Clinical and Biological Features of *Cutibacterium* (Formerly *Propionibacterium*) *avidum*, an Underrecognized Microorganism

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SUMMARY The recent description of the genus *Cutibacterium* has altered the taxonomy of *Propionibacterium* species. These organisms still belong to the genera of the skin coryneform group, and the most-studied species remains *Cutibacterium acnes*. *Cutibacterium avidum* is also a known skin commensal. This underrecognized microorganism can, however, act as a pathogen after bacterial seeding and can be considered opportunistic, causing either superficial or deep/invasive infections. It can

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cause numerous infections, including but not limited to breast infections, skin abscesses, infective endocarditis, and device-related infections. The ecological niche of *C. avidum* is clearly different from that of other members of the genus: it is found in the axillary region or at wet sites rather than in dry, exposed areas, and the number of microorganisms increases during puberty. Historically, it has been used for its ability to modulate the immune response and for its antitumor properties. Conventional microbial culture methods and identification processes allow for its accurate identification and characterization. Thanks to the modern omics tools used for phylogenomic approaches, understanding *C. avidum* pathogenesis (including host-bacterium interactions and virulence factor characterization) is becoming easier, allowing for more thorough molecular characterization. These analyses have revealed that *C. avidum* causes diverse diseases mediated by multiple virulence factors. The recent genome approach has revealed specific genomic regions within this species that are involved in adherence and biofilm formation as well as fitness, survival, and defense functions. Numerous regions show the presence of phages and horizontal gene transfer. *C. avidum* remains highly sensitive to a broad spectrum of antibiotics, such as β -lactams, fluoroquinolones, macrolides, and rifampin, although erythromycin and clindamycin resistance has been described. A long-term treatment regimen with a combination of antibiotics is required to successfully eliminate the remaining adherent bacteria, particularly in the case of deep infections after debridement surgery.

KEYWORDS *Cutibacterium avidum*, abscess, biofilm, immunostimulation, genomic, identification, clinical infections, antibiotic resistance, biofilms, clinical infection, genomics, genotypic identification, immune regulation, phenotypic identification

INTRODUCTION

The genus *Propionibacterium*, initially described by Orla-Jensen in 1909 (1), is made up of species that produce propionic acid during the fermentation process (2). It belongs to the class *Actinobacteria* of the order *Propionibacteriales* (3). Following its discovery in a patient with a chronic skin disease called “acne vulgaris,” *Propionibacterium acnes*, henceforth called *Cutibacterium acnes*, underwent a series of taxonomic changes. It was successively placed in the genus *Bacillus* and then the genus *Corynebacterium* (4, 5). However, in 1946, Douglas and Gunter were able to demonstrate that this microorganism was more closely related to the *Propionibacterium* genus members since, like other species of this genus, it ferments lactose to propionic acid in an anaerobic atmosphere (6, 7). Recently, a significant taxonomic revision was proposed by Scholz and Kilian, placing all *Propionibacterium* species from the skin microbiota within a new genus (8). As a result, *Propionibacterium* is replaced by *Cutibacterium* for *P. avidum*, *P. acnes*, *P. granulosum*, and the more recently discovered species *P. namnetense* (9) and *P. humerusii* (10). Too often ignored or considered a contaminant in cultures (especially in hemolin performance diphasic medium for blood cultures), these species are the subject of renewed interest, with literature results on these organisms increasing from 100 papers per year in 2000 to some 230 to 240 per year since 2013.

In this review, I focus on *Cutibacterium avidum*, a Gram-positive, anaerobic-aerotolerant rod which is a minor colonizer and resident of the human skin. Its ecological niche is clearly different from that of other members of this genus due to a specific tropism for wet areas (11). Although often defined as a commensal (12, 13), *C. avidum* has likely been underestimated, unrecognized, and misidentified in more than a few clinical cases. Despite its low frequency in human infections, numerous associated or invasive infections have been reported: bone infections, infective endocarditis (IE), breast infections, abdominal infections, prostate infections, and splenic and skin abscesses have been described, sometimes with significant collateral damage for the patient (14–17). In my experience, although one cannot avoid bias according to the identification method used and the awareness of microbiologists, there has been a

clearly observed increase in *C. avidum*-positive samples over the past years. A plausible explanation for the increased awareness of this microorganism is probably the introduction of matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) technology in numerous laboratories. Most positive samples have been from blood cultures and valve, bone, tissue, and deep perioperative specimens. Interestingly, most of them were recovered from deep tissue samples taken from immunosuppressed patients or patients receiving chemotherapy or radiotherapy.

In the 1970s, *C. avidum* was considered a less virulent bacterium or culture contaminant (3), but a specific dedicated preparation was used as an adjuvant in antitumor therapies (18) or as an immunity stimulant (19). Later, following various studies, the key role played by *Cutibacterium* species, especially *C. avidum*, in immune response modulation was demonstrated (20). Indeed, this species has been reported to be an immunomodifier, stimulating the various cell subset populations involved in nonspecific antibacterial, antiviral, or antitumor abilities (21).

