Hearing impairment in young and middle-aged septicemia survivors

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Abstract

The ability of sepsis to induce acute phase hearing impairment has been evaluated in septic and sepsis-surviving mice. The relationship between septicemia and long-term hearing impairment remains unknown in humans.

The data were obtained from the Taiwan Longitudinal National Health Insurance Database from 2000 to 2013. We identified patients suffering from septicemia after discharge, excluding those younger than 18 years old and older than 65 years old. The comparison group was matched based on age, sex, and comorbidities. The outcome was hearing impairment occurring after septicemia. The risk factors associated with hearing impairment were established using multivariate Cox proportional hazard regression.

Our study found that septicemia associated with hearing impairment had an adjusted hazard ratio (HR) of 53.11 (95% confidence interval [CI]: 41.74–67.59). The other factors related to hearing impairment in young and middle-aged septicemia survivors included male sex (adjusted HR 1.31 [95% CI: 1.14–1.5]), chronic kidney disease (adjusted HR 1.63 [95% CI: 1.38–1.94]), and otosclerosis (adjusted HR 231.54 [95% CI: 31.61–1695.8]).

Our study revealed that septicemia was associated with increased development of hearing impairment in young and middle-aged humans in the long term. Clinicians should be aware of long-term septicemia-related hearing impairment and provide prevention strategies for otopathy in septicemia survivors.

Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database.

Keywords: hearing impairment, risk, septicemia

1. Introduction

Septicemia is a severe life-threatening disorder that can cause short- and long-term major adverse cardiovascular events, including myocardial infarction, ischemic stroke, and death.⁰¹–⁰³ Septicemia has a high incidence of critical care hospitalization. Septicemia survivors display a range of disabilities and problems that can alter quality of life.⁰⁴ Acute hearing loss is related to sepsis and sepsis survival in mice,⁰⁵,⁰⁶ but a correlation between septicemia and long-term hearing impairment has not been previously addressed in humans. The aim of this study was to identify whether hearing impairment is related to septicemia in humans.

Potential causes of hearing loss include aging, genetics, trauma, ototoxic medication, local infections, vascular diseases, autoimmune disorders, and noise. In animal studies, general inflammation leads to apoptosis in Corti organ-supporting cells, which then induces glutamate overstimulation in the inner hair cells in septic mice.⁰⁵,⁰⁶ Aminoglycoside antibiotics are employed for broad-spectrum gram-negative bacterial infection, but they are associated with nephrotoxicity and ototoxicity.⁰⁷ A previous study found that mammalian hair cell repair was limited, and persistent hearing impairment can occur after hair cell injury.⁰⁸ Understanding the risk factors for hearing impairment is important for preserving function.

We hypothesized that septicemia increases the risk of hearing impairment in young and middle-aged humans. We used the Taiwanese National Health Insurance Research Database (NHIRD) to explore whether a history of septicemia is associated...
with a subsequent increase in the long-term risk of developing hearing impairment.

2. Methods

National health insurance has been implemented in Taiwan since 1995; it is composed of a unified government supportive health care system and covers approximately 99% of Taiwan’s 23 million citizens. All medical care providers must submit computerized data claims for insurance payments. The Taiwanese NHIRD contains all outpatient and inpatient medical insurance payment records. For each visit, the system includes up to 5 International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) inpatient diagnosis and procedure codes and 3 outpatient ICD-9-CM diagnosis and procedure codes. The data extracted included each patient’s age, sex, comorbid conditions, hearing impairment codes, and times of admission and discharge.

The dataset used in this study was obtained from the Taiwan Longitudinal Health Insurance Database, which randomly selects patients from the population. We identified patients with diagnosis codes for septicemia (ICD-9-CM as 038, 003.1, 036.1), which were collected from January 1, 2000, to December 31, 2013. The diagnosis code of septicemia in the NHIRD was used for verification.[2,9–11] Furthermore, hearing loss in children and older patients was reported in 1 pneumococcal meningitis survey.[12] Age-related hearing loss is caused by the loss of inner ear hair cells over time. In addition, 40% of elderly adults have hearing impairment after age 65.[13] We excluded patients based on the following criteria: younger than 18 years, older than 65 years, death during admission, hospitalization for septicemia, hearing impairment before the index date and unknown sex. The date of admission for septicemia was defined as the index date of the study group. Four controls were matched to each case based on age, sex, and comorbidities. Hearing impairment events were defined with the ICD-9-CM diagnostic code 389. Patients were followed until the first event or December 31, 2013. The flow chart of the study is presented in Figure 1.

