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Short Research Communication

Is Gram staining still useful in prosthetic joint infections?

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Abstract

Introduction: *Staphylococcus aureus* is an independent risk factor for DAIR failure in patients with a late acute prosthetic joint infection (PJI). Therefore, identifying the causative microorganism in an acute setting may help to decide if revision surgery should be chosen as a first surgical approach in patients with additional risk factors for DAIR failure. The aim of our study was to determine the sensitivity of Gram staining in late acute *S. aureus* PJI.

Material and methods: We retrospectively evaluated all consecutive patients between 2005-2015 who were diagnosed with late acute PJI due to *S. aureus*. Late acute PJI was defined as the development of acute symptoms and signs of PJI, at least three months after the index surgery. Symptoms existing for more than three weeks were excluded from the analysis. Gram staining was evaluated solely for synovial fluid.

Results: A total of 52 cases were included in the analysis. Gram staining was positive with Gram positive cocci in clusters in 31 cases (59.6%). Patients with a C-reactive protein (CRP) > 150 mg/L at clinical presentation had a significantly higher rate of a positive Gram stain (30/39, 77%) compared to patients with a CRP ≤ 150 mg/L (4/10, 40%) (p=0.02). A positive Gram stain was not related to a higher failure rate (60.6% versus 57.9%, p 0.85).

Conclusion: Gram staining may be a useful diagnostic tool in late acute PJI to identify *S. aureus* PJI. Whether a positive Gram stain should lead to revision surgery instead of DAIR should be determined per individual case.

Key words: Prosthetic joint infection, acute, hematogenous, Gram staining, *Staphylococcus aureus*

Introduction

Late acute prosthetic joint infections (PJI), which are presumed to be mostly hematogenous in origin, have a relatively high failure, especially when caused by *Staphylococcus aureus* [1-5]. In an acute setting, surgical debridement is often performed for immediate load reduction, but revision surgery might be the preferred treatment modality in certain patient groups. We recently demonstrated in a large cohort of late acute PJIs that patients with a preoperative

CRIME80 score (i.e. C-reactive protein >150 mg/L, Chronic obstructive pulmonary disease, Rheumatoid arthritis, fracture as Indication for the prosthesis, Male gender, not Exchanging the mobile components during debridement and an age above 80 years) above 2, have an average failure rate of 64% and increases to 77% when *S. aureus* is involved. [1]. In addition, *S. aureus* was an independent risk factor for failure in the multivariate analysis. For this reason, identifying the

causative micro-organism preoperatively might be helpful to choose the best primary surgical approach per individual case. In this respect, rapid microbiological detection, preferably within a couple of hours, is mandatory. So far, Gram staining has shown a poor sensitivity (~30%) in diagnosing PJI, and therefore, its clinical utility appears to be low [6-23]. However, most of the performed studies have been conducted in revision surgeries comprising mostly chronic PJIs. Considering the above mentioned clinical implications, we evaluated the sensitivity of Gram staining in a cohort of late acute PJIs caused by *S. aureus*.

Material and Methods

We retrospectively collected data of all consecutive patients diagnosed with a late acute *S. aureus* PJI between January 2005 and December 2015 in four University Hospitals. The studied cohort comprised a part of a larger analysis on late acute PJI treated with DAIR [1]. Late acute PJI was defined as the development of acute symptoms and signs of a PJI (i.e. a sudden onset of pain and/or swelling of the prosthetic joint) in a prior asymptomatic joint more than 3 months after the index arthroplasty. Patients with symptoms existing for longer than 3 weeks before surgery was performed were excluded from the analysis. Surgery consisted of a DAIR procedure (with or without the exchange of mobile components) or revision surgery (i.e. one- or two-stage exchange). During surgery, multiple intraoperative tissues and synovial fluid were obtained for culture and used as gold standard. As tissue samples are not available preoperatively, Gram staining performed on intraoperative biopsies was excluded from the analysis and solely analyzed for synovial fluid. In every case, one Gram staining on synovial fluid was performed. A Gram stain was considered positive for *S. aureus* when Gram positive cocci in clusters were observed by the medical microbiologist. *S. aureus* infection was confirmed with ≥ 1 positive culture of periprosthetic intraoperative tissue or synovial fluid. PJI was defined according to the diagnostic criteria described by the Musculoskeletal Infection Society (MSIS) [24]. Multiple variables on patient characteristics, clinical presentation and outcome were collected and analyzed.

