Impact of Nosocomial Infections on Medical Costs, Hospital Stay, and Outcome in Hospitalized Patients

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Background and Purpose: Nosocomial infections have been shown to be associated with increased attributable mortality, length of hospital stay, and health care costs in studies mainly conducted in western populations. However, the health care system in Taiwan differs from the typical situation in western countries, with longer hospitalization times and lower daily costs. The purpose of this study was to understand the economic and clinical impacts of nosocomial infections in Taiwan.

Methods: Between June 1, 2001 and December 31, 2001, every hospitalized patient (age ≥ 16 years) with nosocomial infections (case group) and matched control patients without nosocomial infections of the same age, gender, underlying medical illness, clinical diagnosis at admission and disease severity (control group) were recruited. Demographic characteristics, length of hospitalization, costs and final outcomes of both groups were collected for analysis.

Results: A total of 482 patient-pairs with median age of 68 years were studied. The median length of hospital stay was 40 days for the case group and 22 days for the control group ($p < 0.0001$). The median hospital cost for the case group was 363,425 New Taiwan Dollars (NTD) and 165,965 NTD for the control group ($p < 0.0001$). The median additional hospital stay for patients with nosocomial infection was 15 days, which amounted to 127,354 NTD. The extra hospital costs were not only associated with accommodation but also fees for materials, and costs relating to pharmacy, laboratory tests and diet. Patients with nosocomial infections were more likely to have shock, organ failure and death (all $p < 0.0001$). Additional hospital stay and costs were not related to various infection sites and bacterial pathogens causing nosocomial infections; however, medical costs attributable to nosocomial fungal infection were higher than that of bacterial infections.

Conclusions: Nosocomial infections have a significant impact on the length of hospital stay and medical care cost. Extra costs of nosocomial infections resulted not only from prolongation of hospital stay, but also other medical costs. Infection control for preventing nosocomial infections may play an important role in reducing medical costs, hospital stay, and mortality in hospitalized patients.

Key words: Cost of illness; Cross infection; Health care costs; Length of stay; Mortality

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Nosocomial infections are of importance in terms of patient morbidity, mortality, and hospital costs.[1–3] Incremental costs in nosocomial infections are important to both clinicians and health care managers.[4,5] Depending on the type and etiology of nosocomial infections, the extra cost was reported to have increased from 600 US dollars (USD) per patient in 1976 to 1250 USD per patient in 1983.[6–9] For some special circumstances, such as nosocomial *Staphylococcus aureus* bacteremia, it had a much higher cost (5580 USD).[10] However, data on hospital costs are primarily derived from western countries and most attributed extra cost of nosocomial infection is due to additional stays. Few studies had compared the relative contribution of nursing care, laboratory use, drugs and diet towards total cost. Nevertheless, the proportion of nosocomial infection sites and pathogens causing these infections altering the prolonged stay and extra cost of nosocomial infections were discrete and the causal link between antibiotic resistance and fatal outcome remain unclear.

Nationwide nosocomial infection surveillance data in Taiwan showed that nosocomial infection rate was 4.2 episodes per 1000 patient-days in medical centers and 3.4 episodes per 1000 patient-days in regional hospitals among all hospitalized patients during

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1999-2002.[11] Amount of extra costs incurred for these patients with nosocomial infection has never been studied in detail in Taiwan. As Taiwan's government moves towards the global budget payment system, analyzing the financial impact of nosocomial infections is thus important for medical personnel, hospital administrators, and the government. The aim of our study was to evaluate the additional hospital stays, incremental charges and outcomes due to nosocomial infection in order to estimate the potential impact of infection control measured in an area where health insurance was covered by the government. We also evaluate whether different sites and pathogens of nosocomial infections would alter the length of stays and amount of extra costs and provide information for infection control policy.

Methods

Hospital setting and data collection

The study was performed at National Taiwan University Hospital (NTUH), a 2000-bed medical center located in northern Taiwan with 60,000 to 70,000 admissions annually. Active surveillance of nosocomial infections has been continued at NTUH by reviewing medical records and laboratory data since 1980 to identify patients with nosocomial infection. All hospitalized patients aged ≥ 16 years with nosocomial infections between June 1, 2001 and December 31, 2001 were enrolled. If the patient had more than 1 episode of nosocomial infection during the study period, data from all episodes were analyzed. All types of nosocomial infections at NTUH were identified from daily surveillance by infection control nurses according to the definition from the Centers for Disease Control and Prevention, United States,[12] which defined nosocomial infection as an infection occurring at least 48 h after hospital admission or within 1 week of discharge with evidence of infection being related to previous hospitalization. Bloodstream infection was defined as having positive blood culture obtained in the presence of fever (≥ 38°C).

Nosocomial pneumonia was defined as positive physical or radiographic examinations of chest and either of new onsets of purulent sputum, positive blood culture and isolation of pathogen from transtracheal aspirate, bronchial brushing, or biopsy. Complications occurring during hospitalization were reviewed by infectious diseases specialists as follows: respiratory failure was defined as development of hypoxia necessitating mechanical ventilation; renal failure was defined as the need for dialysis; hepatic failure was defined as presence of jaundice, prolonged prothrombin time, and hepatic encephalopathy; heart failure was defined as deterioration of cardiac function necessitating administration of inotropic agents for life support; and neurologic failure was defined as development of comatous consciousness.