We used the ICD-9-CM codes to identify diagnoses in the NHIRD for hearing impairment comorbidities. Hearing impairment comorbid disorders mapped by ICD-9-CM codes included hypertension (401–405); diabetes mellitus (250); chronic kidney disease (580–589); hyperlipidemia (272); autoimmune disorders (710); anemia (280, 285); hematological disorders, including coagulopathies and platelet disorders (286–287); coronary artery disease (410–414); ischemic stroke (433–437); meningitis (320–322, 013.0, 036.0, 053.0, 047); traumatic brain injuries (800, 803–805, 850–854); encephalopathy (293, 348.3, 780.01, 780.09); chronic otitis media (381–382); otosclerosis (387); and osteoporosis (733.0). The study was approved by TSGH IRB 2-105-05-025.

2.1. Statistical analyses

Continuous variables are displayed as the means ± standard deviations and were evaluated with Student t tests, while categorical variables are displayed as percentages and were evaluated with the Chi-square (X²) test. The risk factors for

| Inclusion criteria | Septicemia 9,949 individuals |
|--------------------|--------------------------------|
| Exclusion criteria | 1. Septicemi before index date 2. Hearing impairment before tracking 3. Presbyacusis / Family history of hearing loss 4. Mortality 5. Age <18 years, Age ≥65 years 6. Sex unknown 5,593 individuals |
| With septicemia (Study cohort) 4,356 individuals |
| Without septicemia (Comparison cohort) 17,424 individuals |
| Tracking endpoint (2013.12.31) 793 individuals with hearing impairment |
| 75 individuals with hearing impairment |

Figure 1. The flowchart of study sample selection from the National Health Insurance Research Database in Taiwan.
hearing impairment were assessed using Cox proportional hazard regression. The statistical significance was set at \( P < .05 \). The statistical analyses were performed with SPSS version 21 software.

3. Results

We investigated 4356 septicemia survivors in the study group and 17,424 septicemia-free patients in the control group. The median hearing impairment detection times were 3.51 years in the study group and 7.72 years in the control group. Table 1 presents the demographic variables for the septicemia and control groups. Compared with the control patients, more septicemia patients were admitted to medical centres, lived in southern Taiwan and had a higher urbanization level. In total, 18.2% (793/4356) of the patients in the study group had hearing impairment versus 0.43% (75/17,424) in the control group (log-rank test: \( P < .001 \)) (Fig. 2).

The majority of hearing impairment cases occurred within 1 year after septicemia (Table 2).

Our study revealed a relationship between septicemia and hearing impairment, with an adjusted hazard ratio (HR) of 53.11 (95% confidence interval [CI]: 41.74–67.59). Other risk factors included male sex (adjusted HR 1.31 [95% CI: 1.14–1.5]), chronic kidney disease (adjusted HR 1.63 [95% CI: 1.38–1.94]), and otoscleroisis (adjusted HR 231.54 [95% CI: 31.61–1695.8]), after adjustment for age and other comorbidities. Some underlying diseases were associated with a lower risk of hearing impairment, including hypertension (adjusted HR 0.462 [95% CI: 0.376–0.569]), anemia (adjusted HR 0.646 [95% CI: 0.446–0.937]), and traumatic brain injury (adjusted HR 0.422 [95% CI: 0.233–0.766]) (Table 3). The overall and subgroup-specific incidence rates and incidence rate ratios of hearing impairment between septicemia and septicemia-free patients were performed in Table 4. The overall incidence rates of hearing impairment in septicemia patients were 1477.96 per 10^5 person-years and 39.11 per 10^5 person-years in septicemia-free patients. The incidence rate ratio of hearing impairment was 37.79 between septicemia

