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SHORT REPORT
Changing aetiology of healthcare-associated bloodstream infections at three medical centres in Taiwan, 2000–2011

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SUMMARY

This multicentre surveillance study was conducted to investigate the trends in incidence and aetiology of healthcare-associated bloodstream infections (HCA-BSIs) in Taiwan. From 2000 to 2011 a total of 56 830 HCA-BSIs were recorded at three medical centres, and coagulase-negative staphylococci (CoNS) were the most common pathogens isolated ($n = 9465$, 16·7%), followed by *E. coli* ($n = 7599$, 13·4%). The incidence of all HCA-BSIs in each and all hospitals significantly increased over the study period owing to the increase of aerobic Gram-positive cocci and Enterobacteriaceae by 4·2% and 3·6%, respectively. Non-fermenting Gram-negative bacteria, *Bacteroides* spp. and *Candida* spp. also showed an increase but there was a significant decline in the numbers of methicillin-resistant *S. aureus*. In conclusion, the incidence of HCA-BSIs in Taiwan is significantly increasing, especially for Enterobacteriaceae and aerobic Gram-positive cocci.

Key words: Enterobacteriaceae, healthcare-associated bloodstream infection, MRSA, non-fermentative Gram-negative bacilli, Taiwan.

Healthcare-associated (HCA) infections, including ventilator-associated pneumonia, catheter-related urinary tract infections, surgical site infections, and bloodstream infections (BSIs), are notorious complications in hospitalized patients [1]. Of those infections, healthcare-associated bloodstream infections (HCA-BSIs) are significant causes of morbidity and mortality. However, the incidence of antibiotic resistance in pathogens causing HCA-BSIs can be affected by multiple factors, including the use of antibiotics and the implementation of infection control policy. For example, we have previously shown a positive correlation between the use of teicoplanin and the

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prevalence of vancomycin-resistant enterococci (VRE) [2]. Knowledge of the aetiology and epidemiology of HCA-BSIs is a critical issue for infection control. Although surveillance systems such as the National Healthcare Safety Network (NHSN) [3] and the International Nosocomial Infection Control Consortium (INICC) [4] provide regular reports on national trends of HCA infections and associated causative pathogens, reported data on HCA infections from Taiwan are scarce and much of these data are outdated [5, 6]. Thus, we conducted this multi-centre study to investigate the trend in incidence of HCA-BSIs and their causative pathogens.

Annual inpatient-days (AIPDs), the incidence of all HCA-BSIs, and the incidence of HCA-BSIs caused by specific pathogens during the period 2000–2011 were calculated at three affiliated medical centres that provide both primary and tertiary care in Taiwan. The hospitals included National Taiwan University Hospital (NTUH, 2500 beds) located in northern Taiwan, National Cheng Kung University Hospital (NCKUH, 1200 beds) in southwestern Taiwan, and Kaohsiung Medical University Chung-Ho Memorial Hospital (KMUH, 1700 beds), in southern Taiwan. Definitions of HCA-BSIs were in accordance with National Nosocomial Infection Surveillance guidelines [1]. Isolates of each species from each patient recovered within 7 days were considered as a single isolate. Data were collected by infection control nurses in each hospital. The annual incidence of HCA-BSIs was calculated as the number of HCA-BSIs during a given year/10 000 AIPD in that year. Some of the data were reported previously [7].

Data on disk diffusion susceptibilities of *Staphylococcus aureus* to oxacillin in isolates recovered from 2000 to 2011 were retrieved from annual summary documents. *S. aureus* ATCC 25 923 was used as a control strain for routine disk susceptibility testing and followed Clinical and Laboratory Standards Institute (CLSI) guidelines [8].

