections is significant worldwide. Interestingly, data from the US Centers for Disease Control and Prevention (CDC) demonstrates a decrease in reported cases and incidence of hepatitis B and C in the United States (Table 1.2) [17]. The incidence per 100,000 population of acute hepatitis B has decreased from 3.8 in 1998 to 1.3 in 2008. Also, the incidence per 100,000 population of acute hepatitis C has decreased from 1.3 in 1998 and has been ≤ 0.3 since 2003. The cause of these secular trends remains unclear, but may reflect changing practices in the IV drug user community, or a cohort effect.

Table 1.2 Incidence per 100,000 population of acute hepatitis B and hepatitis C in the United States by year, 1998–2008

	Hepatitis B		Hepatitis C	
Year	Number	Incidence	Number	Incidence
1998	10,258	3.8	3,518	1.3
1999	7,694	2.8	3,111	1.1
2000	8,036	2,9	3,197	1.1
2001	7,844	2.8	1,640[c]	0.7[c]
2002	8,064	2.8	1,223[d]	0.5[d]
2003	7,526	2.6	891[d]	0.3[d]
2004	6,212	2.1	758	0.3
2005	5,494	1.8	694	0.2
2006	4,713[a]	1.6[a]	802	0.3
2007	4,519	1.5	849	0.3
2008	4,033[b]	1.3[b]	878[b]	0.3[b]

Source: CDC Viral Hepatitis Statistics and Surveillance.
[a]Excludes cases from Arizona.
[b]Excludes cases from Delaware.
[c]Excludes cases from New Jersey and Missouri.
[d]Excludes cases from Missouri.

Liver cancer

Liver cancer is the third most common gastrointestinal cancer and the fifth most common cancer worldwide. Almost 750,000 new liver cancer cases and 700,000 deaths are estimated to have occurred in 2008, with over 80 % of new cases and deaths occurring in less developed regions. There were an estimated 694,000 deaths from liver cancer in 2008, and because of its high fatality (overall ratio of mortality to incidence of 0.93), liver cancer is the third most common cause of death from cancer worldwide. Within liver cancers, hepatocellular carcinoma constitutes the major histological subtype, accounting for 70–85 % of the total liver cancer toll worldwide. Cholangiocarcinomas (intra- and extrahepatic bile duct cancers) are relatively rare, but high rates have been found in areas such as Thailand and other parts of eastern Asia secondary to endemic liver fluke infection [8].

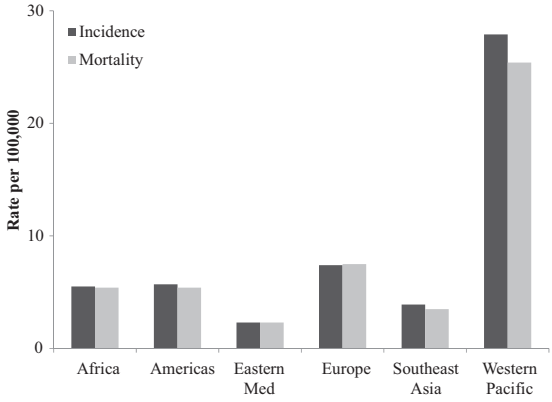

Figure 1.2 Incidence and mortality rates of liver cancer by WHO region, 2008. Source: GLOBOCAN 2008.

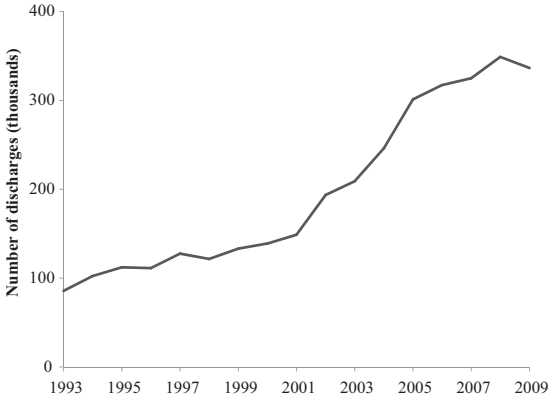

Figure 1.3 Trend of *Clostridium difficile* infection discharge diagnoses from hospital admissions, 1993–2009. Source: HCUP Nationwide Inpatient Sample (NIS), 1993–2009.