Thereafter, biochemical characterization of the cell wall (22) and specific interactions with reticuloendothelial cell systems (23), including various lymphocyte subpopulations, demonstrated its medical significance. Following the culture-centric period, which focused on developing new tools to better understand bacterial growth, metabolism, and immunogenicity, we are now entering a new genomic era. This new period will allow us to decipher virulence factors, genome organization, genome plasticity, and specific features of several *C. avidum* clinical strains by using next-generation sequencing (13, 14) and confirming hypotheses through various *in vitro* and *in vivo* models. As a result, deeper genomic analyses and comparisons will provide key information about the organism's phylogeny and the potential existence of subpopulations within this species. Such results have been described for *C. acnes* clinical strains, with a correlation of different clusters or lineages involved in specific clinical entities. Although a whole-genome synteny has been reported for propionibacteria originating from the skin, a certain plasticity of the genome has revealed *C. avidum*-specific genomic regions. This observation demonstrated the importance of these genomic regions, which include exopolysaccharide gene synthesis functions, prophage regions, and other gene-specific clusters involved in diverse fitness, survival, and defense functions (14). Although only 2 of 14 complete genomes are publicly available, *C. avidum* genomic studies remain relevant to furthering the understanding of the pathogenesis of this organism.

In light of the growing number of *C. avidum* infections, I review both the physiopathology and the clinical/microbiological significance of *C. avidum* as the causative agent of invasive and deep infections and provide an extended view of its biochemical features, immune responsiveness, and culture and identification methods as well as a genomic analysis based on publicly available data. This bacterium is therefore a new rod that needs to be monitored as a potential opportunistic pathogen.

MICROBIOLOGY OF *C. AVIDUM*

Microbiota

Anaerobic diphtheroid bacteria are typical residents of the human sebaceous follicles and are certainly almost all implicated in the pathogenicity of acne or other skin disorders. Following multiplication in the lumen, they move from the follicles over the sebum-covered skin surface, forming dense populations in sebum-rich areas of the skin (24–26). The three most prevalent species (*C. avidum*, *C. acnes*, and *C. granulosum*) can be found on the skin surfaces of both healthy individuals and acne patients. Their spread and distribution are related to the skin region studied, patient age, and presence of skin lesions (papules, pustules, and nodules), as previously reported (6, 27). However, skin microbiome data did not focus on *C. avidum*'s relative abundance, leading to the absence of available data about its prevalence and location. Recent comparative genomics studies revealed distinct host-interacting traits of the three major human-associated propionibacteria, including *C. avidum*. They have evolved specific characteristics to interact with their human hosts, and their various surface properties

probably determine their colonizing capability and pathogenicity at the cutaneous level and also at nonskin sites (13).

The ecological niche of *C. avidum* has been previously analyzed. *C. avidum* tends to reside in regions containing eccrine sweat glands (28). It is most frequently detected in wet areas (nares, axilla, groin, and rectum, which include areas populated with enteric Gram-negative bacteria, suggesting an intestinal reservoir), compared to an oily and wet distribution for *C. granulosum* (29). In contrast, *C. acnes* is the most prevalent and ubiquitous in sebum-rich areas. Indeed, other *Cutibacterium* species, especially *C. acnes* and *C. granulosum*, need skin surface lipids to be present and are involved in acne vulgaris, whereas *C. avidum* is rarely or generally not associated with acne (28). Using immunohistochemical staining of acne samples or confocal laser scanning microscopy with specific antibodies, Jahns et al. reported the absence of *C. avidum* in all acne samples, whereas *C. acnes* and *C. granulosum* were found as distinct populations within the same follicles (30). While *C. acnes* requires reduced sulfur, which can be found *in vivo* thanks to its constant availability in the form of sulfhydryl groups in the sebaceous glands during keratinization (31), water plays a crucial role in *C. avidum* ecology (11). Thus, the relationship between *C. acnes* and its nutritional substrate may provide this microorganism a selective advantage in this ecological niche, whereas modifications in the axillary environment, possibly changes of the moist environment and nutritive substance availability, are key variables in the *C. avidum* ecology (11, 28). These local modifications suggest the existence of various skin environments differing in moisture, sweat density, sebaceous gland content, and extent of anaerobiosis (11). Consequently, looking at the distribution of cutaneous *Cutibacterium* species, regional qualitative and quantitative differences have been demonstrated. Thus, a real-time PCR technique for accurate assessment of the presence of some *Cutibacterium* species (inhabitants of human skin) has also been developed to detect the three main species (12).

Interestingly, the prevalence of *C. avidum* recovery increases with age and is associated with the onset of puberty. This bacterium is clearly recovered less from young females or males aged between 5 and 10 years (5% and 4.5%, respectively), while female and male teenagers (15- to 16-year-olds) are colonized at 45% and 58%, respectively. Females tend to be colonized earlier in life than males. In fact, it has been suggested that increases in axillary moisture with age and in nutritive substance availability may act as key points during the colonization process. This finding constitutes a possible explanation for the most relevant routes of contamination during a breast abscess (see references 15, 17, and 32).

