# FIVE CASES OF HIGH-LEVEL AMINOGLYCOSIDE RESISTANT ENTEROCOCCAL SEPTICAEMIA IN SINGAPORE

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*ABSTRACT*

***Five clinical cases of enterococcal septicaemia were studied retrospectively including determination of high-level aminoglycoside resistance (HLAR) to gentamicin, streptomycin and kanamycin. This is the first study of its kind in Singapore. The clinical features and risk factors for this illness were analysed and found to be very similar to enterococcal bacteremia in general. It is important to carry out tests to detect HLAR so that unnecessary aminoglycoside toxicity can be prevented or to decide on the appropriate aminoglycoside to combine with a cell wall-active agent in severe enterococcal sepsis.***

***Keywords:*** *enterococcus, high-level aminoglycoside resistance*

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## INTRODUCTION

Enterococci have gained worldwide attention because they are common nosocomial agents[1,2] and their eradication is fraught with resistances to many antibiotics[3]. Many have inherent or acquired resistance to the cephalosporins, clindamycin, semisynthetic penicillinase-resistant penicillins and chloramphenicol. It is also important to combine a cell wall-active agent with an aminoglycoside for their synergistic activity in severe enterococcal sepsis[4,5]. Unfortunately this synergy is lost in enterococci exhibiting HLAR, due to production of aminoglycoside-modifying enzyme[6] or to ribosomally-mediated resistance[7]. HLAR was first detected between 1970-1971 by Standiford et al[8], Watanakunakorn[9] and Moellering et al[10]. Moellering et al[10] devised a simple screening method using an aminoglycoside incorporated agar screen at a concentration of 2000 µg/ml and growth of enterococci in this agar is said to demonstrate HLAR thus reflecting synergy-resistance. Despite the numerous investigations into HLAR, including comparison of different methodologies using broth, high content aminoglycoside discs, automated systems and aminoglycoside incorporated agar as well as the studies of medium and inoculum variations, the first clinical case report of gentamicin HLAR enterococcal septicaemia from England appeared only in 1989[11]. There is a relative paucity of clinical reports on HLAR enterococcal septicaemia in Singapore and this paper addresses the problem in the hope that more awareness could ameliorate the outcome of this condition by choosing the appropriate aminoglycoside and offsetting the unnecessary aminoglycoside toxicity in the management of HLAR enterococcal septicaemia.

The five cases were the first blood-borne isolates positive for enterococci in 1992 obtained from the National University Hospital (NUH), Singapore. They were collected as part of a study of the prevalence of HLAR in NUH[12]. Altogether 225 isolates of enterococci were collected from March to June 1992: 22% showed HLAR to gentamicin, 38% to streptomycin and 36% to kanamycin. The cases were studied retrospectively by reviewing the medical records of the patients.

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## MATERIALS AND METHODS

A total of 225 isolates of enterococci were collected during the period from March to June 1992. Three methods were carried out to determine HLAR:

(a) *Agar screen*

According to the method described by Sahm and Torres[13], brain-heart infusion agar plates were prepared to contain either 500µg/ml of gentamicin, 2000 µg/ml of streptomycin or 2000 µg/ml of kanamycin. Inocula of $10^6$ colony-forming units (CFU) per shot were placed onto the brain heart infusion plates. Following incubation in ambient air at 35°C, the agar screens were examined for the presence of bacterial growth after 24 and 48 hours incubation.

(b) *Broth microdilution*

The susceptibilities of isolates to gentamicin and streptomycin were determined using multiple-step dilutions in catin-adjusted Mueller-Hinton broth in accordance with the NCCLS M7-A2 recommendation[14]. The concentrations for the three aminoglycosides were similar to the agar screen method (a).

(c) *High content aminoglycoside discs.*

Preparation of the discs and testing of the isolates followed the recommendations of Sahm and Torees[15].

### Case 1

A 59-year-old Chinese diabetic man had fever due to bacteremic *Enterococcus faecalis* urinary tract infection. He suffered a left-sided stroke and bleeding peptic ulcer 2 months ago. The isolate was sensitive to ampicillin only. HLAR was positive to streptomycin and kanamycin. Infection was cured with parenteral ampicillin and gentamicin. He was in hospital for 15 days.

