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ORIGINAL ARTICLE

Is *Cutibacterium acnes* early surgical site infection rate related to the duration of antibiotic prophylaxis in adolescent idiopathic scoliosis surgery?

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Abstract

Purpose *Cutibacterium acnes* (*C. acnes)* is a gram-positive anaerobic bacillus located in pilosebaceous glands, usually responsible for late postoperative surgical site infections (SSI). A recent study performed in our institution highlighted an unexpected emergence of *C. acnes* early SSI. One potential explanation was the change of the perioperative antibioprophylaxis (ATB) protocol, which switched from 48 h postoperative cefamandole to intraoperative only cefazoline. The aim of this study was therefore to investigate the influence of the ATB duration on the occurrence of *C. acnes* early SSI, by comparing the incidence rates during 3 consecutive ATB protocols.

Methods Between January 2007 and September 2017, all patients who underwent posterior fusion for AIS were retrospectively reviewed. Early *C. acnes* SSI were reported and compared between 3 periods, during which the ATB protocols were modified.

- January 2007–February 2012: Intraoperative Cefamandole continued 48 h (protocol 1)
- March 2012–August 2016: Single shot of intraoperative Cefazoline (protocol 2)
- September 2016–September 2017: Intraoperative Cefazoline continued 48 h (protocol 3).

Results Fifty-three early SSI (7.2%) were reported among the 732 posterior AIS fusions included. Global incidence of *C. acnes* infection was 2.9%. The incidence of *C. acnes* in early SSI increased from 0 to 4.9% between protocol 1 and 2, but was reduced to 1.7% with protocol 3.

Conclusions Early *C acnes* SSI can be explained by the difficulty to eradicate this pathogen with current skin preparation procedures and some Beta-lactam antibiotics tolerance. Longer duration antibioprophylaxis is preferable to prevent from early *C. acnes* SSI.

Keywords Adolescent idiopathic scoliosis · Surgical site infection · Antibiotic prophylaxis · *Cutibacterium acnes*

Introduction

Surgical site infection (SSI) is the most common complication after posterior fusion for adolescent idiopathic surgery (AIS), with incidence rates ranging from 1 to 7% [1–3]. *Staphylococcus aureus* (*S. aureus*) remains to date the main pathogen reported in early SSI (within 30 days postoperative), but a recent study has emphasized the non-negligible

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and underreported role of *Cutibacterium acnes* (*C. acnes*), found in 18% of SSI after pediatric scoliosis surgery [1–3].

Cutibacterium acnes (formely *Propionibacterium acnes*) is a commensal Gram-positive anaerobic bacillus, located in human skin with a predilection for pilosebaceous follicles of the back and the upper body [4, 5]. Historically considered as a contaminant when isolated from surgical wounds, it is now identified as a pathogen implicated in deep postoperative SSI, mostly reported in the orthopedic literature in late periprosthetic infections [6–8].

In a previous study, we reported the efficacy of preoperative staphylococcal nasal decontamination to reduce *Staphylococcus aureus (S aureus)* early SSI after AIS surgery [9]. At the same time, in 2012, the antioprophylaxis (ATB) protocol was shortened following the recommendation of our national anesthesiology society [10, 11]. The intra- and 48 h postoperative cefamandole was reduced to single shot intraoperative cephazoline. However, this new protocol led to an unexpected emergence of *C. acnes* early SSI. One hypothesis was that it was due to the reduction of the length of the perioperative ATB protocol. Indeed, in vitro tests have shown that *C. acnes* isolates were highly susceptible to most antibiotics, but that beta-lactams antibiotics were only bactericidal after 48 h of exposure at 2 times minimum inhibitory concentration (MIC) [12]. As a consequence, the ATB protocol was switched back to cefazolin 48 h postoperative in 2016. The aim of this study was therefore to investigate the influence of the ATB duration on the occurrence of *C. acnes* early SSI, by comparing the incident rates during 3 consecutive ATB protocols

Materials and methods

Patients

All patients who underwent primary posterior fusion for AIS between January 2007 and September 2017 were included, with a minimum 2-year follow-up. Patients with previous spinal surgery, or any past medical history affecting the risk of SSI (sickle cell disease, diabetes, corticotherapy) were excluded. Demographic and perioperative data were collected prospectively but retrospectively analyzed. Blood saving strategy (erythropoietin, tranexamic acid, cell saver) and operative techniques were not modified during the entire study period [13, 14]. Surgery was performed by one of the 2 senior spine surgeons of the department, consisting in posterior segmental spinal correction and fusion using hybrid constructs (lumbar pedicle screws and thoracic sublaminar bands) with CoCr rods [13–15]. Local autograft was used for fusion and the wound was always closed over 2 deep drains.