Finally, *C. avidum* has also been reported to be present in the hen intestine (poultry microbiota). This ecological niche had never been described previously, even though the presence of other *ex-Propionibacterium* species, especially *Acidipropionibacterium acidipropionici*, was known. Compared to the latter species, *C. avidum* seems to be better adapted to the scarce nutrients of cecal water, most likely due to its proteolytic activity (33).

Genetic and Genomic Analyses

Though propionic acid-producing bacteria were initially reported by von Freudreich and Orla-Jensen at the beginning of the last century (1906) (1), in the 1970s DNA similarities were investigated to classify the *Propionibacterium* species. Over the past decade, in light of their frequency in human samples, various molecular typing techniques have been promoted and used to classify subgroups of *P. acnes*/*C. acnes* clinical strains. Phylotype determination was first performed by *recA* or *tly* gene sequencing (34). Recently, Barnard et al. proposed a multiplex PCR method to identify the six major phylotypes (IA1, IA2, IB, IC, II, and III) (35). To be more accurate, multilocus sequence typing (MLST) methods were developed, leading to the differentiation of clusters within *P. acnes*/*C. acnes* populations, called sequence types (ST) or clonal complexes (CC) (36, 37). Recently, a new method, single-locus sequence typing (SLST), has been endorsed for identification of *P. acnes*/*C. acnes* subpopulations, with an excellent degree of correlation (38). Moreover, over the past 3 years, a *Propionibacterium* taxonomy mod-

FIG 1 Genome relatedness of *C. avidum* to various *Cutibacterium* species, based on orthologous average nucleotide identity (orthoANI) values. The dendrogram was created using Oat 0.93 software.

ification was proposed, with three subspecies for *Cutibacterium acnes*. Indeed, regarding the different phylotypes and based on morphological features, it has been proposed that phylotype I corresponds to *C. acnes* subsp. *acnes*, phylotype II to *C. acnes* subsp. *defendens*, and phylotype III to *C. acnes* subsp. *elongatum* (39, 40).

Finally, in 2016, Scholz and Kilian proposed a reclassification of the genus *Propionibacterium* as *Cutibacterium* for cutaneous propionibacteria, based on genomic evidence (8). These changes were consistent with species habitats, genomic topology, DNA G+C content, and peptidoglycan composition. Thus, *Cutibacterium* is the genus for *C. avidum*, *C. acnes*, and *C. granulosum* and two recent *Cutibacterium* species, *C. namnetense* and *C. humerusii*. For more information, the NamesforLife website can be useful to better understand the *Cutibacterium* species (<http://doi.namesforlife.com/10.1601/tx.6610>). In comparing the three species belonging to a homology group, *C. acnes*, *C. granulosum*, and *C. avidum*, this work demonstrated a 62 to 63% GC content in the DNA from the *C. avidum* group. In contrast, the *C. acnes* group revealed a 59 to 60% GC content and only 50% homology with strains belonging to the *C. avidum* group, along with a low level of similarity with *C. granulosum* group strains (41).

More recently, genome availability among *Cutibacterium* species revealed several differences. Compared with the *C. acnes* genome GenBank database, *C. avidum* genome data remain poor. Indeed, there are only 14 of these genomes available in GenBank, two of which are complete genomes, for *C. avidum* 44067 and DPC 6544. Consequently, although more than 120 *C. acnes* genomes are available, in accord with their significance in the medical field, including complete ($n = 16$), chromosome ($n = 3$), scaffold ($n = 71$), and contig ($n = 25$) data, *C. avidum* and *C. granulosum* are still less studied at the genomic level despite new and easy access to the genomic platform. Only 14 *C. avidum* genomes (complete [$n = 2$], scaffold [$n = 2$], and contigs [$n = 10$]) and three *C. granulosum* genomes (complete [$n = 1$] and contigs [$n = 2$]) are available.

Interestingly, phylogenetic analysis confirms the close relationship between *C. avidum* and *C. acnes*, whereas *C. granulosum* is more distant, as shown in Fig. 1. Based on orthologous average nucleotide identity (orthoANI), analysis of the genome relatedness of the five *Cutibacterium* species was performed and revealed a closer relationship between *C. acnes*, *C. namnetense*, and *C. humerusii* (orthoANI values between 80.6 and 88.5%; the validated threshold for the species definition is 95%). In contrast, *C. avidum* represents another branch of the dendrogram. The same observation is true for the *C. granulosum* genome, which is much smaller (about 400 kb smaller), with fewer than 1,865 genes, on average, coding for 1,592 proteins, whereas *C. avidum* and *C. acnes* possess 2,362 and 2,357 genes, respectively, on average, and 2,207 and 2,267 proteins, respectively, on average (Table 1). The core genome shared between these three species encodes almost 1,400 proteins. The genes corresponding to these pro-

TABLE 1 Genomic comparison and characteristics of *Cutibacterium* sp. genomes available in GenBank

