Gastroenteritis of unknown etiology (GUE) is a significant cause of mortality in the United States. In the present study, the demographic and medical characteristics of people who died of GUE were examined, using the 1995–1997 Multiple Cause of Death files to calculate GUE death rates and proportionate mortality ratios. There were 13,153 GUE deaths during the period, or ~4400 deaths per year. Death rates were highest among infants and elderly persons, especially nursing home residents, and increased during the winter months. Compared with all decedents, GUE decedents were more likely to have certain other medical conditions, including bacteremia, volume depletion, renal failure, and human immunodeficiency virus/acquired immunodeficiency syndrome. Fatal GUE often appeared to be infectious in origin, but death certificates provide insufficient information to determine whether the causative agents were unknown or foodborne. The accuracy of GUE reporting on death certificates and the etiology of fatal GUE merit further investigation.

Gastroenteritis of unknown etiology (GUE) is a significant cause of mortality in the United States. Mead et al. [1] recently estimated that there are 5000 annual deaths due to GUE and attributed these deaths to unknown, predominantly foodborne agents. Information about deaths due to GUE is limited, hindering efforts to identify the sources of foodborne illness and improve the safety of the US food supply. The purpose of the present study is to examine the demographic and medical aspects of GUE mortality, using the 1995–1997 Multiple Cause of Death (MCD) files. GUE death rates by age, sex, and other factors were calculated to assess differences within the US population in exposure or susceptibility to unidentified infectious agents. The medical conditions associated with fatal GUE were also examined using information about the other causes of death for GUE decedents.

Previous studies of gastroenteritis mortality examined deaths due to all categories of gastroenteritis, including GUE, but did not describe GUE deaths in detail [2–7]. GUE is the most important category of gastroenteritis mortality, accounting for 77% of all gastroenteritis deaths in 1992–1996 [1]. Mead et al. [1] proposed that unknown agents were the sole cause of fatal GUE and estimated that 67% of GUE deaths were due to the foodborne transmission of these agents. There is evidence that unknown agents affect human health, because population-based surveillance has detected unexplained deaths that appeared to be caused by infections but were not associated with known pathogens [8]. There is also evidence that unknown agents may be transmitted by food, because the etiology of some well-documented outbreaks of foodborne illness has not been determined despite intensive investigations [9, 10], which suggests that unknown agents were responsible.

**MATERIALS AND METHODS**

**Source of data and definition of GUE.** Information about deaths due to GUE was obtained from the 1995–
1997 annual MCD files, which include most of the information recorded on death certificates [11]. The causes of death reported by physicians were coded by state vital statistics offices and the National Center for Health Statistics (NCHS), according to the International Classification of Diseases, Ninth Revision (ICD-9), and were listed on the entity-axis of each death record in the same sequence as on the death certificate [11, 12]. NCHS also assigned an underlying cause of death, defined as the medical condition that initiated the events leading to death. The 1995–1997 MCD files were combined for the present analysis, to reduce random variation in the number of deaths in small subpopulations. There were no significant changes in MCD coding or processing procedures during the 1995–1997 period.

Five ICD-9 codes identify GUE: 009.0–009.3 and 558 (table 1). The codes for gastroenteritis and diarrhea of presumed infectious origin (009.1 and 009.3) are invalid under World Health Organization and NCHS mortality coding procedures and were coded instead as 558 on the MCD files [12]. ICD-9 558 (other noninfectious gastroenteritis and colitis) also includes conditions described simply as “gastroenteritis” or “diarrhea,” as well as radiation, toxic, and allergic gastroenteritis. Most of the conditions coded as 558 are thought to be infectious in origin, despite the title for this category [13]. NCHS assigned additional ICD-9 codes on the MCD files that distinguished between radiation and toxic gastroenteritis. Conditions due to medical exposure to radiation, such as radiation gastroenteritis, were also coded as E879.2 (abnormal reaction to a radiological procedure or therapy) [12]. Conditions qualified as “toxic,” such as toxic gastroenteritis, were assigned 2 additional codes that specified the nature of poisoning and the external cause whenever poisoning was also mentioned on the death certificate [12].

A GUE death was defined as any death of a US resident with an ICD-9 code of 009.0, 009.2, or 558 on the entity-axis of the death record, excluding deaths with a 558 code that were due to radiation or toxic gastroenteritis. Deaths with a 558 code were considered to be radiation or toxic gastroenteritis deaths if a code for toxic poisoning or an abnormal reaction to a radiological procedure or therapy appeared on the same line or 1 line after 558 on the death certificate, when 558 was an immediate or intervening cause of death, or on the same line when 558 was an underlying or contributing cause. Deaths due to allergic gastroenteritis, coded as ICD-9 558, could not be distinguished from GUE deaths, but the number of such deaths likely was small. Previous studies of gastroenteritis mortality have also used ICD-9 009.0, 009.2, and 558 to identify GUE deaths but did not exclude radiation or toxic gastroenteritis deaths [1–3, 6].

**Analysis of GUE mortality.** The causes of death for GUE decedents were examined to determine how often GUE was the underlying cause of death and how often physicians reported that GUE was infectious in origin, as indicated by ICD-9 codes 009.0 (infectious gastroenteritis) or 009.2 (infectious diarrhea). Average annual age-adjusted GUE death rates by age, sex, race, and region were calculated to identify variations in the risk of fatal GUE. Population denominators for death rates were obtained from 1995–1997 annual postcensal estimates of the US resident population by age, sex, race, and state [14–16].

Death rates were computed by dividing the number of GUE deaths during 1995–1997 by the sum of the midyear (July) 1995–1997 populations for the specified group and age-adjusting on the basis of the 2000 US standard population [17]. Infant deaths were divided into neonatal and postneonatal deaths, and average annual neonatal and postneonatal mortality rates were calculated using the sum of 1995–1997 births as the denominator [18]. Three race categories (whites, blacks, and other races) were examined, but death rates were only calculated for whites and blacks, because mortality is known to be underestimated for other races [19]. Deaths were classified by residence using the 9 US census divisions, each of which consisted of 3–9 contiguous states [20].