Preoperative management

All patients underwent preoperative skin preparation, consisting in 2 integral showers with povidone-iodine scrub (day − 1 and day 0). Surgery was postponed in case of significant acne. Preoperative staphylococcal nasal screening was introduced in January 2014. In case of swab culture positive for Meticillin-Sensitive *S.aureus* (*MSSA*), nasal and cutaneous decontamination were performed during 5 days preoperative.

Intraoperative management and antibiotic prophylaxis

Skin preparation of the surgical site was the same during the entire study period. It consisted on one povidone-iodine scrub followed by two scrubs with a 5% alcoholic povidone-iodine solute until drying. The surgical field was covered by an adhesive iodine-impregnated plastic drape.

Three distinct consecutive ATB protocols were used during the study period:

- From January 2007 to February 2012 (protocol 1): cefamandol 30 min before incision (40 mg/kg, maximal dose 1.5 g), with half-dose reinjected every 2 h during surgery), and continued for 48 h (20 mg/kg/8 h).
- From March 2012 to September 2016 (protocol 2): cefazolin 30 min before incision (50 mg/kg, maximal dose 2 g), with and half-dose reinjected every 4 h.
- From October 2016 to September 2017 (protocol 3): cefazolin 30 min before incision (50 mg/kg, maximal dose 2 g) with half-dose reinjected every 4 h, and continued for 48 h (25 mg/kg/8 h).

In cases of penicillin allergy or methicillin-resistant *S. aureus* (*MRSA*) isolated on nasal swab, clindamycin (10 mg/kg/6 h) or vancomycin (15 mg/kg/6H) were used with the same changes in duration over the 3 periods.

Postoperative care

Dressing was changed under sterile conditions with drains removal at day 2, and then left untouched until day 21. Patients were encouraged to stand erect with physiotherapists on the first day postoperative and discharged after 4 or 5 days to a rehabilitation center.

Diagnosis and management of early surgical site infections

Early SSI occurring within 30 days postoperatively were defined according to international guidelines: purulent scar discharge, fluctuating abscess or fever associated with swelling or leaking of the scar [16]. All suspected early SSI underwent surgical revision for debridement, irrigation with povidone-iodine and saline solution and deep drainage without implant removal. Multiple samplings (three to five) of the entire surgical field with deep soft tissues were sent for microbiology analyses. Probabilistic antibiotherapy was started intraoperatively after microbiological samplings, followed by an adapted treatment discussed in a multidisciplinary meeting for a total of 3 months.

Pathogens were identified for all deep samplings by using standard cultures.In case of negative cultures, 16S ARN gene amplification and sequencing were performed. SSI was confirmed if the micro-organism was isolated in at least 2 deep samples for commensal bacteria (such as *Coagulase Negative Staphylococcus (CoNS), Enterococcus faecalis, C. acnes*), or 1 deep sample for pathogens such as *S. aureus, P. aeruginosa or Enterobacteriacae.*

Antibiotic susceptibility tests were performed according to the CASFM guidelines [17]. Cefazolin minimal inhibitory concentration (MIC) was determined for all *C. acnes* isolates from positive deep cultures using E-tests method on MH-F Agar (Biomerieux®).

Statistical analysis

All continuous variables were expressed as mean ± standard deviation (SD) and percentages. Early SSI global incidence and rate of early *C. acnes* SSI were analyzed and compared between the 3 different periods. Unvaried analysis was performed with *Chi-2* test or *Fisher* test according to their normal distribution or not, whereas continue variables analysis was performed using *Student*'s *T* test. A $p < 0.05$ was considered significant.

Results

Patients and SSI

Seven hundred thirty-two AIS posterior fusions (83% female) were included. Mean age at surgery was 15.8 ± 1.8 years. Fifty-three early SSI (7.2%) occurred during the study period, at a mean follow-up of 18 ± 5 days after surgery. Surgical debridement was performed in all cases within 24 h after diagnosis. No surgical revision was needed. Early SSI was cured in all cases by the combination of surgery and antibiotics, and no recurrence of infection was reported at 2-year follow-up.

Microbiological results and evolution during the different ATB protocols

The distribution of the pathogens is reported in Table 1. *C. acnes* and *MSSA* were the 2 most frequent pathogens over the study period. The overall incidence of *C acnes* early SSI in the entire cohort was 2.9%, but *C.acnes* was responsible for 39.6% of the infections over the study period. Polymicrobial infections were reported in nine cases (17%).

Early SSI incidence rate was 6.6% during ATB protocol 1. A significant increase was observed with the shorter protocol 2 (8.5%, $p < 0.05$), but protocol 3 significantly reduced the early SSI rate to 4.2% (5 SSI out of 119 patients).