Species	Strain	Genome size (Mb)	GC%	No. of scaffolds	No. of genes	No. of proteins
<i>Cutibacterium avidum</i>	44067	2.52614	63.5		2,297	2,184
	DPC 6544	2.72985	63.4		2,505	2,312
	ATCC 25577	2.55396	63.3	7	2,290	2,200
	MJR 7694	2.46715	63.4	16	2,235	2,118
	TM16	2.53972	63.4	420	2,441	2,133
	UCD-PD2	2.66729	63.4	51	2,442	2,304
	T13	2.46397	63.4	15	2,223	2,109
	T15	2.46279	63.4	14	2,223	2,110
	T14	2.52207	63.4	9	2,290	2,184
	CI878	2.54154	63.4	73	2,371	2,201
	CI855	2.54166	63.5	51	2,376	2,190
	CI853	2.53246	63.5	41	2,375	2,191
	CI882	2.49707	63.4	66	2,309	2,129
	CI828	2.47614	63.4	30	2,303	2,130
<i>Cutibacterium granulosum</i>	NCTC11865	2.17524	64.2		1,857	1,749
	TM11	2.14036	64.2	98	1,820	1,619
	DSM 20700	2.12823	64.1	372	1,911	1,566
<i>Cutibacterium acnes</i>	KPA171202	2.56026	60		2,371	2,277
	SK137	2.49533	60.1		2,353	2,278
	266	2.49458	60		2,332	2,250
	66609	2.56028	60		2,378	2,282
	ATCC 11828	2.48863	60		2,318	2,198
	Type IA2 Pacn33	2.48962	60		2,327	2,241
	Type IA2 Pacn17	2.52289	60.1		2,354	2,274
	Type IA2 Pacn31	2.49877	60		2,324	2,246
	C1	2.519	60.1		2,377	2,276
	HL096PA1	2.54977	60.15		2,414	2,336
	hdn-1	2.49456	60		2,327	2,247
	KCOM 1861	2.52244	60		2,337	2,208
	PA_15_1_R1	2.54796	60.15		2,409	2,324
	PA_21_1_L1	2.56035	60		2,380	2,276
	PA_15_2_L1	2.54001	60.1		2,382	2,300
	PA_12_1_L1	2.49196	60		2,337	2,261
<i>Cutibacterium namnetense</i>	NTS31307302	2.36966	60.5	24	2,188	2,052
	SK182B-JCVI	2.43067	60.2	50	2,242	2,053

teins code for main metabolic pathways, in particular the propionate formation pathway (characteristic of this genus), the respiratory chain, and fatty acid metabolism (13).

Each species has specific traits. *C. avidum* is characterized by the production of an exopolysaccharide-like structure, encoded by a targeted region corresponding to a species-specific genomic island. This region harbors more than 30 genes, including 19 encoding glycosyltransferases and enzymes implicated in mono- or polysaccharide modification (14). In contrast, *C. granulosum* is able to produce pilus-like structures, appendices that have never been described for either *C. avidum* or *C. acnes*. Rather, *C. acnes* pathogenesis is likely associated with the secreted and surface-associated proteins (42, 43). The detection of a genetic region encoding proteins or enzymes implicated in exopolysaccharide synthesis and modification may explain the ability of *C. avidum* strains not only to produce biofilm following adherence to foreign surfaces or devices but also to evade phagocytosis, along with the ensuing reduced or limited immune response. Consequently, *C. avidum* persistence in infection can be explained. In fact, the chronic status (see the clinical section of this report) of several reported cases can be ascribed to the lack of clearance by the immune system and to frequently described abscess formation, especially after surgery. According to genomic analysis, *Cutibacterium* species have developed different colonization/invasive strategies leading to host interactions or damage. Depending on the genetic background, each species appears to be able to become a potential pathogen, either at a cutaneous level or at nonskin sites.

FIG 2 Overall similarities among the publicly available genomes of *C. avidum*, based on orthoANI values. The dendrogram was created using Oat 0.93 software. Note that two of the genomes, for strains DPC 6544 and UPC-PD2, lie very close to the species boundary of 95% orthoANI, which suggests the presence of a subtype population in the species.

The recent description of the genome sequence of *C. avidum* strain 44067, recovered from a human skin abscess, revealed the presence of clustered regularly interspaced short palindromic repeat (CRISPR) loci (44). This microbial adaptive immune system has been described extensively for *Streptococcus thermophilus* (45). This powerful system restricts the potential for foreign DNA acquisition and therefore limits horizontal gene transfer. This system confers an immune response to invasion by a variety of foreign mobile elements, such as viruses and plasmids (46). The *C. avidum* CRISPR system is related to the *C. acnes* CRISPR system, mostly present in phylotype II isolates. They belong to the same subtype (subtype 1-E), and their *cas* genes are homologous, with 78% identity at the nucleotide level (GenBank accession number [NC021064](#) for *C. avidum* and GenBank accession number [NC006085](#) for *C. acnes*). Moreover, the *C. avidum* CRISPR sequence has two nucleotide substitutions compared to the *C. acnes* sequence. For *C. avidum* ATCC 25577, the CRISPR sequence has previously been reported, with 28 copies along the genome. This sequence appears in 58 copies in *C. avidum* DPC6544 and in 20 copies in *C. avidum* 44064, suggesting potential diversity among *C. avidum* isolates. Moreover, a 100% match has also been noticed in the *C. granulosum* NCTC11865 genome, with 31 copies. However, ATCC 25577 does not possess any of the 18 predicted spacers of isolate 44067. Interestingly, regarding the spacers in *C. avidum* species, one matches a sequence within a gene located on a plasmid (strain HL096PA1) or on a tight adherence locus-containing mobile element (strain 15.1.P1) (46, 47). Further studies are needed to determine whether spacers are predicted to target any known phages or other plasmids in *C. avidum* strains.

