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SHORT REPORT
The pyogenic potential of the different *Streptococcus anginosus* group bacterial species: retrospective cohort study

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SUMMARY

Streptococcus anginosus Group (SAG) bacteria are common causes of pyogenic infections (PIs). We examined the association between SAG species and the presence of a PI through a retrospective, observational, cohort study, between the years 2009 and 2015. All adults with clinically significant SAG infections in one hospital in Israel were assessed for association between SAG species and the presence of a PI defined as an abscess, empyema, or deep/organ space surgical site infection. Risk factors for PI were assessed using multivariate backward stepwise logistic regression analysis. We identified 263 patients with significant SAG infections, 182 (69%) of which were caused by *S. anginosus*, 45 (17·1%) by *Streptococcus constellatus* and 36 (13·7%) by *Streptococcus intermedius*. The mean age of the patients was 56·8 ± 19·1 years. PIs were identified among 160 (60%) of the patients and were mostly non-bacteraemic (147/160, 91·8%), while most non-PI patients had bacteraemia (70/103, 68%). *S. anginosus* and *S. constellatus* were associated with a significantly lower incidence of PI than *S. intermedius*, OR 0·18 (95% CI 0·06–0·53) and 0·14 (0·04–0·48), respectively. Patients with PI were younger and, in general, had less co-morbidities. *S. intermedius* was associated with pyogenic non-bacteraemic infections, while *S. anginosus* and *S. constellatus* were associated with bacteraemia with no abscess or empyema formation. These data may indicate differences in virulence mechanisms of these SAG bacteria.

Key words: Pyogenic infections, *Streptococcus anginosus* Group.

Streptococcus anginosus Group (SAG) infections are the most common streptococcal species causing pyogenic infections (PIs) and have variable clinical manifestations [1, 2]. Few data are available on the differences in clinical virulence of the different SAG species (*S. anginosus, Streptococcus intermedius* and *Streptococcus constellatus*) and their differential ability to cause a PI. In one retrospective cohort, 35% of 245 SAG infections presented as a PI infection, with no reported differences between the species [3]. In another retrospective study of 118 patients with SAG infection, the proportion of patients with abscesses was 51% and *S. anginosus* was associated less frequently with abscess formation than the other SAG species [4]. *S. intermedius* has been linked to a worse prognosis, longer hospital stay [5] and disseminated PI [6]. However, these studies did not adjust for

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underlying clinical characteristics of patients infected with different SAG species.

Our objective was to examine retrospectively the association between SAG species and the presence of a PI in a relatively large cohort of patients over a 7-year period.

A retrospective, observational, cohort study was performed at Rambam Health Care Campus (RHCC) between the years 2009 and 2015. RHCC is a primary and tertiary care university-affiliated hospital of 960 beds, in northern Israel. The study was approved by the hospital's ethics committee with a waiver of informed consent given the observational nature of the study.

We included all consecutive adults (>18 years) with clinically significant SAG infection. Patients were identified by the microbiology laboratory reports of all SAG isolates from all sites. From these, all patients fulfilling Systemic Inflammatory Response Syndrome criteria [7] accompanied by symptoms or signs of infection at the site of isolation or blood cultures positive for SAG were included. The dependent variable was the presence of a PI, defined as a deep tissue abscess, empyema, joint or bone infection or a surgical site infection (SSI) involving the operated organ or bone (organ/space SSI [8]) from which SAG was isolated (thereafter termed 'PI'). Other outcomes included disseminated infection, defined as a PI involving two or more organs, length of hospital stay, all-cause 30-day and in-hospital mortality. The exposure variable was the species of SAG; *S. anginosus, S. intermedius* or *S. constellatus*. We collected a large dataset of potential predictors for PIs including patients' demographics, background conditions, place of infection acquisition, infection presentation and presence of polymicrobial infection.

Data were collected from patients' medical records. RHCC operates a full electronic patient file that includes all clinical, laboratory and radiological data in the study years. Mortality data are updated by the national registry of the Ministry of Health.

SAG were identified to the species level using the Vitek 2 system (bioMerieux, Marcy l'Etoile, France).

