Propionibacterium acnes: from Commensal to Opportunistic Biofilm-Associated Implant Pathogen

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SUMMARY

Propionibacterium acnes is known primarily as a skin commensal. However, it can present as an opportunistic pathogen via bacterial seeding to cause invasive infections such as implant-associated infections. These infections have gained more attention due to improved diagnostic procedures, such as sonication of explanted foreign materials and prolonged cultivation time of up to 14 days for periprosthetic biopsy specimens, and improved molecular methods, such as broad-range 16S rRNA gene PCR. Implant-associated infections caused by *P. acnes* are most often described for shoulder prosthetic joint infections as well as cerebrovascular shunt infections, fibrosis of breast implants, and infections of cardiovascular devices. *P. acnes* causes disease through a number of virulence factors, such as biofilm formation. *P. acnes* is highly susceptible to a wide range of antibiotics, including beta-lactams, quinolones, clindamycin, and rifampin, although resistance to clindamycin is increasing. Treatment requires a combination of surgery and a prolonged antibiotic treatment regimen to successfully eliminate the remaining bacteria. Most authors suggest a

course of 3 to 6 months of antibiotic treatment, including 2 to 6 weeks of intravenous treatment with a beta-lactam. While recently reported data showed a good efficacy of rifampin against *P. acnes* biofilms, prospective, randomized, controlled studies are needed to confirm evidence for combination treatment with rifampin, as has been performed for staphylococcal implant-associated infections.

INTRODUCTION

Propionibacterium acnes is a Gram-positive, facultative, anaerobic rod that is a major colonizer and inhabitant of the human skin along with *Staphylococcus*, *Corynebacterium*, *Streptococcus*, and *Pseudomonas* spp. Although often defined as a commensal

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(1), *P. acnes* is infrequently associated with invasive infections of the skin, soft tissue, cardiovascular system, or deep-organ tissues and is an important opportunistic pathogen causing implant-associated infections (2).

More than 100 years ago, *P. acnes* was first isolated from a patient with the chronic skin disease “acne vulgaris.” *P. acnes* was originally misclassified as a *Bacillus* species and then as a *Corynebacterium* species (3). However, in 1946, Douglas and Gunter were able to demonstrate that this microbial species was more closely related to members of the genus *Propionibacterium* (4), which ferment lactose into propionic acid under anaerobic conditions.

Acne vulgaris is a chronic skin disease of the pilosebaceous unit. There are four contributing factors for developing the disease: (i) inflammation caused by inflammatory mediators released into the skin, (ii) alteration of the keratinization process leading to comedone development, (iii) increased and altered sebum production under androgen control, and (iv) follicular colonization by *P. acnes* (5). The anaerobic and lipid-rich conditions within the pilosebaceous unit provide an optimal microenvironment for *P. acnes* growth (6), especially in cases where there is a blocked follicle. However, the role of *P. acnes* in acne vulgaris remains controversial, since it fails to fulfill all of Koch’s postulates, thereby allowing one to potentially question this bacterial species as the etiological agent (7). In particular, *P. acnes* is found in both acne-affected and normal hair follicles along with other skin commensals such as *Staphylococcus aureus* and *Malassezia* spp. Although present in healthy and diseased follicles, it may be a matter of the threshold number of bacterial cells that are required to cause disease. However, a recently published skin microbiome study by Fitz-Gibbon et al. observed no differences in the relative abundances of *P. acnes* in patients with and those without acne (8). This may be a reflection of the difficulty in determining relative or absolute quantities of skin bacteria (9). In addition, the study by Fitz-Gibbon et al. has been contrasted by a number of other studies that have shown an association between the quantity of *P. acnes* bacteria and acne vulgaris, but these associations were found only in a young population aged 10 to 14 years (10), in young subjects aged 11 to 20 years (11), and in infants (12).

Another property of acne vulgaris disease that brings into question the role of *P. acnes* as the etiological agent is that therapeutic options such as topical or systemic antimicrobial treatments to reduce the bacterial burden often show incomplete responses. Following treatment failure, there is a recurrence of inflammation. This recalcitrance to therapy may be an indication that *P. acnes* is not the lone player in the pathogenesis of this disease, since the particular antibiotic therapy may not be effective against other bacterial species (13). However, the failure of antibiotic therapy has been associated with the emergence of antibiotic resistance in clinical isolates from these patients (14, 15). Treatment failure may also be the result of biofilm-mediated tolerance. Recent studies propose that biofilm formation in *P. acnes* might play a significant role in the chronic course of acne vulgaris (16–18). The direct visualization of *P. acnes* with tissue-invasive patterns and macrocolonies on the follicle wall by fluorescence *in situ* hybridization (FISH) and immunofluorescence microscopy (IFM) strengthens the theory of biofilm pathogenesis (19), as defined by Parsek and Singh (20). In addition, decreased antimicrobial susceptibility and the chronic character of this disease support the idea that *P. acnes* exists in a biofilm mode of growth.

While the role of *P. acnes* biofilms in acne vulgaris is still somewhat controversial, the transition of *P. acnes* as a commensal to an opportunistic pathogen in implant-associated infections and the role of biofilms in pathogenesis have been widely accepted (21, 22). The numbers of these infections are increasing, likely due to improved diagnostic modalities, such as sonication of explanted foreign materials and prolonged cultivation time of periprosthetic tissue biopsy specimens for up to 14 days, and improved molecular methods, such as broad-range 16S rRNA gene PCR. It is now recognized that *P. acnes* is the most frequently isolated pathogen in prosthetic shoulder joint infections (23–27) and is also an important pathogen in cerebrovascular infections (28–31), fibrosis of breast implants (32–34), and infections of cardiovascular devices (35–37). In a descriptive study of 92 patients with invasive infection caused by *P. acnes*, Brook and Frazier noted that 29 (32%) had an implant as a potential predisposing condition (38). In view of the growing population undergoing implantation of foreign materials, we review the pathogenicity and clinical and microbiological relevance of *P. acnes* as the cause of implant-associated infections and provide an overview of the transition of the bacterial species *P. acnes* from a common commensal to an opportunistic pathogen in implant-associated infections.

MICROBIOLOGY

Microbiota

P. acnes is an aerotolerant, anaerobic, Gram-positive, non-spore-forming, pleomorphic rod belonging to the phylum *Actinobacteria*, class *Propionibacteriales* (39). This bacterial species is part of the normal microbiota of the skin, oral cavity, and gastrointestinal and genitourinary tracts (Fig. 1) (40) and is usually not pathogenic. Other cutaneous *Propionibacterium* species include *P. avidum*, *P. granulosum*, *P. lymphophilum*, *P. propionicum* and dairy or so-called “classical” species such as *P. freudenreichii*, *P. jensenii*, *P. thoenii*, and *P. acidipropionici*, which are used industrially for the production of Swiss cheese and propionic acid (41). *P. acnes* can be cultivated on different media, such as blood, brucella, chocolate, or brain heart infusion agar, under anaerobic-to-microaerophilic conditions (42). No single particular medium seems to be superior for the detection of *P. acnes* in prosthetic joint infections (PJIs) (43). Colonies on blood agar are 1 to 2 mm in diameter, typically glistening, circular, and opaque (44). Most strains are catalase and indole positive (convert the amino acid tryptophan into indole) in the absence of glucose.

P. acnes grows better at a pH range of 6.0 to 7.0 than in a more acidic or alkaline milieu (45). In blood cultures, *P. acnes* grows better in anaerobic bottles but is also able to grow in aerobic bottles because of the anaerobic microenvironment that develops at the bottom of nonshaken bottles (46). The optimal temperature for growth is between 30°C and 37°C (47). To distinguish between contamination of the skin and bloodstream infection, more than one blood culture sample has to be positive with the same isolate to consider this commensal the etiologic agent of infection. The mean times to detection of growth of *Propionibacterium* species in blood cultures are 6.4 days in anaerobic bottles and 6.1 days in aerobic bottles (range, 2 days to 15 days) (46). Tissue cultures need more time until growth occurs and should be incubated for 10 to 14 days (48–50).

FIG 1 Relative abundances of *Propionibacterium* species in different skin areas determined by 16S rRNA gene sequence analysis of 10 individuals. Blue, sebaceous gland; red, dry areas; green, moist areas. +++, relative abundance of >50%; ++, relative abundance of ≥5 to ≤50%; +/-, relative abundance of <5%. (Adapted [estimated] from reference 40 with permission from AAAS.)

