Proprionibacterium acnes in shoulder surgery

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Abstract

Proprionibacterium (*Cutibacterium*) *acnes* is the organism most commonly associated with deep infection after shoulder surgery, including shoulder arthroplasty. It is abundant in the sebaceous follicles of the axilla and skin around the shoulder girdle, being implicated in the pathology of acne. It is adapted to the environment of the hair follicle, where it secretes enzymes that digest sebum and provide nutrients. However in this location it is unaffected by skin preparation immediately prior to the skin incision and can therefore be carried into deeper layers Indeed, it is so commonly found in the deep tissues around the shoulder in cases with no suspected infection that the line between contaminant and pathogen can be extremely difficult to draw. To add to this, it is slow growing and culture in anaerobic conditions often does not yield a positive result until the second week of culture or later. An understanding of the organism and its impact on shoulder surgery is therefore crucial to those operating in this region.

Keywords *Cutibacterium acnes*; infection; *Proprionibacterium acnes*; revision arthroplasty; shoulder arthroplasty

Introduction

Proprionibacterium acnes is a Gram-positive facultative anaerobe that is part of the normal skin flora, but is most abundant in sebaceous glands and hair follicles. It is the most abundant organism on human skin and is named because of its proposed role in the pathogenesis of acne vulgaris and its ability to generate proprionic acid. However it can cause blepharitis and endophthalmitis after eye surgery and is implicated in a number of conditions (endocarditis, disc herniation, SAPHO syndrome to name a few) though its precise role is unclear and often implicated simply by the detection of organisms in affected patients. However, modern 'nextgeneration' sequencing techniques can detect its presence in virtually all samples of human tissue.[1] It is frequently found associated with infection after shoulder surgery but the precise role it plays in the interplay between host and infecting organisms is yet to be fully elucidated. Since it is the predominant organism found in a large proportion of infections after shoulder surgery much work is being done to minimize the risk of infection directly, in parallel with establishing the mechanisms that allow commensal to become virulent.

The organism

P. acnes (recently reclassified and therefore becoming known as *Cutibacterium acnes*) lives deep within the hair follicles and associated sebaceous glands where it secretes enzymes that digest sebum to provide nutrients. Pore blockage, hyperactive production of sebum or immune responses to the proteins produced by *P. acnes* are thought to produce overgrowth and inflammation that leads to acne. Once inflammation begins secondary colonization of the pore by *Staphylococcus* species can occur. However, even in healthy skin with no active inflammation there is a thriving population of this organism deep in the follicles, often several millimetres below the skin surface, where staphylococci and other potential pathogens are absent. Notably it will be shielded from skin preparation compounds in this deep location before surgery but will come into contact with the scalpel blade during the skin incision, affirming the practice of changing blades if using a scalpel for deeper dissection.

It is sensitive to a range of antibotics, those most frequently being used to treat infections caused by *P. acnes* being doxycycline, clindamycin, minocycline and erythromycin. Quinolones, cephalosporins, penicillins and others may also be active. However there is an increase in antibacterial resistance in Europe and North America, especially to the macrolides such as erythromycin and to the tetracyclines such as doxycycline and minocycline. It is also susceptible to topical antibacterial agents including benzoyl peroxide, triclosan and chlorhexidine. It is killed by ultraviolet light, hence the use of phototherapy to treat acne, and its photosensitivity is increased by administering aminolevulinic acid before exposure.