GUE death rates excluding decedents with human immunodeficiency virus (HIV)/AIDS were also calculated to determine the effect of HIV/AIDS on GUE mortality patterns. Decedents with HIV/AIDS included any death with an ICD-9 code for HIV/AIDS (042.0–044.9). Seasonal variations in GUE mortality were analyzed by computing monthly GUE death rates. Population denominators were obtained from monthly postcensal estimates of the US resident population by age [14]. The monthly death rates were age-adjusted and plotted to identify seasonal patterns.

The number of GUE deaths was subject to random variation, so a 95% confidence interval (CI) was calculated for each death rate. Deaths were assumed to be distributed as a Poisson variable when there were <100 deaths in a group and as a binomial variable in other cases, in conformity with NCHS procedures [21]. The postcensal population estimates used to compute death rates were not subject to sampling error.

The proportion of GUE deaths in medical facilities, nursing homes, and other places was examined using information about the place of death. Approximate GUE death rates for elderly persons (≥65 years old) who lived in nursing homes and other

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**Table 1. International Classification of Diseases, Ninth Revision (ICD-9) codes for gastroenteritis of unknown etiology.**

<table>
<thead>
<tr>
<th>ICD-9 code</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>009.0</td>
<td>Infectious colitis, enteritis, and gastroenteritis</td>
</tr>
<tr>
<td>009.1a</td>
<td>Colitis, enteritis, and gastroenteritis of presumed infectious origin</td>
</tr>
<tr>
<td>009.2</td>
<td>Infectious diarrhea</td>
</tr>
<tr>
<td>009.3a</td>
<td>Diarrhea of presumed infectious origin</td>
</tr>
<tr>
<td>558</td>
<td>Other noninfectious gastroenteritis and colitis</td>
</tr>
</tbody>
</table>

*a* Invalid code on 1979–1998 Multiple Cause of Death files.
settings were also calculated. Exact death rates could not be determined, because an unknown number of nursing home residents were transferred to medical facilities before death, and a medical facility was reported as the place of death. Instead, a lower limit of the death rate for nursing home residents and an upper limit of the death rate for other elderly persons were calculated by assuming that GUE deaths in nursing homes included all nursing home residents who died from GUE. The true GUE death rate was likely to be higher for nursing home residents and lower for other elderly persons, depending on how many fatal GUE cases were transferred from nursing homes to medical facilities before death. The size and age distribution of the elderly nursing home population was estimated using the 1995 and 1997 National Nursing Home Surveys (NNHS) [22, 23]. The 1995 and 1997 NNHS estimates were averaged to obtain the 1996 nursing home population, and the other elderly population was determined by subtraction from the total elderly population. The GUE death rate for each population was age-adjusted, and approximate 95% CIs were calculated using a formula provided by NCHS, because the public-use version of the NNHS files does not include the information needed to determine exact SEs [21, 24].

Other causes of death. The association between fatal GUE and other medical conditions was investigated by examining every condition reported on ≥2% of GUE death records. Each of the 5570 ICD-9 codes used on the MCD files was treated as a separate condition, with 2 exceptions. The codes for HIV/AIDS (042.0–044.9) were combined, because the individual codes were not relevant for the analysis. The codes for extreme immaturity (765.0) and other preterm infants (765.1) were also combined, because these conditions were unlikely to be consistently differentiated on death certificates. The combined codes identify infants with short gestations (<38 weeks) or low birth weights (<2500 g).

The relationship between GUE and each medical condition was evaluated using a proportionate mortality ratio (PMR) to determine whether GUE decedents were more likely to have the condition than all decedents. Previous studies have used PMRs in this manner to investigate hemochromatosis and neurofibromatosis mortality [25, 26]. The PMR for a specified condition was defined as the observed number of GUE deaths associated with the condition divided by the expected number of GUE deaths associated with the condition [27]. The expected number of deaths was determined by multiplying the number of GUE deaths by the proportion of all deaths associated with the specified condition. Each PMR was standardized by sex and age, using 8 age groups (<1, 1–4, 5–14, 15–44, 45–64, 65–74, 75–84, and ≥85 years). Following procedures used by the National Institute for Occupational Safety and Health, 95% CIs were computed by assuming that GUE deaths were distributed as a Poisson variable when there were ≤1000 deaths with the specified condition and as a binomial variable in other cases [28]. The value of each PMR indicates whether GUE decedents were more likely (PMR > 1.0), equally likely (PMR = 1.0), or less likely (PMR < 1.0) to have the specified condition than all decedents. The conditions associated with GUE were likely to vary by age, so PMRs were also calculated for each condition reported on ≥5% of the GUE death records for infants, nonelderly persons (aged 1–64 years), or elderly persons (aged ≥65 years). The expected number of GUE deaths associated with each condition was determined in comparison to all deaths for the relevant age group.

RESULTS

There were 13,153 deaths involving GUE during 1995–1997, an average of 4384 GUE deaths/year. This estimate excludes 818 deaths from radiation gastroenteritis and 11 deaths from toxic gastroenteritis. GUE was the underlying cause of death for 34.2% of GUE decedents (table 2). GUE was more likely to be the underlying cause of death for decedents aged <15 years old than for older decedents. Only 10.3% of fatal GUE cases were reported to be infectious in origin, but the proportion of infectious cases was much higher for infants (81.1%) than other age groups. Approximately 2 of every 1000 deaths involved GUE. GUE was a more important cause of death for young children than older persons and was mentioned in 1.0% of all deaths of persons aged <5 years old, including 2.7% of postneonatal deaths (data not shown).

The characteristics of GUE decedents are summarized in table 3. Most (74.3%) were elderly. A majority (57.1%) were female, and most (86.1%) were white. Only a small proportion (1.5%) were other races, a category that included American Indians, Native Alaskans, Asians, and Pacific Islanders.