Figure 1.2 shows the distribution of liver cancer incidence and mortality by WHO region. The highest incidence and mortality rates are found in the Western Pacific, with more than half of new cases and deaths occurring in China [9]. Incidence and mortality rates are significantly lower in all other regions. The significantly higher incidence of liver cancer in the Western Pacific is largely due to the elevated prevalence of chronic hepatitis B virus (HBV) infection. HBV infection is responsible for approximately 60 % of total liver cancer in developing countries and for about 23 % of total liver cancer in developed countries [18]. Similarly, chronic hepatitis C virus (HCV) infection accounts for about 33 % and 20 % of total liver cancers in developing countries and developed countries, respectively.

Selected gastrointestinal diseases

Clostridium difficile infections

Clostridium difficile is a spore-forming, gram-positive bacillus that can cause disease ranging from mild diarrhea to fulminant colitis and death. This pathogen is recognized as the most common infectious cause of healthcare-related diarrhea [19]. Mutations that confer antibiotic resistance, increase toxin production, or facilitate sporulation have substantially increased the prevalence and virulence of this opportunistic pathogen [20]. During the mid and late 1990s, the reported incidence of *C. difficile* infection (CDI) in acute care hospitals in the United States remained stable at 30–40 cases per 100,000 population. In 2001, this number rose to almost 50 and continued to increase, resulting in 84 per 100,000 reported cases in 2005, a nearly threefold increase since 1996 [21]. Figure 1.3 displays the trend of US hospital discharge diagnoses of CDI over a 17-year period (1993–2009). Parallel to the increasing prevalence of this disease is its increasing severity and fatality. For example, in England, CDI was listed as the primary cause of death for 499 patients in 1999, 1998 patients in 2005, and 3393 patients in 2006 [21].

In addition, while CDI has traditionally affected elderly or severely ill hospital and nursing home patients, a 2005 US CDC advisory noted increased infection in populations not previously considered at risk, including young and healthy persons who have not been exposed to a hospital or healthcare environment or antimicrobial therapy [22]. Transmission in such cases may be attributable to close contact with patients who have CDI and direct person-to-person spread.

Gastroesophageal reflux disease

A major trend in gastroesophageal reflux disease (GERD) is an observed increase in its prevalence over the past two decades. Europe and North America have shown an increase in the prevalence of reflux symptoms, and studies of the same source population

over time have demonstrated an increase in prevalence in the United States, Singapore, and China [23]. Prevalence in Western countries has been estimated at 10–20 %, using criteria of at least weekly heartburn and/or acid regurgitation [24]. According to a review using the US National Ambulatory Medical Care Survey (NAMCS), the rate of US ambulatory care visits for GERD increased from 1.7 per 100 persons to 4.7 per 100 persons from 1990–1993 to 1998–2001 and continues to be a frequent cause of consultation in primary care [25].

The incidence of a GERD diagnosis and the demographic factors associated with the diagnosis were assessed using the UK General Practice Research Database [26]. In this study, 7159 patients were identified with a new GERD-related diagnosis in 1996, corresponding to an incidence among individuals aged 2–79 years of 4.5 new diagnoses per 1000 person-years. The incidence was age-related and increased with age until 69 years, with a slight decrease thereafter. Women had a slightly higher risk of developing GERD than men in patients over 50 years of age (rate ratio = 1.3).

Inflammatory bowel disease

Although a major cause of gastrointestinal illness and healthcare utilization, reliable data on inflammatory bowel disease rates are not available in most regions of the world. When examining the age-adjusted time trends of US physician visits secondary to Crohn's disease and ulcerative colitis (UC) from 1960–2006, physician visits for Crohn's disease increased almost fourfold over a 30-year period from the early 1960s to the early 1990s, from about 120 to 400 physician visits per 100,000 people. Since then, the rates of Crohn's disease visits appear to have leveled off. Physician visits for UC actually slightly decreased during the same 30-year period from about 400 to 300 physician visits per 100,000 people. With respect to sex differences, physician visits for Crohn's disease remained about 1.4-fold more frequent in women than men. Between 1960 and 1984, physician visits for UC were 1.3-fold more frequent by women than by men; however, during more recent periods, the rates of physician visits for UC by men and women have become more similar [27].