Based on the same orthologous average nucleotide identity method reported previously (48), a genomic comparison of the first nine *Cutibacterium avidum* genomes available in the GenBank database was performed. Figure 2 shows a significant relatedness among seven genomes, with orthoANI values between 98.4 and 100%. I can, however, also highlight the presence of a cluster including two genomes (*C. avidum* DPC6544 and UPC-PD2), which might constitute a subpopulation or a subtype of this species, as recently suggested (14, 49). These data should be investigated further with more diverse and numerous clinical isolates to better investigate *C. avidum* pathogenicity, but also the group or cluster delineation of strains with specific potential for abscess formation, for example, or biofilm production, as previously reported for the *C. acnes* phylotype groups (50–52).

FIG 3 Whole-genome comparison of the publicly available genomes of *C. avidum*. The comparison was performed using the BLAST algorithm and visualized with BRIG 0.95 software. The complete genome of *C. avidum* 44067 was used as a reference sequence. Note the presence of multiple isolate-specific regions, which indicates significant genome plasticity. A representative set of these regions (labeled 1 to 10) was chosen for further analysis and suggested an active involvement of *C. avidum* in horizontal gene transfer (see Table 2 for details).

A detailed comparison of available *C. avidum* genomes was also conducted to investigate the possible presence of species-specific traits as well as whether the differences observed within the dendrogram are linked to horizontal gene transfer or mobile genetic elements. I decided to use the complete genome of *C. avidum* 44067 as a reference sequence. I clearly observed the presence of multiple isolate-specific regions, indicating significant genome plasticity (Fig. 3). Interestingly, the 10 most representative genomic regions investigated revealed the presence of transposases, phages, or mobile genetic elements (Table 2). From this point forward, new isolates with a typical clinical presentation should be investigated to study the impact of gene content according to tropism (skin, bone, prostate, etc.) and to highlight the possibility of phylogenetically distinct clusters within the *C. avidum* population. Lastly, a genomic

TABLE 2 Putative nature and distribution of a representative set of genomic regions specific to *C. avidum* 44067^a

Region	Coordinates	Size (bp)	Putative nature	BLAST search result
1	52500–57400	4,900	Mobile element	<i>C. avidum</i>
2	232700–234300	1,600	Acid phosphatase	<i>C. avidum</i> , <i>C. acnes</i> , <i>Bifidobacterium bifidum</i>
3	309100–310400	1,300	Transposase	<i>C. avidum</i> , <i>C. acidipropionici</i>
4	603400–638200	34,800	Mobile element	<i>C. avidum</i>
5	801000–830000	29,000	Phage	<i>C. avidum</i>
6	953300–956200	2,900	Mobile element	<i>C. avidum</i>
7	1215800–1228000	12,200	Phage	<i>C. avidum</i>
8	1256600–1261700	5,100	Mobile element	<i>C. avidum</i>
9	1792700–1806200	13,500	Horizontal gene transfer hot spot	<i>C. avidum</i>
10	2008000–2016000	8,000	Mobile element	<i>C. avidum</i>

^aCoordinates are specified according to the *C. avidum* 44067 genome numbering. The distribution of the genomic regions was determined using BLAST searches with the nr/nt database of NCBI's GenBank.

comparison should also be performed because of the recent report of a *C. avidum* strain isolated from a feline anal sac (49), corresponding to the first description of *Cutibacterium* carriage in animals other than poultry.

PATHOGENESIS

Virulence Factors

Some virulence factors are presented here, but the reader should keep in mind that these factors are predicted or putative virulence factors/host interaction factors. Indeed, to the best of my knowledge, very few data (presented below) are available for *C. avidum* strains compared to the literature on *C. acnes*. I found no molecular-level investigations describing the creation of knockout *C. avidum* strains for putative virulence factors in order to test their functions, properties, and interactions with eukaryotic cells. Nevertheless, *C. avidum* is able to produce several biologically active substances, including enzymes that break down mucopolysaccharides, such as hyaluronidase and neuraminidase (53). Propionins and bacteriocins are also produced by *C. avidum* strains, some of which are able to inhibit all the *C. acnes* or *C. granulosum* strains tested (54).

Lipase

In *Cutibacterium* species, the triacylglycerol lipase gene is one of the most-studied and most significant virulence factors. This extracellular enzyme is produced by most *Cutibacterium* species. By comparing the *C. avidum*, *C. acnes*, and *C. granulosum* lipase gene sequences, I found a higher degree of identity between the *C. avidum* and *C. acnes* *gehA* genes, with 94% similarity. The *GehA* and *GehB* proteins, on the other hand, share 96% and 86% similarities, respectively, between *C. avidum* and *C. acnes* sequences.