A standardized case record form was used to retrieve clinical and demographic data, hospital costs for diagnostic and therapeutic services, length of stay, complications, and final outcomes of case patients and controls. All patients were tracked and data were collected until death or discharge from the hospital. Post-discharge surveillance was performed at follow-up visits and by retrospective review of medical records.

Case-control matching

One out of every 2 consecutive adult patients who developed nosocomial infections (case) was identified daily from infection control surveillance data, and patients without nosocomial infection (controls) who were admitted to the hospital during the same study period were identified from daily hospital admission lists. We used more strict criteria to match cases and controls to prevent possible confounding. Each case patient was matched with a control of the same age (± 2 years), gender, underlying medical illness, types of surgery, diagnosis at admission, admission date (± 28 days) and types of wards and disease severity. Recording of systemic underlying medical illnesses included malignancies (solid tumors or leukemia, localized tumor or distant metastasis), diabetes (with oral hypoglycemic agents or insulin injection), chronic heart diseases (coronary arterial disease, valvular heart diseases and cardiac arrhythmia), the severity of heart failure as defined by the classification of the New York Heart Association, chronic lung disease (oxygen supported or not), chronic renal disease (dialysis or not), chronic liver disease (cirrhosis or not), neurologic disease (bedridden or not), steroid use (more than 3 months), recent operation (within 3 months) and admission category (medical or surgical, scheduled or unscheduled operation).

Severity of underlying disease was classified using the modified risk stratification proposed by Kreger et al[13] as rapidly fatal (death expected within 1 year), ultimately fatal (death expected within 5 years), or non-fatal (death expected after more than 5 years or no underlying disease). When several potential controls were found, the one with the nearest birth date and date of admission to the case was selected.

Microbiology and identification of causative pathogens

Routine processing of specimens was done at the Department of Microbiology laboratory at NTUH.

Bacteria were identified using conventional methods — VITEK system or API system (bioMerieux, Marcy l'Etoile, France). Antimicrobial susceptibility testing was determined by Kirby-Bauer disk-diffusion technique, as described by the National Committee for Clinical Laboratory Standards (NCCLS) of USA.[14] Antibiotic resistance was determined according to the criteria for disk-diffusion testing recommended by the NCCLS. Multiple drug resistance was defined when the antimicrobial susceptibility tests showed resistance of the isolated sample to at least 3 or more classes of antimicrobial agents. Pathogens of nosocomial infection were defined if pathogens were identified from sterile body fluids (such as blood, pleural effusion, ascites, cerebrospinal fluid, deep respiratory tract secretion or joint effusion), tissue of biopsy or pus which was compatible with sites of nosocomial infections. Patients with nosocomial infections but unidentified microorganisms were carefully reviewed. Patients showing coagulase-negative staphylococci, diphtheroids, *Bacillus* species, *Propionibacterium* species and micrococci in one of the blood cultures were excluded from analysis.

Prolongation of hospital stay and cost analysis

The length of hospital stay and cost for hospitalization were compared between each case and control. Data of the costs related to hospitalization were retrieved from the central financial service at NTUH. This data contains information of the total cost of each hospital stay, as well as fees for accommodation at Emergency Service Department, Intensive Care Unit (ICU), and general wards; fees for medications, laboratory examinations, materials and services — which included catheters, implants, materials for procedure and operations, rehabilitation programs, respiratory care, dialysis and other special services, physician care, nursing care, and consultations; and fees for diet. To prevent the bias of different costs in accommodation and diet (because patients could choose different classes of accommodation and diet), we adjusted the costs of accommodation according to the fees defined by National Health Insurance in Taiwan (6400 New Taiwan Dollars [NTD] per day for ICU, 1035 NTD per day for general ward) and only calculated the cost of nasogastric milk feeding diet. To better understand the impact of different infection sites on excess length of hospital stay and costs, we analyzed the data of patients with nosocomial respiratory tract, urinary tract, bloodstream and surgical site infections. Furthermore, patients with nosocomial infections due to the 4 most common nosocomial pathogens, including *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans*, were compared to assess the duration of hospital stay and costs.

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (Version 8.1, SAS Institute Inc., Cary, NC, USA) and the extra hospital stay and cost were calculated based on per patient-pair. Because of the skewed distribution of hospital stay and cost data, we used medians and interquartile ranges (25th and 75th percentiles) as a measure of central tendency and non-parametric statistics (Wilcoxon's signed rank test) were used to test the differences. Conditional logistic regression was used for analysis of differences in complications and outcomes of patients with nosocomial infection and their controls. To prevent confounding by other factors, patient-pairs with only 1 site/pathogen of nosocomial infections were analyzed for comparison between various infection sites and pathogens. All tests were 2-tailed and a p value < 0.01 was considered significant.