GUE death rates. The average annual age-adjusted GUE

<table>
<thead>
<tr>
<th>Age at death, years</th>
<th>Underlying cause of death was GUE</th>
<th>GUE was infectious</th>
<th>Proportion of all deaths due to GUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>34.2</td>
<td>10.3</td>
<td>0.2</td>
</tr>
<tr>
<td>&lt;1</td>
<td>74.6</td>
<td>81.1</td>
<td>1.1</td>
</tr>
<tr>
<td>1–4</td>
<td>61.2</td>
<td>14.6</td>
<td>1.0</td>
</tr>
<tr>
<td>5–14</td>
<td>51.9</td>
<td>13.0</td>
<td>0.2</td>
</tr>
<tr>
<td>15–44</td>
<td>15.4</td>
<td>5.8</td>
<td>0.2</td>
</tr>
<tr>
<td>45–64</td>
<td>27.0</td>
<td>6.9</td>
<td>0.1</td>
</tr>
<tr>
<td>≥65</td>
<td>32.6</td>
<td>4.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

NOTE. Data are % of deaths.

a The International Classification of Diseases, Ninth revision codes assigned for GUE were either 009.0 (infectious gastroenteritis) or 009.2 (infectious diarrhea).
postneonatal mortality was 7 times higher than neonatal mortality (P < .001). GUE mortality was 12% higher for males than females (P < .001) and 21% higher for blacks than whites (P < .001). GUE mortality also varied by region. The death rate was higher than the national average in the New England (P < .001) and East North Central (P = .006) census divisions but lower than the national average in the Mountain (P = .004) and West North Central (P = .014) census divisions.

The sex and racial differences in GUE mortality were reduced when the 740 decedents with HIV/AIDS were excluded, because these individuals were disproportionately male (84%) and black (39%). In contrast, the age and regional differences were largely unaffected. When HIV/AIDS decedents were excluded, the GUE death rate was 4% higher for males than females (P = .020) and 8% higher for blacks than whites (P = .020) (data not shown). The racial difference in mortality was greatest during infancy, when the death rate was >4 times higher for blacks than whites (P < .001) (figure 1). The racial difference decreased after infancy and was reversed at the oldest ages, with the white death rate exceeding the black death rate at ages 75–84 years (P = .025) and ≥85 years (P < .001). The age pattern of mortality was J-shaped for whites but U-shaped for blacks because of the higher mortality among black infants and lower mortality among blacks aged ≥75 years.

There were regular seasonal variations in the monthly age-adjusted GUE death rate during 1995–1997 (figure 2). For each year, the death rate increased during the winter months and decreased during the summer months. The maximum monthly death rate, in December or January, was 52%–70% higher than the minimum monthly death rate, in August or September. Approximately 47% of GUE deaths occurred during the 5 months from December through April, a period that included 41% of the calendar year.

Most GUE deaths occurred in inpatient hospital facilities (63%) or other medical settings (6%), but 18% were in nursing homes and 11% were in residences. Nearly all (96%) of the deaths per 100,000 persons during 1995–1997 was 1.70 (95% CI, 1.67–1.73) (table 3). The death rate was higher for infants and elderly persons than other age groups, reaching a maximum of 32.73 for persons aged ≥85 years. Among infants, postneonatal mortality was 7 times higher than neonatal mortality (P < .001). GUE mortality was 12% higher for males than females (P < .001) and 21% higher for blacks than whites (P < .001). GUE mortality also varied by region. The death rate was higher than the national average in the New England (P < .001) and East North Central (P = .006) census divisions but lower than the national average in the Mountain (P = .004) and West North Central (P = .014) census divisions.

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**Table 3.** Distribution of deaths due to gastroenteritis of unknown etiology (GUE) and average annual GUE death rate, United States, 1995–1997.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Deaths due to GUE, no. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Average annual GUE death rate (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>13,153 (100.0)</td>
<td>1.70 (1.67–1.73)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>913 (6.9)</td>
<td>8.04 (7.51–8.56)</td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>108 (0.8)</td>
<td>0.93 (0.75–1.11)</td>
</tr>
<tr>
<td>1–11 months</td>
<td>805 (6.1)</td>
<td>6.90 (6.42–7.38)</td>
</tr>
<tr>
<td>1–4 years</td>
<td>178 (1.4)</td>
<td>0.38 (0.33–0.44)</td>
</tr>
<tr>
<td>5–14 years</td>
<td>54 (0.4)</td>
<td>0.05 (0.04–0.07)</td>
</tr>
<tr>
<td>15–24 years</td>
<td>50 (0.4)</td>
<td>0.05 (0.04–0.07)</td>
</tr>
<tr>
<td>25–34 years</td>
<td>308 (2.3)</td>
<td>0.26 (0.23–0.29)</td>
</tr>
<tr>
<td>35–44 years</td>
<td>554 (4.2)</td>
<td>0.43 (0.39–0.47)</td>
</tr>
<tr>
<td>45–64 years</td>
<td>533 (4.1)</td>
<td>0.55 (0.50–0.60)</td>
</tr>
<tr>
<td>55–64 years</td>
<td>795 (6.0)</td>
<td>1.24 (1.15–1.33)</td>
</tr>
<tr>
<td>65–74 years</td>
<td>2103 (16.0)</td>
<td>3.76 (3.60–3.92)</td>
</tr>
<tr>
<td>75–84 years</td>
<td>3934 (30.9)</td>
<td>11.44 (11.08–11.80)</td>
</tr>
<tr>
<td>≥85 years</td>
<td>3731 (28.4)</td>
<td>32.73 (31.68–33.78)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5642 (42.9)</td>
<td>1.80 (1.75–1.84)</td>
</tr>
<tr>
<td>Female</td>
<td>7511 (57.1)</td>
<td>1.60 (1.56–1.63)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>11,330 (86.1)</td>
<td>1.66 (1.63–1.69)</td>
</tr>
<tr>
<td>Black</td>
<td>1622 (12.3)</td>
<td>2.01 (1.91–2.11)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;c&lt;/sup&gt;</td>
<td>201 (1.5)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Census division&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New England</td>
<td>822 (6.2)</td>
<td>1.92 (1.79–2.05)</td>
</tr>
<tr>
<td>Middle Atlantic</td>
<td>1959 (14.9)</td>
<td>1.62 (1.55–1.69)</td>
</tr>
<tr>
<td>East North Central</td>
<td>2333 (17.7)</td>
<td>1.81 (1.74–1.89)</td>
</tr>
<tr>
<td>West North Central</td>
<td>951 (7.2)</td>
<td>1.57 (1.47–1.67)</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>2341 (17.8)</td>
<td>1.63 (1.57–1.70)</td>
</tr>
<tr>
<td>East South Central</td>
<td>822 (6.2)</td>
<td>1.76 (1.64–1.88)</td>
</tr>
<tr>
<td>West South Central</td>
<td>1347 (10.2)</td>
<td>1.75 (1.66–1.85)</td>
</tr>
<tr>
<td>Mountain</td>
<td>633 (4.8)</td>
<td>1.52 (1.40–1.64)</td>
</tr>
<tr>
<td>Pacific</td>
<td>1945 (14.8)</td>
<td>1.74 (1.66–1.82)</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; NA, not applicable.