Failure was defined as: i) the need for prosthesis removal (in case revision surgery was applied as first surgical strategy, removal of the revised prosthesis was considered as failure), ii) the need for suppressive antibiotic therapy because of persistent or recurrent clinical or biochemical signs of infection, or iii) infection-related death.

Differences in patient characteristics between

Gram positive versus Gram negative cases were analyzed using a Fisher exact test with categorical variables and a Mann Whitney U test with continuous variables. A p-value < 0.05 was considered as statistically significant. Data were presented as medians \pm the interquartile range (IQR).

Results

In the studied period, a total of 66 patients were diagnosed with late acute *S. aureus* PJI. Gram staining on synovial fluid was not performed in 15 cases, leaving a total of 52 cases for analysis, comprising 2 shoulders, 18 hips and 32 knees. The majority of cases were monomicrobial infections (50 cases, 96.1%). One of the two polymicrobial infections included a co-infection with *Staphylococcus epidermidis*, the other case was a co-infection with a Gram-negative rod. Gram staining was positive with Gram positive cocci in clusters in 31 cases, resulting in an overall sensitivity of 59.6% (CI 45.1 - 73.0). Excluding missing data, patients with a C-reactive protein (CRP) > 150 mg/L at clinical presentation had a significantly higher rate of a positive Gram stain (30/39, 77%) compared to patients with a CRP ≤ 150 mg/L (4/10, 40%) ($p=0.02$). The sensitivity of Gram staining was also higher in patients with a BMI > 35 (8/10, 80%) compared to patients with a BMI ≤ 35 (15/27, 55.6%), a temperature > 38.5 degrees Celsius (15/19, 78.9%) compared to a temperature ≤ 38.5 degrees Celsius (19/31, 62.0%) and in patients with *S. aureus* bacteremia (22/28, 78.6%) compared to patients with negative bloodcultures (12/22, 54.5%). However, all these differences were not statistically different. Combining the presence of fever and a CRP > 150 mg/L, resulted in a sensitivity of 83.3% (CI 51.9 - 95.7). The median duration of symptoms was 3 days (IQR 1 - 7) in Gram positive cases versus 2 days (IQR 1 - 9.5) in Gram negative cases ($p=0.61$). The sensitivity of Gram staining did not differ for the infected joint (knee or hip).

Forty-seven patients (90.4%) were treated with irrigation and debridement (DAIR). The remaining patients were treated with revision surgery. Overall, failure within the debrided group was 68.1% (32/47). All of the 32 failed cases, failed during antibiotic therapy. The failure rate of the revised cases was: 1 out of 5 (20%). A positive Gram stain was not related with a higher failure rate compared to a negative Gram stain (65.5% versus 72.2%, $p=0.75$).

Discussion

We demonstrated a moderate sensitivity (i.e. 60%) of Gram staining in synovial fluid to detect *S. aureus* in late acute PJIs. Sensitivity was significantly higher in patients with a high CRP, probably due to a

higher bacterial inoculum. Although the sensitivity of Gram staining was moderate, it was significantly higher in our study compared to previous reports (Table 1) [6-23]. To illustrate, a meta-analysis conducted by Ouyang et al. including a total of 4647 patients, demonstrated an overall sensitivity of Gram staining of merely 19%. Although the type of infection was not always clearly defined in the included studies, it is most likely that the majority of these cases comprised chronic infections as all studies were performed in revision surgeries. This may explain the higher diagnostic yield of Gram staining in our study analyzing solely (late) acute infections.