Results

Characteristics of study population

During the study period, a total of 1176 patients developed nosocomial infections at NTUH, which accounted for a crude nosocomial infection rate of 4.5 per 100 discharges (5.6 episodes per 1000 patient-days). Of those patients, 588 patients were randomly selected as the case group. A total of 482 matched pairs could be identified with a matching rate of 82%; 106 patients without suitable controls were excluded because of unusual combination of medical condition or uncommon diseases. The age, gender, systemic medical illnesses (e.g., proportion of malignancy) and disease severity were similar between matched and unmatched cases (p = 0.86, 0.92, 0.77, 0.89). Of the matched cases, a total of 642 episodes of nosocomial infections were diagnosed and multiple episodes were found in 130 patients, including 2 episodes in 106 patients, 3 episodes in 18, and 4 episodes in 6. The infection sites of the 642 episodes were bloodstream (235 episodes, 37%), urinary tract (195, 30%), surgical site (75, 12%), respiratory tract (74, 12%), and others, (63, 9%).

The clinical and demographic characteristics of patients and their controls are the same except the median age (25th, 75th percentile) was 68 years (55, 76 years) for the cases and 68 years (56, 76 years) for controls, respectively (Table 1). Fifty five percent were male. Eighty seven percent of the patients had underlying systemic medical illnesses and 40% of them had been operated on in the past 3 months. Malignancy (including solid tumors and leukemia, 45%) and chronic heart disease (including coronary heart disease, valvular heart disease and arrhythmia, 41%) were the most common underlying medical

Table 1. Demographic and clinical characteristics of 482 patient-control pairs with or without nosocomial infections (NI).

Characteristic	Patients with NI (n = 482)	Patients without NI (n = 482)
Median age (25th, 75th percentile)	68 (55, 76)	68 (56, 76)
Male gender	264 (54.8%)	264 (54.8%)
Disease severity		
Rapidly fatal	92 (19.1%)	92 (19.1%)
Ultimately fatal	185 (38.4%)	185 (38.4%)
Non-fatal	205 (42.5%)	205 (42.5%)
Underlying medical illness	419 (86.9%)	419 (86.9%)
Malignancy	217 (45.0%)	217 (45.0%)
Solid tumors	180 (37.3%)	180 (37.3%)
Leukemia	37 (7.7%)	37 (7.7%)
Chronic heart disease	196 (40.7%)	196 (40.7%)
Diabetes mellitus	140 (29.0%)	140 (29.0%)
Chronic lung disease	116 (24.1%)	116 (24.1%)
Chronic renal diseases	88 (18.3%)	88 (18.3%)
Chronic liver disease	79 (16.4%)	79 (16.4%)
Neurologic disorders	67 (13.9%)	67 (13.9%)
Steroid use	31 (6.4%)	31 (6.4%)
Recent operation*	194 (40.2%)	194 (40.2%)
Admission category		
Medical	332 (68.9%)	332 (68.9%)
Surgical	150 (31.1%)	150 (31.1%)
Unscheduled operation	57 (11.8%)	57 (11.8%)
Scheduled operation	93 (19.3%)	93 (19.3%)

* Recent operation was defined as operation within 3 months.

illnesses, followed by diabetes mellitus (29%), chronic lung diseases (24%) and chronic renal diseases (18%). More than half of the patients (57%) had severe and moderate underlying diseases and nearly 20% of these were rapidly fatal. One-third of the patients were hospitalized for surgical intervention and 12% of them received emergency operation (Table 1).

Microbiologic results

Among the 642 episodes of nosocomial infection, causative pathogens were identified in 612 episodes of infection. The causative microorganisms included *C. albicans* (n = 83), *E. coli* (71), *P. aeruginosa* (70), *S. aureus* (63; 52 methicillin-resistant), *Enterobacter* species (55), *Acinetobacter baumannii* (50), *Klebsiella pneumoniae* (50), enterococci (48), *S. epidermidis* (24), *Candida tropicalis* (13), *Stenotrophomonas maltophilia* (12), *Serratia marcescens* (12), *Proteus mirabilis* (11), *Candida glabrata* (11), *Bacteroides fragilis* (11) and others (122). 193 episodes (30%) were caused by more than 1 pathogen in a single episode of infection. Of the 527 aerobic bacterial isolates causing nosocomial infections, 395 (75%) were multiple drug-resistant.

Prolongation of hospitalization and extra costs

The median length of hospital stay for case patients was 40 days (25th, 75th interquartile percentile; 24, 65) and 22 days (13, 44) for the controls; cases had longer hospital stay than controls by 15 days ($p < 0.0001$), including 11 days extra stay at ward. Patients with nosocomial infection occurring at ICU had a median of 7 days of extra ICU stay than the controls. Patients with any kind of pathogen and any site of nosocomial infection had a significantly longer hospital stay than controls (all $p < 0.0001$) [Table 2]. Nosocomial infection of various sites had an extra 14-16 days of hospitalization. Nosocomial infections caused by *P. aeruginosa* had the longest extra hospital stay (median, 19 days), while infections caused by *E. coli* had the shortest extra stay (median, 8 days).