The density of *P. acnes* is not uniform across the skin surface and the bacterial load is increased where sebaceous glands are more developed. It was shown that *P. acnes* is more common in the skin of the shoulder than elsewhere, and more so in men than women.[2] It was identified in the capsule of the shoulder in patients undergoing primary shoulder replacement for osteoarthrosis[3] was most commonly seen in men (8% women and 73% men had positive cultures from the shoulder capsule at primary shoulder replacement), though recognized as a frequent contaminant.[4] Later it was shown to be detectable more commonly in the glenohumeral joint than in the subacromial space at routine arthroscopy. Questions have been raised, and remain only partly answered, as to its role in postoperative complications including infection.[5]

Detection

P. acnes can be cultured on a variety of media under anaerobic or microaerophilic conditions and no particular agent has demonstrated superiority for its detection in prosthetic joint infections. However the incubation period is longer than for many other potential pathogens and cultures should be continued for up to 14 days.[6]

Genetic sequencing of several strains of *P. acnes* opened up highly sensitive methods of detection as well as providing a deeper understanding of the properties of the organism implied from its genes. For example, proteomic investigations revealed a number of adhesins as bacterial products, and the capacity of different strains to produce a range of such molecules is linked to virulence. The most virulent are capable of producing biofilms whilst strains from healthy skin were poor biofilm formers.[7]

The recognition of the importance of biofilms in prosthesis-related infections preceded by some margin the recognition of *P. acnes* as an organism that could produce infection through the

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mode of biofilm. A biofilm is a sessile community of bacteria attached to a substrate or each other and embedded in a matrix of extracellular polymeric substances at least partly produced by the organisms. Organisms in a biofilm exhibit an altered phenotype compared to planktonic cells of the same bacterial species. The biofilm often has a complex network of channels through the extracellular matrix allowing the flow of nutrients and waste materials between deeper layers and the surface. Like all biofilm-related organisms, detection of *P. acnes* on explanted prostheses with suspected infection is facilitated by sonication of the implant to release the biofilm and its contained organisms. Centrifugation of the sonicate and culture of the sediment obtained further improves the likelihood of detecting organisms when present.

Next-generation sequencing techniques have been shown to be able to detect *P. acnes* DNA in almost all biopsy samples[1] demonstrating the care that has to be taken in the acquisition of samples and the assumptions made from positive tests using these techniques. This can make decisions about antibiotic treatment in the face of positive cultures even more tricky. Recently there have been positive reports on the use of α-defensin and synovial interleukin (IL)-6 to assist in the detection of significant infection at revision surgery.

The clinical problem

Although the boundary between infective agent and commensal is blurred, there is nevertheless a genuine and significant problem of *P. acnes* infection in shoulder surgery that is not seen elsewhere in orthopaedic surgery. *P. acnes* has been shown to be one of the most common causes of periprosthetic joint infection and implant loosening in shoulder arthroplasty[8] and is responsible for up to half of all cases of infected rotator cuff repair.[9] A large cohort study of more than half a million shoulder arthroscopies, in which the overall infection rate was only 0.25%, indicated that in addition to male sex, a history of steroid injections, chronic anaemia, malnutrition, morbid obesity and depression were independent risk factors for infection.[9] A study of more than 3000 all arthroscopic rotator cuff repairs at one institution revealed an infection rate of only 0.85% and the infecting organism most commonly identified were *Staph. epidermidis* (39%), *P. acnes* (29%) and *Staph. aureus* (7%). Given the observation that *P. acnes* may be an initiator of inflammation and local immune compromise, allowing secondary infection with species such as *Staphylococcus*, the importance of further research into the roles of *P. acnes* in shoulder infection is obvious.

Aside from overt infection, however, there is another potential manifestation of the organism that is poorly understood. That is, the painful stiff joint with absent radiological and often haematological evidence of infection after previous shoulder surgery. In arthroplasty this is the painful prosthesis with positive *P. acnes* cultures on open biopsy. Even less well understood is the painful, stiff shoulder after previous non-arthroplasty procedures. A study of 68 revision shoulder arthroscopy cases from a cohort of 1591 primary procedures, where the indication for revision was pain and stiffness, revealed that 29% had positive tissue cultures from biopsies and 80% of these were positive for *P. acnes*.[10]