The lipase encoded by the *gehA* gene has a crucial impact by hydrolyzing triglycerides of sebum, which partially explains acne pathogenesis. The release of irritating free fatty acids within the pilosebaceous follicles can explain the inflammatory skin disorder commonly observed in acne. Whether *C. acnes* and, to a lesser extent, *C. granulosum* have clearly been involved in acne, the role of *C. avidum* remains unclear. However, despite the different ecological niches, Nakamura et al. were able to use gas-liquid chromatographic analysis to demonstrate higher activity of the *C. avidum* ATCC 25577 lipase (3-fold more butyric acid produced) than that of the *C. acnes* ATCC 11827 lipase (55). Moreover, while the lipase activity of *C. acnes* has been reported to be expressed during the early phase of growth, various investigations have revealed an effect of substrates present in the medium on lipase activity expression. That is, lipase expression is reduced by glucose addition (56).

In *C. avidum* strains, lipase is able to metabolize various substances, giving rise to the free fatty acids responsible for bad odor, especially in axillary osmidrosis (58). To avoid or limit these disadvantages, various substances (*jumi-haidoku-to* or *unsei-in*) are used to decrease or suppress propionic and butyric acid production (57). Although *C. avidum*

is still considered a weak pathogen, the degradative properties of lipase may cause host tissue and cell damage. Other Gram-positive bacteria with lipase activity have also been described, such as *Staphylococcus caprae* (59) and *Staphylococcus aureus* USA300, for which a contribution to colonization and persistence on human skin is likely to be the most plausible role. Moreover, a lipase-deleted *S. aureus* strain revealed a decreased ability to produce biofilm compared to that of the parent strain. Likewise, by using an intraperitoneal infection model in mice, the same group demonstrated reduced formation of peritoneal abscesses, probably correlated with a reduced bacterial load compared to that with the wild type (60).

Other Gram-positive pathogens are able to produce lipase, such as bacteria of the *Burkholderia cepacia* complex, with an impact in lung epithelial cell invasion (61), and *Candida parapsilosis*, a skin commensal for which lipase modulates the immune response of macrophages (62). Future studies clearly need to be performed to investigate the pathogenesis of *C. avidum* infection, especially in liponecrotic breast abscess or skin necrosis (15–17, 32).

Hyaluronate Lyase

Hyaluronate lyase, commonly referred to as hyaluronidase, is an extracellular enzyme involved in bacterial pathogenesis (63). This enzyme has been described for several Gram-positive bacteria, such as *Streptococcus pneumoniae* and *Streptococcus pyogenes*. Initially, it was described as a spreading factor due to its capacity to hydrolyze extracellular matrix in eukaryotic hosts. One of its main substrates remains hyaluronan, a major extracellular matrix component in vertebrates. CD44 is the hyaluronan cell surface receptor molecule. This receptor is present on various cell types, and its importance has been reported previously for the normal immune response process (64).

The three main *Cutibacterium* species recovered from the skin can produce hyaluronidase. Even though *C. acnes* strains are the most active (68.8%), with clearly measurable hyaluronidase activity, *C. avidum* (45%) and *C. granulosum* (33.3%) strains are also positive, despite significantly lower activity (65). The impact of *C. avidum* hyaluronate lyase is still poorly understood. *C. acnes* carries two hyaluronate lyase gene alleles. The HYL-IB/II variant was reported as a highly active allele of hyaluronate lyase resulting in total hyaluronic acid degradation. In contrast, the low activity of the HYL-IA variant resulted in partial hyaluronic acid degradation (66). The first *C. acnes* hyaluronate lyase gene (*hyl* gene in type IB/II strains) has been cloned and sequenced to better understand its structure, binding domains, and homology. Nevertheless, in *Escherichia coli*, the active enzyme was reported to be only cell associated, not secreted. The 2,256-bp gene encodes an 82-kDa enzyme with a leader sequence of 32 amino acids that is cleaved to produce the extracellular form of the mature protein (67).

Further studies with *C. avidum* strains are needed to investigate the role of *C. avidum* hyaluronate lyase in skin or deep infections, the impact of potential variants, its involvement in penetrating the extracellular matrix found in the tissues, and its relationship with the immune system, as recently suggested for *C. acnes* (66).

Hemolysins

Like many other microorganisms, *C. avidum* is able to produce hemolysins, leading to significant beta-hemolysis on blood agar plates (Fig. 4) and resulting in potential side effects in the host. In 1977, Hoeffler demonstrated the most active hemolytic activity of *C. avidum* strains compared to those of *C. acnes* and *C. granulosum* strains, regardless of erythrocyte origin (68). Nevertheless, sheep erythrocytes seemed to be the most resistant. These differences in erythrocyte susceptibility may indicate that there are several substances with distinct hemolytic specificity but also differences in erythrocyte membrane composition.