The median total cost of hospitalization for patients with nosocomial infections and controls was 363,425 NTD and 165,965 NTD, respectively ($p < 0.0001$). Therefore, cases had a median extra cost of 127,354 NTD compared to their matched controls. In the subcategories, all types of medical cost (median) were significantly higher in cases than in controls: accommodation, 64,195 *vs* 27,889 NTD; laboratory examinations, 46,259 *vs* 20,374 NTD; medication, 114,963 *vs* 37,675 NTD; fees for services and materials, 110,287 *vs* 62,491 NTD; and diet, 1870 *vs* 0 NTD (all $p < 0.0001$).

Similarly, patients with nosocomial infections had significantly higher costs for hospitalization regardless of causative pathogens and sites of infection (all $p < 0.0001$) [Table 3]. Of the sites of nosocomial infection, the patients with respiratory tract and surgical site infections had higher extra costs (median, 117,100 and 117,802 NTD, respectively), while the patients with bloodstream infection had the least extra charges (101,536 NTD). Nosocomial infection caused by *C. albicans* had the highest extra

Table 2. Prolonged hospital stay of patients with or without nosocomial infections (NI).

Category	Hospital stay [median (25th, 75th percentile)]		Extra days of hospitalization [median (25th, 75th percentile)]	*p* value (Wilcoxon's signed rank test)
	With NI (cases)	Without NI (controls)		
Total days	40 (24, 65)	22 (13, 44)	15 (0, 33)	< 0.0001
Intensive care unit (overall)	0 (0, 14)	0 (0, 2)	0 (0, 7)	< 0.0001
Wards (overall)	32 (17, 51)	18 (9, 37)	11 (–4, 29)	< 0.0001
NI occurred at ICU (n = 110)	22 (10, 39)	9 (4, 22)	7 (2, 21)	< 0.0001
Sites of nosocomial infections*				
Urinary tract (n = 117)	37 (23, 61)	22 (14, 47)	14 (–2, 33)	< 0.0001
Respiratory tract (n = 35)	40 (25, 63)	23 (12, 38)	15 (0, 33)	< 0.0001
Surgical site (n = 51)	39 (24, 64)	22 (12, 25)	15 (–1, 33)	< 0.0001
Bloodstream (n = 142)	40 (23, 63)	28 (14, 44)	16 (1, 34)	< 0.0001
Pathogens caused nosocomial infections†				
Staphylococcus aureus (n = 27)	36 (14, 62)	22 (15, 38)	16 (–7, 42)	< 0.0001
Escherichia coli (n = 36)	33 (20, 53)	21 (12, 47)	8 (–1, 19)	< 0.0001
Pseudomonas aeruginosa (n = 30)	40 (27, 57)	21 (13, 39)	19 (4, 33)	< 0.0001
Candida albicans (n = 44)	43 (26, 56)	25 (14, 45)	15 (1, 39)	< 0.0001

* Data of patient-pairs with single site of nosocomial infection were recruited for analysis.
† Data of patient-pairs with single pathogen were recruited for analysis.
ICU = intensive care unit.

Table 3. Comparison of charges for accommodation, materials and services, medications and diet between cases and controls.

Category	Charges in NTD*, median (25th, 75th percentile)		Extra costs (NTD*) [median (25th, 75th percentile)]	*p* value (Wilcoxon's signed rank test)
	With NI (cases)	Without NI (controls)		
Total charges	363,425 (1,172,808, 708,815)	165,965 (79,058, 405,877)	127,354 (–12,792, 377,754)	< 0.0001
Accommodation	64,195 (30,628, 141,449)	27,889 (12,826, 64,495)	28,023 (–969, 82,431)	< 0.0001
Laboratory	46,259 (21,877, 93,453)	20,374 (8918, 48,664)	16,065 (–1971, 50,935)	< 0.0001
Pharmacy	114,963 (37,441, 229,859)	37,675 (13,160, 138,343)	36,072 (–5244, 124,014)	< 0.0001
Materials and services†	110,287 (51,703, 219,004)	62,491 (21,009, 125,617)	36,373 (–7315, 111,356)	< 0.0001
Diet	1870 (0, 12,659)	0 (0, 1870)	0 (0, 8550)	< 0.0001
Sites of NI				
Urinary tract (n = 117)	354,608 (160,654, 670,271)	159,953 (79,592, 417,233)	114,662 (–37,876, 359,417)	< 0.0001
Respiratory tract (n = 35)	368,435 (163,794, 676,617)	180,059 (95,758, 428,255)	117,100 (–12,692, 358,449)	< 0.0001
Surgical site (n = 51)	357,013 (169,639, 708,815)	126,519 (62,491, 240,580)	117,802 (–18,170, 364,895)	< 0.0001
Bloodstream (n = 142)	323479 (147227, 642315)	199,365 (93,553, 405,877)	101,536 (–11,089, 327,955)	< 0.0001
Pathogens that caused NI				
Staphylococcus aureus (n = 27)	279,612 (90,948, 592,115)	168,737 (83,066, 464,928)	75,785 (–116,700, 171,208)	< 0.0001
Escherichia coli (n = 36)	218,135 (114,996, 428,088)	142,518 (57,214, 286,906)	51,002 (–12,291, 148,396)	< 0.0001
Pseudomonas aeruginosa (n = 30)	250,968 (125,250, 394,053)	165,029 (79,592, 302,170)	53,741 (59,018, 203,874)	< 0.0001
Candida albicans (n = 44)	472,577 (274,481, 656,778)	191,916 (100,467, 498,562)	144,154 (–10,822, 324,080)	< 0.0001

* Exchange rate in 2001; United States Dollar = 34 NTD.
† Fees for materials and services included catheters, implants, materials for procedure and operations, rehabilitation programs, respiratory care, dialysis and other special services, physician care, nursing care, and consultations.
NTD = New Taiwan Dollars; NI = nosocomial infection.

cost during hospitalization (144,154 NTD), and infection caused by *E. coli* was the lowest (51,002 NTD) [Table 3].