### Case 2

A 79-year-old Chinese man was admitted for backache and was subsequently assessed for continuous ambulatory peritoneal dialysis. He had hypertension, abdominal aortic aneurysm and chronic renal failure. He went into cardiogenic shock 13 days after admission and required mechanical respiratory support and urinary catheterisation. Urine and blood cultures on the 14th and 16th day of admission respectively grew *E. faecalis* which was moderately sensitive to ampicillin and had HLAR to gentamicin, streptomycin and kanamycin. The patient did not recover from the shock, developed anuria and died 21 days after admission probably from the myocardial infarct and septicaemia.

### Case 3

A 54-year-old Indian woman was admitted with fever and

lethargy. A diagnosis of second relapse of acute myeloid leukaemia (AML) was confirmed on bone marrow biopsy and aspiration. On admission, a subclavian catheter was inserted to administer blood products, ceftriaxone, gentamicin and cytotoxic therapy. Blood culture on the 10th day of admission grew *Enterococcus faecium* which was resistant to ampicillin and had HLAR to gentamicin, streptomycin and kanamycin. The patient died on the 16th day of admission from the relapse of AML and sepsis.

**Case 4**

A 76-year-old Chinese diabetic women had fever due to urinary tract infection and *Escherichia coli* was cultured from the urine and blood specimens. The sepsis was complicated by disseminated intravascular coagulation and required central lines monitoring and urinary catheterisation. She was prescribed ceftriaxone and gentamicin. Two blood cultures on day 19 grew *E. faecalis* which was resistant to chloramphenicol and amikacin and moderately sensitive to ampicillin. HLAR was positive for all the three aminoglycosides. She was treated with chloramphenicol and amikacin because repeat urine cultures grew *Klebsiella pneumoniae*. Ultrasound showed swollen left kidney with multiple cystic spaces suggesting left renal papillary necrosis. Left antegrade nephrostomy yielded pus when grew a *Candida spp.* Irrigation of the bladder with amphotericin B and oral fluconazole were prescribed. Blood cultures on day 61 grew *E. faecalis* again which had the same antibiotic susceptibility pattern as the initial blood isolate. She was given a course of unasyn (combination of ampicillin and sulbactam) towards the end of her hospitalisation which totalled 92 days.

**Case 5**

A 75-year-old Chinese diabetic man had bacteraemic *E. coli* chest infection and colon carcinoma. He responded to gentamicin and parenteral hyperalimentation. He was discharged after palliative right hemi-colectomy but was readmitted 3 days after surgery because he developed right subphrenic empyema which was drained. *K. pneumoniae* was cultured from sputum on day 1 and day 4 of the second admission. Blood cultures grew *E. faecalis* with HLAR to all three aminoglycosides and *Enterobacter cloacae* on day 1. Subphrenic collection grew *K. pneumoniae* and *E. faecalis*. The patient succumbed to multi-organ failure after 42 days of hospitalisation.

## DISCUSSION

A summary of the clinical features of the 5 cases are given in Table I. All the cases had underlying diseases which were diabetes mellitus (Cases 1,4), malignancies (Cases 3, 5) and chronic renal failure from hypertension (Case 2). All except Case 1 were nosocomial infections. Four of the 5 cases (Cases 2 to 5) had instrumentation such as urinary catheterisations, colonoscopy and CVP line insertions. The portal of entry was genitourinary (Cases 1, 2, 4), skin (Cases 3, 4, 5) and gastrointestinal (Case 5). Whilst the portal of entry is single in Cases 1, 2 and 3, it was possibly multiple in Cases 4 and 5.