Microbiome Studies

P. acnes colonizes primarily sebaceous glands and hair follicles of human skin, but it may also be found in the mouth, nares, genitourinary tract, and large intestine. In 2009, Patel et al. described semiquantitative cultures of *P. acnes* and *Staphylococcus* species from hip, knee, or shoulder skin areas in order to define the bacterial prevalence and burden. They found that *P. acnes* colonizes the shoulder more frequently than hip and knee and that men have a higher bacterial burden than women (51). These results are in accord with the clinical observation that *P. acnes* is more commonly isolated in shoulder than hip and knee PJIs (52). In that same year, Grice et al. studied the human skin microbiome of 10 patients by using 16S rRNA gene phylotyping and found 19 bacterial phyla. The most common sequences belonged to the *Actinobacteria* (51.8%), *Firmicutes* (24.4%), *Proteobacteria* (16.5%), and *Bacteroidetes* (6.3%). The three genera most commonly identified accounted for >62% of the sequences: propionibacteria (23%; *Actinobacteria*), corynebacteria (22.8%; *Actinobacteria*), and staphylococci (16.8%; *Firmicutes*) (40). Propionibacteria predominated in sebaceous gland-rich sites such as face, scalp, chest, and back (Fig. 1) but were also present at dry and moist skin sites such as buttocks, forearm, inner elbow, and umbilicus (40, 42).

Phylogenetic Studies

In 2004, the whole genome of *P. acnes* was sequenced by Brüggemann et al. (53). Subsequently, *P. acnes* strains from patients with various infections such as acne vulgaris, ophthalmic-related infections, soft tissue infections, surgical wound and blood infections, and dental infections were divided into three different divisions known as types I, II, and III based on nucleotide sequencing of the

tly (putative hemolysin) and *recA* (repair and maintenance of DNA) genes (54, 55). *recA* sequence analysis also identified a sub-cluster of strains within type I (types IA and IB) (56). Multilocus sequence typing (MLST) with either seven (57) or nine (58) housekeeping genes confirmed these four highly distinct evolutionary lineages (types IA, IB, II, and III) (<http://pubmlst.org/pacnes/>), which show differences in virulence determinants and inflammatory properties (54–57, 59, 60).

By using MLST, McDowell et al. (57) identified 37 sequence types (STs) in a collection of strains from diverse sources. ST6 (lineage IA) and ST10 (lineage IB1) were most frequently found (64% of all samples). ST6 was associated with acne vulgaris, while ST10 strains were isolated from a range of sources, including implant-associated infections. By using an expanded eight-gene MLST scheme (six housekeeping genes and two putative virulence genes, hemolysin and Christie-Atkins-Munch-Petersen [CAMP] factor homologue [*camp2*] (61), those researchers were able to distinguish 91 STs. Acne vulgaris seems to be associated predominantly with type IA1, and in contrast, types IB and II were more frequently recovered from patients with soft tissue- and medical device-related infections (61, 62). A new phylogenetic lineage (type IC cluster) of an antibiotic-resistant *P. acnes* strain from a patient with acne vulgaris was described in 2012 (63). In order to reduce the time and expense of the MLST method, McDowell et al. reported a four-gene MLST scheme (two putative virulence factors, *tly* and *comp2*, and two housekeeping genes, *arcE* and *guaA*) that still provided valuable data for genetic analysis (64).

Besides MLST, other methods for strain classification are ribosomal or whole-genome sequencing. In 2013, Fitz-Gibbon et al. reported a study in which they sequenced the 16S rRNA genes of *P.*

P. acnes strains from acne patients and healthy individuals (8). Of the 10 most common strain types, 6 were found more often in acne patients. Subsequently, they selected 66 *P. acnes* isolates from seven major and two rare ribotypes and sequenced and assembled the whole genomes. Following phylogenetic tree construction using single nucleotide polymorphisms of these 66 strains (as well as 5 other *P. acnes* genomes publicly available), they found that those genomes from the same ribotypes clustered together. Therefore, ribotyping was shown to be a reliable marker for determining the lineage of *P. acnes* strains. Also, the strains able to cause disease usually had a predictable complement of virulence factors within their genome, allowing future prevention or treatment studies to target these gene products.

PATHOGENESIS

P. acnes produces a number of putative virulence factors and also causes disease by bacterial seeding, modification and manipulation of the host immune response, and biofilm formation. However, there are relative few studies of this organism compared to studies of other bacterial species, since its pathogenic potential has been recognized only recently. Therefore, the significance of many putative virulence factors and strategies in implant-associated infections can only be extrapolated from closely related species until a more complete understanding of this opportunistic pathogen is attained.

Virulence Factors

The sequencing of a first *P. acnes* isolate (KPA171202, a type IB strain recovered from skin) in 2004 (53) led to a better understanding of a number of putative virulence factors involved in host tissue-degrading activities, cell adhesion, inflammation, and slime/capsular polysaccharide biosynthesis. These factors included host tissue-degrading enzymes such as lipases/esterases, hyaluronate lyase (degrades hyaluronan, a constituent of the extracellular matrix of connective tissue), endoglycoceramidas, four sialidases, and various extracellular peptidases. These enzymes may contribute to nutrient acquisition and immunoavoidance and may aid in bacterial seeding.

Within the *P. acnes* genome, five genes with approximately 32% sequence homology to the cohemolytic CAMP factor of *Streptococcus agalactiae* were found (65). This factor is known to be able to bind to immunoglobulin G and M classes and act as a pore-forming toxin (56). CAMP also has cohemolytic activity with sphingomyelinase, which can confer cytotoxicity to keratinocytes and macrophages (66), enhancing virulence by degrading and invading host cells. Therefore, these CAMP-associated actions could also be responsible for the hemolysis seen in *P. acnes*, where it is synergistically intensified similarly to the classical CAMP reaction (67). Some *P. acnes* strains have beta-hemolytic activity, causing complete lysis of red blood cells, which may be related to the *tly* gene (54). The genome sequence also encodes other factors with pathogenic potential (e.g., proteins containing signals for surface localization and attachment to the cell wall) predicted to be involved in cell adherence and host interaction.

In addition to strain KPA171202, four strains belonging to different phylotypes of *P. acnes* (strains 266, SK137, SK187, and J139) were also sequenced, and a number of genes contained within the genomes showed homology to demonstrated virulence factors in closely related species (68). However, island-like genomic regions encoding putative virulence- and fitness-associated traits differed

between phylotypes. In particular, there were two loci on a linear plasmid in the acne-associated strains but not in healthy skin-associated strains: a tight adhesion (Tad) locus and a Sag gene cluster on locus 2 that contributes to hemolytic activity in pathogens (8). In addition to these genomic islands, a potential major genetic mechanism for variable expression in *P. acnes* is slipped-strand mispairing (59). Brzuszkiewicz et al. noted small differences by point mutation or phase variation that could affect the expression of adhesins (68). The results of this study may explain the differences between *P. acnes* as a commensal and as an opportunistic pathogen. However, further confirmatory studies assessing their virulence properties in appropriate animal models are needed to confirm their role in pathogenesis.

In addition to genomic studies, Holland et al. used *in vitro* proteomic investigations to identify approximately 20 proteins that were secreted in the mid-exponential growth phase of *P. acnes*. Most of the proteins had obvious activities within the host (glycoside hydrolases, esterases, lipases, and proteases). Other secreted proteins were CAMP factors, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), putative adhesins, and several hypothetical proteins that may play a role in host tissue inflammation (69).

Biofilm formation is one of the major virulence properties of *P. acnes* implant-associated infections and is apparently independent of the phylotype of *P. acnes*. Phase variation that affects the expression of adhesins (e.g., dermatan-sulfate adhesins PPA2127 and PPA2210) seems to be a major factor that explains strain differences (68, 70). In 2009, Holmberg et al. reported data showing that most of the invasive *P. acnes* isolates with different phylotypes tested were able to form biofilms, while strains from healthy skin were poor biofilm formers (70). Biofilm formation as an important virulence factor is discussed in greater detail below.