When infections involving different sites or caused by different pathogens were compared, there were no significant differences in length of hospital stay and cost between various sites (all $p \geq 0.01$) [Table 4]. No differences in prolongation of hospital stay or extra hospital costs were observed between different pathogens, with the exception that patients with nosocomial infection due to *C. albicans* showed borderline higher extra costs than other bacterial infections ($p = 0.05$) [Table 4].

Clinical outcomes

Nosocomial infection was associated with more complications, such as shock ($p < 0.0001$; Conditional odds ratio [COR], 3.44; 95% confidence interval [CI], 2.24-5.29) and organ failure ($p < 0.0001$; COR, 3.95; 95% CI, 2.45-6.38) during hospitalization (Table 5). Patients with nosocomial infections had a higher probability of renal and respiratory failures than

Table 4. Comparison of extra length of stay (LOS) and extra hospital costs between different pathogens and sites of nosocomial infection.

	Hospital stay, *p* value				Hospital costs, *p* value				
	Total extra LOS	Extra ICU stay	Extra ward stay	Total extra charges	Extra costs of accommodation	Extra laboratory costs	Extra costs of medication	Extra costs of materials and services	Extra costs of diet
Infection sites*									
RTI/BSI	0.20	0.34	0.30	0.14	0.16	0.11	0.23	0.20	0.06
RTI/UTI	0.42	0.16	0.28	0.14	0.06	0.03	0.26	0.27	0.01
RTI/SSI	0.36	0.37	0.38	0.32	0.13	0.04	0.39	0.25	0.05
BSI/UTI	0.12	0.17	0.03	0.42	0.15	0.14	0.37	0.47	0.05
BSI/SSI	0.21	0.46	0.14	0.22	0.42	0.14	0.28	0.13	0.07
UTI/SSI	0.41	0.21	0.35	0.27	0.27	0.36	0.39	0.04	0.28
Pathogens†									
C. albicans/E. coli	0.09	0.19	0.21	0.04	0.01	0.01	0.02	0.38	0.06
C. albicans/P. aeruginosa	0.16	0.04	0.18	0.12	0.08	0.03	0.08	0.46	0.09
C. albicans/S. aureus	0.10	0.12	0.35	0.07	0.11	0.10	0.03	0.21	0.07
E. coli/P. aeruginosa	0.04	0.11	0.08	0.47	0.15	0.48	0.49	0.34	0.11
E. coli/S. aureus	0.34	0.41	0.29	0.42	0.12	0.40	0.50	0.39	0.14
P. aeruginosa/S. aureus	0.38	0.35	0.48	0.35	0.30	0.38	0.47	0.37	0.27
C. albicans/bacteria‡	0.12	0.16	0.23	0.05	0.08	0.06	0.04	0.30	0.05

* Analysis was performed by sites of nosocomial infections including bloodstream (n = 142), urinary tract (n = 117), surgical site (n = 51) and respiratory tract (n = 35).
† Analysis by pathogens causing nosocomial infections including *Candida albicans* (n = 44), *Escherichia coli* (n = 36), *Pseudomonas aeruginosa* (n = 30) and *Staphylococcus aureus* (n = 27).
‡ Bacteria including *E. coli* (n = 36), *P. aeruginosa* (n = 30) and *S. aureus* (n = 27).
ICU = intensive care unit; RTI = respiratory tract infection; BSI = bloodstream infection; UTI = urinary tract infection; SSI = surgical site infection.

Table 5. Complications of 482 patient-pairs with or without nosocomial infections (NI).

Characteristic	Cases with NI (n = 482)	Cases without NI (n = 482)	Conditional odds ratio (95% CI)	*p* value
Shock	112 (23%)	46 (10%)	3.44 (2.24-5.29)	< 0.0001
Organ failure	117 (24%)	55 (11%)	3.95 (2.45-6.38)	< 0.0001
Renal failure	50 (10%)	24 (5%)	3.36 (1.72-6.59)	0.0004
Respiratory failure	43 (9%)	11 (2%)	5.00 (2.34-10.68)	< 0.0001
Heart failure	31 (6%)	26 (5%)	1.28 (0.69-2.37)	0.44
Neurologic failure	26 (5%)	10 (2%)	6.33 (1.87-21.38)	0.003
Liver failure	15 (3%)	10 (2%)	1.56 (0.67-3.59)	0.30
Renal failure, ever received dialysis	31 (6%)	14 (3%)	3.25 (1.80-5.29)	0.002
Tracheostomy on ventilator	16 (3%)	4 (0.8%)	6.99 (1.59-30.74)	0.001
Death	207 (43%)	68 (14%)	8.72 (5.36-14.27)	< 0.0001