Table 1. Studies performed on Gram staining in revision surgery. This Table was partially duplicated from the meta-analysis performed by Ouyang et al. [25].

Author	Year	N	N (%) of <i>S. aureus</i>	Sample	Sens	Spec	PPV	NPV
Kraemer et al. [12]	1993	55	1 (1.8)	Tissue	23%	100%	100%	81%
Feldman et al. [11]	1995	33	3 (9)	Synovial fluid	20%	ND	ND	ND
Chimento et al. [10]	1996	169	No data	Tissue	0%	0%	0%	0%
Barrack et al. [9]	1997	67	6 (8.9%)	Synovial fluid	10%	100%	ND	ND
Atkins et al. [22]	1998	297	3 (1)	Synovial fluid and tissue	6%	100%	ND	ND
Della Valle et al. [21]	1999	413	14 (3.4)	Tissue	15%	99%	71%	85%
Spanghel et al. [20]	1999	202	No data	Tissue	19%	98%	63%	89%
Virolainen et al. [18]	2002	68	15 (22)	Synovial fluid	67%	100%	ND	ND
Banit et al. [19]	2002	121	10 (8%)	Tissue swab	43%	100%	ND	ND
Ko et al. [17]	2005	40	7 (17.5)	Tissue	0%	0%	0%	0%
Trampuz et al. [23]	2007	326	10 (12.6)	Sonication fluid	45%	100%	100%	86%
Parvizi et al. [8]	2006	70	26 (27.6)	Synovial fluid	35%	97%	94%	54%
Ghanem et al. [7]	2009	1004	No data	Tissue	31%	100%	99%	75%
Morgan et al. [6]	2009	921	No data	Synovial fluid and tissue	27%	100%	99%	79%
Johnson et al. [16]	2010	202	No data	Tissue swab	10%	100%	100%	62%
Oethinger et al. [15]	2011	269	No data	Synovial fluid and tissue	9%	99%	ND	ND
Schindler et al. [14]	2011	62	15 (24.2)	NS	2%	ND	ND	ND
Zywiel et al. [13]	2011	347	No data	Tissue swab	7%	99%	92%	57%

Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, ND: not determined.

As late acute *S. aureus* PJI treated with DAIR is associated with a relatively high failure rate, especially in patients with a high preoperative CRIME80 score [1], a Gram stain with Gram positive cocci in clusters may be useful in an acute setting to consider revision surgery instead of DAIR. Previous studies have shown that late acute PJI caused by microorganisms other than *S. aureus*, have a better outcome, and a DAIR procedure may be feasible in

the majority of these patients [1, 3-4]. Therefore, especially when immediate load reduction is warranted, rapid preoperative identification of the causative microorganism might be helpful to determine the primary surgical approach. Until now, molecular detection does not show any benefit in acute PJIs [26]. Although a negative Gram stain does not exclude an infection caused by *S. aureus* as indicated by our results, the specificity and positive predictive value of Gram stain appears to be very high as previously demonstrated [25.] Therefore, a high CRIME80 score combined with a Gram stain containing Gram positive cocci in clusters may guide the orthopaedic surgeon to consider revision surgery instead of DAIR. Although the presence of coagulase negative staphylococci (CoNS) cannot be excluded in Gram stains with positive cocci in clusters, these microorganisms are very rare in causing late acute infections [1]. Moreover, if CoNS are isolated, the chance that the PJI is a previously unrecognized chronic PJI, instead of a late acute PJI, is much more likely. In these cases, a revision surgery instead of a DAIR would be the preferred treatment modality as well [27]. Obviously, the ultimate decision to perform revision surgery should be made per individual case and preferably discussed within a multidisciplinary team as several factors needs to be taken into account.

In conclusion, our results indicate that implementing Gram staining in routine diagnostics may have additional clinical value in late acute PJIs as the presence of Gram positive cocci in cluster may warrant the surgeon to intensify surgical treatment in certain patient groups.

Competing Interests

The authors have declared that no competing interest exists.

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