<sup>a</sup> Percentages within categories may not equal 100.0 because of rounding.

<sup>b</sup> No. of deaths/100,000 population except for infants <1 and 1–11 months old, where denominator is 100,000 births. Age-adjusted using the 2000 US standard population.

<sup>c</sup> American Indians, Alaskan Natives, Asians, and Pacific Islanders.

<sup>d</sup> States included in each census division are New England: CT, MA, ME, NH, RI, and VT; Middle Atlantic: NJ, NY, and PA; East North Central: IL, IN, MI, OH, and WI; West North Central: IA, KS, MO, MN, NE, ND, and SD; South Atlantic: DC, DE, FL, GA, MD, NC, SC, VA, and WV; East South Central: AL, KY, MS, and TN; West South Central: AR, LA, OK, and TX; Mountain: AZ, CO, ID, MT, NM, UT, and WY; and Pacific: AK, CA, HI, NV, OR, and WA.
Gastroenteritis of Unknown Etiology. Twenty-one conditions had a PMR fluid disorders. anemia, short gestation/low birth weight, and electrolyte and a variety of disorders—notably, shock, renal failure, HIV/AIDS, was volume depletion. The other associated conditions included comparison with all deaths. The second most common condition 3.93 times (95% CI, 3.84–4.01) more often than expected, in which was mentioned in 16.4% of GUE deaths and occurred associated condition was unspecified septicemia (bacteremia), were associated with fatal GUE (table 4). The most common conditions were short gestation/low birth weight and bacter- arrest, and pneumonia in 2 age groups. The most common failures in all 3 age groups and with respiratory arrest, cardiac characteristics are consistent with gastrointestinal infections of unknown etiology, United States, 1995–1997.

DISCUSSION

The present study confirms that GUE is a significant cause of death in the United States. GUE was associated with ~4400 deaths/year during 1995–1997. The annual number of GUE deaths was comparable to the mortality burden from 3 diseases with infectious etiologies: cervical cancer (4400 deaths), rheumatic fever and heart disease (4800 deaths), and hepatitis B virus infections (4400–6000 deaths) [29–31]. The estimate of 4400 annual GUE deaths is 12% lower than the estimate of 5000 annual GUE deaths by Mead et al. [1], in part because the present study excluded nearly 300 annual radiation and toxic gastroenteritis deaths. The present study also relied exclusively on death certificate data, whereas Mead et al. [1] averaged separate estimates on the basis of death certificate and hospital discharge data. The use of hospital discharge data to estimate the number of GUE deaths is problematic, because 29% of the GUE deaths reported on death certificates occurred outside medical facilities.

The MCD files provide considerable information about the demographic and medical characteristics of GUE deaths. The underlying cause of death for 66% of GUE decedents was a medical condition other than GUE, which suggests that fatal GUE usually occurred in individuals who were already ill and were probably more susceptible to infection. However, only 10% of fatal GUE cases were reported to be infectious, as indicated by the proportion of deaths with ICD-9 009.0 or 009.2 codes. Physicians may have described other GUE cases as presumed infections, but these cases could not be identified because the ICD-9 codes for gastroenteritis and diarrhea of presumed infectious origin (009.1 and 009.3) were not used on the MCD files.

GUE deaths in children had strikingly different characteristics from other GUE deaths. GUE was the predominant underlying cause of death for GUE decedents <15 years old, and most fatal GUE in infants was reported to be infectious. Both characteristics are consistent with gastrointestinal infections that were recognized at the time of death, although the causative agent was not reported on death certificates. GUE was also a more important cause of mortality for infants and young children than older persons, particularly during the postneonatal
Table 4. Medical conditions associated with ≥2% of deaths due to gastroenteritis of unknown etiology (GUE), United States, 1995–1997.