We assessed changes in the incidence densities of HCA-BSIs caused by specific pathogens to describe changes in the burden of disease in each hospital over the study period. Incidence densities were calculated as the number of events/10 000 inpatient-days. The Cochran–Armitage trend test was used to assess temporal trends in incidence densities. We also modelled temporal trends of incidence densities using Poisson regression, presenting yearly change in incidence density as a rate ratio (RR) with 95% confidence interval (CI). Data were analysed using SPSS version 11.0 (SPSS Inc., USA) and R version 2.15.2 (R Foundation, Austria).

During the study period, a total of 56 830 HCA-BSIs were recorded, including 23 271 at NTUH, 7884 at NCKUH, and 25 675 at KMUH. Overall, coagulase-negative staphylococci (CoNS) was the most common pathogen ($n = 9465$ 16·7%), followed by *Escherichia coli* ($n = 7599$, 13·4%) *S. aureus* ($n = 5471$, 9·6%), and *Klebsiella* spp. ($n = 5430$, 9·6%). Aerobic Gram-positive cocci (GPC) accounted for the majority of HCA-BSI episodes ($n = 18\,407$ 32·4%), followed by various Enterobacteriaceae ($n = 16\,907$ 29·8%), non-fermenting Gram-negative bacteria (NFGNB) ($n = 9789$, 17·2%), *Candida* spp. ($n = 4967$, 8·7%), and anaerobes (*Bacteroides* spp.; $n = 642$, 1·1%). Overall, Gram-negative bacteria (GNB) were the most common pathogens (26 696, 47%), followed by GPC, and *Candida* spp. Some differences in the frequency distribution of pathogens was evident between the three hospitals but the most common were *S. aureus*, CoNS, *Acinetobacter* spp., *Klebsiella* spp., and *Candida* spp. in varying rank order. The top five common pathogens at NTUH were *Candida* spp., *S. aureus, Acinetobacter* spp., *Klebsiella* spp., and *E. coli*. At NCKUH, they were *Candida* spp., CoNS, *Acinetobacter* spp., *S. aureus*, and *Klebsiella* spp. At KMUH, the top five pathogens were CoNS, *E. coli, Klebsiella* spp., *S. aureus*, and *Candida* spp. (Supplementary Table S1).

Table 1 and Figure 1 show that the incidence of all HCA-BSIs in each hospital and in all hospitals increased significantly during 2000–2011 (all $P < 0·001$). For each pathogen in all hospitals, the incidence of HCA-BSIs caused by CoNS, enterococci, *E. coli, Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Acinetobacter* spp., *Stenotrophomonas maltophilia*, other NFGNB, *Bacteroides* spp., and *Candida* spp., increased significantly (all $P < 0·05$). The incidence of *Serratia* spp. and *Pseudomonas* spp., however, remained stable. Overall, the annual incidence of Enterobacteriaceae and aerobic GPC showed a significant increase of 4·2% (95% CI 2·9–5·5), and 3·6% (95% CI 2·4–4·9), respectively (Supplementary Fig. S1).

Of 56 830 episodes of HCA-BSI, 5471 were caused by *S. aureus*, and 58·3% ($n = 3187$) were due to methicillin-resistant *S. aureus* (MRSA). For MRSA, the incidence significantly decreased ($P < 0·001$) from 2·28 to 1·28/10 000 inpatient-days, with an annual decrease of 6·1% (95% CI 4·2–7·9) over the study period. By contrast, the incidence of methicillin-susceptible

Table 1. *Incidence (the number of episodes during a given year/10 000 AIDP of healthcare-associated bloodstream infections in three hospitals located in different parts of Taiwan, 2000–2011*

