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agr Dysfunction as an Independent Risk Factor for In-hospital Mortality in Persistent Methicillin-resistant *Staphylococcus aureus* Bacteremia

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Abstract

Background: Although methicillin-resistant *Staphylococcus aureus* bacteremia (MRSAB) often persists, little is known about microbiological risk factors for poor clinical outcomes in persistent MRSAB (pMRSAB). We aimed to elucidate microbiological risk factors of in-hospital mortality in pMRSAB and to compare in-hospital mortality of non-pMRSAB and of pMRSAB according to such a microbiological characteristic.

Summary: pMRSAB was defined as an MRSAB of ≥ 3 days despite of administration of susceptible antibiotic. SCC*mec* type, *spa* type, *agr* type, presence for genes for PVL and PSM-*mec*, vancomycin MIC, and functionality of *agr* locus were tested in all 207 pMRSAB blood isolates. Of them, 71 (34.3%) were in-hospital mortality. *agr* dysfunction was the only microbiological factor which was more frequent in in-hospital mortality than in survival (73.2%, 52/71 vs. 51.5%, 70/136, *P*=0.003). In multivariable analysis with clinical factors including Charlson's comorbidity weighted index score, Pitt bacteremia score, and pneumonia as a primary infection foci, *agr* dysfunction was independently associated with in-hospital mortality (adjusted odds ratio, 2.27; 95% confidence interval, 1.15-4.45; *P*=0.017). In-hospital mortality was not different between *agr* functional pMRSAB and non-pMRSAB (22.4%, 19/85 vs. 26.9%, 180/670, *P*=0.375) while that of *agr* dysfunctional pMRSAB was significantly higher (42.6%, 52/122 vs. 26.9%, 180/670, *P*=0.001).

Conclusions: *agr* dysfunction was an independent risk factor for in-hospital mortality in pMRSAB. *agr* functional pMRSAB was not associated with higher in-hospital mortality than non-pMRSAB.

Methods

Data from all non-duplicate episodes of MRSAB between 2009 and July 2016 in adult patients (≥ 15 years) were prospectively collected at 11 secondary- or tertiary-hospitals in South Korea. pMRSAB was defined as an documented MRSAB of ≥ 3 days duration while the patient was receiving antibiotic to which the isolate was susceptible. non-pMRSAB was defined as an MRSAB of < 3 days with or without susceptible antibiotic therapy. pMRSAB cases of unavailable blood isolates were excluded from the study.

Multiplex PCR for SCC*mec* type, typing of *spa* polymorphism, typing of the *agr* locus, vancomycin minimal inhibitory concentration (MIC), and PCR for the *lukS-PV* and *lukF-PV* genes for PVL and PSM-*mec* were performed for all the blood pMRSAB isolates: The function of *agr* locus was investigated by δ-hemolysin expression assay using *S. aureus* RN4220, and the absence of, or barely detectable, synergistic hemolysis was defined as *agr* dysfunction.

Results

1. Patients

Among a total of 1037 MRSAB, 279 and 670 cases were pMRSAB and non-pMRSAB, respectively, after excluding 29 of suspected contamination, 46 of polymicrobial infection, 13 of ≥ 3 days duration without susceptible antimicrobial therapy . Of pMRSAB, blood isolates were available in 207 (74.2%) cases. In-hospital mortality were 34.3% (71/207) among them.

2. Comparisons of clinical factors between survival and in-hospital mortality

	Survival (n=136)	In-hospital mortality (n=71)	*P*
Female	52 (38.2)	25 (35.2)	0.669
Age	64.6 (± 13.9)	67.9 (± 10.9)	0.084
Charlson's comorbidity-weighted index	**4.6 (± 2.6)**	**5.9 (± 2.5)**	**0.002**
Nosocomial infection	75 (55.1)	48 (67.6)	0.084
ICU location at first positive blood culture	19 (14.0)	18 (25.4)	0.085
Acute severity of illness			
Pitt bacteremia score, median (IQR)	**1.0 (0.0-2.0)**	**2.0 (1.0-4.0)**	**<0.001**
SOFA score, mean (± SD)	**4.1 (± 3.6)**	**7.6 (± 4.6)**	**<0.001**
Presentation with septic shock	**14 (10.3)**	**18 (25.4)**	**0.006**
Site of infection			
Central line associated infection	37 (27.2)	21 (29.6)	0.718
Surgical site infection	14 (10.3)	11 (15.5)	0.279
Skin & soft tissue infection	18 (13.2)	9 (12.7)	0.910
Pneumonia	**4 (2.9)**	**12 (16.9)**	**0.001**
Bone & joint infection	23 (16.9)	5 (7.0)	0.056
Infective endocarditis	8 (5.9)	4 (5.6)	0.942
Unknown primary site of infection	15 (11.0)	4 (5.6)	0.210
Hours to appropriate antibiotic, median (IQR)	1780.5 (484.8-3620.8)	1669.0 (295.0-4213.0)	0.976

3. Comparisons of microbiological factors between survival and in-hospital mortality

	Survival (n=136)	In-hospital mortality (n=71)	*P*
SCC*mec* type IV (vs. type II/III)	55 (40.4)	21 (29.6)	0.125
***agr* dysfunction**	**70 (51.5)**	**52 (73.2)**	**0.003**
Genes for PVL	4 (2.9)	1 (1.4)	0.505
psm-mec	13 (9.6)	5 (7.0)	0.543
Vancomycin MIC ≥ 1.5 μg/mL (E-test)	76 (55.9)	38 (53.5)	0.746

4. Independent risk factors for in-hospital mortality in pMRSAB

	aOR (95% CI)	*P*
Charlson's comorbidity-weighted index	**1.19 (1.05-1.34)**	**0.005**
Pitt bacteremia score	**1.31 (1.11-1.55)**	**0.001**
Pneumonia	**4.65 (1.31-16.48)**	**0.017**
***agr* dysfunction**	**2.27 (1.15-4.45)**	**0.017**

5. In-hospital mortality in non-pMRSAB and pMRSAB according to *agr* functionality

non-pMRSAB (n=670)	pMRSAB (n=207)		*P* (vs. non-pMRSAB)	
	agr(+) (n=85)	*agr*(-) (n=122)	*agr*(+) pMRSAB	*agr*(-) pMRSAB
180 (26.9)	19 (22.4)	52 (42.6)	0.375	0.001

Conclusions

Among many microbiological characteristics explored in this study, only *agr* dysfunction was revealed as an independent risk factor for in-hospital mortality in pMRSAB. *agr* functional pMRSAB was not associated with higher in-hospital mortality than non-pMRSAB. This is the first study not only exploring microbiological risk factors of in-hospital mortality in pMRSAB but also underscoring the importance of classification of pMRSAB according to microbiological features of the isolate.

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