CI = confidence interval.

controls ($p = 0.0004$ and < 0.0001, respectively). Some of the patients with nosocomial infections developed irreversible organ failure necessitating dialysis ($p = 0.002$; COR, 3.25; 95% CI, 1.80-5.29) and ventilator support ($p = 0.001$; COR, 6.99; 95% CI, 1.59-30.74). Sixteen patients (3%) had undergone operations for the management of nosocomial infections. Seventy six (16%), 34 (7%) and 33 (6%) of patients had septic shock, multiple organ failure syndrome and disseminated intravascular coagulation, respectively, related to their nosocomial infections. The crude mortality rates at the end of the study were 43% for cases and 14% for controls, respectively ($p < 0.0001$; COR, 8.72; 95% CI, 5.36-14.27) [Table 5]. Fourteen patients with nosocomial infections died within 3 days after onset despite intensive care being given. These patients had a shorter hospital stay and lower costs because of early mortality from severe sepsis. Patients with multiple episodes of nosocomial infections had a longer extra hospital stay and extra costs than those with only 1 episode of nosocomial infection (median, 25 days *vs* 13 days, $p = 0.003$; 288,576 NTD *vs* 81,028 NTD, $p < 0.0001$) [Table 6]. The mortality was also higher for patients with multiple episodes of nosocomial infections (60.8% *vs* 36.4%, COR, 2.83; 95% CI, 1.89-4.73, $p < 0.0001$). Patients with nosocomial infections caused by multiple drug-resistant bacteria also had a longer extra hospital stay and extra hospital costs than those with susceptible bacteria (median, 16 days *vs* 6 days, $p = 0.005$; 114,834 NTD *vs* 54,345 NTD, $p = 0.006$) [Table 6]. Patients infected by multiple drug-resistant bacteria also had higher mortality (48.7% *vs* 29.8%, COR, 2.22; 95% CI, 1.49-3.29, $p = 0.01$).

Table 6. Comparison of impact of multiple (≥ 2) episodes of nosocomial infections and multiple drug-resistant bacterial infections on hospital stay, costs and mortality.

Characteristic	All patients with nosocomial infections (n = 482)				Patients with single aerobic bacterial nosocomial infections* (n = 258)			
	Patients with multiple NI (n = 130) [median (25th, 75th percentile)]	Patients with single NI (n = 352) [median (25th, 75th percentile)]	Conditional odds ratio (95% CI)	*p* value	NI caused by multiple drug-resistant bacteria (n = 201) [median (25th, 75th percentile)]	NI caused by susceptible bacteria (n = 57) [median (25th, 75th percentile)]	Conditional odds ratio (95% CI)	*p* value
Hospital stay (days)	47 (19, 72)	31 (16, 65)	-	0.02	39 (14, 67)	12 (4, 51)	-	0.004
Extra hospital stay	25 (4, 33)	13 (–2, 33)	-	0.003	16 (–21, 75)	6 (–15, 43)	-	0.005
Costs (NTD)	454,608 (160,654, 870,271)	279,612 (90,948, 592,115)	-	< 0.0001	238,985 (11,698, 775,758)	126,248 (6428, 516,003)	-	0.0007
Extra costs	288,576 (–11,292, 597,754)	81,028 (–17,090, 271,208)	-	< 0.0001	114,834 (–17,406, 408,068)	54,345 (–12,642, 345,719)	-	0.006
Mortality	79 (60.8%)	128 (36.4%)	2.83 (1.89-4.73)	< 0.0001	98 (48.7%)	17 (29.8%)	2.22 (1.49-3.29)	0.01

* Patients with a single episode of nosocomial infections caused by aerobic pathogens were enrolled for analysis.
CI = confidence interval; NTD = New Taiwan Dollars.

Discussion

Our data from a referred tertiary medical center show that about 15 extra days of hospitalization and 127,354 NTD (~3746 USD) in extra charges were attributable to nosocomial infections, which accounted for more than two-thirds of overall hospital stays and charges when compared to patients without nosocomial infections. With an average of 2500 patients with nosocomial infections occurring at NTUH yearly, nosocomial infection costs an extra 37,500 days of hospital stay and more than 300,000,000 NTD a year. Patients with nosocomial infection had a much higher incidence of organ failure, such as adult respiratory distress syndrome, disseminated intravascular coagulation, acute renal failure or shock. The resultant increase of morbidity, mortality, and costs of medical care are greater than those anticipated in patients without nosocomial infections. The extra charges and prolongation of hospital stay may be underestimated because some of the patients with nosocomial infection died rapidly, and had lower costs and shorter hospital stays. Furthermore, our data reflected only the costs for medical care; the cost of illness in terms of loss of productivity, incomes, and social burden were not considered. We only measured first admission to the hospital, yet some patients with nosocomial surgical site infection would require multiple hospitalizations over the ensuing months. Thus, nosocomial infections pose an enormous expense to already overburdened health care systems.