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	*P*
NTUH													
AIPD	624 675	631 401	672 676	629 618	720 781	722 913	711 357	709 485	723 255	751 326	763 772	723 505	
S. aureus	4·05	3·23	3·63	3·30	2·89	2·86	2·88	2·65	2·39	2·38	2·23	1·89	**<0·001**
MRSA	2·79	2·50	2·82	2·30	2·11	2·09	2·09	1·79	1·47	1·33	1·24	0·90	**<0·001**
CoNS	2·34	2·31	1·89	2·60	2·58	2·27	2·25	2·54	4·89	2·10	2·03	1·63	0·70
Enterococci	1·65	1·81	1·65	2·46	2·53	1·84	2·00	2·40	2·74	3·14	3·44	3·14	**<0·001**
E. coli	2·07	2·07	1·95	1·94	1·71	2·21	2·60	2·40	2·89	3·21	2·95	3·34	**<0·001**
Klebsiella spp	1·78	1·76	2·11	2·60	2·30	2·10	2·47	3·21	2·93	3·09	2·97	3·15	**<0·001**
Enterobacter spp.	1·44	1·85	1·35	2·02	1·75	1·56	1·83	2·21	1·83	1·88	2·27	2·07	**<0·001**
Citrobacter spp.	0·32	0·32	0·15	0·17	0·21	0·18	0·35	0·31	0·19	0·28	0·41	0·23	0·30
Serratia spp.	0·35	0·48	0·46	0·49	0·43	0·57	0·34	0·58	0·39	0·49	0·62	0·41	0·34
P. aeruginosa	1·58	1·63	1·31	1·56	2·11	1·62	1·70	1·99	1·81	1·72	1·54	1·17	0·60
Acinetobacter spp.	2·69	2·41	2·22	3·02	2·39	2·66	2·32	2·89	2·71	3·29	3·21	2·68	**0·002**
S. maltophilia	0·78	0·79	0·70	1·10	1·10	0·80	0·45	0·87	0·82	0·92	0·88	0·44	0·13
Other NFGNB*	0·98	0·97	1·65	1·19	1·71	1·36	1·03	1·56	1·41	1·46	1·43	1·31	0·058
Bacteroides spp.	0·22	0·22	0·18	0·22	0·21	0·30	0·34	0·38	0·37	0·52	0·46	0·37	**<0·001**
Candida spp.	3·57	3·71	3·29	4·02	3·57	3·11	2·85	3·27	3·39	4·06	3·72	4·23	0·080
NCKUH													
AIPD	282 926	278 558	291 660	278 339	295 228	292 128	289 803	292 128	320 915	320 859	339 133	344 605	
S. aureus	3·25	2·87	2·81	3·16	1·66	2·23	2·62	1·99	1·22	1·71	1·83	1·48	**0·006**
MRSA	2·47	2·15	1·85	2·37	1·15	1·54	1·48	1·20	0·75	0·93	1·06	0·78	**<0·001**
CoNS	2·47	2·87	2·88	3·27	2·98	2·60	2·76	2·64	2·21	2·24	2·51	2·06	**<0·001**
Enterococci	1·06	1·58	1·82	2·08	1·49	1·78	1·38	1·75	2·21	2·49	1·33	1·92	**0·007**
E. coli	1·56	1·97	1·34	1·90	1·25	1·68	1·66	1·78	1·78	1·65	1·68	1·86	**0·029**
Klebsiella spp.	1·31	1·62	1·71	2·19	1·29	2·05	1·79	2·36	2·52	2·15	1·74	1·60	0·46
Enterobacter spp.	1·56	2·01	1·47	1·98	1·29	1·78	1·62	1·40	1·18	1·40	1·33	1·13	0·062
Citrobacter spp.	0·14	0·11	0·17	0·40	0·07	0·10	0·17	0·14	0·25	0·31	0·29	0·20	**0·004**
Serratia spp.	0·60	0·75	0·51	0·36	0·27	0·34	0·21	0·31	0·44	0·16	0·35	0·32	0·12
P. aeruginosa	1·17	1·22	0·82	1·47	0·95	1·10	0·90	1·06	0·87	1·03	1·30	0·84	**0·001**
Acinetobacter spp.	2·09	3·48	2·23	3·56	1·63	2·60	2·14	3·05	2·21	3·18	1·98	2·38	0·36
S. maltophilia	0·39	0·47	0·58	0·43	0·51	0·48	0·62	0·62	0·81	0·62	0·59	0·44	0·34
Other NFGNB*	0·99	1·18	1·13	1·51	0·78	1·20	0·72	1·57	0·90	1·15	0·91	0·70	0·22
Bacteroides spp.	0·46	0·11	0·27	0·18	0·03	0·17	0·10	0·17	0·12	0·19	0·24	0·17	0·11
Candida spp.	1·84	2·51	1·92	3·41	2·78	2·46	1·97	3·83	3·24	3·55	2·45	2·15	0·21
KMUH													
AIPD	331 301	344 125	346 188	345 853	414 173	420 601	383 796	409 444	416 788	404 333	417 525	434 153	
S. aureus	2·29	4·04	6·18	5·15	5·24	4·26	5·68	4·69	5·47	4·97	5·22	5·48	**<0·001**
MRSA	1·15	2·03	3·09	2·57	2·63	2·14	2·84	2·34	1·87	1·98	2·01	2·33	**<0·001**
CoNS	8·63	10·78	8·38	10·09	7·80	11·60	14·20	14·61	17·97	18·45	20·14	20·18	0·97

