

Research Article

Characteristics of *Propionibacterium acnes* Infections in Orthopaedic Surgery: 11 Year Study in a Referral Center, 2004-2014

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Abstract

Propionibacterium acnes has been associated with late, smoldering and healthcare-associated infections of the shoulder and spine. However, the characteristics of *P. acnes* with respect of other anatomical locations, patient populations and bacterial culture characteristics remain largely unknown. This retrospective single center observational study compared ten variables (age, sex, type and site of infection, presence and type of hardware, C-reactive protein levels, immunodeficiency state, rate of polymicrobial cultures and type of co-existent germs) of orthopaedic patients suffering from *P. acnes* infections with those of patients with non-*Propionibacterium* infections. *P. acnes* was isolated intraoperatively in 37 of 2716 (1.36%) orthopaedic infections. The lumbar region (odds ratio 7.4, 95% CI 1.2-46.3), the shoulder (OR 9.9, 1.6-60.1) and the presence of hardware (OR 8.2, 2.4-28.4) were significantly associated with *P. acnes* infection; while sex and age were not. *P. acnes* was rarely identified (3/1008 vs. 34/1708; $p < 0.01$) among immunodeficient patients, in foot infections, prosthetic joints, and tibia nails and never in septic bursitis. Lower CRP serum levels (< 50 mg/l) were observed more often in *P. acnes* cases than in controls (49% versus 31%, $p < 0.01$). *P. aeruginosa* or MSSA were almost never identified as a co-pathogen of *P. acnes*. Combination of these clinical variables should help attending physicians and surgeons to reinforce suspicion for *P. acnes* infection, and take appropriate measures when needed. Further research should shed light on *P. acnes*' tropism for plates and spondylodesis as opposed to arthroplasties.

Keywords: *Propionibacterium acnes*; Orthopaedic; Infection; Characteristics; Co-pathogen

Abbreviations

P. acnes: *Propionibacterium acnes*; CRP: C-Reactive Protein; OR: Odds Ratio; CLSI: Clinical and Laboratory Standard's Institute; EUCAST criteria: European Committee on Antimicrobial Susceptibility Testing; ROC: Receiver Operating Characteristic; MSSA: Methicilline-Susceptible *Staphylococcus Aureus*

Introduction

Propionibacterium acnes is a Gram-positive non-obligate anaerobic bacterium colonizing the lipid-rich sebaceous glands of the skin [1]. It belongs to the clinical group of skin commensals, but can occasionally cause serious infections [2]. Determining the presence of *P. acnes* infection can be difficult. Due to its low virulence, infections are less dolent [3] and markers of infection (fever, sedimentation rate, leucocyte count) are reported of unreliable character in *P. acnes* infections [4]. Infections may remain latent for several months [5]. Histopathological findings of acute inflammation, chronic inflammation or foreign-body reaction are said not to correlate with *P. acnes* [6].

Importantly, *P. acnes* has several particularities, for example, it prefers certain anatomical regions, although it can cause infection in almost any body site [1]. *P. acnes* can be recovered in the presence or

not of devices. Besides its name-giving affection to acne vulgaris, *P. acnes* is linked to many chronic orthopaedic and cardiac prosthetic and implant infections [7-10], as well as breast [11] or eye implant infections [12]. *P. acnes* can produce biofilms [13], and is involved in the mechanism of septic and possibly aseptic loosening of orthopaedic implants [14]. In orthopaedic surgery, *P. acnes* is historically known to infect shoulder and clavicular infections, especially in the presence of implants [1]. A third prevalent anatomic localization is the lumbar spine, in which anaerobic conditions or long term surgery (associated with cutaneous contamination) are reportedly linked to *P. acnes* infections [15,16].

Surprisingly, the characteristics of *P. acnes* with respect to all orthopaedic infection locations, the presence and type of orthopaedic material, patients' characteristics and microbiologic findings remain little documented. The purpose of this study was to compare *P. acnes* infections with other bacteriological infections in an orthopaedic unit and determine whether there is a difference between groups in the proportion of: anatomical sites; the presence and type of hardware; age, sex and immune deficiency status; CRP levels, and identified germs. Identification of these clinical variables should help attending physicians and surgeons to reinforce suspicion for *P. acnes* infection, hence allowing them to take appropriate measures. This retrospective single center observational study tries to address these questions.