### Table 1

| Variables                      | Septicemia | Septicemia-free | \( P \) |
|-------------------------------|------------|-----------------|--------|
| Total                         | 4356       | 17,424          | .999   |
| Sex                           |            |                 |        |
| Male                          | 2161 (49.61%) | 8644 (49.61%) |        |
| Female                        | 2195 (50.39%) | 8780 (50.39%) |        |
| Age (yr)                      | 47.97 ± 11.71 | 47.66 ± 12.72 | .144   |
| Age group (yr)                |            |                 | .999   |
| 18–44                         | 1339 (30.74%) | 5356 (30.74%) |        |
| ≥45                           | 3017 (69.26%) | 12,068 (69.26%) |        |
| Diabetes mellitus             | 1148 (26.35%) | 4498 (25.8%) | .453   |
| Hypertension                  | 275 (6.31%) | 1217 (6.88%) | .117   |
| Chronic kidney disease        | 528 (12.12%) | 2097 (12.04%) | .876   |
| Hyperlipidemia                | 56 (1.29%) | 222 (1.27%) | .94    |
| Coronary heart disease        | 390 (8.95%) | 1557 (8.94%) | .972   |
| Ischemic stroke               | 82 (1.88%) | 272 (1.56%) | .14    |
| Autoimmune diseases           | 46 (1.06%) | 186 (1.07%) | .934   |
| Anemia                        | 171 (3.93%) | 611 (3.51%) | .187   |
| Hematological disorder        | 65 (1.49%) | 241 (1.38%) | .565   |
| Meningitis                    | 20 (0.47%) | 110 (0.63%) | .831   |
| Traumatic brain injury        | 78 (1.79%) | 272 (1.56%) | .281   |
| Encephalopathy                | 5 (0.11%) | 9 (0.05%) | .174   |
| Chronic otitic media          | 681 (15.63%) | 2877 (16.51%) | .162   |
| Otosclerosis                  | 0 | 4 (0.02%) | .59    |
| Osteoporosis                  | 5 (0.11%) | 20 (0.11%) | .999   |
| Location                      |            |                 |        |
| Northern Taiwan               | 1277 (29.32%) | 6951 (39.89%) | <.001* |
| Middle Taiwan                 | 976 (22.41%) | 4753 (27.28%) |        |
| Southern Taiwan               | 1791 (41.12%) | 4663 (26.76%) |        |
| Eastern Taiwan                | 304 (6.98%) | 969 (5.56%) |        |
| Outlets islands               | 8 (0.18%) | 88 (0.51%) |        |
| Urbanization level (\( \leq 40 \)) |            |                 | <.001* |
| 1 (Highest)                  | 1832 (42.06%) | 6334 (36.35%) |        |
| 2                             | 1908 (43.8%) | 7148 (41.02%) |        |
| 3                             | 142 (3.26%) | 1303 (7.48%) |        |
| 4 (Lowest)                   | 474 (10.88%) | 2639 (15.15%) |        |
| Level of care                 |            |                 | <.001* |
| Hospital centre               | 2093 (48.05%) | 5437 (31.20%) |        |
| Regional hospital             | 1483 (34.04%) | 4942 (28.36%) |        |
| Local hospital                | 780 (17.91%) | 7045 (40.43%) |        |

\( * P < .05. \)
and septicemia-free patients. Factors of hearing impairment stratified by variables using Cox regression showed in Supplemental Table 1 (see Table, http://links.lww.com/MD/E524, Supplement Content, which illustrates factors of hearing impairment stratified by variables using Cox regression).

### 4. Discussion

Our study revealed that septicemia is significantly associated with long-term subsequent hearing impairment in young and middle-aged adult humans. Hearing impairment occurred earlier in septicemia survivors than in septicemia-free patients. Hearing impairment results from complex processes and may influence communication, which can be very stressful and lead to social withdrawal, affecting patients’ quality of life.[14]

Septicemia can develop when an infection occurs elsewhere in the body. This is dangerous because the bacteria and their toxins can be carried through the bloodstream to the entire body. Septicemia leads to extensive host defense systemic inflammatory responses to fight the infection; when inflammation fails to resolve, it progresses to chronic inflammation, which can persist for months to years.[15] Inflammation causes blood clots and prevents oxygen from reaching vital organs, resulting in organ failure. Toxins can cause extremely low blood flow, which may result in organ or tissue damage.[16] Chronic inflammation associated with septicemia can cause short- and long-term atherosclerotic events,[1–3] dementia,[4] and multiple sclerosis.[11]