Bacterial Seeding

P. acnes has the ability to adhere to human skin and is most often found in sebaceous sites on the face, scalp, chest (axilla and sternum), and back as a commensal (40). On healthy skin, this microbial species normally does not invade to cause deep tissue infection. However, *P. acnes* can cause deep infections by seeding intraoperatively due to insufficient antisepsis and introduction during surgical incision (71). Antisepsis during surgery is short-lived, and bacteria can recolonize wound edges within 30 to 180 min after the antiseptic treatment of a patient, thereby providing an opportunity for *P. acnes* to seed the wound bed and implant (72). Therefore, it is understandable that a major risk factor for PJI is surgical operations in areas with a high concentration of sebaceous glands colonized by *P. acnes* (e.g., shoulder) (51). However, the source of *P. acnes* contamination may also be exogenous skin microbiota (surgical health care worker) or hematogenous seeding via the bloodstream after insertion of a medical device (73, 74). Once seeded, the microbe must travel to the implant in what has been termed “the race for the surface” by Gristina et al., which describes the process of successful bacterial adhesion with initial nonspecific adhesion facilitated by van der Waals forces, acid-base and electrostatic interactions followed by irreversible adhesion through specific binding to the biomaterial (71, 75).

Recognition by the Host Immune System and Immune Response

The innate immune response first recognizes *P. acnes* by antigen-presenting cells (APCs) through the binding of host pattern

recognition receptors. In the epidermis of acne lesions, the expression levels of Toll-like receptor 2 (TLR-2) and, to a lesser degree, Toll-like receptor 4 (TLR-4) are increased by keratinocytes (76). By using cell culture models and immunohistochemistry, Kim et al. showed that *P. acnes* triggers an inflammatory cytokine response in macrophages by the activation of TLR-2 (77). The ability of *P. acnes* to activate both TLR-2 and -4 might be explained by the distinct composition of peptidoglycan in their cell wall compared to other Gram-positive bacteria (78). Activation leads to the release of proinflammatory cytokines (interleukin-1 β , -8, and -12) and tumor necrosis factor alpha (TNF- α) by immune cells (keratinocytes and monocytes), thereby modulating the host immune response. An inflammatory response is also induced with the secretion of lipases and proteases, such as MMP-9 (protein of the matrix metalloproteinase family involved in the breakdown of extracellular matrix), by keratinocytes (79).

In addition to TLR-2 and TLR-4, priming of the host immune response in mice through the intravenous administration of killed *P. acnes* led to a strong immunomodulatory response that was able to stimulate macrophages via the intracellular receptor TLR-9 (80, 81), which may be important for the induction of gamma interferon (IFN- γ). Further studies need to be performed in order to determine the relative importance of TLR-9 in the pathogenesis of acne or implant-associated infections.

In order to mimic clinical acne lesions, a model that uses a tissue chamber integrated with a dermis-based cell-trapped system was developed (82). Human sebocyte cell lines were grown on this system, which was then implanted into mice. *P. acnes* was injected into the chamber, and the host immune response was monitored. Levels of neutrophils, macrophages, and the proinflammatory cytokine macrophage inflammatory protein 2 (MIP-2) were elevated 3 days after *P. acnes* injection. That study also found that both host proteins (fibrinogen, S100A9, and the serine protease inhibitor A3K) and *P. acnes* proteins (putative peroxiredoxin and proline iminopeptidase) were up- or downregulated after *P. acnes* injections (82).

Besides the innate immune response, the host adaptive immune response with B cell- and T cell-mediated pathways, as well as complement activation (classical and alternative) to promote neutrophil chemotaxis, is important in acne vulgaris (79, 83, 84). In patients with severe acne vulgaris, total IgG and in particular IgG3 levels might be elevated (79, 85, 86). *P. acnes* can escape the immune response by resisting phagocytosis or surviving inside macrophages for up to 8 months under anaerobic conditions *in vitro* (87–89), which may play a role for the development of *P. acnes*-associated inflammatory diseases. However, persistent intracellular survival in clinical situations has yet to be demonstrated. Also, persistence can be readily explained by other virulence strategies of persistence that are well documented, such as biofilm formation.

BIOFILM

P. acnes can act as an opportunistic pathogen causing invasive and chronic implant infections through a biofilm mode of growth. A biofilm is defined as a sessile community of microbial cells that (i) are attached to a substratum, interface, or each other; (ii) are embedded in a matrix of (at least partially self-produced) extracellular polymeric substances; and (iii) exhibit an altered phenotype with regard to growth, gene expression, and protein production compared to planktonic bacterial cells (90). Dunne summarized

the basic ingredients of a biofilm as “microbes, glycocalyx, and surface” (91). The biofilm matrix may be composed of endogenously and exogenously produced polysaccharides, protein, and/or extracellular DNA, in proportions based on the biofilm growth environment and the bacterial genera, species, and strains involved (90). The organized biofilm communities, which can range from a single cell to a thick multicellular layer, have structural and functional heterogeneity (92). The different structures are dependent on localized environmental conditions such as nutrition, waste, gas, and space limitations (91). There is often a complex channel network that flows through the biofilm to provide nutrients to deeper regions.

Biofilm research has focused on a number of other bacterial species besides *P. acnes*, so general knowledge about pathogenesis in biofilm-associated infections is often extrapolated from these microorganisms. In the presence of an implant, the host rapidly coats the device with extracellular matrix proteins, termed a conditioning layer. Subsequently, bacteria rapidly adhere to these implant-coated proteins, and granulocytes may fail to eliminate the pathogen (“the race for the surface”) (75). This is explained by an impaired ingestion rate, low bactericidal activity, and impaired superoxide production of granulocytes surrounding the implant (93, 94). In 2008, Kristian et al. showed that once embedded in a biofilm, *Staphylococcus epidermidis* was killed less efficiently by neutrophil granulocytes and induced more of the complement C3a than planktonic cells (95). This impaired neutrophil-mediated killing has also been seen in *S. aureus* and *Pseudomonas aeruginosa* biofilms (96–102). Since biofilm microorganisms have much greater resistance to antimicrobial killing than do planktonic bacteria (103), implant-associated infections are more difficult to eradicate and generally require both antibiotic and surgical treatment (94, 104).

In Vitro Studies

To study *P. acnes* biofilm formation, *in vitro* biofilm growth experiments have been performed by using microtiter plates (17, 70), glass beads (105), or different biomaterials, including titanium, steel, and silicone (21, 22), as attachment surfaces. These studies showed that *P. acnes* readily forms biofilms on all these surfaces. In Fig. 2 and 3, we show scanning electron microscopy (SEM) images of young *P. acnes* biofilms on glass beads and on a stainless steel pin (both hydrophilic materials). The images revealed *P. acnes* cells embedded within an exopolymeric matrix that appears similar to the polysaccharide intercellular adhesion (PIA) biofilms of staphylococci (106, 107). *In vitro*, a mature *P. acnes* biofilm is first seen at between 18 and 96 h after bacterial inoculation (22, 108), depending on the growth medium and initial bacterial inoculum (70). The presence of plasma also affects *P. acnes* by inhibiting biofilm formation (70). Adherence and biofilm formation are also dependent upon the surface roughness of the biomaterial (108). Qi et al. showed that *P. acnes* adhered best on frosted glass, with the roughest surface, followed by polyethylene and stainless steel, with the smoothest surface. In addition, several studies confirmed that sessile *P. acnes* cells are less susceptible to antimicrobial agents than their planktonic counterparts (17, 22, 105). While these *in vitro* studies were important in studying *P. acnes* biofilm formation properties, the *in vivo* relevance of these microbial communities was found only recently by Tunney et al. (109). They were able to demonstrate the presence of biofilm clumps of *P. acnes* attached to infected and surgically removed hip

FIG 2 Scanning electron micrographs of a *P. acnes* strain ATCC 11827 biofilm on solid soda lime glass beads (Walter Stern Inc., Port Washington, NY), incubated with *P. acnes* for 2 days anaerobically at 37°C under static conditions (magnifications, $\times 2,000$ [A] and $\times 20,000$ [B]; beam accelerating voltage, 1 kV; working distance, 3 mm) (Zeiss Supra 55VP field emission scanning electron microscope).

arthroplasties by using confocal laser immunofluorescence microscopy (109). From these data, it is clear that *P. acnes* can form biofilms *in vitro*, *in vivo*, and on multiple surfaces and that these *P. acnes* biofilms display an increased tolerance to antimicrobial agents.