<table>
<thead>
<tr>
<th>Medical condition (ICD-9 code)</th>
<th>GUE deaths associated with condition, %</th>
<th>Proportionate mortality ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unspecified septicemia (038.9)</td>
<td>16.4</td>
<td>3.93 (3.84–4.01)</td>
</tr>
<tr>
<td>Volume depletion (276.5)</td>
<td>13.1</td>
<td>9.63 (9.48–9.77)</td>
</tr>
<tr>
<td>Respiratory arrest (799.1)</td>
<td>9.7</td>
<td>1.11 (1.05–1.16)</td>
</tr>
<tr>
<td>Pneumonia, organism unspecified (486)</td>
<td>9.6</td>
<td>1.18 (1.13–1.24)</td>
</tr>
<tr>
<td>Chronic airway obstruction, n.e.c. (496)</td>
<td>8.5</td>
<td>1.13 (1.07–1.19)</td>
</tr>
<tr>
<td>Shock without mention of trauma (785.5)</td>
<td>7.3</td>
<td>3.20 (3.00–3.41)</td>
</tr>
<tr>
<td>Renal failure, unspecified (586)</td>
<td>6.5</td>
<td>1.78 (1.67–1.91)</td>
</tr>
<tr>
<td>HIV/AIDS (042.0–044.9)</td>
<td>5.6</td>
<td>4.03 (3.75–4.33)</td>
</tr>
<tr>
<td>Unspecified protein-calorie malnutrition (263.9)</td>
<td>5.1</td>
<td>3.90 (3.61–4.21)</td>
</tr>
<tr>
<td>Anemia, unspecified (285.9)</td>
<td>4.2</td>
<td>2.88 (2.65–3.13)</td>
</tr>
<tr>
<td>Short gestation/low birth weight (765.0, 765.1)</td>
<td>4.0</td>
<td>1.24 (1.13–1.35)</td>
</tr>
<tr>
<td>Hemorrhage of gastrointestinal tract, unspecified (578.9)</td>
<td>3.7</td>
<td>2.56 (2.34–2.80)</td>
</tr>
<tr>
<td>Atrial fibrillation and flutter (427.3)</td>
<td>3.6</td>
<td>1.47 (1.34–1.61)</td>
</tr>
<tr>
<td>Acute renal failure, unspecified (584.9)</td>
<td>3.6</td>
<td>3.32 (3.03–3.64)</td>
</tr>
<tr>
<td>Urinary tract infection, site not specified (599.0)</td>
<td>3.5</td>
<td>2.31 (2.11–2.53)</td>
</tr>
<tr>
<td>Cardiac dysrhythmia, unspecified (427.9)</td>
<td>3.4</td>
<td>1.21 (1.10–1.33)</td>
</tr>
<tr>
<td>Unspecified chronic organic brain syndrome (294.9)</td>
<td>3.3</td>
<td>1.88 (1.71–2.07)</td>
</tr>
<tr>
<td>Unspecified disorder of kidney and ureter (593.9)</td>
<td>2.8</td>
<td>1.91 (1.72–2.11)</td>
</tr>
<tr>
<td>Pneumonitis due to inhalation of food or vomitus (507.0)</td>
<td>2.7</td>
<td>1.39 (1.25–1.54)</td>
</tr>
<tr>
<td>Electrolyte and fluid disorders, n.e.c. (276.9)</td>
<td>2.1</td>
<td>10.03 (8.89–11.29)</td>
</tr>
<tr>
<td>Unspecified vascular insufficiency of intestine (557.9)</td>
<td>2.1</td>
<td>6.03 (5.32–6.79)</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; HIV, human immunodeficiency virus; ICD-9, International Classification of Diseases, Ninth revision; n.e.c., not elsewhere classified.

period. On the basis of the definition used in the present study, GUE would have been the sixth leading cause of death for postneonates in 1997, after sudden infant death syndrome, congenital anomalies, accidents, pneumonia and influenza, and homicide [32]. There were large variations in the risk of death from GUE, especially by age. GUE death rates were substantially higher among infants and elderly persons than other age groups, and the age pattern of mortality resembled that for all categories of gastroenteritis combined [3]. Individuals ≥75 years old had the highest GUE death rates and accounted for 58% of all GUE deaths. Infants had the second highest GUE death rate and accounted for 7% of deaths. The age pattern of GUE mortality may reflect age-related variations in exposure or susceptibility to unknown agents. Elderly persons are particularly susceptible to many foodborne agents because of changes in the immune and gastrointestinal systems during aging [33, 34].

The higher mortality rate from GUE during the postneonatal period than the neonatal period was unusual, because infant mortality from most major causes of death is lower during the postneonatal period [32]. One exception was infectious disease, which caused more deaths among postneonates than neonates [35]. The lower GUE mortality rate among neonates was not an artifact of the modified ICD-9 coding procedures for the MCD files, because the coding of infant gastroenteritis did not depend on age [12].

Elderly nursing home residents had the highest risk of GUE mortality of any group examined in the present study and accounted for 17% of all GUE deaths, although they represent <1% of the US population. The risk of fatal GUE was >4 times higher for elderly nursing home residents than other elderly persons, which confirms that GUE was a special problem for nursing home residents [3]. The difference in GUE mortality between nursing home residents and other elderly persons is almost certainly understated, because some persons with fatal GUE were probably transferred from nursing homes to medical facilities before death and, therefore, were classified in the present study as “other elderly” persons. One study of nursing home residents found that one-fourth of those who died were discharged to a hospital before death [36]. If a similar proportion of nursing home residents with fatal GUE were hospitalized before death, then the GUE death rate has been substantially underestimated for nursing home residents and overestimated for other elderly persons.
Table 5. Medical conditions associated with \( \geq 5\% \) of deaths due to gastroenteritis of unknown etiology (GUE) in specified age group, United States, 1995–1997.