The oxygen stress attributed to reactive oxygen species generation causes mitochondrial dysfunction via adenosine triphosphate depletion in patients with sepsis.[17] Hearing impairment in the context of septicemia occurs due to immune reaction-induced apoptosis and microthrombosis following inner ear destruction. Apoptosis occurs in Deiters’ cells, Claudius’ cells, and Hensen’s cells in the Corti organ due to glutamate overstimulation in the radial dendrites; this is followed by vacuolization of the inner ear cells, which has been observed via immunohistochemical evaluation through a cecal ligation puncture in an induced sepsis mouse study.[15] Sepsis-surviving model mice exhibited an increased threshold of auditory brainstem response.[6] Aminoglycoside antibiotics are widely used for suspected gram-negative bacterial infections. A previous study found that vasodilation due to inflammation increased...
| Table 4 | The overall and subgroup-specific incidence rates and incidence rate ratios of hearing impairment between septicemia and septicemia-free patients. |
|---------|-------------------------------------------------------------------------------------------------------------------------------------|
| Septicemia Stratified | With Event | PYs | Incidence Rate (per 10^5 PYs) | Without Event | PYs | Incidence Rate (per 10^5 PYs) | IRR |
| Total | 793 | 53655.21 | 1477.96 | 75 | 191750.96 | 39.11 | 37.79 |
| Gender | | | | | | | |
| Male | 380 | 21315.97 | 1782.7 | 39 | 94128.71 | 41.43 | 43.03 |
| Female | 413 | 32339.24 | 1277.09 | 36 | 97622.26 | 36.88 | 34.63 |
| Age group (yr) | | | | | | | |
| 18–44 | 152 | 10024.15 | 1516.34 | 6 | 39567.36 | 15.16 | 100 |
| ≥45 | 641 | 43631.06 | 1469.14 | 69 | 152183.61 | 45.34 | 32.4 |
| Diabetes mellitus | | | | | | | |
| Without | 532 | 35006.86 | 1498.3 | 60 | 155996.71 | 38.46 | 38.96 |
| With | 261 | 18148.35 | 1438.15 | 15 | 35754.25 | 41.95 | 34.28 |
| Hypertension | | | | | | | |
| Without | 606 | 40260.55 | 1728.74 | 57 | 144820.11 | 39.36 | 43.92 |
| With | 97 | 13394.66 | 724.17 | 18 | 46930.85 | 38.35 | 18.88 |
| Chronic kidney disease | | | | | | | |
| Without | 626 | 46636.45 | 1342.3 | 74 | 182776.63 | 40.49 | 33.15 |
| With | 167 | 7017.86 | 2379.34 | 1 | 8974.54 | 11.14 | 213.53 |
| Hyperlipidemia | | | | | | | |
| Without | 787 | 52098.84 | 1510.59 | 72 | 184367.54 | 38.95 | 38.79 |
| With | 6 | 1556.37 | 385.51 | 3 | 6883.42 | 43.58 | 8.85 |
| Coronary artery disease | | | | | | | |
| Without | 735 | 48322.06 | 1521.04 | 69 | 174716 | 39.49 | 38.52 |
| With | 58 | 5331.15 | 1087.54 | 6 | 17034.96 | 35.22 | 30.88 |
| Ischemic stroke | | | | | | | |
| Without | 779 | 51613.87 | 1500.28 | 69 | 184326.07 | 37.43 | 40.32 |
| With | 14 | 2041.34 | 685.83 | 6 | 7424.89 | 80.81 | 8.49 |
| Autoimmune diseases | | | | | | | |
| Without | 778 | 52869.96 | 1471.54 | 74 | 191052.77 | 38.73 | 37.99 |
| With | 15 | 785.25 | 1910.22 | 1 | 698.19 | 143.23 | 13.34 |
| Anemia | | | | | | | |
| Without | 770 | 51005.35 | 1500.65 | 69 | 183471.25 | 37.61 | 40.14 |
| With | 23 | 2649.86 | 867.97 | 6 | 8279.72 | 72.47 | 11.98 |
| Hematological disorder | | | | | | | |
| Without | 780 | 53193.13 | 1467.84 | 74 | 190574.53 | 38.83 | 37.8 |
| With | 13 | 516.08 | 2519 | 1 | 1176.44 | 85 | 29.63 |
| Meningitis | | | | | | | |
| Without | 792 | 53549.42 | 1479.01 | 75 | 191510.73 | 39.16 | 37.77 |
| With | 1 | 105.79 | 945.3 | 0 | 240.23 | 0 | – |
| Traumatic brain injury | | | | | | | |
| Without | 785 | 51960.35 | 1510.77 | 72 | 183048.98 | 39.33 | 38.41 |
| With | 8 | 1694.86 | 472.02 | 3 | 8701.98 | 34.47 | 13.69 |
| Encephalopathy | | | | | | | |
| Without | 791 | 53432.48 | 1480.37 | 75 | 191020.36 | 39.26 | 37.7 |
| With | 2 | 222.73 | 897.95 | 0 | 730.6 | 0 | – |
| Chronic otitic media | | | | | | | |
| Without | 789 | 53139.71 | 1484.77 | 68 | 190845.57 | 35.63 | 41.67 |
| With | 4 | 515.5 | 775.94 | 7 | 905.39 | 773.15 | 1 |
| Otosclerosis | | | | | | | |
| Without | 793 | 53655.21 | 1477.96 | 74 | 191743.77 | 38.59 | 38.3 |
| With | 0 | 0 | 0 | 1 | 7.19 | 13910.97 | – |
| Osteoporosis | | | | | | | |
| Without | 793 | 53584.36 | 1479.91 | 75 | 190680.6 | 39.34 | 37.62 |
| With | 0 | 70.85 | 0 | 0 | 1090.36 | 0 | – |
| Urbanization level | | | | | | | |
| 1 (The highest) | 331 | 18290.62 | 1808.67 | 22 | 59695.13 | 36.73 | 49.27 |
| 2 | 303 | 23911.23 | 1267.19 | 40 | 84908.88 | 47.11 | 26.9 |
| 3 | 34 | 3470.57 | 979.67 | 5 | 14458.62 | 34.58 | 28.33 |
| 4 (The lowest) | 125 | 7982.79 | 1565.87 | 8 | 32488.34 | 24.62 | 63.59 |
| Level of care | | | | | | | |
| Hospital center | 322 | 20519.69 | 1569.22 | 30 | 66266.59 | 45.27 | 34.66 |
| Regional hospital | 356 | 23979.04 | 1401.22 | 36 | 83877.64 | 42.92 | 32.65 |
| Local hospital | 135 | 9156.48 | 1474.37 | 9 | 41606.73 | 21.63 | 68.16 |