Incidence of early *C. acnes* SSI followed the same trend, with 0% (0 out of 226 patients) during protocol 1, a significant increase to 4.9% (19 out of 387 patients, $p < 0.05$) with protocol 2, followed by a significant decrease to 1.7% (2 out of 119 patients) ($p < 0.05$) during protocol 3 (Table 2).

C. acnes isolates

In 86% of the cases, *C. acnes* was isolated in more than 3 deep samples and identified in polymicrobial infection in four cases (19% of *C. acnes* SSI) (3 with *CoNS* and 1 with *Enterococcus faecalis*). All *C. acnes* isolates were sensitive to amoxicilline, cephalosporins, levofloxacin and rifampicine, and all but one were sensitive to clindamycine. The susceptibility to cefazolin of 14 *C. acnes* isolates was determined retrospectively. Cefazolin MIC

Table 1 Microbiological results for early surgical site infection after adolescent idiopathic scoliosis posterior fusion

	Number of cases	% of Infections
C. acnes	21	39.6
MSSA	22	41.5
Peptostreptococcus	5	9.4
CoNS	4	7.5
P. aeruginosa	3	5.7
Enterobacter cloacae	2	3.8
Enterococcus faecalis	2	3.8
Klebsielle pneumoniae	1	1.8
C. albicans	1	1.8

9 Polymicrobial infections

C. acnes: *Cutibacterium acnes*

MSSA: Methicillin sensitive *Staphylococcus aureus*

CoNS: Coagulase negative *Staphylococcus*

P. aeruginosa: *Pseudomonas aeruginosa*

C. albicans: *Candida albicans*

Table 2 Global and *Cutibacterium acnes* early surgical site infection after adolescent idiopathic scoliosis surgery during the 3 different ATB protocols

ATB protocol	Total AIS	Early SSI	Incidence of early SSI (%)	Early *C. acnes* SSI	Incidence of early *C. acnes* SSI (%)	% of early SSI due to *C. acnes*
Protocol 1	226	15	6.6	0	0	0
Protocol 2	387	33	8.5	19	4.9	57.6
Protocol 3	119	5	4.2	2	1.7	40.0
Total	732	53	7.2	21	2.9	39.6

ATB antibioprophylaxys, *SSI* surgical site infection, *C. acnes Cutibacterium acnes*

Protocol 1: 1st long ATB protocol: From January 2007 to February 2012

Protocol 2: Short ATB protocol: From March 2012 to August 2016

Protocol 3: 2nd long ATB protocol: From September 2016 to September 2017

raised between 0.094 and 0.5 ug/ml (median 0.19 µg/ml). All *C. acnes* isolates could be considered sensitive to cefazolin.

Discussion

Incidence and emergence of *C. acnes* in early spinal SSI

This study is the first to report *C. acnes* as a major agent in early SSI after posterior AIS fusion. Responsible for 40% of infections over the entire study period, its incidence reached 4.9% during the 2nd protocol period. *C. acnes* is a Gram + anaerobic bacillus mostly located in the pilosebaceous follicles of the upper trunk, which had been to date mostly described as a low-virulent pathogen responsible for late spinal or prosthetic infections [7, 18–20]. However, recent literature has pointed out the emergence of this pathogen in early SSI after spine surgery, which is still probably underestimated [1, 7, 21, 22]. *C. acnes* has the capacity to produce a biofilm on different biomaterial used in AIS surgery, including titanium, 48 h after bacterial inoculation [23]. Warner et al. found *C. acnes* responsible for 18% of SSI after pediatric spine surgery, with a global incidence of 0.6% over a 12-year period [1]. This is much lower than the 2.9% described in our more recent 10-years study. However, whether this increase is due to a commensal flora modification, to different identification methods or to different ATB protocols remains unclear. *C. acnes* is indeed difficult to detect in postoperative culture due to its slow growth, and prolonged incubation periods > 7 days may be required [7, 18, 24]. This could explain the underestimated *C. acnes* infection rate reported in the current literature [1].In the current study, bacteriological identification was positive for all cases of early SSI, so the actual *C. acnes* incidence rate can be considered accurate.

Influence of the ATB protocol length on *C. acnes* early SSI

The optimal length and type of ATB for AIS surgery remain unclear. The American Academy of Orthopaedic Surgeons guidelines suggest the use of cephalosporin, initiated 1 h before incision and continued for 24 h postoperatively [25].

In the current study, the duration of the ATB protocol significantly affected the occurrence rate of *C. acnes* early SSI (Table 2). No case of *C. acnes* was reported during protocol 1, before nasal screening and when 48 h of cefamandol were used, and the vast majority of identified germs at the time were *S Aureus* (responsible for 73% of the SSI during that period).