<table>
<thead>
<tr>
<th>Age group, medical condition (ICD-9 code)</th>
<th>GUE deaths in age group with condition, %</th>
<th>Proportionate mortality ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants, &lt;1 year old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short gestation/low birth weight (765.0, 765.1)</td>
<td>56.2</td>
<td>1.21 (1.11–1.32)</td>
</tr>
<tr>
<td>Unspecified septicemia (038.9)</td>
<td>20.4</td>
<td>12.13 (10.45–14.00)</td>
</tr>
<tr>
<td>Shock without mention of trauma (785.5)</td>
<td>11.3</td>
<td>4.70 (3.83–5.71)</td>
</tr>
<tr>
<td>Respiratory arrest (799.1)</td>
<td>10.8</td>
<td>3.61 (2.93–4.39)</td>
</tr>
<tr>
<td>Cardiac arrest (427.5)</td>
<td>9.9</td>
<td>3.37 (2.72–4.14)</td>
</tr>
<tr>
<td>Renal failure, unspecified (586)</td>
<td>8.3</td>
<td>3.74 (2.95–4.69)</td>
</tr>
<tr>
<td>Chronic respiratory disease arising in perinatal period (770.7)</td>
<td>6.6</td>
<td>3.61 (2.76–4.65)</td>
</tr>
<tr>
<td>Other specified disorders of intestine (569.8)</td>
<td>6.0</td>
<td>21.17 (15.91–27.58)</td>
</tr>
<tr>
<td>Volume depletion (276.5)</td>
<td>5.4</td>
<td>17.61 (13.01–23.30)</td>
</tr>
<tr>
<td>Nonelderly persons, 1–64 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS (042.0–044.9)</td>
<td>29.5</td>
<td>4.07 (3.78–4.37)</td>
</tr>
<tr>
<td>Unspecified septicemia (038.9)</td>
<td>17.2</td>
<td>4.45 (4.04–4.90)</td>
</tr>
<tr>
<td>Cardiac arrest (427.5)</td>
<td>14.2</td>
<td>1.25 (1.12–1.39)</td>
</tr>
<tr>
<td>Volume depletion (276.5)</td>
<td>11.7</td>
<td>33.58 (29.80–37.69)</td>
</tr>
<tr>
<td>Respiratory arrest (799.1)</td>
<td>10.0</td>
<td>1.37 (1.20–1.55)</td>
</tr>
<tr>
<td>Diabetes mellitus without mention of complicaton (250.0)</td>
<td>8.4</td>
<td>1.40 (1.22–1.60)</td>
</tr>
<tr>
<td>Pneumonia, organism unspecified (486)</td>
<td>8.3</td>
<td>2.01 (1.74–2.30)</td>
</tr>
<tr>
<td>Cytomegalic inclusion disease (078.5)</td>
<td>7.6</td>
<td>14.55 (12.55–16.77)</td>
</tr>
<tr>
<td>Shock without mention of trauma (785.5)</td>
<td>7.1</td>
<td>3.47 (2.97–4.02)</td>
</tr>
<tr>
<td>Cachexia (799.4)</td>
<td>6.9</td>
<td>9.25 (7.91–10.75)</td>
</tr>
<tr>
<td>Renal failure, unspecified (586)</td>
<td>5.8</td>
<td>2.18 (1.84–2.57)</td>
</tr>
<tr>
<td>Elderly persons, ( \geq 65 ) years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified septicemia (038.9)</td>
<td>15.8</td>
<td>3.52 (3.43–3.61)</td>
</tr>
<tr>
<td>Volume depletion (276.5)</td>
<td>14.2</td>
<td>8.27 (8.12–8.42)</td>
</tr>
<tr>
<td>Pneumonia, organism unspecified (486)</td>
<td>10.6</td>
<td>1.10 (1.04–1.16)</td>
</tr>
<tr>
<td>Chronic airway obstruction, n.e.c. (496)</td>
<td>10.3</td>
<td>1.10 (1.04–1.17)</td>
</tr>
<tr>
<td>Shock without mention of trauma (785.5)</td>
<td>7.0</td>
<td>3.00 (2.77–3.23)</td>
</tr>
<tr>
<td>Renal failure, unspecified (586)</td>
<td>6.6</td>
<td>1.62 (1.49–1.75)</td>
</tr>
<tr>
<td>Unspecified protein-calorie malnutrition (263.9)</td>
<td>5.6</td>
<td>3.54 (3.25–3.85)</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; HIV, human immunodeficiency virus; ICD-9, International Classification of Diseases, Ninth revision; n.e.c., not elsewhere classified.

The elevated risk of fatal GUE in the nursing home population is not surprising, because nursing home residents have high rates of chronic illness, malnutrition, and functional impairments, such as bowel incontinence, that are conducive to the spread of infection [37]. Outbreaks of acute gastroenteritis are common in nursing homes [38], including many attributed to unidentified foodborne agents [39]. Recent studies based on new molecular diagnostic methods have indicated that most gastroenteritis outbreaks of unknown etiology in nursing homes were actually caused by Norwalk-like viruses [40, 41]. This finding suggests that some GUE deaths in nursing homes were also due to Norwalk-like viruses. The role of Norwalk-like viruses in adult gastroenteritis mortality has not yet been established, but these agents might eventually emerge as an important cause of sporadic cases of acute gastroenteritis, as well as mass outbreaks [42].

The risk of GUE mortality varied by sex, race, and region, as well as by age and nursing home residence. Much of the difference in mortality by sex and race was due to the high proportion of males and blacks among GUE decedents with HIV/AIDS. Even after decedents with HIV/AIDS were excluded, the risk of fatal GUE was higher for males than females and for blacks than whites. The reason why the risk was higher for males is unclear, but sex differences in behavior affecting exposure to unknown
The present study did not examine age differences in the seasonality of GUE mortality, because the monthly number of GUE deaths for most age groups was subject to a high degree of random variation. Other studies have found that deaths from all categories of gastroenteritis were higher during the winter among young children and elderly persons, although the winter peak among children became less prominent after 1985, probably because of a decrease in rotavirus mortality [3, 52]. Rotavirus often causes severe gastroenteritis in children, but many rotavirus infections are never identified [53]. However, few GUE deaths were likely to be unidentified rotavirus infections, because rotavirus is estimated to cause only ~20 deaths/year [54].