Table 1 (*cont.*)

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	*P*
Enterococci	1·00	1·05	1·21	1·45	1·23	1·33	1·25	1·54	2·11	2·35	2·30	3·34	**<0·001**
E. coli	7·70	8·14	8·49	8·88	7·94	10·89	11·99	12·19	11·80	12·93	12·19	11·91	**<0·001**
Klebsiella spp	3·62	4·18	4·48	5·03	5·72	6·54	6·54	6·28	6·24	6·13	5·39	5·97	**<0·001**
Enterobacter spp.	0·94	1·02	0·84	1·13	0·89	1·66	1·35	1·56	1·90	2·00	1·48	1·54	**<0·001**
Citrobacter spp.	0·15	0·20	0·20	0·40	0·19	0·07	0·23	0·27	0·48	0·47	0·38	0·39	**<0·001**
Serratia spp.	0·30	0·32	0·32	0·17	0·46	0·48	0·50	0·42	0·38	0·47	0·31	0·53	0·081
P. aeruginosa	1·81	1·86	1·79	1·88	1·76	2·02	2·14	2·15	2·14	2·32	1·96	2·07	0·070
Acinetobacter spp.	0·72	1·02	1·07	1·39	1·30	1·28	1·25	1·76	2·30	2·47	1·89	1·47	**<0·001**
S. maltophilia	0·24	0·46	0·32	0·49	0·48	0·76	0·99	0·56	1·78	1·48	0·65	0·85	**<0·001**
Other NFGNB*	0·63	0·38	0·26	0·43	0·60	0·62	1·02	1·25	1·25	1·85	1·60	1·11	**<0·001**
Bacteroides spp.	0·81	0·61	0·35	0·75	0·53	0·36	0·31	0·27	0·12	1·26	1·32	1·11	**<0·001**
Candida spp.	2·78	2·91	0·78	2·28	0·80	0·90	1·69	1·44	2·76	4·15	2·35	3·09	**<0·001**

AIPD, Annual inpatient-days; CoNS, coagulase-negative staphylococci; KMUH, Kaohsiung Medical University Chung-Ho Memorial Hospital; MRSA, methicillin-resistant *Staphylococcus aureus*; NCKUH, National Cheng Kung University Hospital; NFGNB, non-fermentative Gram-negative bacilli; NTUH, National Taiwan University Hospital.

* Includes NFGNB other than *P. aeruginosa, Acinetobacter* spp., and *S. maltophilia.*

S. aureus (MSSA) rose significantly ($P<0·001$), with an annual increase of 2·9% (95% CI 1·1–4·7). In addition, the ratio of MRSA isolates to all *S. aureus* isolates decreased from 67·0% in 2000 to 45·3% in 2011 ($P<0·001$). Moreover, the incidence of MRSA decreased significantly from year to year during the study period in all hospitals ($P<0·001$).