From 1951 to 2005, there has been a nearly 80 % decrease in mortality from UC from approximately 5.6 to 1.2 deaths per million population in a total of 21 countries [28]. On the other hand, from 1951 to 1975, mortality from Crohn's disease increased almost twofold from 0.8 to 1.5 deaths per million population. Since then, mortality from Crohn's disease has been decreasing and paralleling the trend of UC.

Gastrointestinal diseases responsible for hospitalization

While gastrointestinal illness is a major cause of hospitalization throughout the world, reliable data on hospitalization rates for various illnesses are not available internationally. Table 1.3 demonstrates the most common gastrointestinal and liver causes of hospitalization, ordered by number of reports at discharge, using the National Inpatient Sample, a 20 % stratified sample of US community hospitals. Acute pancreatitis, gallstone diseases, diverticulitis without hemorrhage, and acute appendicitis were each responsible for over 200,000 hospitalizations. Aspiration pneumonia was the fifth cause of hospitalization, and was also in the overall top 30 causes of hospitalization for any disease entity.

Limitations of the data

The data that were used for the above analyses are of the highest quality information available to assess the overall global burden of gastrointestinal diseases. However, there are some limitations that merit attention.

Ideally, all data would come from vital registries with complete coverage and medical certification of cause of death. For countries with incomplete or no vital registration system, epidemiologic studies, systematic reviews, and statistical modeling were used. For countries with incomplete data or no data regarding cause of death, the distribution of deaths was estimated using statistical models, proportional mortality, and natural history models. The 2008 estimates made available by the WHO were created using WHO's extensive databases and based on information provided by Member States, as well as on systematic reviews and analyses carried out by CHERG (the Child Health Epidemiology Reference Group).

Table 1.3 Most common gastrointestinal principal discharge diagnoses from hospital admissions, 2009*

Rank among GI dx	Rank among all dx	ICD-9-CM code(s)	Principal diagnosis	Total # Admissions	% Δ from 2000	Median LOS (days)	Total hospital days† (thousands)	Median costs (USD)	Aggregate cost (USD, thousands)	In-hospital deaths n (%)
1	21	577.0	Acute pancreatitis	274,119	+30	4.0	1,409	6,096	2,599,686	2,631 (1.0)
2	41, 76	574.0, 574.1	Cholelithiasis with cholecystitis‡	226,216	−14	3.0§	819	8,322§	2,208,531	959 (0.4)
3	27	562.11	Diverticulitis without hemorrhage	219,133	+41	4.0	1,099	6,077	2,115,989	1,235 (0.6)
4	29	540.9	Acute appendicitis	207,345	+22	1.0	362	6,592	1,491,402	90 (0.04)
5	30	507.0	Aspiration pneumonia	188,930	+6	6.0	1,475	9,030	2,523,299	22,273 (11.8)
6	37	558.9	Noninfectious gastroenteritis/colitis	151,856	+36	2.0	462	4,090	775,020	486 (0.3)
7	44	578.9	Gastrointestinal hemorrhage NOS	140,497	+22	3.0	612	6,090	1,155,971	4,914 (3.5)
8	46	560.9	Intestinal Obstruction NOS	134,431	+44	3.0	600	5,098	1,018,437	2,812 (2.1)
9	47	278.01	Morbid obesity	132,448	+314	2.0	288	10,689	1,642,293	137 (0.1)
10	57	8.45	*Clostridium difficile* infection	110,553	+237	5.0	761	6,774	1,119,213	4,038 (3.7)
11	73	560.81	Intestinal adhesions with obstruction	83,183	+23	7.0	736	11,853	1,453,238	2,265 (2.7)
12	94	8.8	Viral gastroenteritis	66,842	+29	2.0	181	3,677	298,507	108 (0.2)
13	96	530.81	Esophageal reflux	65,634	−32	2.0	162	4,366	386,229	n/a**
14	100	562.12	Diverticulosis with hemorrhage	64,222	−6	3.0	291	5,818	552,906	713 (1.1)

*Weighted national estimates from HCUP Nationwide Inpatient Sample (NIS), 2009, Agency for Healthcare Research and Quality (AHRQ). Total number of weighted discharges in the United States based on HCUP NIS = 39,434,956.

†Total hospital days per year for all persons with each diagnosis, estimated by the product of number of discharges and mean LOS.

