



Risk factors of Multidrug-resistant Gram-negative Bacterial Bloodstream Infections in Children's Hospitals in Japan

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Abstract

Background: Although multidrug resistant (MDR) gram-negative bacilli (GNB) are a serious and growing concern worldwide, the epidemiological data on children are still limited. Our aim was to evaluate the risk factors for MDR GNB bloodstream infections (BSI) in children.

Methods: Patients with GNB BSI were enrolled between April 2010 and March 2017 at eight children's hospitals in Japan. Clinical and microbiological data were collected retrospectively. The 2012 criteria of the Centers for Disease Control and Prevention were used to define MDR. MDR and non-MDR GNB BSI were then compared in terms of risk factors.

Results: In total 629 GNB BSI cases were identified. The median age and proportion of males was 2 years (IQR 0.3-8.7) and 50.7%, respectively. Underlying diseases were found in 94% of the patients. The proportion of GNB BSI cases developing after >48 hours from admission was 76.2%. The most common GNB was *Escherichia coli* (29.3%, 184/629), followed by *Klebsiella pneumoniae* (19.7%, 124/629) and *Pseudomonas aeruginosa* (16.4%, 103/629). MDR comprised 24.5% (154/629) of cases. The MDR rate for *E coli*, *K pneumoniae*, and *P aeruginosa* was 44.0% (81/184), 23.4% (29/124) and 16.5% (17/103), respectively. The coverage rate of the initial empiric therapy for the MDR and non-MDR GNB BSI cases was 60.4% and 83.4%, respectively (P<0.001). The all-cause mortality rate at 28 days of GNB BSI was 10.7% (67/629), 13.6% (21/154) and 9.7% (46/475) for MDR-, and non-MDR GNB BSI, respectively (P=0.167). The all-cause mortality rate at 28 days was 10.4% (14/135) and 7.7% (27/351) for MDR and non-MDR *Enterobacteriaceae* BSI, (P=0.341) and 41.2% (7/17) and 18.6% (16/86) for MDR- and non-MDR *P aeruginosa* BSI, respectively (P=0.056). Multivariate logistic regression analysis showed that MDR GNB BSI was independently associated with anticarcinogenic drug use within 30 days (OR: 43.90; 95%CI: 4.69-411.08), older age (OR: 1.05; 95%CI: 1.02-1.09), and admission to the neonatology ward (OR 0.019; 95%CI: 0.005-0.076).

Conclusions: One-fourth of GNB BSI cases were MDR. Anticarcinogenic drug use and older age were risk factors for MDR GNB BSI in children's hospitals. MDR *P aeruginosa* infections were associated with higher all-cause mortality.

Backgrounds and Aim

- MDR GNB infections are associated with an elevated risk of mortality in adults, and it is also threatening children.
- Reports on impacts and risk factors of MDR GNB BSI in children are still limited or conducted in small studies.
- The purpose of this study was to investigate risk factors and impact of MDR in children with larger sample size of GNB BSI episodes as a multicenter study in Japan.

Patients & Methods

Patients

Inclusion criteria

- Children (<18 years of age) presenting with GNB BSI at 8 Japanese children's hospitals between April 2010 and March 2017.
- The detection of different species 72 hours after the previous positive blood culture in a single patient was considered as an another episode.

Exclusion criteria

- Haemophilus* spp., *Salmonella* spp. and *Yersinia* spp. were excluded, as either they were not included in the CDC definition or they were foodborne pathogen.
- GNB with failed identification.
- In case the same bacterium was recovered within 4 weeks of the previous positive blood culture in a single patient.
- In case the positive blood culture was considered contamination and not treated as BSI.

MDR Definitions

- The definitions of MDR by CDC and ECDC in 2012 were used.

Statistical analysis

- The clinical characteristics and outcomes of patients with MDR and non-MDR GNB BSI were compared.
- Logistic regression analysis was used to identify the risk factor for the development of MDR GNB BSI.

Results

Table 1. Bacteria isolated in blood cultures

Bacteria	n (%)	MDR, n (%) *
Total	629 (100)	154 (24.5)
<i>Escherichia coli</i>	184 (29.3)	81 (44.0)
<i>Klebsiella</i> spp.	167 (26.6)	34 (20.4)
<i>Pseudomonas aeruginosa</i>	103 (16.4)	17 (16.5)
<i>Enterobacter</i> spp.	81 (12.9)	14 (17.3)
<i>Acinetobacter</i> spp.	40 (6.4)	2 (5.0)
<i>Serratia</i> spp.	29 (4.6)	2 (6.9)
<i>Citrobacter</i> spp.	13 (2.1)	3 (23.1)
<i>Morganella morganii</i>	6 (1.0)	0 (0)
<i>Pantoea</i> spp.	3 (0.5)	0 (0)
<i>Proteus</i> spp.	3 (0.5)	1 (33.3)

* The percentage indicates the proportion of MDR in each bacterium.

Table 2. Comparison of MDR and non-MDR GNB BSI

	Total (n = 629)	MDR (n = 154)	Non-MDR (n = 475)	P values
Age	2.0 (0.3-8.7)	3.0 (0.6-10.1)	1.8 (0.2-8.3)	.003*
Male	50.7	55.2	49.3	
Underlying diseases	94.1	97.4	93.1	
Days from admission to the positive blood culture	33 (3-118)	70.5 (10-176.8)	26.0 (1-80.5)	.75
Hematology-oncology ward	24.0	34.4	20.6	.82
PICU	17.0	15.6	17.5	
General ward	16.5	15.6	16.8	
NICU	15.4	9.1	17.5	<.001*
Surgical ward	13.8	18.2	12.4	
Antibiotic use within 30 days	63.0	64.3	62.5	
Corticosteroids use within 30 days	31.0	38.3	28.6	.195
Immunosuppressive agents use within 30 days	8.6	9.1	8.4	
Anticarcinogenic drug use within 30 days	22.6	33.4	18.9	.001*
Surgery within 30 days	17.5	13.0	18.9	
Hemodialysis within 30 days	3.5	2.6	3.8	
Mechanical ventilation	26.9	25.3	27.4	
CV catheter	69.5	76.0	67.4	.872
Urinary catheter	17.3	17.5	17.3	
ECMO	2.4	1.3	2.7	
IVH	22.9	22.1	23.2	
Effective empiric therapy	74.4	60.4	83.4	
All-cause mortality at 28 days	10.7	13.6	9.7	

Age and Days from admission to the positive blood culture were described as median (IQR). Others indicate percentage.

* Statistically significant by multivariate analysis (P < 0.05)

Age, OR: 1.054; 95%CI: 1.018-1.092; NICU, OR: 0.019 (0.005-0.076); Anticarcinogenic drug use within 30 days, OR: 43.904 (4.689-411.079)

Conclusion

One-fourth of GNB BSI cases were MDR. Anticarcinogenic drug use and older age were risk factors for MDR GNB BSI in children's hospitals in Japan.