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This article by Choi et al. describes the findings from 19 tertiary-care teaching hospitals in South Korea. At first, the finding that infectious diseases are attributed to 29% of all in-hospital deaths seems unexpected. Then we realize that the numbers, while surprising, are not unusual.

In the United States, hospital-acquired infections are a countrywide problem. It has been estimated that each year nearly two million patients get an infection while being treated in our nation's hospitals, and almost 100,000 of them die in the U.S. The Centers for Disease Control and Prevention estimates the cost of hospital-acquired infections to be as high as $27.5 billion each year.[1] The findings in this study and elsewhere bring to light the fact that even the "most developed" countries, such as South Korea, the United Kingdom,[2] and the United States, still face a constant and, in some cases, increasing threat from infection-related mortality in hospital settings. It is also interesting to note that pneumonia and septicemia remain the most common causes of death.

The sentinel hospital-based surveillance system is an important step toward developing and maintaining a useful monitoring system to control routine and extraordinary infectious diseases. Other studies in the literature set up a standardized methodology for the mining and investigation of infection control surveillance.[3] This article, however, is the first to evaluate the proportions of infectious diseases among all in-hospital mortality cases as either the direct or underlying cause of death and investigate the description of infectious causes of in-hospital death in South Korea.

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HOSPITAL-BASED SURVEILLANCE OF INFECTION-RELATED MORTALITY IN SOUTH KOREA

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During the 20th century, developing countries have experienced substantial declines in mortality and increases in life expectancy. In the 19th century, the mortality pattern was dominated by high rates of infectious disease-related deaths, especially in the young, although mortality from chronic diseases predominated. According to estimates from the Global Burden of Disease study, infectious diseases account for only 4% of all disability-adjusted life years (DALYs)—a measure of the burden of diseases and injuries—lost in countries with established market economies (e.g., the United States), whereas chronic and neoplastic diseases account for 81% of all DALYs.[1]

Until recently, it was assumed that the epidemiologic transition brought about a permanent reduction in infectious disease mortality in developed countries. However, emerging and reemerging diseases such as acquired immunodeficiency syndrome (AIDS) and tuberculosis (TB) demonstrate that gains against infectious diseases cannot be taken for granted. Currently, avian influenza, which is caused by the influenza A virus (H5N1), continues to cause outbreaks among poultry and wild birds worldwide. These outbreaks have raised

serious global concerns about the imminent arrival of an influenza pandemic,[2] making the surveillance of infectious diseases essential.

Following the increase in emerging and reemerging infectious diseases since the late 1990s, the Korean government has strived to enhance its surveillance and response system. Since 2000, sentinel surveillance programs, such as the influenza sentinel surveillance, pediatric sentinel surveillance, school-based sentinel surveillance, and ophthalmological sentinel surveillance programs, have been introduced to improve surveillance activities. In 2007, we developed the sentinel hospital-based surveillance system for infection-related mortality.

The immediate cause of mortality in patients with diverse underlying diseases can be infectious disease. However, the proportion of infectious diseases as either the immediate or underlying cause of mortality has not been clearly evaluated in Korea. This article describes the sentinel hospital-based surveillance system for infection-related mortality and evaluates the proportions and characteristics of infectious diseases as either the immediate or underlying causes of in-hospital mortality in Korea.

METHODS

In 2007, the Korean Centers for Disease Control and Prevention and the Korean Society of Infectious Diseases developed a sentinel hospital-based surveillance system for infection-related mortality. The sentinel hospital-based surveillance system consisted of 19 tertiary-care teaching hospitals in Korea with nationwide distribution. The objectives of this surveillance system were to monitor outbreaks of severe infectious diseases and deaths by unidentified pathogens, evaluate the disease burdens of infectious diseases, and conduct multicenter clinical studies for infectious diseases.