We targeted a sample of at least 140 patients, assuming a 50% rate of PIs to include five independent variables in a multivariate analysis in addition to the exposure variable and compared between patients with and without pyogenic SAG infection. Categorical variables were compared using the χ^2 test or the Fisher exact test, and continuous variables were compared using the *t* test or the Mann–Whitney *U*-test, as appropriate. Variables found significant on univariate analysis ($P < 0{\cdot}05$) were examined for statistical and clinical correlations and non-correlated variables were entered into a multivariate backward stepwise logistic regression analysis, in which the dependent variable was pyogenic infection. SAG species was forced into the analysis multiple imputations of blood urea nitrogen (BUN) were used for 19 patients to allow its inclusion in the regression model. Variables not contributing to the model's predictive ability were excluded from the final model. The goodness of fit and predictive ability of the model were examined using the Hosmer–Lemeshow and the receiver operating characteristics (ROC) curve, respectively. Analyses were performed using SPSS 20.

Over the study period, SAG bacteria were isolated from 301 adult patients, of which 263 had clinically significant infections, caused by *S. anginosus* in 182 patients (69·2%), *S. constellatus* in 45 (17·1%) and *S. intermedius* in 36 (13·7%). Male predominance was noted (168/263, 63·9%). The mean age of the patients was 56·8 ± 19·1 years. All-cause 30-day and in-hospital mortality rates were 45/263 (17·1%) and 39/263 (14·8%), respectively.

PIs were identified among 160/263 (60%) patients, and among these, 13 (8·1%) had bacteraemia and eight (5%) had disseminated infection. PIs included intra-abdominal abscesses or peritonitis (69 patients, 43·1%), skin/soft-tissue abscesses, arthritis or osteomyelitis (44 patients, 28·1%), empyema or lung abscesses (32 patients including one with both empyema and intra-abdominal infection, 20%) and intracranial abscesses (15 patients, 9·4%). Most patients with non-pyogenic infections had bacteraemia (70, 68%); none had endocarditis. Patients with PIs were generally younger and had fewer co-morbidities (Table 1). Most infections were acquired in the community, similarly in both groups. Surgical procedures were performed for abscess or empyema drainage in most patients with PI (141/160, 88·1%). Infection severity and mortality were higher in patients with non-pyogenic infections.

PIs were observed most commonly with *S. intermedius* (31/36, 86·1%) compared with 57·1% (104/182) with *S. anginosus* and 55·6% (25/45) with *S. contellatus*, $P = 0{\cdot}04$. The final multivariate model predicting PIs included age, baseline cognitive or functional impairment, acute mental alternation and raised BUN at infection presentation and SAG species. Congestive heart failure, diabetes and other laboratory values failed to improve the model. *S. anginosus* (OR 0·18,

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Table 1. *Patient characteristics and outcomes of patients with pyogenic vs. non-pyogenic SAG infection*

	Pyogenic infection $N = 160$	Non-pyogenic infection $N = 103$	P value
Demographics and background conditions			
Mean age, years (s.d.)	52·3 (18·8)	63·8 (17·4)	>0·001
Male (%)	104 (65%)	64 (62·1%)	0·366
Heart failure (%)	13 (8·1%)	16 (15·7%)	0·057
Diabetes mellitus (%)	23 (14·4%)	31 (30·1%)	0·02
COPD (%)	4 (2·5%)	4 (3·9%)	0·52
Connective tissue disease (%)	7 (4·4%)	2 (1·9%)	0·29
Dementia (%)	6 (3·8%)	15 (14·6%)	0·02
Liver disease (%)	13 (8·1%)	8 (7·8%)	0·9
Cognitive/physical impairment (%)	16 (10%)	24 (23·3%)	0·03
Active malignancy (%)	34 (21·2%)	26 (25·2%)	0·45
Community-acquired infection (%)	129 (80·6%)	82 (78·6%)	0·85
Infection presentation and characteristics			
SAG species			0·004
Streptococcus anginosus	104 (65%)	78 (75·7%)	
Streptococcus constellatus	25 (15·6%)	20 (19·4%)	
Streptococcus intermedius	31 (19·4%)	5 (4·9%)	
Polymicrobial infection (%)	102 (63·8%)	66 (64·1%)	0·95
Bacteraemia	13 (8·1%)	70 (68%)	<0·001
Acute renal failure (%)	11 (6·9%)	11 (10·7%)	0·27
Tachycardia (%)	63(39·4%)	42 (41·2%)	0·77
Hypotension (%)	28 (17·5%)	36 (35·3%)	0·01
Mental alternation (%)	11 (6·9%)	17 (16·5%)	0·01
WBC median (IQR 25–75)	13 (9·5–17)	12 (9–16)	0·23
Platelet, median (IQR 25–75)	255·5 (198–381)	248·5 (173–359)	0·34
Blood urea nitrogen (mg/dl) median (IQR 25–75)	13 (9–19·5)	19 (14–32)	0·01
Creatinine, median (IQR 25–75)	0·84 (0·7–1·1)	1 (0·73–1·43)	0·11
Clinical outcomes			
Lengths of hospitalisation (days), median (IQR 25–75)	10 (6–20)	12 (6–20)	0·7
In hospital mortality (%)	14 (8·8%)	25 (24·3%)	0·01
30 days mortality (%)	15 (9·4%)	30 (29·1%)	>0·001