Table 1: Comparison of *P. acnes* infections with other infections in orthopaedic surgery.

n = 2716	<i>P. acnes</i> infection n = 37	Comparison p value*	non- <i>P. acnes</i> infection (control) n = 2679
Male gender	29 (78%)	> 0.05	1827 (68%)
Median age	46 (range 17-84)	-	57 (range 17-99)
Age group ≤ 50 years	20 (54%)	> 0.05	1065 (40%)
Age group 51 - 80 years	16 (43%)	> 0.05	1296 (48%)
Age group > 80 years	1 (3%)	> 0.05	318 (12%)
Immune deficiency+	3 (8%)	< 0.000	1005 (37%)
Spine	10 (27%)	< 0.00	69 (3%)
Shoulder	6 (16%)	< 0.00	87 (3%)
Foot	1 (3%)	0.029	423 (16%)
Other	20 (54%)	> 0.05	2100 (78%)
Presence of hardware	24 (65%)	<0.000	634 (24%)
Plates	6 (16%)	0.004	143 (5%)
Nails	1 (3%)	> 0.05	53 (2%)
Spondylolysis	5 (14%)	<0.000	25 (1%)
Prosthesis	5 (14%)	> 0.05	313 (11%)
Other	7 (19%)	0.004	100 (4%)
Joint and bone	32 (86%)	-	1662 (61%)
Bursitis	0	0.005	468 (17%)
Abscess formation	12 (32%)	> 0.05	1043 (39%)
Serum CRP level <50 mg/L	18 (49%)	0.033	838 (31%)
CRP 51 - 200 mg/L	12 (32%)	0.033	845 (32%)
CRP > 200 mg/L	7 (19%)	0.033	996 (37%)
Polymicrobial	15 (41%)	0.015	552 (21%)
MSSA	1 (3%)	<0.000	1039 (44%)
<i>Pseudomonas aeruginosa</i>	0 (0%)	0.035	253 (11%)

* Pearson- χ^2 or Fisher exact-test; Variables in bold are statistically significant (two-tailed p value <0.05). MSSA = Methicillin-Sensitive *Staphylococcus aureus*; CRP= C-Reactive Protein level on admission. +Immune-suppressive therapy, dialysis, cirrhosis Child C, human immunodeficiency virus infection, active malignancy, pregnancy, splenectomy, agranulocytosis, diabetes mellitus.

Materials and Methods

Study design and setting

The Orthopaedic Service of University of Geneva Hospitals has 132 acute care beds (24 on the Septic Ward). Dedicated infectious diseases consultants (since the year 2000) have established a number of databases regarding orthopaedic infections as approved by our hospital Ethics Committee [15]. We retrospectively analyzed these data over a period of 11 years in regards to the epidemiology of *P. acnes*.

Participants/study subjects

All first clinical infection episodes in adult patients, hospitalized in our orthopaedic and traumatology center between January 2004 and December 2014 were included. All infection types (osteo-articular, cutaneous, subcutaneous, bursitis, with or without hardware or prosthesis) were included. The diagnosis of *P. acnes* infection was based upon the presence of *P. acnes* in at least two intraoperative samples [17], together with clinical signs of infection (novel pain, fever, sinus discharge) and/or radiographic signs [18]. We excluded recurrences, episodes with insufficient data, infections without intraoperative microbiological samples and paediatric cases.

Description of experiment

The databases were cross-matched with the Hospital's Coding Office files for patient identification and retrospectively analyzed was performed. We processed all specimens in our clinical microbiology laboratory and the procedures corresponded mainly to CLSI (Clinical and Laboratory Standard's Institute) recommendations [19] remained unchanged throughout the entire study period except for switching to EUCAST criteria (European Committee on Antimicrobial Susceptibility Testing) in spring 2014 [20]. Sonication was not performed. A median of 5 days of microbiological culture

time was performed in CDC Anaerobe 5% Sheep Blood Agar media, enriched with brain-heart infusion.