Acute *Proprinibacterium acnes* infection

Acute infection of a shoulder arthroplasty is identified when there is purulence surrounding the implant, a sinus tract connecting the implant with the surface or histological evidence of inflammation of tissues surrounding the joint coupled with identification of the relevant organism on preoperative aspiration and/or intraoperative biopsies in at least two separate samples. *P. acnes* has been reported to cause acute infections manifesting in this way within 3 months of surgery in around 1% of shoulder arthroplasty cases, with raised inflammatory markers and radiological evidence of loosening[11] indistinguishable from other forms of such infection. Normally, after an operation such as arthroplasty, the inflammatory markers are raised in any event. The erythrocyte sedimentation rate (ESR) can take several weeks to return to normal levels but the C-reactive protein (CRP) normalizes within about 2 weeks and is a more useful early indicator. Treatment is along the lines described for acute purulent infection of the hip and knee, described elsewhere in this issue.

Similar acute presentations occur after open or arthroscopic non-arthroplasty procedures and the mainstay of surgical treatment is drainage, debridement and irrigation — the principles of management of orthopaedic infections including early consultation with colleagues in microbiology which will not be elaborated on further in this article. The principles of careful acquisition of samples, anaerobic culture and prolonged incubation of the culture for up to 14 days are essential if cases of infection caused by this organism are not to be treated empirically because of culture results stating 'No growth'.

Culture-positive revision shoulder replacement

The deep infection rate for shoulder arthroplasty is variously reported to be up to 4%. Treatment options include excision arthroplasty with or without fusion, antibiotic suppression, debridement with retention of the original prosthesis (changing liners as appropriate), exchange of the prosthesis (one-stage revision) or two-stage revision arthroplasty. The ideal management protocol has not been elucidated and we rely on case series of each management option. Antibiotic suppression may be considered for medically complex cases with organisms of low virulence, but has a failure rate of up to 50%.[12] Excision arthroplasty is successful in controlling infection, but leaves significant functional deficits. More often revision arthroplasty is the choice in managing infection. The principles are as described for lower limb arthroplasty with modifications to accommodate the possible differences in microbiological flora responsible in shoulder arthroplasty. At the moment reports on successful exchange revision in the face of an infected prosthesis are variable, with small case series describing high success rates but other authors reporting recurrence rates of up to 50%.[12] A systematic review suggested favourable outcomes in one-stage revision[13] but the message for now is that one-stage revision should only be considered in the context of research or audited practice by a multidisciplinary team including surgeons and microbiologists.

Revision with positive cultures obtained before surgery

In the case of revision with positive cultures for *P. acnes* (from biopsies and aspiration, with prolonged anaerobic culture as

described) two-stage revision is by far the commonest procedure performed. Stage 1 consists of thorough debridement of all potentially infected tissue and insertion of a cement spacer impregnated with antibiotics active against the causative organism. These can be fabricated by hand, by moulding cement into which antibiotics have been mixed onto a Steinman pin, or commercially available spacers can be used.

The aim of the spacer is to maintain soft tissue tension, induce the formation of a pseudocapsule that can be helpful in defining planes at revision, allow gentle physiotherapy to maintain range of movement and even to allow functional use between stages. It is supplemented with intravenous and/or oral antibiotics as discussed with the microbiology team. Such spacers should be left in situ until all signs and serum indicators of infection have normalised – a minimum of 6 weeks and sometimes significantly longer. In medically complex patients there are even reports of spacers being left indefinitely, and also reports of patients who were sufficiently happy with pain relief and function after spacer insertion that they declined a second stage. Another consideration is that after infection and debridement the rotator cuff is often stiff and scarred, if not incompetent, and revision to a reverse prosthesis may have to be considered in cases of cuff deficiency.