‡ICD-9-CM codes for "calculus of gallbladder with acute cholecystitis" (574.0) and "calculus of gallbladder with other cholecystitis" (574.1) combined for this diagnosis. Total number of discharges, aggregate charges and costs, and in-hospital deaths represent sum from both.

§Median LOS and median costs presented for most common ICD-9-CM codes in this category (574.0).

**Too few events to generate a stable estimate in this category [(standard error/weighted estimate) > 0.30].

Dx, diagnosis; ICD-9-CM, *International Classification of Diseases*, 9th edition, Clinical Modification; %Δ, percent change; LOS, length of stay; USD, US dollars; NOS, not otherwise specified.

Incidence data for cancers are associated with some level of delay as this type of data requires time to be compiled; while the numbers within this chapter are the most current available, there is a several year time lag. More recent data about individual regions may be found in reports from the registries themselves. Information from most of the developing countries may be considered of relatively limited quality, but this information remains the only source of information for these regions. Mortality statistics collected and made available by the WHO have the advantages of national coverage and long-term availability; however, some datasets are of lesser quality than others. For some countries, coverage of the population is incomplete, resulting in low estimated mortality rates. In other countries, the quality of cause of death information is poor. While almost all the European and American countries have comprehensive death registration systems, most African and Asian countries (including the populous countries of Nigeria, India, and Indonesia) do not. Of course, a major concern regarding data from developing countries is detection bias. In countries with limited medical technology and resources, the burden of undiagnosed cancer is likely substantial and is not quantifiable.

Data for some of the selected gastrointestinal illnesses was not readily available from regional databases; therefore, the data in the above discussion is largely from studies that have accessed such primary databases and performed their own analyses.

Data derived from administrative databases, such as the NIS data, may suffer from the use of data primarily for billing purposes. Therefore, the fidelity of coding data to clinical information must be considered. The median and aggregate costs are estimates, calculated from hospital charges, and the data are by level of discharge (e.g. a single patient could be represented by multiple discharges). Also, in analyzing the trends, some trends may represent epiphenomena. For example, an increase in morbid obesity discharges may be due to increasing popularity of obesity surgery, for which morbid obesity is the principal coded discharge diagnosis.

Implications

Gastrointestinal and liver diseases are responsible for significant morbidity and mortality worldwide. The above statistics attest to the toll of these diseases. Beyond merely describing the terrible impact of these diseases, an understanding of the epidemiology of gastrointestinal and liver disease allows consideration of improvement of systems-based practices and public policy. Many individuals suffer from preventable disease states such as childhood diarrhea, malignancy, and various liver diseases. Millions of children annually die preventable deaths due to diarrheal disease. Cancer prognosis may be poorer in developing countries due to late detection and lack of access to resources and standard treatment. Numerous cases of gastrointestinal cancers could be prevented by vaccinations for viral hepatitis and improved screening, as well as by promoting physical activity, implementing programs for tobacco control, and healthier dietary intake. In addition, data should be updated regularly in order to track progress, as well as to spot temporal trends in disease burden that might merit reallocation of resources to address the changes.

Multiple choice questions

1 Which of the following is not associated with an increased incidence of childhood diarrhea?

A Inconsistent access to a clean water supply
B Residing in the WHO Africa or Southeast Asia region
C Chronic nutritional deficiencies
D Availability of oral rehydration solutions

2 Which GI-related malignancy resulted in the most estimated number of deaths in the year 2008?

A Colorectal cancer
B Stomach cancer
C Liver cancer
D Esophageal cancer
E Pancreatic cancer

3 Which gastrointestinal principal discharge diagnosis has had the greatest percentage increase from 2000 to 2009?

A *Clostridium difficile*
B Acute pancreatitis
C Morbid obesity
D Intestinal obstruction NOS
E Diverticulitis without hemorrhage

Appendix 1.A

Sources

Diarrheal disease

Estimates used in this section are based on data from the Global Health Observatory (GHO), a repository that provides access to over 50 datasets on priority health topics including mortality and burden of disease, produced by the World Health Organization (WHO) (http://apps.who.int/ghodata/). Estimates for the distribution of causes of death among children aged <5 years can be accessed through "World Health Statistics" → "Cause-specific mortality and morbidity" → "Causes of death among children" of the GHO data repository. Measurement and estimation methods can be found at: http://apps.who.int/gho/indicatorregistry/App_Main/view_indicator.aspx?iid=89.