Variables, outcome measures, data sources, and bias

Ten variables (age, gender, type and site of infection, presence and type of hardware, C-reactive protein levels, immunodeficiency state, rate of polymicrobial cultures and type of co-existent germs) were collected per episode on an EXCEL™ sheet, and compared between cases and controls. To confront our findings with data from other centers, we performed a literature review. A computerized strategy using MEDLINE, EMBASE, EFFORT and AAOS, from January 1946 until March 2015, searched for the following key words: 'infections', '*Propionibacterium acnes*', 'orthopaedic', 'trauma', and 'incidence'. The search was limited to *in vivo* human studies of adults published in the English language concerning the field of orthopaedic surgery. We also hand searched the reference lists of the retrieved studies. After having eliminated all duplicates, we retained 28 original articles. 14 articles concerned shoulder infections, 4 concerned spine infections, 4 articles discussed hip and knee prosthesis infections and 3 articles related to positive *P. acnes* cultures in orthopaedic implants. Of particular interest, 3 papers addressed the overall incidence of *P. acnes* in post-operative osteoarticular infections and associated risk factors [7-9].

Statistical analysis, study size

Group comparisons were performed using the Pearson- χ^2 , the Fisher-exact or the Wilcoxon-ranksum-tests, as appropriate. An unmatched logistic regression analysis determined associations with the outcome "*P. acnes* infection". Independent variables with a p value ≤0.30 in univariate analysis were introduced stepwise in the multivariate analysis. We included 5-10 outcome events per predictor variable [21]. Key variables were checked for confounding, co-linearity and interaction, the latter by Mantel-Haenszel estimates

Table 2: Unmatched logistic regression analyses with outcome “*P. acnes* orthopaedic infection”.

	Univariate analysis (OR)	Multivariate analysis (OR)
Female gender	0.6 (0.26-1.30)	n.a.
Age (continuous variable)	1 (0.97-1.00)	n.a.
Immune deficiency*	0.1 (0.04-0.48)	n.a.
CRP levels (continuous variables)	1 (0.99-1.00)	n.a.
Spine	7.3 (2.96-18.12)	7.4 (1.18-46.06)
Shoulder	5.7 (2.34-14.28)	9.9 (1.61-60.6)
Foot	0.1 (0.02-1.08)	1.0 (0.13-9.40)
Hardware	6 (3.01-11.76)	8.2 (2.35-28.33)
Plates	3.4 (1.40-8.36)	n.a.
Nails	1.4 (0.18-10.22)	n.a.
Spondylodesis	16.6 (5.97-46.06)	n.a.
Prosthesis	1.5 (0.60-3.53)	n.a.
Abscess	0.7 (0.38-1.50)	1.4 (0.40-4.72)

Results as OR (odds ratio) with 95% confidence interval. n.a.= not applicable due to interaction.

Variables in bold are statistically significant (two-tailed *p* value <0.05).

*Immune-suppressive therapy, dialysis, cirrhosis Child C, human immunodeficiency virus infection, active malignancy, pregnancy, splenectomy, agranulocytosis, diabetes mellitus.

and interaction terms. Age and CRP levels were analyzed as continuous and categorized variables. *P* values ≤0.05 (all two-tailed) were significant. STATA™ software (9.0; College Station, USA) was used. The goodness-of-fit-value was 0.99 and the ROC-value 0.85, indicating a high accuracy of our final model.

Results

Demographics, description of study population

2716 infection episodes were retained for analysis. The median age of all patients was 57 years (range 17-99 y); 1845 (69.93%) were males and 1008 (37.11%) were immunodeficient. 665 surgical procedures (24%) involved hardware. Hardware were arthroplasties (n=319; 11.75%), plates (n=149; 5.49 %), nails (n=54; 2%), spondylodesis material (n=30; 1.10%), screws (n=20; 0.74%), cerclage cables or wires (n=14; 0.51%) or hip screws (n=5; 0.18%). 1055 (38.84%) infectious episodes were associated with abscesses, and 468 (17.23%) were septic bursitis cases. 567 infections (20.87%) were polymicrobial. Common pathogens were MSSA (n=1040; 38.29%), *Streptococcus* (n=434; 15.97%) and *P. aeruginosa* (n=253; 9.31%).

P. acnes population

P. acnes was isolated intraoperatively in 37 of 2716 (1.36%) infection episodes (Table 1).

Hardware was present in 24 cases (64.86%) and mainly involved plates (n=6; 25.00%), spondylodesis (5; 20.83%) and arthroplasties (5; 20.83%). 32 cases (86, 48%) were joint or bone infections, 5 were cutaneous or subcutaneous infections. 12 episodes (32.43%) presented an abscess. We found no septic bursitis cases linked to *P. acnes*. *P. acnes* was more frequently identified during procedures in the presence compared with the absence of foreign orthopaedic material (24/665 vs. 13/2051; *p*<0.01). After multivariate logistic regression analysis, the presence of hardware (OR 8.2, 2.4-28.4) remained significantly associated with *P. acnes* infection. A significant association was found between *P. acnes*, plates (Odds Ratio 3.4, 95% CI 1.40-8.36) and spondylodesis (OR 16.6, 95% CI 5.97-46.06). In contrast, differences concerning prosthetic joints, tibia nails and the presence of abscesses were found not to be significant (*p*>0.05).