Although it is known that *P. acnes* forms biofilm on different biomaterials, detailed mechanisms and steps in biofilm formation

remain to be fully elucidated. Binding of extracellular matrix and plasma proteins, like fibronectin (Fn), laminin, and fibrinogen, may be an initial step of infection in association with foreign materials like those seen in staphylococcal biofilms (110). In particular, Yu et al. reported that fibronectin binding protein is an important surface adhesin but that other adhesins might play an important role as well (111). *P. acnes* also produces a lipoglycan-

FIG 3 Scanning electron micrographs of a *P. acnes* strain ATCC 11827 biofilm on a biofilm-coated 0.25-mm-diameter stainless steel insect pin, incubated with *P. acnes* for 2 days anaerobically at 37°C under static conditions (magnifications, $\times 371$ [A], $\times 352$ [B], and $\times 33,800$ [C]; beam accelerating voltage, 1 kV; working distance, 5 mm) (Zeiss Supra 55VP field emission scanning electron microscope).

based cell envelope that may also be important for adherence to skin tissue and for biofilm formation (112). In addition, the increased lipase activity in supernatants derived from *P. acnes* biofilms attracts neutrophils, and these host immune cells often suffer from frustrated phagocytosis, thereby lysing and adding to the exopolymeric substances of the biofilm (113). Lastly, three separate clusters of genes in the *P. acnes* genome are known to play roles in biofilm matrix formation in other microbial species. The clusters encode UDP-*N*-acetyl-D-mannoseaminuronate dehydrogenase, UDP-*N*-acetylglucosamine-2-epimerase, mannose-1-phosphate guanylttransferase, ExoA (succinoglycan biosynthesis protein), and various glycosyltransferases (53, 65).

Animal Models

To date, animal models of implant-associated infections with *P. acnes* are rare and have been performed only with a subcutaneous tissue cage model in guinea pigs (93, 105) and with hematogenous infection of a total knee arthroplasty in rabbits (114). In the latter study, the authors proved that *P. acnes* was able to cause PJIs by hematogenous seeding in 50% of the animals. All of the infected animals showed elevated levels of antibodies against *P. acnes*, demonstrating an active but ineffective adaptive immune response to infection. Presently, there is no implant-associated animal model of *P. acnes* infection in mice, but due to the decreased expense, ease in handling, and availability of genetic knockout strains, a convenient working bone-associated implant model in mice would be of interest.

CLINICAL PRESENTATION

Implant-associated infections are an enormous medical and economic problem because of the increased use of implants and an aging population (115). In the past 15 years, the emerging role of *P. acnes* in implant-associated infections has gained more attention due to improved diagnostics, such as sonication of explanted foreign material (27, 116–118), prolonged cultivation time of peri-implant biopsy specimens (43, 48, 49), and broad-range 16S rRNA gene PCR as a molecular method (109, 119, 120). Invasive infections with *P. acnes* most often manifest themselves as infections of indwelling medical devices (Fig. 4 and 5), but *P. acnes* is also responsible for a number of other chronic infections, such as periodontitis, endodontic infections, endophthalmitis/keratitis, chronic rhinosinusitis, prostatitis, and folliculitis associated or not with acne vulgaris (Table 1). While the major focus of the present review is on implant-associated infections with *P. acnes*, a clinical overview of the most common biofilm-mediated infections (prosthetic joint infections, breast fibrosis, cardiovascular device-related infections, and spinal osteomyelitis) is also presented.

Prosthetic Joint Infections

A periprosthetic joint infection is clinically and microbiologically defined by (i) the presence of a sinus tract that communicates with the prosthesis, (ii) the presence of acute inflammation seen upon histopathological examination of periprosthetic tissue at the time of surgical debridement or prosthesis removal, (iii) the presence of purulence surrounding the prosthesis, and (iv) two or more intraoperative cultures or a combination of preoperative aspiration and intraoperative cultures that result in the detection of the same microorganism (121). Among prosthetic joint infections, *P. acnes* is the dominant pathogen found after shoulder arthroplasty, with a general infection rate of between 0.9 and 1.9% after primary

FIG 4 Left shoulder PJI with abscess formation in an 82-year-old woman 3 months after primary shoulder arthroplasty. Shown is clinical presentation (A and B) with sudden swelling and pain above left acromioclavicular joint without radiological signs of osteolysis or loosening of the implant (C and D) but with a 2.8- by 1-cm large fluid collection periarticular (E) (A, acromion; C, clavicle). *P. acnes* was cultivated in 2 of 2 joint aspirates, 1 of 3 tissue biopsy specimens, and sonication fluid of the mobile part of the implant (>500 CFU/ml). (Courtesy of M. Clauss, Liestal, Switzerland.)

implantation (23, 25, 52, 122–127). Infections first present with pain and stiffness of the shoulder, followed by local swelling or localized redness (122). Wang et al. described 17 shoulder PJIs caused by *P. acnes*, for which the time to infection after index surgery was <3 months (122). They found that inflammatory markers (erythrocyte sedimentation rate and C-reactive protein level) are elevated in most patients. Imaging studies such as X ray or computed tomography often showed joint subluxation or loosening, and joint ultrasound detected effusion in 24% of cases.

Pottinger et al. retrospectively examined potential risk factors

FIG 5 Pacemaker endocarditis 15 years after pacemaker revision surgery in a 58-year-old man. Shown are a large vegetation (3.5 by 5 cm) on the pacemaker lead (A) and an echogenic mass (EM) in the right ventricle (RV) seen by transthoracic echocardiography (B and C). *P. acnes* endocarditis was diagnosed by conventional tissue culture and broad-spectrum PCR of the vegetation around the pacemaker lead. RA, right atrium. Blue-green arrows show pacemaker leads in the cross section. (Courtesy of C. Starck, Zurich, Switzerland.)

for shoulder PJI with *P. acnes* and found that intraoperatively observed cloudy synovial fluid, gender (increased risk for males), and humeral osteolysis were all associated with at least a 6-fold-increased likelihood of obtaining a positive *P. acnes* culture (128).

Humeral loosening, glenoid wear, and membrane formation were associated with an increased likelihood of about 300% (128). Wang et al. demonstrated that male patients suffered from shoulder PJI caused by *P. acnes* more frequently than females but did not have an explanation for that finding (122).

Breast Fibrosis

Breast implants are used for reconstruction after mastectomy due to breast cancer and for cosmetic breast augmentation. Capsular contracture is a known local complication and is reported in 5.2% to 30% of patients (129, 130). A recent study found that the implant placement, surface, and sizes; the incision site; hematoma or seroma development; and surgical bra impact the incidence significantly (129). Contracture is classified according to the Baker system (grade I, breast absolutely natural; grade II, minimum contracture; grade III, moderate contracture; grade IV, severe contracture). It is well established that *P. acnes* has a role in subclinical infection in capsular contracture (33, 34). Del Pozo found that 33% of breast implants removed due to capsular contraction had >20 CFU bacteria/10 ml sonication fluid. They isolated mainly *Propionibacterium* spp., coagulase-negative staphylococci, and *Corynebacterium* species (34). Rieger et al. showed that the use of sonication allowed the detection of bacteria in 41% of 22 removed breast implants with Baker capsular contracture grades III and IV (32). Also, positive bacterial culture following sonication of the breast implant was significantly correlated with the degree of capsular contracture ($P < 0.001$), and the most frequently isolated organisms were *P. acnes* and coagulase-negative staphylococci (33).