Physicians reported more causes of death, on average, for GUE decedents than other decedents, which suggests that GUE cases were relatively more complicated. The PMRs comparing GUE deaths with all deaths indicate that a variety of different medical conditions were associated with fatal GUE. Many of these conditions were indicative of incomplete reporting of the causes of death. Ten conditions had ICD-9 codes with the term “unspecified” in the title, because physicians did not provide enough information to allow coders to assign a more specific code. Two other conditions—respiratory arrest and shock—are cited on the US standard death certificate as examples of modes of dying that should not be reported as causes of death [11]. It was unclear why physicians reported these nonspecific conditions. One possible explanation is that the conditions were caused by the same unknown agents responsible for fatal GUE, precluding a complete diagnosis. Alternatively, nonspecific diagnoses may have been erroneously recorded on death certificates in place of specific diagnoses [55].

Bacteremia was the condition most commonly associated with fatal GUE. The etiology of bacteremia was apparently undetermined, because bloodstream infections were coded as ICD-9 038.9 (unspecified septicemia) when there was no mention of a causative agent on the death certificate. Gastroenteritis is a possible complication of bacteremia [56], so some cases of GUE may have resulted from infections of sites other than the gastrointestinal tract. However, the association between GUE and bacteremia may also indicate that unknown agents that caused GUE could invade the bloodstream, like certain gastrointestinal pathogens, notably Salmonella species.

Several other conditions associated with GUE were possible complications of severe gastroenteritis, including volume depletion, shock, electrolyte and fluid disorders, and cardiac arrest [3]. Volume depletion occurred 9.6 times more often than expected and was present in 13% of GUE deaths, making it the second most common condition associated with GUE. The frequent mention of volume depletion may indicate that GUE decedents did not always receive timely treatment for gastrointestinal fluid losses. Volume depletion was less likely to be present in GUE deaths among infants (5%) than nonelderly (12%) or elderly (14%) persons, perhaps because infants were more likely to receive rehydration therapy.

Some conditions associated with GUE could also be caused by Shiga toxin–producing pathogens (Shigella dysenteriae type 1, Escherichia coli O157:H7, and other Shiga toxin–producing E. coli strains). Infection by these pathogens may result in hemorrhagic colitis or hemolytic uremic syndrome (characterized by acute renal failure, hemolytic anemia, and thrombocytopenia), as well as gastroenteritis. Nearly 4% of GUE decedents had gastrointestinal hemorrhage and 2% had vascular insufficiency of
the intestine (ischemic colitis), conditions similar to hemorrhagic colitis. GUE was not associated with hemolytic uremic syndrome but was associated with acute renal failure (7% of decedents) and unspecified anemia (4% of decedents). Overall, 13% of GUE decedents had gastrointestinal hemorrhage, ischemic colitis, acute renal failure, or unspecified anemia.

Shiga toxin–producing pathogens are estimated to cause ~160 deaths per year [1], assuming that S. dysenteriae type 1 is responsible for most of the estimated deaths due to Shigella species. However, only ~20 deaths/year are reported on death certificates, under the assumption that all of the deaths on the 1995–1997 MCD files with ICD-9 codes for shigellosis (004.0–004.9), E. coli infections (008.0), or other bacterial food poisoning (005.8) were caused by Shiga toxin–producing pathogens. The discrepancy between the numbers of reported and estimated deaths implies that most fatal infections due to Shiga toxin–producing pathogens were not reported on death certificates. Some of these unreported infections may have been included instead among the GUE deaths involving gastrointestinal hemorrhage, ischemic colitis, acute renal failure, or unspecified anemia.

GUE was associated with unspecified renal failure and disorder of the kidney and ureter, as well as acute renal failure. One or more of these conditions was reported in 13% of GUE deaths. GUE decedents were more likely than all decedents to have certain conditions that could result in renal failure, including bacteremia, volume depletion, and gastrointestinal hemorrhage. GUE decedents who were hospitalized before death were also at risk of nosocomial renal insufficiency [57].

Other conditions associated with GUE made individuals more susceptible to infection. The most important example was HIV/AIDS, which was present in 6% of GUE deaths and occurred 4.0 times more often than expected. Nearly all (99%) of the GUE decedents with HIV/AIDS were nonelderly persons. Some (24%) of the nonelderly persons with HIV/AIDS also had cytomegalovirus infections, a common cause of diarrhea in patients with HIV/AIDS [58]. It was unclear whether cytomegalovirus was responsible for gastroenteritis in these decedents, because cytomegalovirus can affect other organs without involving the gastrointestinal tract.

Chronic illness may also predispose individuals to infection. Five of the conditions associated with GUE typically occurred in chronically ill or debilitated individuals, including pneumonia due to unspecified organisms, chronic airway obstruction, malnutrition, organic brain syndrome, and pneumonitis due to inhalation of food or vomitus. Overall, 25% of GUE deaths involved ≥1 of these 5 conditions, including 33% of the deaths among elderly nursing home residents. The association with GUE was strongest in the case of malnutrition, which occurred 3.9 times more often than expected.

The association between GUE and pneumonia might also indicate that fatal pneumonia due to unidentified agents sometimes involved gastrointestinal symptoms. Acute gastroenteritis of unknown etiology accompanied by respiratory symptoms has traditionally been attributed to respiratory, rather than gastrointestinal, pathogens [1]. If the 420 annual GUE deaths associated with pneumonia due to unspecified organisms were classified as respiratory rather than gastrointestinal mortality, the number of GUE deaths would be reduced by nearly 10%. The classification of GUE deaths involving pneumonia is less consequential for estimates of respiratory mortality, because this group of GUE deaths represented only 0.2% of the 187,000 annual deaths on the 1995–1997 MCD files with ICD-9 code 486 for pneumonia due to unspecified organisms.