In 2010, the French society of anaesthesia and reanimation (SFAR) recommended to shorten the use of cefazolin for orthopedic surgery, with a single injection performed 30 min before incision, eventually associated to a second one if the surgical procedure lasted more than 4 h [10, 11]. These recommendations were based on a Cochrane database publication, focusing on proximal femoral and closed long bone fractures, which found no benefit of repeated cefazolin injections on deep SSI incidence [26]. Moreover, first generation cephalosporin (such as cefazolin) seems to be optimal for orthopedic ATB because of its efficient bone diffusion and bone concentration. Studies reported that cefazolin achieved the highest total peak level in bone tissue, reached 25 to 40 min after injection, with a peak concentration at 16 times the median minimal concentration inhibition (MIC) against *S. aureus* [27, 28].

For these reasons, our ATB protocol was modified in March 2012, but the change led to an unexpected significant increase in *C. acnes* early SSI (4.9%). The higher number of *C. acnes* infections was initially assigned to the efficacy of the nasal swab program, which reduced dramatically the incidence of *S. aureus* SSI [9] but the overall SSI incidence rate remained stable and the number of *C. acnes* SSI kept increasing. The reason protocol 3 was adopted in October 2016, with a step back to 48 h of cefazolin postoperatively,

was that some papers suggested that pharmacodynamics properties of betalactams against *C. acnes* were not optimal [12, 29].

In fact, several studies have determined cefazolin MIC from *C. acnes* samples isolated from positive deep cultures, and found a low mean value from 0.32 µg/ml to 0.094 µg/ml [24, 30]. However, in vitro studies have recently emphasized the betalactam tolerance of *C. acnes*, with a bactericidal effect only obtained after 48 h at 2 times MIC [12]. This finding was confirmed by Hall et al., who tested 6 *C. acnes* isolates for several antibiotics: 5 isolates were killed after 48 h of vancomycin (shorter time kill effect [10]), versus 1 with penicillin and surprisingly none of the isolates was killed with 48 h of cefazolin [29]. The tolerance of *C. acnes* to cefazolin, and the importance of contact duration in betalactam pharmacodynamics can therefore explain the significant increase in early *C. acnes* SSI when the shorter protocol 2 was adapted, but also the subsequent drop (1.7%) when the ATB protocol was extended again to 48 h (protocol 3).

Other perioperative measures to reduce *C. acnes* SSI

Another reason to explain the failure to eliminate *C. acnes* inoculation is the difficulty to eradicate the pathogen from the skin (deep derm) with current recommended surgical preparation [24, 31, 32]. Nandyala et al. obtained 23% positive tissue cultures from pediatric patients undergoing posterior spinal fusion after standard skin preparation, and *C. acnes* represented the most common organism (70%) [33]. Its presence was significantly associated with back acne and AIS fusion should therefore be postponed if the patient's skin status is not optimal.

Several prevention strategies have been suggested to reduce early *C. acnes* SSI, including dermatological consultation and treatment for skin acne prior to spine surgery, adequate skin preparation with either betadine or chlorhexidine solution, hemostasis, copious irrigation with saline containing antibiotic, use of postoperative drains and perioperative antibiotic prophylaxis, but the scientific evidence remains poor [18, 22, 25].

Limitations

This study has several limitations that need to be considered. First, it was retrospective and the duration of each ATB protocol periods was not consistent. However, data were collected prospectively and both perioperative anesthesiologic preparation and operative technique were similar along the entire study period Second, the cohort was historical and the 3 periods compared were consecutive, while a prospective randomized study with a control group would have provided better evidence. Operative time and estimated blood loss, which are important parameters regarding infection risk, were not specifically investigated in this study, but they have been previously reported [14, 34, 35]. However, the surgical technique remained unchanged during the entire study. Period and blood saving strategies were applied all over the 3 ATB periods. Last, multiple factors remain involved in the occurrence of postoperative SSI, and we are aware that the duration of the antibioprophylaxis can not be considered as the only parameter affecting SSI rates, so further studies should be performed to improve preventive strategies in spinal surgery.

This study reports *C. acnes* as a major agent in early SSI after AIS posterior fusion. The failure to eliminate this pathogen can be explained by (1) the difficulty to eradicate *C. acnes* from the surgical wound with current skin preparation, and (2) the *C. acnes* betalactam tolerance, with a killing effect only appearing after 48 h of antibiotics administration. ABP protocols using cephalosporins should therefore be extended to 2 days postoperative to optimize *C. acnes* early SSI prevention.

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Compliance with ethical standards

Conflict of interest Pr B. Ilharreborde reports personal fees and consulting for Zimmer Biomet, Medtronics and Implanet, outside the submitted work. The others authors have nothing to declare.

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