In this study, the average length of hospital stay of the control group (22 days) was much longer than the national average for medical centers under National Health Insurance[15] (8.3-10.2 days) because the patients in the control group had to match the case group who had high disease severity and multiple underlying diseases, including malignancies. The average length of hospital stay for patients with or without nosocomial infection in Taiwan is much longer than that in western countries. For example, median hospitalized days for patients with surgical site infection and their controls at Duke University Medical Center[16] were 15 days and 7 days compared with 39 days and 22 days at NTUH (this study); hospital stay for patients with bloodstream infection and their controls at a 2000-bed university hospital in Rome, Italy[17] was 30 days and 10 days compared with 40 days and 28 days at NTUH, respectively. One reason for this is that patients only need to pay very little even with very long hospital stays under the Taiwan National Health Insurance, which is responsible for the majority of the costs. Lack of reasonable reimbursement for chronic beds in Taiwan is considered to be another reason. We found that in a different health care system with longer patient hospitalization and lower daily cost of accommodation, extra costs of nosocomial infections were not only due to prolongation of hospital stay, but also due to other medical costs. Our study demonstrates similar findings as those in western countries[6–9,12] and reveals the common importance of infection control to prevent extra medical costs in areas with different health care systems.

The methodology of matching multiple variables associated with length of stay is commonly used.[2,3,10] In this study, we used strict criteria to match case and control groups in order to estimate the prolongation of hospital stay, extra costs and complications due to nosocomial infections. It is unlikely that underlying comorbidities could influence the outcomes. Previous case-control studies have demonstrated clearly that nosocomial infection prolongs hospitalization significantly,[18–21] and they suggest that accommodation costs account for more than half (even up to 90%) of the total additional charges[10,12,22] and most of these studies have used the length of hospitalization as an indicator of resource utilization attributable to nosocomial infections.[18–22] In this study, the proportion of expenses for materials, operations, physicians and drugs were much higher than that of accommodation. Therefore, extra charges attributed solely to extra length of hospital stay are likely to underestimate the total amount charged. The impact of nosocomial infection on various components of hospital costs should be emphasized.

Resistance of nosocomial pathogens to multiple classes of antimicrobials has become a major problem in the management of nosocomial infections. Duration of hospital stay and costs of nosocomial infection were significantly increased in patients infected with drug-resistant bacteria.[20,23–25] Our study showed that patients with multiple episodes of nosocomial infections and nosocomial infections caused by multiple drug-resistant bacteria had a longer extra hospital stay, higher extra costs and higher mortality rate than those did not. Recent study has shown that antibiotic resistance in nosocomial bacteremia caused by Gram-negative bacteria did not increase the need for hospital resources and did not adversely affect the outcome for critically ill patients.[26,27] However, the study was conducted with patients in ICU with high Acute Physiology and Chronic Health Evaluation II scores and expected high mortality at entry. Because of differences among the populations in various studies, comparison among studies of the causality of antimicrobial resistance and mortality is difficult.

The cost of nosocomial infections may depend on the site of infection.[16,17] In this study, we investigated whether the site of infection and the responsible organism had a different impact on extra hospital stay.[4,5] We did not find significant differences of extra cost and hospital stay between various sites and causative pathogens of nosocomial infection, with the exception of nosocomial fungal infection. It had a higher cost than bacterial infections, partly due to the complicated hospital courses and superinfection with fungi that usually developed after use of broad-spectrum antibacterial agents for previous bacterial infections. As nosocomial fungal infection has been increasingly common in recent years in Taiwan,[11] policies to reduce fungal infection such as improving host immunity, reducing use of broad-spectrum antibiotics and unnecessary devices (e.g., urinary catheterization) are mandatory.

Previous studies estimated that the outcome of hospitalization for patients with nosocomial infection was slightly, albeit not significantly, worse than in their matched controls.[21,28,29] However, recent advances in therapies for cancers and immune suppression have resulted in a significantly elevated risk of mortality and organ failure in patients with nosocomial infections. After matching for severity of illness, we detected an association between nosocomial infections and increased in-hospital morbidities and mortality compatible with others.[30,31]

In conclusion, nosocomial infections have a significant impact on the length of extra hospital stay and extra costs for medical care at medical centers. Extra costs of nosocomial infections were not only due to prolongation of hospital stay, but also due to other medical costs. Hospital administrators and the government should provide sufficient human resources for infection control programs and develop policy for early detection of patients who have higher risk of nosocomial infections.