Cardiovascular Device-Related Infections

P. acnes causes several cardiovascular device-related infections, such as prosthetic valve endocarditis and pacemaker and cardiac implantable cardioverter-defibrillator (ICD) infections. Infections can be divided into local infections (pocket infections) or

TABLE 1 Common diseases associated with *P. acnes*

Disease	Reference(s)
Indwelling medical device infection	
Prosthetic joint infection (particularly shoulder prosthesis)	23, 25, 50, 52, 116, 122, 124, 128, 166, 205–207
Orthopedic devices	207, 208
Cerebrovascular devices (cerebrospinal fluid shunts or external ventricular drainages)	28, 29, 146, 209–215
Postoperative craniotomy infections	146
Breast implants	32–34
Cardiovascular devices (e.g., pacemakers, ICDs, mechanical or biological heart valves, vascular grafts)	35, 74, 146
Endophthalmitis after implantation of a lens	146
Peritoneal catheters	216
Spine osteomyelitis with or without an implant	135, 138, 140, 146, 188
Endodontic infections	217–219
Periodontitis	220–222
Folliculitis associated or not with acne vulgaris	16, 18, 79, 223.
Prostatitis, prostate cancer	19, 160, 224–226
Endophthalmitis/keratitis	227, 228
Chronic rhinosinusitis	229

device-related bloodstream infections, including device-related endocarditis (35, 38, 73, 74, 131, 132). Endocarditis caused by *P. acnes* has been associated with both native and prosthetic valves but more often develops on valve prostheses, most commonly on the aortic valve (46, 133). A review of the literature showed that symptoms of endocarditis were often subtle due to the low virulence and slow growth of *P. acnes* (73, 74). This makes a proper diagnosis difficult, especially because *P. acnes* found in blood cultures can also be interpreted as a contaminant. One study by Park et al. examined 522 patients with *P. acnes* bacteremia, only 18 (3.5%) of whom had clinically significant bacteremia (134). The mortality rate is relatively high (15 to 27%) due to major valvular and perivalvular destruction associated with a delayed diagnosis of disease (74, 133).

Spinal Osteomyelitis

Spinal osteomyelitis (also termed vertebral osteomyelitis, spondylodiscitis, septic discitis, or disc space infection) is an infection of the vertebral body and/or the intervertebral disc space and can be associated or not with indwelling hardware. In general, spinal osteomyelitis presents acutely, within a few days or weeks; with delayed onset, within a few weeks to a month; or, most frequently, late, years following spine surgery (135). The rate of infection by *P. acnes* after spine surgery is generally low but increases to up to 12% of all infections when instrumentation is used (136–139). In 2010, Uckay et al. reported 29 patients with spondylodiscitis caused by *P. acnes* who presented with back pain (29/29) but were mostly afebrile, and only 1 of the 29 patients had positive blood cultures (140). Recent surgery was a major risk factor for 28 of 29 patients (97%), and osteosynthesis material was present in 22 of 29 patients (75.9%). This study also found a long interval between spinal surgery and either the onset of symptoms (34 months; range, 1 to 156 months) or diagnosis of infection (19.5 weeks; range, 1 to 104 weeks). Therefore, this type of disease should be part of the differential diagnosis when patients with any history of back surgery present with back pain, even when blood cultures are negative. The long-term prognosis for these patients is favorable with 6 weeks of antimicrobial therapy, osteosynthesis material removal, and appropriate debridement of devitalized bone and tissue. There are many reports of *P. acnes* vertebral osteomyelitis in the spine after spine stabilization using the dynamic neutralization system (141). Screw loosening observed by conventional X ray was seen in 73.5% of cases.

Although not associated with an implant, the role of *P. acnes* in disc degeneration has also been highlighted. In 2001, Stirling et al. found positive cultures for *P. acnes* in debrided tissue from 84% of microdiscectomy patients treated for lower back pain (142). Albert et al. found an association of Modic type I changes of disc atrophy (fissuring and edema of the endplates) of previously herniated discs and *P. acnes*-positive tissue cultures (143). A double-blind study including 162 patients with chronic lower back pain and Modic type I changes investigated the effect of a 100-day-long antibiotic treatment with amoxicillin-clavulanate. That study showed significant improvements in disease-specific disabilities (according to the Roland Morris questionnaire), in back and leg pain (e.g., pain rating scale or hours with pain), days with sick leave, and magnetic resonance imaging in patients taking antibiotics (144). These results emphasize the potential role of *P. acnes* in disc degeneration.

S. aureus is the most common microorganism found in acute

early or hematogenous spinal osteomyelitis, followed by *Escherichia coli* (135, 137, 139, 145–147). Coagulase-negative staphylococci and *P. acnes* are typical microorganisms that have a delayed presentation after surgery, in particular if fixation devices (instrumentation) are used (135, 137, 139, 145–147). There is no prospective study on specific risk factors for *P. acnes* infections in vertebral osteomyelitis. A retrospective case-control study of bacterial infections following spinal fusion surgery by Rao et al. showed that a longer duration of closed suction drains (unit odds ratio [OR], 1.6 per day drain present; 95% confidence interval [CI], 1.3 to 1.9), body mass index (OR, 1.1; 95% CI, 1.0 to 1.1), and male gender (OR, 2.7; 95% CI, 1.4 to 5.6) were significant risk factors in a multivariate analysis (148).

DIAGNOSTIC PROCEDURES

For successful microbiological diagnosis of implant-associated infections, multiple conventional tissue cultures, sonication of the removed implant or its mobile parts, and/or synovial fluid aspiration is recommended.

Conventional Microbial Cultures

In general, several intraoperative tissue samples (soft tissue and bone) from different parts of the peri-implant region should be taken for meaningful microbiological sampling. It is recommended that at least three and optimally five to six periprosthetic intraoperative tissue samples be taken for aerobic and anaerobic cultures (149, 150) due to the heterogeneous biofilm distribution and to improve the exclusion of contamination from the skin. Ideally, antimicrobial treatment should be withheld for at least 2 weeks prior to the collection of microbiological samples (117, 150, 151), in order to increase the sensitivity. With *P. acnes*, a prolonged incubation time of 10 to 14 days for periprosthetic tissue and synovial fluid is mandatory to optimize the detection of the pathogen (48). Swabs are, in general, not appropriate for diagnosing infections because of the lower sensitivity and the difficulty in performing a PCR after a negative culture result due to the sparse cell material (152). If the implant-associated infection includes a joint, percutaneous aspiration of synovial fluid should be performed. In periprosthetic knee joint infections, an increased synovial fluid leukocyte count of $>1,700$ leukocytes/ μ l and/or $>65\%$ granulocytes is a strong indicator of a PJI (153).

Sonication

If infection necessitates the removal or exchange of an implant, a sonication bath is recommended for the diagnosis of an implant-associated infection. The sonication method dislodges bacteria from the surface of an implant (154) and breaks biofilm clumps into suspensions of single cells, as described by Trampuz et al. for hip and knee PJIs (155). In brief (116, 117), the implant is aseptically removed and transported to a microbiological laboratory in a solid, airtight, sterile container. Once in the laboratory, 50 to 200 ml sterile Ringer solution is added to the container under a laminar airflow biosafety cabinet. The container with the implant is vortexed for 30 s, followed by sonication for 1 min using an ultrasound bath (e.g., BactoSonic [Bandelin GmbH, Berlin, Germany]). The frequency of sonication is usually 40 ± 2 kHz, with a power density of 0.22 ± 0.04 W/cm². After sonication, the container with the implant is vortexed for another 30 s to remove any residual microorganisms and to homogeneously distribute them in the sonication fluid. The sonication fluid is plated in 0.1-ml

aliquots onto aerobic and anaerobic sheep blood agar plates, and 1 ml is inoculated into thioglycolate broth. After 7 days of incubation, the CFU/ml in the sonication fluid is calculated. Because of the possibility of *P. acnes* lysis by the chosen acoustic energy in sonication, an additional centrifugation step for the fluid and cultivation of the sediment with concentrated *P. acnes* bacteria may improve the sensitivity of sonication (116).

In a study by Trampuz et al., the sensitivity of sonicate fluid culture was superior to that of conventional tissue culture (78.5% versus 60.8%; $P < 0.001$), especially when preoperative antimicrobial therapy was stopped 4 to 14 days before obtaining the tissue samples (117). A study comparing conventional tissue cultures, sonication fluid cultures, and multiplex PCR demonstrated that *P. acnes* could be detected either in conventional tissue cultures (incubation time, 10 days) or in sonication cultures (incubation time, 7 days) but not by multiplex PCR because of the absence of specific primers for this microbial species, resulting in low specificity. In general, the sonication method shows a trend of being more sensitive than vortexing alone to remove biofilm bacteria (156, 157), and it has been applied to hip and knee PJIs as well as shoulder and elbow PJIs (27, 118), cardiovascular implants (35), breast implants (32–34), ureteral stents (158), and spinal implants (136).

Molecular Biological Testing

In 2004, Brüggemann et al. reported the whole genome sequence of *P. acnes* (53). Since then, a broad-range set of primers against the highly conserved regions of the 16S rRNA gene has allowed PCR amplification and subsequent sequencing for species identification. In a study by Sfanos and Isaacs using *P. acnes*-specific primers (159), PCR detection of *P. acnes* showed good specificity and sensitivity.