This 12-year multi-centre surveillance study has shown that the annual incidence of HCA-BSIs in Taiwan gradually increased from 26·96/10 000 AIPD in 2000 to 38·54/10 000 AIDP in 2011. This increase is markedly higher than that seen during the period 1993–2006 in Taiwan (23·0–25·6/10 000 AIPD) [6]. Our finding is consistent with the results of a study in the USA, which showed annual increases of 3·8% for all nosocomial BSIs in antibiotic-resistant bacteria (ARB)-non-endemic hospitals and 5·4% in ARB-endemic hospitals ($P<0·001$) [9]. Furthermore, our incidence was higher than reported from a university hospital in France between 2005 and 2007, which ranged from 9·96 to 13·1 HCA BSIs/10 000 AIPD [10]. In addition the overall incidence of 26·3/1000 admissions (range 23·6–29·3/1000 admissions) found here exceeded the national estimated incidence of adult nosocomial BSIs in the USA in 2003 (21·6 cases/1000 admissions) [11] which suggests that the burden of HCA-BSIs is not only on the increase in Taiwan but is greater than in other global regions.

The incidence and aetiology of HCA-BSIs varied between the three study hospitals with the highest and lowest incidence at KMUH and NCKUH, respectively. This supports the observation of an earlier study of 11 hospitals in Taiwan [6] of a changing epidemiology of HCA-BSIs over time and that the incidence in different hospitals is the result of several factors such as patient demographics, medical and surgical specialities provided, the bed number of haematology-oncology wards and intensive-care units and the contribution of outbreaks to the dissemination of pathogens. Studies from other regions also report comparable, but hospital-/country-specific aetiologies such as the high frequency of CoNS (31%) and *S. aureus* (20%) in a survey of 49 US hospitals [12], and the predominance of *E. coli* (17·4%), *S. aureus* (15·2%), and *K. pneumoniae* (12·3%) in a Thailand hospital [13]. In this survey almost half (47%) of all HCA-BSI cases were due to GNB, including 17·2% NFGNB, and 32·4% aerobic GPC, a situation in contrast to US data where 65% of infections were caused by GPC and 25% by GNB [12]. Most importantly, the incidence of these GNB and GPC