In collaboration with the Child Health Epidemiology Reference Group (CHERG), the WHO Department of Health Statistics and Informatics prepared country-level estimates of child deaths under 5 years of age by cause for the year 2008. These estimates are derived from WHO databases, information provided by Member States, as well as systematic reviews and analyses carried out by CHERG. Country-level data was combined to achieve data for each WHO region. Mortality data on diarrheal disease and other causes of death in children aged <5 years, as well as the methods used to obtain these estimates can be accessed at: http://www.who.int/healthinfo/statistics/mortality_child_cause/en/index.html.

Gastrointestinal malignancies

The estimates used in this section are based on GLOBOCAN 2008, a standard set of worldwide estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC) under the auspices of WHO. This project was developed to provide up-to-date estimates of the incidence of, and mortality from major cancers for all nations in the world. GLOBOCAN allows individuals to obtain current estimates for major cancers categorized by region, sex, and age groups.

Incidence data were derived from population-based cancer registries, either national or subnational areas. In developing countries, incidence data is often available only from major cities. Mortality data was collected and provided by WHO. While not all datasets are complete and of the same quality (coverage of the population is incomplete or cause of death is inaccurate), it is the most accurate and thorough information available. Provisional estimates of age- and sex-specific deaths from cancer for 2008 have been used for regions without death information or where statistics are considered unreliable. National population estimates for 2008 were extracted from the United Nation (UN) population division's 2008 revision using geographical definitions as defined by the UN. The methods used to estimate incidence and mortality of cancers for each country can be found at GLOBOCAN data sources and methods: http://globocan.iarc.fr/.

Selected diseases of the liver

The data used in the discussions of hepatitis B and C are derived from WHO estimates of burden of disease. The WHO media center has over 100 fact sheets on various health-related topics such as different infections, disease states, and health risks, which can be found at: http://www.who.int/mediacentre/factsheets/en/. The hepatitis B and hepatitis C fact sheets were last updated in July 2012. The data included in the discussion about liver cancer is derived from GLOBOCAN 2008, discussed in the previous sources section.

Hepatitis B and hepatitis C trend data were obtained from the Centers for Disease Control and Prevention (CDC) – Viral Hepatitis Statistics and Surveillance, which can be found at: http://www.cdc.gov/hepatitis/Statistics/index.htm.

Gastrointestinal diseases responsible for US hospitalization

The most common inpatient gastroenterology and hepatology discharge diagnoses for the United States may be compiled using the Nationwide Inpatient Sample (NIS). The NIS is one of the databases in the Healthcare Cost and Utilization Project (HCUP) (http://hcupnet.ahrq.gov/). NIS is the only national hospital database with charge information on all patients, regardless of payer, including persons covered by Medicare, Medicaid, private insurance, and the uninsured. The most recent version, NIS 2009, contains all discharge data from 1050 hospitals located in 44 states, representing a 20 % stratified

sample of US community hospitals. The sampling frame for the 2009 NIS sample is a sample of hospitals that comprises approximately 95 % of all hospital discharges in the United States.

The NIS database was queried for the rank order of the principal discharge diagnosis (i.e. *International Classification of Diseases Clinical Modification*, 9th edition (ICD-9-CM) for all patients in all hospitals. From the top 100 diagnoses, we identified the gastroenterology and hepatology diagnoses among them, which were subsequently rank-ordered after combining related diagnosis codes. We then performed a separate query for each individual ICD-9-CM code (or group of codes) to acquire data on mean and median length of stay (LOS), median charges and costs, aggregate charges (i.e. "the national bill") and aggregate costs, and number of inpatient deaths associated with each diagnosis or diagnosis group. We also performed a temporal analysis for the number of admissions for the top principal GI diagnoses between the years 2000 and 2009 to identify relevant trends.

Total hospital days were estimated by the product of the mean LOS and the number of discharges for each diagnosis. Total charges were converted to costs by HCUP using cost-to-charge ratios based on hospital accounting reports from the Centers for Medicare & Medicaid Services (CMS). Cost data are presented preferentially, as costs tend to reflect the actual costs of production, while charges represent what the hospital billed for the case.