FISH

Fluorescence *in situ* hybridization (FISH) techniques may offer a more rapid solution for microscopic visualization of bacteria using fluorescently labeled oligonucleotide probes, which bind to unique complementary target sites on rRNA. For research purposes, Alexeyev et al. (160) and Yamada et al. (161) performed FISH for the detection of *P. acnes* in prostate and lymph nodes. For diagnostic purposes, Poppert et al. described a specific *P. acnes* FISH probe for rapid identification of *P. acnes* in 111 blood cultures showing Gram-positive rods by Gram staining (162). After hybridization, washing, and mounting, they identified *P. acnes* within 1 h with sensitivity and specificity of 100% in subcultures and with a sensitivity of 95% in cultures directly. Presently, FISH analysis does not play a role in the routine diagnosis of implant-associated infections in general and *P. acnes* specifically due to the technical difficulties of the procedure.

PREVENTION AND TREATMENT

Prevention

At present, there are no specific preventative measures to avoid implant-associated infections caused by *P. acnes*. However, since these infections are usually acquired intraoperatively, methods that reduce indwelling medical device infection from other bacteria are also effective at reducing the risk of *P. acnes* infection. Therefore, general prevention recommendations include proper skin preparation (disinfection), antibiotic prophylaxis, reduced

surgical suite traffic, minimal time between initial incision and closing, use of antibiotic-laden bone cement, and performance of a thorough postoperative evaluation (150, 163).

While there have been a number of studies evaluating the potential for a vaccine to prevent *P. acnes*-mediated acne vulgaris, no studies have tested the ability to prevent implant-associated infections by this microbial species. However, one study evaluated the efficacy of the antigen sialidase (identification number gi|50843033), a cell wall-anchored protein produced by *P. acnes* (164), in providing protection against challenge in a murine ear/skin infection model following vaccination. Mice vaccinated with sialidase and then challenged with *P. acnes* had reduced ear swelling and redness and reduced levels of the inflammatory cytokine macrophage inflammatory protein 2 (MIP-2). Later, this same group evaluated the protective efficacy of vaccination with the Christie-Atkins-Munch-Peterson (CAMP) virulence factor (CAMP factor 2; identification number gi|50842175) antigen against *P. acnes* challenge (66, 165). This secreted protein was shown to have cohemolytic activity with sphingomyelinase, which conferred cytotoxicity to keratinocytes and macrophages (66). Although this study showed promising results, *P. acnes* infections were not eliminated, and because this study was performed by using a mouse skin model, it is difficult to extrapolate these results to deep musculoskeletal and indwelling medical device biofilm infections.

Susceptibility Testing and Emergence of Resistance

P. acnes is highly susceptible to a wide range of antibiotics (Table 2), including beta-lactams, quinolones, clindamycin, and rifampin (166, 167). However, resistance is beginning to emerge. In 1983, Denys et al. tested 104 clinical isolates of *P. acnes* against 22 antimicrobial agents (168), and *P. acnes* showed resistance to only metronidazole. Recent reports note an increasing emergence of resistance to macrolides, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole. The first report concerning antimicrobial resistance in *P. acnes* described resistance to clindamycin and erythromycin (169, 170), followed by reports of tetracycline resistance (14) and, more recently, several reports of the emergence of macrolide-clindamycin-resistant *P. acnes* in Europe, South Korea, and Japan (166, 171–173). A European surveillance study, including 13 countries with 314 *P. acnes* isolates, showed resistance rates of 2.6% for tetracycline, 15.1% for clindamycin, and 17.1% for erythromycin. No resistance to linezolid, benzylpenicillin, or vancomycin was observed (167). Highly variable rates of resistance between European countries, 83% in Croatia, 60% in Italy, and 0% in The Netherlands, have been noted. The emergence of macrolide-clindamycin resistance was attributed to widespread topical and oral use in therapy for acne vulgaris (174). In 2013, Schafer et al. reported the emergence of trimethoprim-sulfamethoxazole resistance in 26.3% of patients with acne vulgaris seen in a dermatological department in Santiago, Chile, which was associated with an increased severity of acne vulgaris (174).

Antimicrobial susceptibility breakpoints for *P. acnes* have been published by the Clinical and Laboratory Standards Institute (CLSI) in the United States (175) and by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (176). The CLSI and EUCAST breakpoints are not always equivalent (177) (Table 3), which in part explains differences in reported resistance rates. The MIC₅₀ and MIC₉₀ values for *P. acnes* are summarized in

TABLE 2 Reported susceptibilities of *Propionibacterium acnes* to various antibiotics from selected English-language reports^a

Drug	Yr	Country or continent	No. of isolates	Source	MIC range (µg/ml)	MIC _{50/90} (µg/ml)	Reference(s)
Amoxicillin	2010–2012	USA	28	Shoulder	0.028/0.117		166
Ampicillin	1995–1996	Japan	50	Acne	0.025–0.2	0.05/0.05	230
	1996–2002	USA	12	Various	≤0.03–0.125	0.06/0.06	231
Ampicillin-sulbactam	2008	USA	14	DFI	<0.03–0.125	0.06/0.125	232, 233
Azithromycin	2007–2010	Sweden	24	Prostate	0.125–2	1/1	225
	2007–2010	Sweden	25	Various	0.125–1	0.25/0.5	225
	2010	Mexico	49	Acne	≤0.03–≥256	64/≥256	234
Cefepime	2006	USA	23	Ophthalmic	1.0–12	6.0/8.0	235
Ceftriaxone	2006	USA	23	Ophthalmic	0.19–1.0	0.38/0.75	235
	2010–2012	USA	28	Shoulder		0.016/0.45	166
Cephalothin	2010–2012	USA	28	Shoulder		0.047/0.94	166
Cephalexin	1995–1996	Japan	50	Acne	0.2–1.6	0.4/0.4	230
Ciprofloxacin	2007–2010	Sweden	24	Prostate	0.125–0.0.5	0.25/0.5	225
	2007–2010	Sweden	25	Various	0.125–0.5	0.25/0.5	225
	2010–2012	USA	28	Shoulder		0.25/0.5	166
Clindamycin	1992–1993	Japan	17	Acne	0.05–>100	0.1/>100	236
	1995–1996	Japan	50	Acne	0.2–50	0.2/0.2	230
	1999–2000	Sweden	201	Treated acne	<0.008–64	0.03/4	237
	1999–2000	Sweden	79	Untreated acne	<0.008–16	0.03/0.03	237
	2005	Europe	304	Various	<0.06–64	<0.06/0.25	167
	2006	USA	23	Ophthalmic	0.03–0.75	0.06/0.06	235
	2005–2007	South Korea	31	Acne	≤0.016–0.25	0.03/0.125	238
	2007–2010	Sweden	25	Various	0.032–≥256	0.064/≥256	225
	2007–2010	Sweden	24	Prostate	0.32–0.125	0.064/0.064	225
	2008–2009	Chile	80	Acne	0.125–>8	0.125/1	174
	2010	Mexico	49	Acne	≤0.03–≥256	0.5/>256	234
	2010–2012	USA	28	Shoulder		0.03/8.5	166
	2011	Chile	53	Acne	≤0.03–32	0.03/0.03	239
Daptomycin	1996–2002	USA	12	Various	0.125–1	0.5/1	231
	2007–2010	Sweden	24	Prostate	0.125–2	1/1	225
	2007–2010	Sweden	25	Various	0.125–1	0.25/0.5	225
Doripenem	2008	USA	14	DFI	0.03–0.25	0.06/0.12	232
	2008	USA	18	Various	0.06	0.06	240
Doxycycline	1995–1996	Japan	50	Acne	0.2–12.5	0.4/0.78	230
	2005–2007	South Korea	31	Acne	≤0.016–0.5	0.09/0.25	238
	2008–2009	Chile	80	Acne	0.03–0.5	0.06/0.125	174
	2010	Mexico	49	Acne	0.06–16	2/8	234
	2011	Chile	53	Acne	0.06–8	0.06/0.06	239
Ertapenem	2006	USA	23	Ophthalmic	0.094–0.75	0.125/0.38	235
	2008	USA	14	DFI	≤0.06–0.5	0.125/0.25	232
	2008	USA	18	Various	0.06–0.5	0.06	240
	2010–2012	USA	28	Shoulder		0.03/0.14	166
Fusidic acid	2007–2010	Sweden	24	Prostate	0.5–2	2/4	225
	2007–2010	Sweden	25	Various	1–2	4/4	225
Imipenem	1996–2002	USA	12	Various	≤0.03	≤0.03	231
	2007–2010	Sweden	24	Prostate	0.016–0.064	0.032/0.032	225
	2007–2010	Sweden	25	Various	0.125–2	0.25/1	225