IRR = Incidence rate ratio, PYs = person-years.
cellular damage in the blood-labyrinth barrier, which facilitates aminoglycoside transfer to hair cells.\textsuperscript{[18]} Male humans who perform work that involves exposure to loud noises exhibit an increased risk of hearing loss associated with pneumococcal meningitis.\textsuperscript{[12]} Our study had a similar finding: men exhibited an increased risk of hearing impairment after septicemia. Sepsis induces apoptosis in various organs, potentially leading to multiple organ failure. The moderate renal impairment-related increased risk of hearing impairment occurs via apoptosis, with an odds ratio of 1.43 (95% CI: 1.1–1.84).\textsuperscript{[19]} and our study reported a similar finding. A past study reported that otosclerosis related to sensorineural hearing loss occurred in 34% of patients,\textsuperscript{[20]} and our study showed that otosclerosis also increases hearing impairment. The otosclerosis was the highest association with hearing impairment, but it would not be the major cause instead of septicemia with low prevalence in our study group. Septicemia patients with more comorbid conditions will experience increased mortality during hospitalization\textsuperscript{[10]} and an increased number of comorbid conditions seems to cause an increased risk of septicemia-induced hearing impairment in our study.

Patients with a higher urbanization level have a lower risk of hearing impairment. Potential reasons include the possibility that these patients are more concerned about their health status and frequently seek health care providers to improve their quality of life. Patients with hypertension, anemia, and traumatic brain injury exhibited relatively fewer hearing impairment events in the present study. The potential reason may be adequate treatment indicated by the diagnostic codes for hypertension and anemia in the claims data. Higher mortality from traumatic head injury leads to a lower risk of hearing impairment. More in-depth research in this field is necessary.