We retrospectively reviewed clinical data of patients who had in-hospital mortality from November 2007 to May 2008. Infectious disease specialists evaluated the cause of death (COD) of each patient during the week of mortality. We defined infectious disease-related mortality as death that could be attributed to infectious disease as either the immediate or underlying cause. The term "immediate cause of death" is defined as the disease or injury directly leading to death, and the term "underlying cause of death" is defined as the disease or injury that initiated the sequence of events leading directly to death or the circumstances of the accident or violence that produced the fatal injury.[3] In cases with infection-related mortality, infectious disease specialists defined the underlying and immediate causes of mortality according to standardized algorithms. Only one caused disease was entered in each cause. If the underlying COD was the same as the immediate COD, the codes were reintroduced in both causes.

We used the International Classification of Diseases, 10th Revision (ICD-10) codes to define underlying diseases and immediate causes of mortality.[3] Individual assignments were subjective, as the ICD-10 codes are not well defined. For this article, we used a list of 28 infectious CODs from the National Vital Statistics System at the Centers for Disease Control and Prevention (CDC) for tabulation and analysis, although with modifications.[4]

We defined hospital-acquired infection as infection that occurred more than 48 hours after hospital admission, infection that occurred less than 48 hours after hospital admission in patients who had been hospitalized within two weeks prior to admission, or infection in patients who had been transferred from an outside hospital or nursing home. We also compared underlying diseases and immediate CODs between community- and hospital-acquired infections.

We used Chi-square tests, Fisher's exact tests, and linear-by-linear association to compare categorical variables as needed. We compared continuous variables using the student's *t*-test. All *p*-values were two-tailed and we considered $p<0.05$ to be statistically significant. We used SPSS® version 11.0 for this analysis.[5]

RESULTS

During the study period—November 4, 2007, to April 26, 2008—there were 6,051 in-hospital mortality cases, 1,756 of which were infection-related, accounting for 29% of all in-hospital mortalities. Among these patients, 685 were considered to have infectious diseases as underlying diseases, which was 16% of all in-hospital mortalities. The mean age of patients with infection-related mortality was 65.4 ± 17.2 years (range: 0–100), and 68% of patients with infection-related mortality were male (Table 1). The proportions of community- and hospital-acquired infections among infection-related mortalities were 41% and 49%, respectively. In 10% of infection-related mortalities, we could not determine whether the infectious diseases were community acquired. There were 120 patients aged 0–39, 777 aged 40–69, and 859 aged 70–109 (Table 2). We found a significant correlation between decade of life and proportion of community-acquired infection ($p=0.002$). Demographic data on noninfectious mortality were not available during the study duration.

As shown in Table 3, pneumonia was the most common underlying cause of infection-related mortality,

Table 1. Baseline characteristics of 1,756 deaths (29% of total deaths) related to infection at 19 tertiary-care teaching hospitals in Korea, November 2007 to May 2008

Characteristic	*Value*
Age (in years): mean ± SD (range)	65.4 ± 17.2 (0–100)
Gender male: *N* (percent)	1,185 (68)
Community- or hospital-acquired infections: *N* (percent)	
Community-acquired infections	718 (41)
Hospital-acquired infections	854 (49)
Undetermined	184 (10)

SD = standard deviation

and septicemia was the most common direct cause of infection-related mortality. Table 4 shows comparisons between community- and hospital-acquired infection-related mortality. The mean age was higher in community-acquired infection-related mortality than in hospital-acquired infection-related mortality ($p<0.001$). Septicemia was less common in community-acquired infection-related mortality as the underlying cause of infection-related mortality.