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TABLE 2 (Continued)

Drug	Yr	Country or continent	No. of isolates	Source	MIC range ($\mu\text{g/ml}$)	MIC _{50/90} ($\mu\text{g/ml}$)	Reference(s)
	2008	USA	14	DFI	≤ 0.015	≤ 0.015	232
	2008	USA	18	Various	0.016–0.064	0.032/0.064	240
Levofloxacin	2010	Mexico	49	Acne	0.125– ≥ 256	0.5/8	234
Linezolid	2005	Europe	304	Various	0.25–2	0.5/1	167
	2007–2010	Sweden	24	Prostate	0.064–0.5	0.25/0.25	225
	2010–2012	USA	28	Shoulder		0.25/0.93	166
	2007–2010	Sweden	25	Various	0.016/0.25	0.25/0.25	225
Meropenem	2006	USA	23	Ophthalmic	0.094–1.5	0.25/0.75	235
	2008	USA	14	DFI	0.06–0.5	0.125/0.25	232
	2008	USA	18	Various	0.06–0.06	0.06/0.06	240
Metronidazole	2006	USA	23	Ophthalmic		> 256	235
	2007–2010	Sweden	24	Prostate	> 256	$> 256/ > 256$	225
	2007–2010	Sweden	25	Various	> 256	> 256	225
Minocycline	1992–1993	Japan	17	Acne	0.01– ≥ 100	0.8/25	236
	1995–1996	Japan	50	Acne	0.1–3.1	0.2/0.2	230
	2001	Chile	53	Acne	0.03–1	0.03/0.03	239
	2005–2007	South Korea	31	Acne	0.02–0.5	0.06/0.125	238
	2010	Mexico	49	Acne	0.125–8	0.5/2	234
Moxifloxacin	2007–2010	Sweden	25	Various	0.125–0.5	0.125–0.25	225
	2010–2012	USA	28	Shoulder		0.125/0.38	166
	2007–2010	Sweden	24	Prostate	0.125–0.5	0.25/0.5	225
Penicillin	2001	Chile	53	Acne	≤ 0.03 –2	0.03/0.03	239
	2005	Europe	304	Various	0.008–0.125	0.032/0.064	167
	2007–2010	Sweden	24	Prostate	0.016–0.125	0.032/0.064	225
	2007–2010	Sweden	25	Various	0.016–0.125	0.032/0.064	225
	2010–2012	USA	28	Shoulder		0.006/0.125	166
Piperacillin-tazobactam	1996–2002	USA	12	Various	≤ 0.03 –0.5	0.125/0.5	231
	2007–2010	Sweden	24	Prostate	0.125–1	0.5/1	225
	2007–2010	Sweden	25	Various	0.125–2	0.25/1	225
Rifampin	2007–2010	Sweden	24	Prostate	≤ 0.016	$\leq 0.016/ \leq 0.016$	225
	2007–2010	Sweden	25	Various	≤ 0.016	$\leq 0.016/ \leq 0.016$	225
Televancin	1996–2002	USA	12	Various	0.06–0.125	0.125/0.125	231
Tetracycline	1995–1996	Japan	50	Acne	0.78–25	0.78/1.56	230
	1999–2000	Sweden	201	Treated acne	0.06–32	0.5/8	237
	1999–2000	Sweden	79	Untreated acne	0.06–4	0.25/0.5	237
	2001	Chile	53	Acne	0.03–8	0.06/0.06	239
	2005	Europe	304	Various	0.064–32	0.5/1	167
	2005–2007	South Korea	31	Acne	0.09–0.4	0.19/0.25	238
	2007–2010	Sweden	24	Prostate	0.064–0.5	0.125/0.25	225
	2007–2010	Sweden	25	Various	0.064–0.25	0.125/0.25	225
	2008–2009	Chile	80	Acne	0.25–2	0.25/0.5	174
	2010	Mexico	49	Acne	0.5– ≥ 256	2/32	234
Tigecycline	2007–2010	Sweden	24	Prostate	0.016–0.064	0.032/0.064	225
	2007–2010	Sweden	25	Various	0.016–0.032	0.016/0.032	225
Trimethoprim-sulfamethoxazole	1999–2000	Sweden	201	Treated acne	0.016–0.5	0.125/0.25	237
	1999–2000	Sweden	79	Untreated acne	0.06–0.5	0.06/0.125	237
	2007–2010	Sweden	25	Various	0.016–0.25	0.032/0.064	225
	2007–2010	Sweden	24	Prostate	0.016–0.125	0.064/0.125	225

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TABLE 2 (Continued)

Drug	Yr	Country or continent	No. of isolates	Source	MIC range (μg/ml)	MIC _{50/90} (μg/ml)	Reference(s)
Vancomycin	2008–2009	Chile	80	Acne	0.25–>4	0.25/4	48
	2010	Mexico	49	Acne	0.125–≥256	≥256	234
	1996–2002	USA	12	Various	0.25–0.5	0.5	231
	2005	Europe	304	Various	0.25–2	0.5/1	167
	2007–2010	Sweden	24	Prostate	0.064–0.5	0.25/0.25	225
	2007–2010	Sweden	25	Various	0.016–0.25	0.25/0.25	225
	2010–2012	USA	28	Shoulder		0.38/0.5	166

^a Selected studies were chosen from a Medline search of “*P. acnes* and susceptibility or resistance.” Studies were excluded if no MIC data were presented. DFI, strains from diabetic foot infections; Various, strains from multiple specified sites.

Table 2. Table 3 shows the breakpoints according to CLSI and EUCAST guidelines. These data were evaluated by agar dilution, broth microdilution, or Etest. Beta-lactams, tigecycline, and rifampin show the strongest activity against *P. acnes* strains.

The causes of resistance to tetracycline and erythromycin-clindamycin are associated with point mutations in rRNA (178). Mac-

rolide resistance of *P. acnes* is caused by a mutation in domain V of the 23S rRNA or by an alteration of the target site by the 23S dimethylase, which is encoded by the erythromycin ribosomal methylase [*erm*(X)] gene (15, 171, 179). Erythromycin-resistant propionibacteria were classified based on their pattern of cross-resistance to a panel of macrolide-lincosamide-streptogramin B (MLS) antibiotics (15). The mechanism of trimethoprim-sulfamethoxazole resistance is unknown. The theory of a modified form of dihydrofolate reductase caused by a plasmid is unlikely (174), since only a mobile genetic element and no plasmid has been isolated from *P. acnes* (180). There are as yet no *in vivo* data on the emergence of rifampin resistance in *P. acnes*. In 2013, Furustrand Tafin et al. reported an *in vitro* study on the emergence of rifampin resistance (181). Resistance was associated with mutations in the *rpoB* gene, which encodes the bacterial RNA polymerase. The mutations were detected in cluster I (amino acids 418 to 444) and cluster II (amino acids 471 to 486).