HLAR against gentamicin, streptomycin and kanamycin was demonstrated in 4 of the 5 cases; streptomycin and kanamycin in Case 1. The antibiotic regime was appropriate in Case 1 but inappropriate in the rest of the cases for HLAR enterococcal bacteraemia. Though vancomycin was prescribed in Case 5, it was added too late in the course of the illness. Ceftriaxone was prescribed in all the cases except Case 2. The aminoglycosides had no beneficial effects because of the HLAR phenomenon in Cases 2 to 5. Polymicrobial infection was seen in Case 5 and the organisms were *K. pneumoniae* and *E. cloacae*. The occurrence of other bacteria in enterococcal bacteraemia is not uncommon[16,17]. Four of the 5 enterococcal septicaemia were due to *E. faecalis*. This reflected the predominance of *E. faecalis* isolated in most laboratories. In the study on the prevalence of HLAR in NUH[12], 90% of the 225 isolates of enterococci were *E. faecalis*. The mortality in this study is 60% compared to other reports of 34%[18] to 78%[19]. It is difficult to determine in this study and other similar studies[16,17] the clinical significance of enterococci because the patients often also had severe underlying diseases and it is also difficult to establish the independent role of the enterococci which are present in polymicrobial bacteraemia. The average duration of hospital stay was 37 days, ranging from 15 to 92 days. Enterococcal bacteremia may be transient as in Case 4 which occurred after the insertion of intra-arterial and CVP lines and recurred after the antegrade nephrostomy.

In summary, the major risks for HLAR enterococcal septicaemia in the 5 cases are: (1) immunosuppression with debilitation such as diabetes mellitus, cancer or a breakdown in local barriers secondary to central lines; (2) prior instrumentation of the gastrointestinal, genitourinary tracts; (3) long-term

**Table I – Clinical features of 5 cases of HLAR enterococcal septicaemia[a]**

| Case | Age/Sex | Underlying Disease | Clinical Features | Portal of entry[b] | Micro-organisms | Antimicrobial Agents given | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | 59/M | Diabetes mellitus<br>Renal calculus | Fever, pyuria | Genitourinary tract | *E. faecalis* (S,K)[c] | Ceftriaxone<br>Ampicillin<br>Gentamicin | Alive |
| 2 | 79/M | Hypertension<br>CRF[d]<br>Aortic aneurysm | Cardiogenic shock | Genitourinary tract | *E. faecalis* (G, S, K)[c] | None | Died |
| 3 | 54/F | Second relapse of AML | Fever, bruising | Skin | *E. faecium* (G,S,K)[c] | Ceftriaxone<br>Gentamicin | Died |
| 4 | 67/F | Diabetes mellitus | Fever, pyuria, RPN[e] | Genitourinary tract,<br>Skin | *E. faecalis* (G, S, K)[c]<br>*K. pneumoniae*<br>*E. cloacae* | Ceftriaxone<br>Gentamicin<br>Chloramphenicol<br>Amikacin | Alive |
| 5 | 75/M | Carcinoma of the colon | Chest infection, subphrenic abscess | Gastrointestinal tract<br>Skin | *E. faecalis* (G, S, K)[c] | Gentamicin<br>Amikacin<br>Metronidazole<br>Vancomycin | Died |

a : Medical records of the 5 cases were reviewed retrospectively.
b : Mode of instrumentation: genitourinary tract, urinary catheterisation; skin, central line insertion; gastrointestinal, colonoscopy.
c : G, S, K refers to HLAR to gentamicin, streptomycin and kanamycin respectively.
d : CRF = chronic renal failure
e : RPN = renal papillary necrosis.

hospitalisation, and (4) use of broad spectrum antibiotic agents (especially cephalosporins) that have little or no enterococcal activity for patients in the above risk groups, and these agree with the findings of Gullberg et al[16] who studied enterococcal bacteraemia. Many of these risks can be reduced by the alert clinician who will carry out modifications in the management of the patient such as cessation of inappropriate antibiotics and unnecessary instrumentations.

The prevalence of HLAR enterococci[20] is increasing and because there are also reports of beta-lactamases and resistance to vancomycin[21]; enterococcal sepsis should receive the same attention meted out to other nosocomial agents such as methicillin-resistant *Staphylococcus aureus*. It is therefore recommended that prospective studies on human enterococcal infections should be carried out to evaluate the requirement for one or two drug therapy in non-endocarditis enterococcal bacteraemia instead of largely retrospective studies that have been reported so far. HLAR detection should be carried out more frequently to avoid unnecessary aminoglycoside toxicity and it may improve the outcome of the disease with the appropriate aminoglycoside that is truly synergy-sensitive.

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