References

1 Global Health Observatory [Internet database]. World Health Organization (2008). Available from: http://apps.who.int/ghodata/ (accessed July 27, 2011).
2 Johansson E, Wardlaw T. (2009) *Diarrhoea: Why children are still dying and what can be done*, UNICEF/World Health Organization, New York/Geneva.
3 Boschi-Pinto C, Lanata CF, Black RE. (2009) The global burden of childhood diarrhea, in *Maternal and Child Health: Global Challenges, Programs, and Policies* (ed. J Ehiri), Springer, pp. 225–43.
4 Child mortality by cause [Internet database]. World Health Organization (2008). Available from: http://www.who.int/healthinfo/global_burden_disease/cod_2008_sources_methods.pdf (accessed July 27, 2013).
5 Snyder JD, Merson MH. The magnitude of the global problem of acute diarrhoeal disease: a review of active surveillance data. *Bull World Health Organ* 1982;60(4):605–13.
6 Bern C, Martines J, de Zoysa I, Glass RI. The magnitude of the global problem of diarrhoeal disease: a ten-year update. *Bull World Health Organ* 1992;70(6):705–14.
7 Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ* 2003;81(3):197–204.
8 Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA: Cancer J Clin* 2011;61(2):69–90.
9 Ferlay J, Shin HR, Bray F, et al. (2010) GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet database]. International Agency for Research on Cancer, Lyon, France. Available from: http://globocan.iarc.fr (accessed August 11, 2011).
10 Sandler RS. Editorial: colonoscopy and colorectal cancer mortality: strong beliefs or strong facts? *Am J Gastroenterol* 2010;105(7):1633–5.
11 Lee KJ, Inoue M, Otani T, et al. Gastric cancer screening and subsequent risk of gastric cancer: a large-scale population-based cohort study, with a 13-year follow-up in Japan. *Int J Cancer* 2006;118(9):2315–21.
12 Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 2006;45(4):529–38.
13 Hepatitis B [Internet database]. WHO Media centre. Available from: http://www.who.int/mediacentre/factsheets/fs204/en/index.html (last accessed May 6, 2013).
14 Ahmed F, Foster GR. Global hepatitis, migration and its impact on Western healthcare. *Gut* 2010;59(8):1009–11.
15 Te HS, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. *Clin Liver Dis* 2010;14(1):1–21, vii.
16 Hepatitis C [Internet database]. WHO Media centre. Available from: http://www.who.int/mediacentre/factsheets/fs164/en/index.html (accessed August 19, 2011).
17 Viral Hepatitis Statistics and Surveillance [Internet database]. Centers for Disease Control and Prevention (CDC). Available from: http://www.cdc.gov/hepatitis/Statistics/index.htm (accessed September 08, 2011).
18 Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006;118(12):3030–44.
19 Dubberke ER, Wertheimer AI. Review of current literature on the economic burden of *Clostridium difficile* infection. *Infect Control Hosp Epidemiol* 2009;30(1):57–66.

20 Freeman J, Bauer MP, Baines SD, et al. The changing epidemiology of *Clostridium difficile* infections. *Clin Microbiol Rev* 2010;23(3):529–49.
21 Kelly CP, LaMont JT. *Clostridium difficile* – more difficult than ever. *New Engl J Med* 2008;359(18):1932–40.
22 Centers for Disease Control and Prevention (CDC). Severe *Clostridium difficile*-associated disease in populations previously at low risk – four states, 2005. *MMWR Morb Mortal Wkly Rep* 2005;54(47):1201–5.
23 El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol* 2007;5(1):17–26.
24 Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;54(5):710–7.
25 Altman KW, Stephens RM, Lyttle CS, Weiss KB. Changing impact of gastroesophageal reflux in medical and otolaryngology practice. *Laryngoscope* 2005;115(7):1145–53.
26 Ruigomez A, Garcia Rodriguez LA, Wallander MA, et al. Natural history of gastro-oesophageal reflux disease diagnosed in general practice. *Aliment Pharmacol Ther* 2004;20(7):751–60.
27 Sonnenberg A, Chang J. Time trends of physician visits for Crohn's disease and ulcerative colitis in the United States, 1960–2006. *Inflamm Bowel Dis* 2008;14(2):249–52.
28 Sonnenberg A. Time trends of mortality from Crohn's disease and ulcerative colitis. *Int J Epidemiol* 2007;36(4):890–9.

Answers to multiple choice questions

1. D
2. B
3. C