A majority (56%) of infant GUE deaths were premature or low birth weight. Fatal GUE might be associated with short gestations because the immune response is more deficient in premature infants than other infants [56], increasing the risk of infection. Low birth weight has also been identified as a risk factor for infant mortality from all categories of gastroenteritis [6]. The association between GUE and 2 other conditions in infants might be related to the use of dexamethasone; infant GUE deaths were 3.6 times more likely to involve bronchopulmonary dysplasia and 21.2 times more likely to involve other specified disorders of the intestine than all infant deaths. Bronchopulmonary dysplasia develops in premature infants receiving mechanical ventilatory support and is sometimes treated with dexamethasone, an adrenocortical steroid that impairs the immune response [59]. Low-birth-weight infants treated with dexamethasone are also at risk of perforation of the intestine, one of the conditions classified under other specified disorders of the intestine [60].

Possible explanations for the association between GUE and 2 other conditions can also be identified. The most likely explanation for the association with cardiac dysrhythmia was disturbance of cardiac function by electrolyte imbalances resulting from severe diarrhea [56]. Dysrhythmia might also result from the use of drugs with proarhythmic effects, such as erythromycin, a macrolide antibiotic recommended for treating diarrhea due to Campylobacter species, the most common cause of foodborne gastroenteritis [61, 62]. The most likely explanation for the association between GUE and urinary tract infections was nosocomial infection, because diarrhea is a risk factor for nosocomial urinary tract infections, particularly in patients with an indwelling catheter [63]. Alternatively, the unknown agents that caused GUE may have been able to invade the urinary tract, like one of the most common gastrointestinal pathogens, Salmonella species [64].

In summary, the information reported on death certificates suggests that fatal GUE was often due to infectious agents. All of the GUE deaths where gastroenteritis was described as infectious in origin and coded as ICD-9 009.0 or 009.2 probably
Infectious agents likely were also present when GUE was the underlying cause of death and when GUE occurred together with bacteremia or pneumonia. Other aspects of GUE mortality that were consistent with an infectious etiology included the seasonal increase in mortality during the winter months [3] and the association with HIV/AIDS and certain chronic conditions, such as malnutrition, that increased susceptibility to infection.

Although fatal GUE was often due to infectious agents, the information provided on death certificates was insufficient to determine whether GUE was caused by unknown, predominantly foodborne agents, as proposed by Mead et al. [1]. Death certificates do not indicate why physicians ruled out known causes of gastroenteritis or record how the agents that caused GUE were transmitted. More research is needed to assess how GUE was diagnosed and to identify the risk factors for fatal GUE to determine whether the agents that caused GUE were unknown or transmitted by food.

The most important limitation of the present study is the uncertain accuracy of death certificate data on causes of death. Reported causes of death may be incomplete or even inaccurate [65–68]. The most frequent errors made by physicians include omitting some causes of death and listing nonspecific rather than specific diagnoses [55, 66]. Infectious conditions are particularly likely to be underreported, including conditions due to gastrointestinal pathogens such as *Vibrio vulnificus* and *Cryptosporidium parvum* [1, 69, 70]. The accuracy of gastroenteritis reporting on death certificates has not been investigated and merits attention, in view of the effect on estimates of GUE mortality. One important issue is whether physicians correctly ruled out known causes of gastroenteritis, such as Shiga toxin–producing pathogens or adverse drug reactions [71]. Another important issue is whether physicians sometimes erroneously reported a nonspecific diagnosis of gastroenteritis or diarrhea, rather than a specific cause such as a known pathogen.

Other shortcomings of death certificate data include the unreliable information about American Indian, Native Alaskan, Asian, and Pacific Islander mortality, the errors in age reporting for elderly blacks, and the absence of a variable identifying nursing home residents. In addition, information about whether GUE was described as a presumed infection on death certificates was not available, because ICD-9 codes 009.1 and 009.3, for gastroenteritis and diarrhea of presumed infectious origin, were not used on the MCD files.

The PMRs used in the present study also have limitations. A high PMR for one condition will necessarily result in a low PMR for other conditions, because the PMR is a ratio and the number of deaths from all causes is fixed [27]. This relationship may explain why GUE decedents were less likely to have certain cardiovascular conditions than all decedents. However, PMRs are a good approximation of standardized mortality ratios when the 2 groups being compared have the same overall death rate from all causes [27]. The true group at risk of fatal GUE is unknown, but the results from the present study indicate that most or all of the US population was likely to be at risk, because GUE deaths occurred in every age, sex, race, and geographic category examined. Therefore, the group at risk of fatal GUE probably had the same overall death rate as the US population, and the PMRs reported here are likely to approximate standardized mortality ratios.

The PMR analysis involved multiple comparisons, increasing the likelihood that GUE would be significantly associated with some conditions simply by chance. At the conventional significance level of $P = .05$, 1 or 2 of 31 conditions reported in $\geq 2\%$ of GUE deaths would be associated with GUE by chance. In fact, 21 conditions were associated with GUE, so most of the associations were unlikely to be due to chance. Many of the conditions associated with GUE were possible complications of gastroenteritis, disorders that could be caused by known gastrointestinal pathogens or conditions that increased susceptibility to infection, further increasing confidence in the validity of the analysis.

The GUE death rates reported here are provisional, because the postcensal population estimates for 1995–1997 will ultimately be superseded by intercensal estimates. The postcensal estimates are projections based on the 1990 census, whereas the intercensal estimates are interpolations based on the 1990 and 2000 censuses. At the time of the study, intercensal estimates were available only for the US population by state and age [72]. The intercensal estimate of the 1995–1997 US population was 1.6% higher than the postcensal estimate, because the population enumerated in 2000 was larger than had been projected [73]. As a result, the GUE death rates reported here would be slightly lower if intercensal population estimates were used for the denominator in place of the postcensal estimates.

The findings from the present study have important implications for efforts to reduce gastroenteritis mortality. Many GUE deaths occurred in individuals who were susceptible to infection, including patients with HIV/AIDS, persons with chronic illness, and nursing home residents. Other GUE deaths were associated with serious conditions, such as bacteremia or acute renal failure, that may have been caused by the same unknown agents responsible for GUE. It may be difficult or impossible to prevent such deaths without first achieving a better understanding of the etiology of GUE.

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References