Table 3: Principal pathogens identified in microbial cultures.

	Cases (<i>P. acnes</i>) 37	Control (non- <i>P. acnes</i>) 2679
<i>Propionibacter acnes</i>	37	0
<i>Methicilline-susceptible Staphylococcus aureus</i>	1	1039
<i>Streptococcus</i>	0	434
<i>Pseudomonas aeruginosa</i>	0	253
<i>Methicillin-resistant Staphylococcus aureus</i>	0	172
<i>Staphylococcus epidermidis</i>	8	97
<i>Corynebacterium</i>	4	12
<i>S. agalactiae</i>	1	70
<i>S. warneri</i>	1	7

Anatomical sites of *P. acnes* infections concerned mostly the spine (n=10; 27.02%) and shoulder (n=6; 16.22%) region (Table 1). Few *P. acnes* infections were caudal to the lumbar region. After group comparison between *P. acnes* (cases) and non-*P. acnes* infections (controls) (Tables 1 & 2), proportion of *P. acnes* in the spine (12%) and shoulder (6%) was found to be significantly different. Due to differences in crude group comparisons, a multivariate logistic regression analysis adjusted for case mix was performed (Table 2). The lumbar region (Odds Ratio 7.4, 95% CI 1.2-46.3) and the shoulder (OR 9.9, 1.6-60.1) remained significantly associated with *P. acnes* infection. Among *P. acnes* infections, 29 (78%) were male; median age was 46 years (range 17-84 y) and 3 patients (8.10%) were immunodeficient. *P. acnes* was rarely identified among immunodeficient patients (3/1008 vs. 34/1708; *p*<0.01). After multivariate logistic regression analysis, sex and age were not associated with *P. acnes* infection. Lower CRP serum levels (< 50 mg/l) were observed more often in *P. acnes* cases than in controls (49% versus 31%, *p*<0.01). 15 (40, 54%) infections were polymicrobial. Microbiological cultures were more often polymicrobial in *P. acnes* infections than compared to controls (*p*=0.015), and *P. aeruginosa* or MSSA were almost never associated to polymicrobial cultures of *P. acnes*. Co-existing microorganisms in polymicrobial cultures (Table 3) were *S. epidermidis* (n=8), *Corynebacterium* (n=4), *S. agalactiae* (n=1), *S. warneri* (n=1) and MSSA (n=1).

Discussion

This retrospective study confirmed a strong association between *P. acnes* infections and bone and joint infections, plate and spondylodesis infections, mainly in shoulder and spine regions. *P. acnes* infections were associated with lower CRP level elevation than other infections. Of interest, immunodeficient patients were more likely to have infections due to other pathogens than *P. acnes*. Microbiological cultures of *P. acnes* were more often polymicrobial, but co-infection with *P. aeruginosa* or MSSA was rare. Age and sex were found not to be correlated with *P. acnes*.

P. acnes deep tissue infection in orthopaedic surgery remains a rare complication outside of eventual nosocomial outbreaks. Our study identified 37 (1.36%) *P. acnes* infections in 2716 orthopaedic infection episodes, which is comparable to literature: Walter et al. [9] retrospectively reviewed anaerobic bone and joint infections of orthopaedic implants in 3144 patients and noted a *P. acnes* infection risk of 0.63% (20/3144). Titécát et al. [7] attributed *P. acnes* to 5.8% of

all orthopaedic infections, with a predilection to prosthetic infections of the upper limb. Kanafani et al. [8] analyzed the global incidence of *P. acnes* after orthopaedic surgery of major joints over a period of 11 years and identified *P. acnes* as responsible for infection in 1.6/1000 procedures.