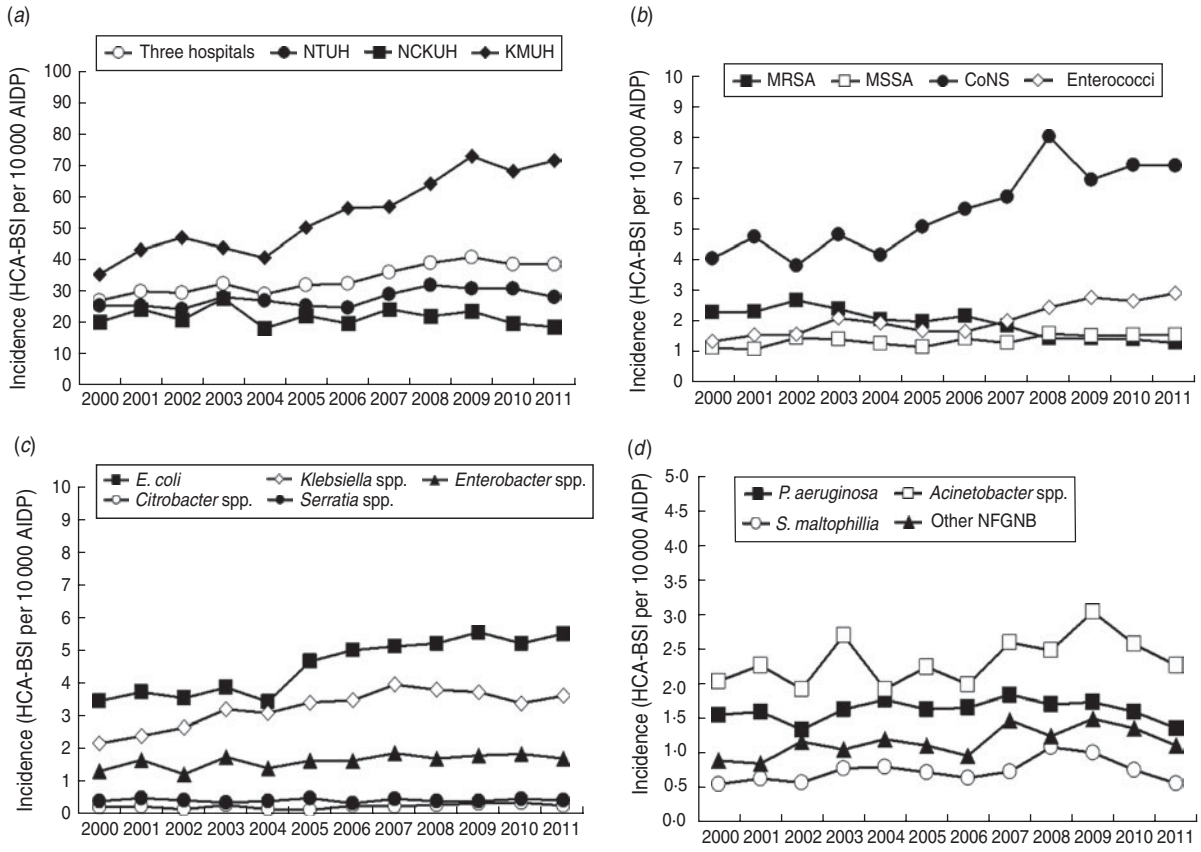

Fig. 1. (*a*) Trend in incidence of healthcare-associated bloodstream infections (HCA-BSIs) in three hospitals (KMUH, Kaohsiung Medical University Chung-Ho Memorial Hospital; NCKUH, National Cheng Kung University Hospital; NTUH, National Taiwan University Hospital) in Taiwan, 2000–2011; (*b*) in Gram-positive cocci, including methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), coagulase-negative staphylococci (CoNS), and enterococci; (*c*) in Enterobacteriaceae; and (*d*) in non-fermentative Gram-negative bacilli (NFGNB).

significantly increased during our study period. This finding may be attributed to an increased number of patients generally or better ascertainment through improved blood culture technique.

Our earlier observation of the decrease in MRSA in HCA BSIs in Taiwan [7] was confirmed in this wider survey, underlining the fact that other pathogens contribute more to the total burden of these infections. This contrasts sharply with the views of Ammerlaan *et al.* [9] who concluded from their study that the total burden of disease was due to an increase in both antibiotic-resistant and susceptible bacteria, but is consistent with some other European countries [14]. This suggests that the threat of MRSA as a causative agent of HCA-BSIs is decreasing in Taiwan.

Finally, *Candida* spp. caused about 8·7% of all HCA-BSI episodes in the present study with an incidence of about 12% in each of two hospitals but four-fold lower in the third hospital. One (KMUH) of the three hospitals had twice and three times more CoNS infections than the other two hospitals (NTHH and NCKUH). Explanation of this difference is difficult but was most likely multifactorial, such as patient mix, proportion of haematological and oncological patients, the annual incidence of central venous line-related infections and use of antifungal agents [15], hospital settings, and infection control measures.

In conclusion, HCA-BSIs are increasing in Taiwan, especially those caused by aerobic GPC and Enterobacteriaceae but the contribution of MRSA appears to be on the wane. This changing aetiology will impact on not only infection control practice but also antimicrobial prescribing policies. The contribution of antimicrobial resistance to the change in aetiology merits further investigation.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268813003166.

DECLARATION OF INTEREST

None.

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