Letters to the Editor

Maintenance haemodialysis and delayed administration of appropriate antibiotics increase 30-day mortality among patients with non-hospital-acquired meticillin-resistant *Staphylococcus aureus* bacteraemia

Sir,

Clinical information is limited regarding the outcome of patients with non-hospital-acquired meticillin-resistant *Staphylococcus aureus* (NHA-MRSA) infections, particularly those undergoing maintenance haemodialysis on an outpatient basis who are prone to healthcare-associated *S. aureus* infections. Moreover, NHA-MRSA is of rising clinical significance because of the potential development of life-threatening bacteraemia and fatal outcome in otherwise healthy persons [1,2].

We conducted a retrospective study in National Taiwan University Hospital (NTUH), a major referral teaching hospital in Taipei, Taiwan, from January 2002 to December 2006. All patients older than 18 years of age presenting to the emergency department or hospitalised at NTUH were screened for eligibility. MRSA bacteraemia was classified as NHA if at least one blood culture was positive within 72 h after hospital arrival [3,4]. Patients residing in long-term care facilities or nursing homes, patients hospitalised during the 30 days preceding bacteraemia and those presenting with out-of-hospital cardiac arrest or lost to follow-up were excluded from the study. The following definitions were applied in the evaluation of each individual patient: (i) vascular access: permanent indwelling catheter, arteriovenous fistula or graft; (ii) time to start antibiotics: the time in days between collection of initial blood culture specimens and administration of the first dose of antibiotics for MRSA infection; patients were grouped by the first administration of antibiotics within 72 h or >72 h (3 days) after hospital arrival; (iii) antibiotics for MRSA bacteraemia: MRSA was susceptible in vitro to the drugs administered; (iv) shock: systolic blood pressure <90 mmHg and requiring medical intervention; (v) consciousness disturbance: changes in orientation or alertness

compared with baseline levels; (vi) 30-day mortality: death occurring within 30 days after hospital arrival; and (vii) vascular access-associated bacteraemia: evidence of inflammation at the insertion site, over arteriovenous fistulas or grafts, and/or a catheter-tip culture positive for *S. aureus* and no evidence of any other focus.

Among a total of 94 patients, 33 (35.1%) were undergoing maintenance haemodialysis and 61 (64.9%) were not on long-term dialysis. The overall 30-day mortality rate was 18.1% (17/94), with 21.2% (7/33) occurring in the haemodialysis group and 16.4% (10/61) in the non-dialysis group. Multivariate analysis of predictors of 30-day mortality was conducted by fitting a stepwise Cox proportional hazards model and the results are shown in Table 1. Among the factors included, undergoing haemodialysis was determined to be the most potent independent risk factor (hazard ratio = 40.517; $P=0.0002$). As early (≤ 72 h) administration of appropriate antibiotics was an important factor in 30-day mortality, we attempted to identify factors associated with early use of antibiotics for MRSA bacteraemia. In logistic regression analysis, the presence of vascular access was the only marginally significant predictor (odds ratio = 4.625; $P=0.056$). Moreover, in haemodialysis patients, vascular access is easily the most suspected primary focus of bacteraemia. Even given the expected poor prognosis in this subgroup of patients, early administration of appropriate antibiotics ought to improve patient survival. This finding coincides with current guidelines advocating the use of an empirical regimen targeting antibiotic-resistant pathogens for patients harbouring risk factors associated with healthcare-associated infections [5].

Regarding microbiological characteristics, because 3 strains were not well preserved, only 91 isolates were tested for their toxin gene profiles. Overall, four isolates (isolates 6, 44, 35 and 16) were identified as carrying the staphylococcal cassette chromosome *mec* (SCC*mec*) type II, SCC*mec* type III, SCC*mec* type IV and Panton–Valentine leukocidin (PVL) genes, respectively. No significant differences in strain characteristics were detected between 30-day survivors and non-survivors. Moreover, in the haemodialysis group, SCC*mec* type II- or SCC*mec* type III-positive isolates were

Table 1

Cox proportional hazards model showing hazard rates for 30-day mortality following hospital arrival^a.