Aging and exposure to loud noise may cause wear and tear on the hairs or nerve cells in the cochlea, which send sound signals to the brain. In addition, the aging immune system and weaker older bodies are more vulnerable to the damaging effects of sepsis, and these patients are more likely to suffer lasting consequences. We excluded older septicemia survivors to reduce the effect of aging on hearing impairment. However, our study found that hearing impairment was not associated with older age in the young and middle-aged groups. Poorly controlled diabetes mellitus induces chronic kidney disease and increases oxidative stress.\textsuperscript{[21]} Diabetes mellitus and hyperlipidemia were not related to hearing impairment in adults in our study. A potential reason is that the NHIRD dataset is generated from insurance payment claims. Patients with a diagnosis of diabetes mellitus and hyperlipidemia are administered suitable treatments according to the payment guidelines. Spiral ganglion loss and a flattened organ of Corti were noted after ischemia in guinea pigs.\textsuperscript{[22]} A previous rat study showed cell damage due to apoptosis in outer hair cells in a carotid ischemia model.\textsuperscript{[23]} However, our study did not find that ischemic stroke increased the risk of hearing impairment. The potential reason is that hearing impairment may be undiagnosed or underestimated in severe ischemic stroke patients who are bedridden or display cognitive impairment without hearing impairment complaints.

Bacterial infection can be prevented with a vaccine\textsuperscript{[24,25]} and treated with antibiotics. Rapid identification of the infection source can facilitate timely treatment with appropriate antibiotics, potentially preserving some hearing function. The administration of third-generation cephalosporin antibiotics to treat acute infection has relatively fewer toxic effects on the ear. Dextran and vasodilators improve inner ear circulation. Aspirin reduces ischemic attacks within 1 month after sepsis.\textsuperscript{[26]} Antioxidants diminish reactive oxygen species levels to reduce hair cell apoptosis.\textsuperscript{[27]}

Our results support the hypothesis of a close correlation between septicemia and hearing impairment in the largest population of participants investigated to date, after adjustment for other contributing factors. Physicians and patients need to pay more attention to this complication of septicemia. The rapid identification of the infection source can quickly facilitate treatment with appropriate antibiotics, and guidelines on the management of chronic kidney disease\textsuperscript{[28]} should be followed to preserve hearing function, thereby enhancing patients’ ability to communicate and relieving their psychological burden. If treatment for hearing loss fails, adults may need a cochlear implant to improve their hearing ability and, thereby, their social interactions. However, this alternative can be uncomfortable and expensive.

5. Limitations

There were some limitations of this study. First, because the NHIRD is a payment claims dataset, detailed data on body mass index, noise environment exposure, family history, potential risk factors, and severity of the hearing loss according to audiometry and otological exams were not available; however, these factors may have an impact on hearing impairment risk.

Second, the diagnoses of septicemia, hearing impairment, and comorbidities were made according to the ICD-9-CM diagnostic codes recorded in the database from the Taiwan NH program, which may vary from study to study. Patients with severe septicemia experience severe inflammation, which may exert a threshold effect on hearing impairment. A prospective audiometry assessment must be undertaken in septicemia survivors to confirm the dose effect.

Third, age-related hearing impairment occurs after 55 years of age. The etiology of hearing impairment needs to be determined in older septicemia survivors.

Fourth, we did not survey ototoxic agents in this study. The effects of ototoxic agents, such as antibiotics or diuretics, on hearing impairment should be assessed in the future.

Fifth, although the data were only collected until 2013, they still provide initial results regarding the risk of hearing impairment among septicemia survivors. One study showed lesser poor hearing in older severe sepsis survivors compared with general population in USA.\textsuperscript{[29]} This pilot study was performed in a Chinese population, and the generalizability of our findings to other ethnic populations is limited. It needs more recent data and further global study to confirm our findings.

6. Conclusions

To the best of our knowledge, this is the first paper to show that septicemia is associated with an increased risk of long-term hearing loss in young and middle-aged humans. Our study suggests that clinicians should be aware of septicemia-related hearing impairment and use optimal prophylaxis strategies to decrease hearing impairment. We recommend determining the hearing of septicemia survivors to enable the earlier identification of hearing impairment. Early aggressive prevention and treatment of septicemia should be used to reduce long-term complications and improve quality of life.
Acknowledgments

The authors thank TSGH-C107-004, TSGH-C108-003, and TSGH-C109-010 for their support and the American Journal Experts for English editing.

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