In 1982, a hemolysin was partially purified from *C. avidum* 1148, isolated from the skin of a healthy adult. The molecular mass was determined to be 32 kDa. The hemolytic spectrum of hemolysin was established by use of different animal erythro-

FIG 4 Colony morphologies of *C. avidum* and related species on Schaedler agar plates after 3 days of incubation in an anaerobic atmosphere.

cytes. Hemolysin activity was completely lost by heating to 60°C for 5 min (53). Various treatments also caused a complete loss of activity (the protein is sensitive to digestion by pronase, DNase, or chymotrypsin), whereas RNase, lysozyme, and lipase did not affect hemolysin activity. Inhibition of hemolysin activity was observed with lecithin but not with cholesterol, which may be a receptor or substrate for hemolysin. Lastly, this *C. avidum* hemolysin is a thiol-activated (oxygen-labile) type of hemolysin, since mercaptoethanol protects it from losing activity in the atmosphere (53).

Historically, the cohemolytic factor has been reported for *C. acnes* strains (69). The CAMP reaction corresponds to the synergistic lysis of erythrocytes by the interaction of an extracellular protein (CAMP factor [for Christie–Atkins–Munch-Petersen]) produced by different species, especially *Streptococcus agalactiae* with the *S. aureus* sphingomyelinase C (β -toxin). Previous investigations of potential hemolytic activity were performed by adding different concentrations of washed animal erythrocytes to a blood agar base (68). Some hemolytic ability differences were observed. For *C. acnes*, various hemolysins were described (69). In order to study the role of each CAMP factor, Sørensen et al. (70) conducted a study on CAMP-deleted strains. Valanne and colleagues (69) demonstrated the presence of the five genes encoding CAMP factors in *C. acnes* subgroups IA, IB, and II. Interestingly, observed differences showed variations at the expression level rather than missing genes (70). Moreover, when the *camp2* or *camp4* gene was deleted, only the $\Delta camp2$ strain revealed reduced hemolytic activity with sheep erythrocytes, suggesting that this CAMP factor is the major active cohemolytic factor, but in the IA phylotype *C. acnes* genetic background. More recently, my group revealed that only strains belonging to IA and IB phylotypes are hemolytic (71), with different behaviors, as previously reported (37).

Concerning *C. avidum*, no such phylogenetic approach has been developed to analyze differences. According to comparative genomic analysis, different CAMP factors, especially the *camp1*, *camp2*, and *camp4* genes, are missing in *C. avidum* genomes. Nevertheless, *C. avidum* isolates contain two CAMP factor genes with high degrees of similarity to the genes for CAMP factors 3 and 5 (HMPREF9153_0708 and HMPREF9153_1759 in strain ATCC 25577) (13). Thus, this characteristic is routinely important for strain identification, since the hemolytic activity of *C. avidum* strains is quite high compared to that of *C. acnes* (71, 72) (Fig. 4).

Biofilm

Bacterial biofilm is a structured bacterial community producing an exopolysaccharide matrix that can allow adherence to foreign devices or viable cell surfaces. The change in behavior (from planktonic cells to an aggregated state or sessile form) is activated by a mechanism of chemical communication that differs between species (73). Biofilm formation has been well studied and characterized for different clinical strains of *Cutibacterium* species, especially *C. acnes* (6, 51, 74, 75). To study the ability of *C. acnes* strains to produce such a structure, various experiments were performed *in vitro*. These experiments used 96-well plates (76, 77), glass beads (75), or various

biomaterials, such as titanium, steel, and silicone (73, 78), as adhesion surfaces. These experiments demonstrated that different *C. acnes* strains are able to form early or mature biofilms on all these surfaces.

In 2009, Holmberg et al. showed that only invasive *C. acnes* strains could produce biofilm, regardless of their phylotype, whereas strains isolated from healthy skin produced less biofilm (77). The ability of *C. acnes* to create a biofilm is also influenced by the presence of plasma and the surface roughness of the biomaterial (77, 79). Although *in vitro* studies are important for analyzing the properties and extrinsic factors influencing the ability of strains to produce biofilm, the clinical relevance of this ability was demonstrated only recently by Tunney et al., by use of immunofluorescence microscopy with a *C. acnes* monoclonal antibody or 16S rRNA gene amplification from sonicate fluids and inflammation cell infiltration in tissues around the implanted device (80). However, the various mechanisms and steps necessary for the synthesis of an exopolysaccharide by *C. acnes* strains remain to be elucidated. Jahns et al. reported that *C. acnes* biofilm composition is similar to that of other bacteria, comprising extracellular DNA, proteins, and glycosylated residues (81). Furthermore, transcriptomic analysis revealed that the genes coding for DNA replication, cell wall synthesis, and cell division were underexpressed in sessile bacteria, whereas the gene encoding the virulence factor CAMP 1 was overexpressed (81).

Conversely, very little clinical and fundamental information is currently available for *C. avidum* strains and associated biofilm production ability. The recent description of device-related infections by genomic analysis revealed new data for this species (14). Indeed, the three *C. avidum* strains analyzed possess a gene involved in the exopolysaccharide synthesis pathway. Consequently, *C. avidum* pathogenicity may be linked to this bacterial property leading to clinically significant infections, including abscess formation, in the presence of foreign-body material, such as prosthetic joint devices. However, according to the study of Achermann et al., no distinction between *C. avidum* and *C. acnes* isolates was reported for the ability to produce a biofilm, despite the presence of an exopolysaccharide island detected in all *C. avidum* clinical strains (72).