With negative cultures before surgery but positive perioperative samples

A problem that remains unsolved for now is management of the patient undergoing revision shoulder replacement for loosening in whom infection is not suspected, but after successful surgery tissue samples taken routinely at surgery grow *P. acnes*. Is this a commensal contaminating the specimens from the layer of sebaceous glands in the skin edge? Is it actually the organism responsible for the patients pain and stiffness that led to revision, a scenario shown to be the case for 56% of patients undergoing revision surgery in one series.[8]

Unexpected positive cultures were found in 107 patients over a 31-year period in one unit[14] and the outcome of these cases was identified. Unfortunately there was no protocol for management, with half receiving antibiotic treatment and half not. The problem was identified more in males, and *P. acnes* was the most common organism. In only 11 cases did an overt infection develop caused by the same organism unexpectedly identified in the biopsy. The general theme of recent publications is that unexpectedly positive cultures at revision surgery are associated with a low risk of overt infection requiring surgery, but higher than those who are culture-negative. Authors invariably report that identification of organisms on culture is followed by a period of antibiotic treatment, often of 6 weeks duration, with enhanced monitoring of inflammatory markers. No studies so far have suggested that positive biopsies should be followed by debridement or any form of routine revision procedure.

Minimizing risk

The general principles of maintaining sterility apply, ranging from theatre design through theatre discipline and the movement of personnel to gowns, gloves and the handling of equipment. This section assumes standard theatre operating procedures are followed and emphasizes only those areas that are particularly important in managing potential *P. acnes* infection. Even a simple soap and water shower at home, before departing to hospital for same-day surgery, reduces the colony count for both *Staphylococcus* and *P. acnes*. Showering with chlorhexidine soap, or following the shower with chlorhexidine wipes, reduces this even further. Shaving the axilla does not seem to make a difference, however. The bacterial count in the axilla after shaving actually seems to increase, so shaving is only recommended if the hair may interfere with visualization or skin closure.

There has been interest in using benzoyl peroxide topically in advance of shoulder surgery, as it is commonly used in dermatology to treat acne. It is able to penetrate the sebaceous glands after topical application, and bacterial resistance does not seem to develop. The bacterial load is significantly reduced if applied in the days leading up to surgery. Its positive effect in skin preparation[15] is yet to be shown to have any effect on clinical infection rates.

As *P. acnes* resides particularly in the sebaceous glands, often several mm below the skin surface, this reservoir is minimally affected by the skin preparation that takes place immediately before the surgical incision is made. The skin knife therefore passes through these glands and becomes contaminated. Although the exposed skin edge remains as a potential contaminant, this observation reinforces the need to follow basic principles including avoidance of using the skin knife to cut deeper layers, changing gloves before handling implants and avoiding contact between the cut skin edge and any prosthesis being inserted. Irrigation of the surgical field and wound edges with antiseptics sounds an attractive idea but there is no convincing evidence that it makes any difference to infection rates. The use of antibiotic-laden bone cement has recently been called into question in lower limb arthroplasty, but the only evidence in shoulder surgery so far is that it does seem to reduce the infection rate in reverse shoulder replacement, which may be a procedure sufficiently different from hip and knee replacement that lessons learned from the latter may not be extrapolatable.[16]

Conclusions

P. acnes is a commensal found abundantly in the sebaceous glands, which in turn are more numerous around the shoulder, and which can become a pathogen responsible for infections after shoulder surgery. It is one of the most frequent organisms found to be responsible for such infections more common even than *Staphylococcus* in many series. The risk of such infections is highest in middle-aged males and the bacterium can be difficult to detect, needing anaerobic culture of aspiration and biopsy specimens to be prolonged beyond 2 weeks. It is a biofilm-forming organism and can be difficult to eradicate, the most accepted form of treatment for infected arthroplasty being two-stage revision. Its habitat in the sebaceous glands means that contamination of the surgical field is extremely difficult to avoid during surgery, and tests relying on the detection of DNA are very frequently positive even in shoulders undergoing primary arthroplasty for osteoarthrosis. The significance of unexpectedly positive biopsy cultures at the time of revision shoulder arthroplasty is yet to be fully elucidated, though usually managed by a period of antibiotic treatment pending further research. ◆

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