Covariate	Estimate	SE	Wald χ^2	P-value	HR	95% CI
Albumin	−2.4140	0.5542	18.9749	<0.0001	0.089	0.030–0.265
Antibiotics for MRSA ≤ 3 days	−2.4150	0.9185	6.9133	0.0086	0.089	0.015–0.541
Vascular access ^b -associated bacteraemia	−2.2319	0.8671	6.6255	0.0101	0.107	0.020–0.587
Haemodialysis	3.7017	0.9798	14.2731	0.0002	40.517	5.938–276.481
PAOD	3.5470	0.9389	14.2730	0.0002	34.708	5.512–218.563
Consciousness disturbance	−1.4935	0.9107	6.2025	0.0128	9.661	1.621–57.578
SBP <90 mmHg	1.5594	0.6694	5.4273	0.0198	4.756	1.281–17.661
Charlson Index	0.6380	0.2070	9.5013	0.0021	1.893	1.262–2.839

SE, standard error; HR, hazard ratio; CI, confidence interval; MRSA, meticillin-resistant *Staphylococcus aureus*; PAOD, peripheral arterial occlusive disease; SBP, systolic blood pressure.

^a Cox proportional hazards model: $n=94$; adjusted generalised $R^2=0.4912$.

^b Permanent indwelling catheters, arteriovenous fistulas or grafts.

detected in 22 of 33 strains, and SCCmec IV genes were identified in 11 of 33 strains. Among the non-dialysis group, SCCmec II or SCCmec III genes were identified in 28 of 58 strains, and the SCCmec IV gene was detected in 30 of 58 strains. This analysis revealed no statistically significant difference between the haemodialysis and non-dialysis groups ($P=0.125$). Irrespective of the molecular characteristics of MRSA strains, timely administration of effective antibiotics could be a more important factor in determining clinical outcome in patients with NHA-MRSA bacteraemia. Similar findings have been reported by Schram et al. [6], who showed that patients with MRSA infections initially receiving inappropriate antibiotic treatments had twice the risk of mortality.

In conclusion, our study suggests that undergoing maintenance haemodialysis is the most potent predictor for 30-day mortality in patients with NHA-MRSA bacteraemia, and administration of appropriate antibiotics within 72 h of hospital arrival may improve patient outcome.

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Free concentration and protein-binding ratio of ceftriaxone in cerebrospinal fluid in paediatric patients with purulent meningitis caused by *Haemophilus influenzae* type b

Sir,

Ceftriaxone (CRO), which penetrates well into the cerebrospinal fluid (CSF), is recommended as the antibiotic of choice for empirical and specific therapy of bacterial meningitis in children [1]. However, there is concern that treatment failure may occur with antibiotics having a high protein-binding ratio, such as CRO, since bactericidal activity is achieved by unbound drug at the site of infection [2]. There have been numerous reports of good total concentrations in CSF [3] but few reports on free concentrations. Therefore, in the present study, free CRO concentrations and protein-binding ratios in CSF were examined to enhance our understanding of the clinical efficacy of CRO against bacterial meningitis.

Between April 2005 and June 2008, 12 paediatric patients aged 2 months to 5 years, suspected of having bacterial meningitis based on pleocytosis, CSF gram stain and latex agglutination antigen detection test results, were admitted to Chiba Children's Hospital and Chiba University Hospital (Chiba City, Japan). In all cases, *Haemophilus influenzae* serotype b (Hib) was recovered from the CSF. In Japan, Hib remains a major cause of childhood bacterial meningitis [4] as introduction of the Hib-conjugated vaccine was delayed. Fourteen CSF samples were collected after written informed consent had been obtained. All patients had normal renal and hepatic functions. In each case, CRO 50 mg/kg body weight was given intravenously for 30 min every 12 h. Because of the difficulty of sampling from infants, CSF samples could not be collected using the same time schedule. All samples were stored at -80°C until assays were performed.

CRO concentrations were determined by an agar well diffusion bioassay as described previously [5]. The test strain, *Escherichia coli* NJHJ JC-2, was cultured in trypticase soy broth at 35°C for 18–20 h and was inoculated into Antibiotic medium No. 1 or No. 2 (Difco, Franklin Lakes, NJ) at 1.0%. A standard solution of CRO was diluted with 1/15 M phosphate buffer solution (pH 7.0) to give a 2000 mg/L CRO solution. Next, 1.0 mL of this 2000 mg/L CRO solution was serially diluted two-fold with 1.0 mL of 1/15 M phosphate buffer solution to give CRO solutions of 200 mg/L to 0.10 mg/L to determine standard curves.

Free drug was separated from bound drug by membrane ultrafiltration using a Centrifree YM-30 membrane (Cat No. 4104; Millipore Corp., Bedford, MA) as CRO does not bind to this mem-