DISCUSSION

From the 1900s to the 1980s, the infectious disease mortality rate in developed countries declined substantially, consistent with the concept of epidemiologic transition.[6] Epidemiologic transition is a phase of development witnessed by a sudden increase in population growth rates brought about by medical innovation in disease treatment, followed by a restabilization of population growth from subsequent declines in procreation rates. Improvements in living conditions, sanitation, and medical care probably accounted for this trend. However, during a 15-year period starting in 1981, this trend reversed, with infectious disease deaths consistently increasing from year to year. At the end of the 20th century, infectious disease-related deaths declined again, largely because of a substantial decline in AIDS mortality.[7] Emerging and reemerging diseases such as AIDS and TB account for the majority of the increased burden of infectious diseases worldwide. In Korea, up until the early 20th century, infectious diseases were the major causes of morbidity and mortality. After 1950, the overall morbidity and mortality from infectious diseases rapidly declined.[8] However, many emerging and reemerging communicable diseases, such as leptospirosis, malaria, endemic typhus, and brucellosis, have recently occurred in Korea.

The mortality statistics presented in this article were compiled in accordance with World Health Organization regulations, which specify that member nations classify and code CODs in accordance with the current version of the ICD-10. The ICD-10 provides the basic guidance used in virtually all countries to code and classify CODs. However, it does not classify infectious diseases as similar codes. For example, codes for pneumonia contain A, B, or J codes. Additionally, we did not define each ICD-10 code. Therefore, we based the COD on the subjective opinions of infectious disease doctors. We should develop definitions for each of the ICD-10 codes for infectious diseases to monitor infection-related mortality objectively.

In this six-month study, we evaluated the proportions of infectious diseases among all causes of mortality and described the causes of infection-related deaths. Infectious disease accounted for 29% of all in-hospital

Table 2. Age distribution of infection-related mortality at 19 tertiary-care teaching hospitals in Korea, November 2007 to May 2008

	Number of subjects			
Age (in years)	*Community-acquired infections*	*Hospital-acquired infections*	*Undetermined*	*Total*
0–9	7	25	4	36
10–19	4	10	2	16
20–29	7	14	1	22
30–39	20	19	7	46
40–49	56	73	13	142
50–59	87	120	19	226
60–69	138	230	41	409
70–79	252	242	60	554
80–89	128	106	35	269
90–99	18	15	2	35
100–109	1	0	0	1

Table 3. Number of infection-related deaths for 28 possible causes at 19 tertiary-care teaching hospitals in Korea, November 2007 to May 2008[a]

	Community-acquired infection		*Hospital-acquired infection*	
Cause of death (ICD-10 codes)	*Underlying cause*	*Direct cause*	*Underlying cause*	*Direct cause*
Certain other intestinal infections (A04, A07–9)	5	3	3	1
Tuberculosis (A15–19)	13	5	8	0
Respiratory tuberculosis (A15–16)	11	4	7	0
Other tuberculosis (A17–19)	2	1	1	0
Septicemia (A40–41)	35	264	70	291
Viral encephalitis (A83–86)	1	2	0	0
Viral hepatitis (B15–19)	1	0	2	0
Human immunodeficiency virus (B20–24)	5	0	1	1
Other and unspecified infectious and parasitic diseases and their sequelae (A00, A05, A20–36, A42–44, A48–49, A54–79, A81–82, A87–B04, B06–09, B25–49, B55–99)	10	8	13	8
Meningitis (G00, G03)	6	3	2	1
Acute and subacute endocarditis (I33)	3	2	2	1
Diseases of pericardium and acute myocarditis (I30–31, I40)	1	0	0	0
Influenza and pneumonia (J10–18)	141	210	175	277
Influenza (J10–11)	0	1	0	0
Pneumonia (J12–18)	141	209	175	277
Infections of the kidney (N10–12, N13.6, N15.1, N39.0)	18	8	2	7
Inflammatory diseases of female pelvic organs (N70–76)	0	0	0	1

[a]There were no deaths from salmonella infections (A01–02), shigellosis and amebiasis (A03, A06), whooping cough (A37), scarlet fever and erysipelas (A38, A46), meningococcal infection (A39), syphilis (A50–53), acute poliomyelitis (A80), malaria (B50–54), rheumatic fever (I00–09), other acute lower respiratory infections (J20–22), acute bronchitis and bronchiolitis (J20–21), or unspecified acute lower respiratory infection (J22).