The median of 5 days microbiological culture time of *P. acnes* in this retrospective study, and the absence of sonication [22] could have resulted in an underestimation of *P. acnes* infection rate: Between 2000 and 2011, a significant increase in the number of *P. acnes* isolates in orthopaedic surgery has been observed [7,23], probably inherent to the prolonged incubation time of the samples. Ideal incubation time observation periods longer than one week are found to have a higher sensitivity for *P. acnes* detection [24,25] and some colleagues propose an optimal incubation period of 13 day [5]. The strength of this study is the requirement for two intraoperative samples with the same *P. acnes* to be counted as infection, together with clinical signs of infections. Deep tissue infection specimens are 6.3 times more likely to have ≥ 2 culture media positive for *P. acnes* than specimens from nondiagnostic events [17]. Gram stain is currently not recommended because of its low sensitivity and negative predictive value [4]. The relative lower CRP levels (<50 mg/l) associated with *P. acnes* infections, as observed in this study, can be explained by a lower inflammatory response of the host to *P. acnes*, inherent to its indolent nature. In this study, *P. acnes* microbial cultures were more often polymicrobial than cultures from controls, compatible with *P. acnes*' tolerance for other germs (Table 3). The primary identified co-existing germ was *S. epidermidis* (22%), known to live in close proximity with *P. acnes* on human skin. Of interest, antagonistic interactions between these two species have been described and it could be envisaged that anti-*P. acnes* activity of *S. epidermidis* could be exploited, for example as a probiotic treatment approach against *P. acnes*-associated diseases [26]. Selective competition in favour of fast growing bacteria like *P. aeruginosa* or MSSA, might make identification of *P. acnes* in presence of these pathogens less likely and can lead to a misidentification or underestimation of *P. acnes* in culture.

The strong association between *P. acnes* and shoulder and lumbar surgery has been explained for shoulder surgery by proximity of *P. acnes*' ecological niche, the lipid-rich sebaceous follicles of the skin [27,28], and a high range of passive motion and extensions during surgery (personal opinion). Another explanation could lie in the use of hardware, especially in spine surgery. Aubin et al. [3] showed a sixty-fold increase in risk of *P. acnes* infections in spine surgery with hardware in comparison to other spine procedures. Mc Lorinan et al. [29] suggested that *P. acnes* detected from spinal wounds by means of immunofluorescence microscopy, originates from patient skin and were due to wound contamination at the time of (primary) spinal surgery. The strong association between *P. acnes* and osteosynthesis material, relates directly to one of *P. acnes*' survival mechanisms: the ability to grow in biofilm [1,30]. Mastronardi et al. [31] emphasized the utmost importance of prevention of infection after spinal surgery and Walter et al. [9] proposed, when infections were suspected, establishment of immediate broad-spectrum antibiotic treatment during the post-surgical period, until accurate microbiological results are obtained. Clindamycin and vancomycin are considered the first line of treatment of *P. acnes* infection [32]. Rifampicin, a small molecule that can easily penetrate the exopolysaccharide matrix, is

considered the gold-standard treatment for infections related to medical devices [27], and is equally proposed, in combination with oral β -lactam for treatment of *P. acnes* prosthetic infections. Recent reports warn for an increasing resistance to Clindamycin [9] and Rifampicin [33]. Routine antimicrobial susceptibility testing should be performed and identification of *P. acnes* genotype could be helpful [33].

Interestingly, unlike other reports in literature [1], we did not observe an association between *P. acnes* and prosthesis. This might be explained that *P. acnes* very rarely infects beneath the pelvis, for which a firm dermatologist explanation remains lacking.

Patient-related risk factors are source of debate in literature. Several reports [9,24,34,35] note male sex to be independently associated with *P. acnes* infections, while others (such as in our study) denied the association with male sex or age [23]. The reason why *P. acnes* infections were less associated with immunodeficient patients than immunocompetent subjects remains unclear. Perhaps, the answer lies in a change of commensal populations in immunodeficient patients in favor of other organisms than *P. acnes*, but impact of the host immune system on microbial composition has yet to be fully explored [36].

Conclusion

In our institution of orthopaedic surgery and traumatology, *Propionibacterium acnes* is very rarely associated with infections. The results of this study confirm an association between *P. acnes* and bone and joint infections, particularly involving shoulder and spine regions. We identified the presence of hardware such as plates and spondylodesis as risk factors. Furthermore, immunodeficient patients or patients presenting high CRP levels were more likely to have infections due to other pathogens than *P. acnes*. Age and sex were found not to be correlated with *P. acnes*. Combination of these clinical variables should help attending physicians and surgeons to reinforce suspicion for *P. acnes* infection, and take appropriate measures when needed. Further research should shed light on *P. acnes*' tropism for plates and spondylodesis as opposed to prosthesis.

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