P1998

Abstract (poster session)

Microarray-based genotyping of Staphylococcus aureus bacteraemia isolates – impact of pathogen- and host-factors on clinical manifestations and outcome

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Objectives: The relative impact of pathogen and host factors on the clinical course of Staphylococcus aureus bacteremia (SAB) is unclear. We aimed to investigate possible associations of genetic determinants of S. aureus with SAB severity and specific clinical manifestations. Methods: At two German tertiary care centers patients with SAB were prospectively identified and followed within the INvasive STapyhlococcus aureus INfections CohorT (INSTINCT). Between Jan 2006 and May 2010, 317 SAB isolates were collected and subsequently analysed by spa typing and DNA microarray-based genotyping (StaphyType, Alere, Germany). Uni- and multivariate regression analysis of factors associated with 30-day mortality, severe sepsis/septic shock, disseminated disease, infective endocarditis and osteoarticular infection was performed. Results: On the basis of hybridisation patterns isolates could be assigned to 21 different clonal complexes (most prevalent CC5, CC45, CC30, CC15 and CC7), spa typing revealed 157 different spa types. 10% of isolates were methicillin-resistant. Of 185 genes/alleles investigated, 49 genes were found in >=95% of isolates, 59 genes were detected in <=5% of isolates. In univariate analysis, there was a significant association between specific clonal complexes and the investigated clinical endpoints, i.e. for CC15 and 30-day mortality and disseminated disease, and for CC22 and osteoarticular infection, respectively. Also, a number of single genes or gene clusters were associated with mortality, severe sepsis/septic shock, disseminated disease and osteoarticular infection. However, after adjusting for patient characteristics only a very limited number of genotypic pathogen factors remained independently associated with the investigated clinical endpoints (table 1). For 30-day mortality these were presence of mecA, beta-lactamase (bla) and ermC genes, and for infective endocarditis presence of sed/sej/ser genes. For most endpoints there was a major independent impact of host factors such as age, comorbidity and particularly community-acquisition of SAB. Conclusion: Individual genotypes and clonal complexes of S. aureus as explanatory variables for the complex clinical phenotype of SAB should be interpreted with caution. Genotype-phenotype association studies need to include adjustments for important host factors such as age, comorbidity and community acquisition (presumably as a proxy for incubation time).

Table 1 Multivariate logistic regression analyses for endpoint day 30 mortality, severe sepsis or septic shock, disseminated disease and infective endocarditis in 317 SAB patients

	day 30 mortality (58 vs. 256 patients) §		severe sepsis/septic shock (102 vs. 215 patients)		disseminated disease (79 vs. 238 patients)		infective endocarditis (35 vs. 282 patients)	
Parameter/Risk factor	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Intercept	-	<0.01	-	<0.01	-	<0.01	-	p<0.01
Age [per year] &	1.06 (1.03-1.10)	<0.01	1.02 (1.00-1.04)	0.02	1.0 (0.98-1.02)	0.99	0.99 (0.97-1.01)	0.55
Study center 2 &	1.81 (0.87-3.77)	0.11	0.91 (0.53-1.54)	0.72	0.47 (0.26-0.87)	0.02	0.77 (0.36-1.67)	0.51
Male Sex &	1.38 (0.64-2.96)	0.42	1.66 (0.93-2.94)	0.08	0.95 (0.52-1.76)	0.88	1.20 (0.53-2.72)	0.66
Comorbidity McCabe ultimately or rapidly fatal &	4.52 (2.09-9.79)	<0.01	1.38 (0.79-2.41)	0.26	0.90 (0.48-1.71)	0.75	0.77 (0.32-1.88)	0.57
Mode of acquisition &								
community-acquired SAB	3.40 (1.31-8.81)	0.01	4.82 (2.50-9.50)	<0.01	5.21 (2.55-10.63)	<0.01	7.08 (2.54-19.74)	<0.01
community-onset healthcare-associated SAB	3.68 (1.58-8.54)	<0.01	2.88 (1.52-5.48)	<0.01	2.70 (1.31-5.57)	0.01	3.62 (1.22-10.68)	0.02
methicillin resistance (*mecA*) &	4.80 (1.43-16.06)	0.01	1.21 (0.46-3.16)	0.70	0.83 (0.26-2.62)	0.75	0.45 (0.09-2.33)	0.32
beta-lactamase (*blaZ/R*) #	3.12 (1.17-8.30)	0.02						
macrolide, lincosamide, streptogr. resist (*ermC*)	4.64 (1.32-16.35)	0.02						
fosfomycin resistance (*fosB*)			1.71 (0.98-2.99)	0.06				
enterotoxin D/J/R (*sed/sej/ser*) §†			2.27 (0.84-6.15)	0.11	1.87 (0.64-5.47)	0.25	5.11 (1.4-18.62)	0.01
enterotoxin A (*sea*)					1.01 (0.51-2.01)	0.97		
leukocidin E (*lukE*)					1.57 (0.66-3.73)	0.31		
staphylokinase (*sak*)					1.55 (0.44-5.48)	0.49		
chemotaxis-inhibiting protein (*chp*)					0.85 (0.40-1.83)	0.68		
hemolysin beta (*hlb*)					1.37 (0.53-3.56)	0.52		
CC15	2.66 (0.96-7.40)	0.06			0.35 (0.04-2.84)	0.33		
CC5	0.38 (0.11-1.36)	0.14						

OR odds ratio, CI confidence interval, CC clonal complex

§ 3 patients were lost to follow-up, & mandatory variable

due to an extremely high correlation of *blaI* and *blaR* (contingency coefficient 1.0 of *blaR* with *blaZ*), only *blaZ* was included in the multivariate model (endpoint day 30 mortality)

§ due to a high correlation of *sed/sej/ser* and *aadD* (contingency coefficient 0.71), only *sed/sej/ser* was included in the multivariate model (endpoint severe sepsis/septic shock), if aadD is included instead, results are OR 4.23 (95% CI 0.91-19.61, p=0.07) for aadD and OR 1.80 (95% CI 1.04-3.10, p=0.03) for fosB

† due to a contingency coefficient of 1.0 of *sed*, *sej*, *ser*, only *sed* was included in the multivariable logistic regression model (endpoint disseminated disease)