ICD-10 = International Classification of Diseases, 10th Revision

mortalities, although it accounted for 16% of underlying diseases. According to the Global Burden of Disease Study in 1990, in developed countries, infectious diseases and respiratory infections accounted for a little more than 4% of DALYs, while in developing countries these same causes accounted for 35% of DALYs.[1] Our study shows that infectious diseases account for substantially large proportions of in-hospital mortalities.

Limitations

Our study had several limitations. Although infection-related mortality as an underlying cause was not so high, infection-related mortality as a direct or underlying COD was substantially high. This finding could be related to the fact that we regarded death as infection-related if either the direct or underlying COD was an infectious disease, and many patients who also have

Table 4. Differences in causes of death between hospital- and community-acquired infection-related deaths at 19 tertiary-care teaching hospitals in Korea, November 2007 to May 2008

Variable	*Community-acquired infection-related deaths*	*Hospital-acquired infection-related deaths*	P-*value*
Age (in years): mean ± standard deviation	67.5 ± 15.7	63.4 ± 18.2	<0.001
Gender male: *N* (percent)	481 (67)	592 (69)	0.328
Underlying causes: *N* (percent)			
Septicemia (A40–41)[a]	35 (5)	70 (8)	0.008
Influenza and pneumonia (J10–18)[a]	141 (20)	175 (21)	0.704
Direct causes: *N* (percent)			
Septicemia (A40–41)[a]	264 (37)	291 (35)	0.264
Influenza and pneumonia (J10–18)[a]	210 (29)	277 (33)	0.187

[a]International Classification of Diseases, 10th Revision codes

noninfectious diseases die due to infectious diseases. Aside from this limitation, this finding revealed that infectious diseases are a major cause of in-hospital mortality in developed countries such as Korea. It is known that nosocomial infections contribute to 88,000 deaths in U.S. hospitals annually.[9] In our study, nosocomial infections accounted for 49% of all infection-related mortality cases. This finding showed that in developed countries, the occurrence of nosocomial infectious diseases contributes to the large burden of infectious diseases.

We performed this study during winter and early spring in a northern temperate climate; we did not evaluate the seasonality of infection-related mortality. Further studies should be conducted to evaluate its effect. Among infectious diseases, pneumonia and sepsis were the most common direct or underlying causes of infection-related deaths. This finding was consistent with other studies on disease burdens.[1,4] The prognosis of many types of infectious diseases has consistently improved; however, the mortality rates of severe sepsis and pneumonia are still high, even in developed countries.[10,11]

There was only one death from influenza, although the six-month study period included the flu season in Korea. We assumed that mortality from influenza could be underestimated and classified as pneumonia.

The causal relationship between mortality and disease was decided by the subjective opinions of infectious disease specialists, and we did not define each ICD-10 code. Therefore, our results were not objective. We had data on numbers of deaths from infections at different ages but did not have the proportions of total deaths due to infection during these decades, so we could not know the age differences for the proportions of infection-related mortality clearly.

In addition to these limitations, a sentinel surveillance system is not representative of the entire population, and this limitation should be considered before generalizing these findings. Moreover, because our study was conducted by tertiary-care hospitals, our results could be different from overall findings in Korea. We could not clearly differentiate a terminal infection in a patient who had inevitably deteriorating underlying disease from an unnecessary infectious death as a complication of curable underlying disease. Further analyses along these lines should be performed.

CONCLUSIONS

Infectious diseases account for a substantially large proportion of in-hospital mortalities, even in developed countries such as Korea. Continuous surveillance of infection-related mortality would be helpful for monitoring outbreaks of severe infectious diseases and deaths by unidentified pathogens and evaluating the disease burdens of infectious diseases.

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