References

1. McGowan JE Jr: Cost and benefit-a critical issue for hospital infection control. Fifth Annual National Foundation for Infectious Diseases Lecture. *Am J Infect Control* 1982;10:100-8.
2. Haley RW: Measuring the costs of nosocomial infections: methods for estimating economic burden on the hospital. *Am J Med* 1991;91(3B):32S-8S.
3. Freeman J, McGowan JE Jr: Methodologic issues in hospital epidemiology. III. Investigating the modifying effects of time and severity of underlying illness on estimates of cost of nosocomial infection. *Rev Infect Dis* 1984;6:285-300.
4. Jarvis WR: Selected aspects of the socioeconomic impact of nosocomial infections: morbidity, mortality, cost and prevention. *Infect Control Hosp Epidemiol* 1996;17:552-7.
5. Wenzel RP: The economics of nosocomial infections. *J Hosp Infect* 1995;31:79-87.
6. Haley RW, Schaberg DR, Crossley KB, et al: Extra charges and prolongation of stay attributable to nosocomial infections: a prospective interhospital comparison. *Am J Med* 1981;70: 51-8.
7. Leroyer A, Bedu A, Lombrail P, et al: Prolongation of hospital stay and extra cost due to hospital-acquired infection in a neonatal unit. *J Hosp Infect* 1997;35:37-45.
8. Girou E, Stephan F, Novara A, et al: Risk factors and outcome of

nosocomial infections: results of a matched case-control study of ICU patients. *Am J Respir Crit Care Med* 1998;157:1151-8.
9. Vegas AA, Jodra VM, Garcia ML: Nosocomial infection in surgery wards: a controlled study of increased duration of hospital stays and direct cost of hospitalization. *Eur J Epidemiol* 1993;9: 504-10.
10. Wakefield DS, Helms CM, Massanari RM, et al: Cost of nosocomial infection: relative contributions of laboratory, antibiotic, and per diem costs in serious *Staphylococcus aureus* infections. *Am J Infect Control* 1988;16:185-92.
11. Chang SC, Tsai CL, Wang JT, et al: Nosocomial infections in medical centers and regional hospitals between 1999 and 2002 in Taiwan. *Infect Control J* 2004;14:1-11.
12. Garner JS, Jarvis WR, Emori TG, et al: CDC definitions for nosocomial infections, 1988. *Am J Infection Control* 1988;16:128-40.
13. Kreger BE, Craven DE, McCabe WR: Gram-negative bacteremia. *Am J Med* 1980;68:344-55.
14. National Committee for Clinical Laboratory Standards: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A4. NCCLS documents, Wayne, Pennsylvania, 2001.
15. Department of Health, Taiwan, ROC. Agency for Healthcare Research and Quality. Available at: URL: http://www.doh.gov.tw/statistic/data
16. Kirkland KB, Briggs JP, Trivette SL, et al: The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. *Infect Control Hosp Epidemiol* 1999;20:725-30.
17. Orsi GB, Stefano LD, Noah N: Hospital-acquired, laboratory-confirmed bloodstream infection- increased hospital stay and direct costs. *Infect Control Hosp Epidemiol* 2002;23:190-7.
18. Haley RW, Schaberg DR, Von Allmen SD, et al: Estimating the extra charges and prolongation of hospitalization due to nosocomial infections: a comparison of methods. *J Infect Dis* 1980;141:248-57.
19. Dietrich ES, Demmler M, Schulgen G, et al: Nosocomial pneumonia: a cost-of-illness analysis. *Infection* 2002;30:61-7.
20. Kim T, Oh PI, Simor AE: The economic impact of methicillin-resistant Staphylococcus aureus in Canadian hospitals. *Infect Control Hosp Epidemiol* 2001;22:99-104.
21. Digiovine B, Chenoweth C, Watts C, et al: The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. *Am J Respir Critic Care Med* 1999; 160:976-81.
22. Coello R, Glenister H, Fereres J, et al: The cost of infection in surgical patients- a case-control study. *J Hosp Infect* 1993;25: 239-50.
23. Carmeli Y, Troillet N, Karchmer AW, et al: Health and economic outcomes of antibiotic resistance in *Pseudomonas aeruginosa*. *Arch Intern Med* 1999;159:1127-32.
24. Kremery V Jr, Spanik S, Krupova I, et al: Bacteremia due to multi-resistant gram-negative bacilli in neutropenic cancer patients- a case controlled study. *J Chemother* 1998;10:320-5.
25. Abramson MA, Sexton DJ: Nosocomial methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* primary bacteremia- at what costs? *Infect Control Hosp Epidemiol* 1999; 20:408-11.
26. Harbarth S, Rohner P, Auckenthaler R, et al: Impact and pattern of gram-negative bacteremia during 6 years at a large university hospital. *Scand J Infect Dis* 1999;31:163-8.
27. Blot S, Vandewoude K, De Bacquer D, et al: Nosocomial bacteremia caused by antibiotic-resistant gram-negative bacteria in critically ill patients: clinical outcome and length of hospitalization. *Clin Infect Dis* 2002;34:1600-6.
28. Freeman J, Rosner BA, McGowan JE Jr: Adverse effects of nosocomial infection. *J Infect Dis* 1979;140:732-40.
29. Whitehouse JD, Friedman ND, Kirkland KB, et al: The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. *Infect Control Hosp Epidemiol* 2002;23:183-9.
30. Pittet D, Tarara D, Wenzel RP: Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;271:1598-601.
31. Liu JW, Su YK, Liu CF, et al: Nosocomial blood-stream infection in patients with end-stage renal disease: excess length of hospital stay, extra cost and attributable mortality. *J Hosp Infect* 2002; 50:224-7.