95% CI 0·06–0·53) and *S. constellatus* (OR 0·14, 95% CI 0·04–0·48) were associated with significantly fewer PIs compared with *S. intermedius*; age was the only other significant factor associated with PIs (Table 2). The model performance was adequate; Hosmer–Lemeshow $P = 0·82$, area under the ROC curve 0·74 (95% CI 0·67–0·8).

Over the course of 7 years, we identified 263 patients with clinically significant SAG infections with *S. anginosus* being the most frequent species (69%) isolated. Overall, there was a relatively high proportion of PIs (60%) and these were associated with younger and healthier patients without bacteraemia, while bacteraemia occurred more frequently in patients without a PI. *S. intermedius* caused significantly more PIs than other SAG species, when adjusted to other differences between patients with and without pyogenic infections. Younger age remained significantly associated with PIs in the adjusted analysis. Survival was higher for patients with PIs, relating to the lower rate of bacteraemia in this group, younger age, fewer co-morbidities and possibly because drainage was performed in most of patients.

In agreement with our study, there is an evolving understanding that *S. intermedius* is more invasive and causes more severe infections than the other SAG species. In a literature review of 12 patients with SAG-disseminated infections (defined as involving two or more major organs), *S. intermedius* was responsible for six infections, while *S. anginosus* and S. *constellatus* caused two each [6]. Likewise, a retrospective single-centre study including 118 patients with SAG infections, *S. intermedius* was the least common but resulted in the highest rate of abscess

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Table 2. *Risk factors for pyogenic infection, multivariate analysis*

Factors predicting pyogenic infection	OR (95% CI)	*P* value
SAG species		
Streptococcus intermedius	Reference	
Streptococcus anginosus	0·18 (0·06–0·53)	0·02
Streptococcus constellatus	0·14 (0·04–0·48)	0·02
Acute mental alteration[a]	0·41 (0·16–1·04)	0·06
Blood urea nitrogen (mg/dl)[a]	0·98 (0·96–1)	0·08
Age (years)	0·97 (0·95–0·99)	0·001

[a] Measured at onset of infection.

formation (10/12, 88% of patients), compared with 41/54 (76%) with *S. constellatus* and 10/52 (19%) with *S. anginosus*, and a higher rate of bacteraemia [4]. In our study, *S. intermedius* was similarly associated with a higher rate of PIs (using a broader definition than abscesses), but was associated with highly significantly lower rates of bacteraemia than *S. constellatus* and *S. anginosus*.

The reasons for the increased pyogenic potential of *S. intermedius* have not been fully elucidated. Genetic mutations resulting in overproduction of intermedilysin, a major virulence factor of SAG, has been described [9], while the presence and activity of hydrolytic enzymes (deoxyribonuclease and chondroitin sulfatase) have been reported to be present more frequently *S. intermedius* and *S. constellatus*, and were associated with infection-related strains [10].

Our study, as most of the reviewed literature, is a retrospective single-centre study with its inherent limitations. The high proportion of PIs reported here may be explained by the fact that we included only clinically significant infections, unlike other studies with lower rates (35–51%) of such infections [3, 4]. We also employed a broader definition for 'pyogenic infections' and the long time span of the study enabled the collection of a relatively large series of patients, therefore allowing us to adjust for confounders when assessing the relative contribution of the individual SAG species to PIs. Throughout this period, the Vitek 2 system was used to identify the SAG isolates to the species level. Although currently molecular identification might be considered more accurate, several studies have confirmed the good performance of Vitek-2 in SAG identification [3, 11–13].

In conclusion, our findings suggest that compared with other SAG species, *S. intermedius* has the highest potential to cause infections involving abscess formation or other deep-seated infections and its identification should trigger an investigation to identify foci requiring surgical interventions. *S. constellatus* and *S. anginosus* caused bacteraemia without an associated pyogenic infection more frequently than *S. intermedius*.

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DECLARATION OF INTEREST

None.

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