Antimicrobial susceptibility is dramatically reduced in biofilms where the microbes are much more tolerant to antibiotics than their planktonic counterparts. Therefore, chronic infections are difficult to cure with antimicrobial treatment alone without removal of the biofilm attached to the implant and devitalized tissue and bone. The antibiotic tolerance and recalcitrance to antimicrobial therapy of sessile *P. acnes* biofilm populations have been shown in a number of *in vitro* and *in vivo* studies (17, 22, 105, 182). One of these studies evaluated the antibiotic sensitivity of *in vitro*-grown sessile and planktonic *P. acnes* (ATCC 11827) to a number of relevant antibiotics. While rifampin, daptomycin, and ceftriaxone were effective against *P. acnes* biofilms, vancomycin, clindamycin, and levofloxacin were less so. An *in vivo* animal model (subcutaneous tissue cage model in guinea pigs) was used to evaluate susceptibility to levofloxacin, vancomycin, daptomycin, and rifampin. This study showed the highest cure rate with the combination of daptomycin plus rifampin (63%), followed by 46% for vancomycin plus rifampin (105). Another study showed that all eight tested clinical *P. acnes* isolates (from hip PJIs) growing in biofilms on either polymethylmethacrylate (PMMA) bone cement or three types of titanium had greater resistance to cefamandole, ciprofloxacin, and vancomycin but that only 50% had increased resistance to gentamicin (22). No differences in increases of resistance were seen between PMMA and titanium. Gentamicin-loaded bone cement was tested in an *in vitro* study in combination with cefuroxime in the fluid phase (182), which simulated prophylactically intravenous antimicrobial treatment at surgery. This treatment did not prevent *P. acnes* biofilm formation

TABLE 3 MIC breakpoints reported by EUCAST for Gram-positive anaerobes and by the CLSI for *Propionibacterium acnes*

Drug(s)	MIC breakpoint (mg/liter) ^d				% resistant <i>P. acnes</i> strains (34 isolates) ^e
	EUCAST		CLSI		
	S	R	S	R	
Penicillin	0.25	0.5	≤0.5	≥2	0
Amoxicillin	4	8			
Ampicillin	4	8	≤0.5	≥2	0
Ampicillin, sulbactam			<8/4	≥32/18	0
Azithromycin	— ^b				
Ceftriaxone, cefepime, cefoxitin					
Cefoxitin			≤16	≥64	0
Cephalothin					
Ciprofloxacin, levofloxacin	— ^a				
Clindamycin	4	4	≤2	≥8	3
Daptomycin	— ^b				
Doripenem	1	1			
Doxycycline, minocycline					
Ertapenem	1	1	≤4	≥16	0
Fusidic acid	— ^b				
Gentamicin	— ^a				
Imipenem	2	8	≤4	≥16	0
Linezolid	— ^a				
Meropenem	2	8		≥16	0
Metronidazole	4	4	≤8	≥32	97
Moxifloxacin	— ^a		≤2	≥8	0
Piperacillin-tazobactam	8	16	<32/4	≥128/4	0
Rifampin	— ^b				
Tigecycline	— ^a				
Trimethoprim-sulfamethoxazole					
Vancomycin	2	2			

^a For the following antibiotics, EUCAST reports non-species-related breakpoints: for gentamicin, resistant at >4 mg/liter and susceptible at ≤4 mg/liter; for ciprofloxacin, resistant at >1 mg/liter and susceptible at ≤0.5 mg/liter; for moxifloxacin, resistant at >1 mg/liter and susceptible at ≤0.5 mg/liter; for tigecycline, resistant at >0.5 mg/liter and susceptible at ≤0.25 mg/liter; and linezolid, resistant at >4 mg/liter and susceptible at ≤2 mg/liter.

^b For antibiotics not included in these categories, the following EUCAST MIC resistance breakpoints established for other Gram-positive organisms were used: >2 mg/liter for azithromycin, >1 mg/liter for fusidic acid, >0.5 mg/liter for rifampin, and >1 mg/liter for daptomycin.

^c CLSI isolates collected from selected U.S. hospitals from 1 January 2007 to 31 December 2009 (233).

^d S, susceptible; R, resistant.

if a high inoculum of bacteria was used, which could occur at the time of a surgical revision of an infected implant.

Treatment Recommendations

Due to the different clinical pictures of *P. acnes* implant-associated infections, there is no general consensus on how to best treat these infections. However, surgical recommendations for implant-associated infections caused by *P. acnes* should not differ dramatically from those for infections caused by other microorganisms (121). Implant-associated infections require the surgical removal of the infected implant and debridement of infected tissue and dead bone. Since *P. acnes* infections often have a delayed presentation after implant surgery due to the indolent nature of the infection, extensive and aggressive debridement of all infected tissue with removal of the implant is recommended. Surgical therapy must be accompanied by prolonged antibiotic treatment to successfully kill the remaining bacteria. The increasing resistance mainly to clindamycin argues for routine antimicrobial susceptibility testing in implant-associated infections.

For PJIs, most authors suggest a course of 3 to 6 months of antibiotic treatment, including 2 to 6 weeks of intravenous treatment with a beta-lactam, depending on the size of the implant (104, 121). A cohort study from Australia with 147 patients with early PJI documented that a shortened treatment course of <3 months in total is a risk factor for treatment failure (183). However, other reported studies favor shorter treatments (184–187), but no randomized controlled trials have been performed. For spinal osteomyelitis, the recommended antimicrobial treatment duration ranges from 4 to 6 weeks (188, 189) to 3 months if an implant is present. For cardiovascular device infections with *P. acnes*, no specific antibiotic treatment is proposed in guidelines (190, 191), but a course of 6 weeks with an intravenous beta-lactam antibiotic alone or in combination with an aminoglycoside for 2 weeks is often given (73, 74). Alternative regimens include vancomycin for patients who are allergic to or intolerant of beta-lactams (74). Because of a common complication with valvular abscesses in *P. acnes* endocarditis, operative revision surgery is often needed to decrease the rate of relapse of infection (73, 74).

Rifampin is known to be active because of its low minimal bactericidal concentration against *S. aureus* and coagulase-negative staphylococci in the stationary phase of growth (192, 193). Successful cure by rifampin therapy in orthopedic device-associated infections has been demonstrated in experimental animal models and in observational and controlled trials (192–200). However, the emergence of resistance (single-step mutation in the DNA-dependent rRNA polymerase) is frequent when given as monotherapy (201–204). The role of rifampin in *P. acnes* has been studied (105); those authors reported *in vivo* data and data from an experimental animal model (subcutaneous tissue cage model in guinea pigs) showing a good efficacy of rifampin alone and in combination with vancomycin, daptomycin, or levofloxacin. While there are currently no randomized controlled human studies on the efficacy of rifampin in a combination antimicrobial treatment for *P. acnes* PJI, the present IDSA guidelines for PJI therapy still recommend monotherapy with either penicillin G, ceftriaxone, clindamycin, or vancomycin intravenously (121).

CONCLUSIONS

Our review has focused on implant-associated infections caused by *P. acnes*, which are an important medical issue due to the in-

creased use of different implants, such as joint arthroplasties or other orthopedic implants, cerebrovascular and cardiovascular devices, and breast implants. All these infections have gained more attention due to improved diagnostic procedures, such as a prolonged cultivation time of up to 14 days for biopsy specimens and explanted medical devices. *P. acnes* causes disease through a number of virulence factors, particularly the ability to form a biofilm. These biofilms are difficult to treat by antibiotics alone and usually require surgery with intensive debridement of infected tissue and the removal of any foreign device. In addition to surgery, prolonged antibiotic treatment is required, where the choice of antibiotic is directed by susceptibility testing against the isolated *P. acnes* strain. While recently reported data showed a good efficacy of rifampin against *P. acnes* biofilms, prospective, randomized, controlled studies are needed to confirm evidence for combination treatment with rifampin, as has been performed for staphylococcal implant-associated infections. In addition, studies should be performed in order to improve and shorten the length of time to diagnosis and to determine potential vaccine candidates in order to develop preventive strategies against these infections.

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Mark E. Shirtliff, Ph.D., is presently an Associate Professor in the Department of Microbial Pathogenesis in the Dental School and an Adjunct Associate Professor in the School of Medicine at the University of Maryland, Baltimore. Dr. Shirtliff began his biofilm infection training at the University of Texas Medical Branch in the Department of Microbiology and Immunology. He received his Ph.D. in 2001 with his thesis entitled “*Staphylococcus aureus*: Roles in Osteomyelitis.” He then traveled to the Center for Biofilm Engineering as a postdoctoral fellow to continue his work using animal models to study infection resolution in biofilm-related diseases. While in Montana, Dr. Shirtliff became an Assistant Research Professor in 2003 in the Department of Microbiology, and later that year, he accepted a position at the University of Maryland, Baltimore. In Maryland, Dr. Shirtliff continues his research and teaching interests in host-pathogen interactions, biofilm infections, and treatment of infections using animal models and was promoted to Associate Professor with tenure in 2009. He funds his research through grants from the State of Maryland, the National Institutes of Health (NIDCR and NIAID), and the Department of Defense. He has published over 100 articles, has more than 20 years of experience using animal infection models to study biofilm infections, and is the Senior Editor of the *Springer Series on Biofilms*.