Future studies are clearly required to analyze the kinetics of biofilm formation and biofilm maturation and the complex existence of biofilm for this species.

Biofilm formation seems to be regulated by the secretion of particular molecules, a process referred to as “quorum sensing” (82, 83). Quorum sensing is a specific type of communication between bacterial cells, based on a self-induced process: when the chemical signals begin to accumulate in the area surrounding the environment of the pathogen, the latter undergoes a series of physiological modifications that permit biofilm formation (14). Thus, it may be interesting to determine if *C. avidum* strains are unable to send or send only “safety” biomolecules when present in “controlled” quantities under commensal conditions but become pathogenic and send “danger” biomolecules via quorum sensing in the form of excess free fatty acid production, which activates different Toll-like receptors (TLRs) (TLRs 2 and 4), as occurs in the *C. acnes* bacterial community (84).

For this reason, genomic, molecular, biofilm kinetics, and endpoint studies are required to investigate the role of biofilm in *C. avidum* infections. Indeed, in daily practice, we clearly know that biofilm-related infections are difficult to eradicate (75, 85). Sessile *C. avidum* cells will be more resistant than their planktonic counterparts to many of the most-prescribed antibiotics, and they are also able to resist antibodies and evade the immune response. Finally, sessile cells seem to synthesize more lipases as well as various molecules involved in quorum sensing, leading to potentially increased inflammation and abscess formation (58, 76). New perspectives for studying biofilm ability by confocal microscopy, by dynamic study of the biofilm bacterial population along with investigations of specific intercellular communications or with animal models (74, 75), are opening up research projects with this poorly known and too often underestimated species.

Other Virulence Factors

While studying other enzymatic properties among a collection of different *C. avidum* strains, Hoeffler demonstrated that this species is also able to produce gelatinase, DNase, lecithinase, and a weak phosphatase (68). The role of gelatinase was previously reported for other species, with the ability of *Enterococcus faecalis* to induce epithelial cell permeability, though its deletion can also prevent biofilm prevention (86). Lecithinase activity may also be involved in bacterial spread in culture. Such enzymes are required during *Listeria monocytogenes* infection of human epithelial cells (87). Finally, extracellular DNases in bacteria can contribute to physiology and pathogenesis by using different significant pathways. In group A streptococci, the DNase Sda1 suppresses both the TLR9-mediated innate immune response and macrophage bactericidal activity, whereas in *S. aureus*, biofilm susceptibility is time dependent: early biofilms prove to be DNase susceptible, while advanced biofilms are more resistant (88, 89). All these putative virulence factors in *C. avidum* strains should be investigated to better understand host-bacterium interactions at the molecular level that lead to abscesses, biofilm formation, or deep or device-related infections.

Host-Bacterium Interaction

For *C. acnes*, innate immune activation occurs at least partially via TLR2 as well as the NLRP3 inflammasome (90); thus, *C. avidum* is also likely to interact with these receptors. Nevertheless, *C. avidum* can also interact with its own environment via the production of chemical compounds. Some types of biologically active compounds may have a crucial role in *C. avidum* disease physiopathology, particularly that of skin abscesses (see the clinical section of this review). In fact, within the skin microbiota but also inside the pilosebaceous duct in moist areas, *C. avidum* PF77 is able to interact with Vero cells, but much more so with skin fibroblasts, with a cytotoxic effect. Investigation of the impact of *C. avidum* propionate production revealed a correlation between cytotoxicity and propionate concentrations in samples (91). The cytotoxic effect could be related to this production and cause damage to various human cells. Moreover, propionate and other carboxylic acid salts (C_1 to C_5) were assessed at the same concentrations and demonstrated various degrees of cytotoxicity depending on chain length. Similar results have also been observed with certain clades of *C. acnes* strains incubated with bone cells (52).

Similarly, proinflammatory molecule production by *C. avidum* was investigated using culture supernatants in two different models: a guinea pig ileum preparation and a rat fundic strip preparation. These tissue models can be considered models for the receptors implicated in the inflammation cascade. This valuable tool showed that the tissue response observed due to histamine, tryptamine, or short-chain fatty acid salts is systematically dose dependent, leading to smooth muscle contraction or relaxation. Interestingly, the levels of histamine-like or tryptamine-like activities measured in *C. avidum* PF77 culture supernatants grown in the presence or absence of histidine or tryptophan revealed less histamine-like activity but more tryptamine-like activity for *C. avidum* than for *C. acnes*. The histamine, tryptamine, and short-chain fatty acids produced by *C. avidum* may therefore play a role, especially in sebaceous follicles, as biologically active substances leading to inflammation (92). Nevertheless, further studies should be conducted to better understand these biological effects *in vivo*, according to the potential microenvironmental differences that can clearly exist between different grades of normal and acne-prone skin (pH, oxygen tension, bacterial competition, resource levels, etc.).

Immune Stimulation

This section and the following one summarize early studies focused on testing immune stimulation and antitumor effects of different *Cutibacterium* strains, which were probably less well characterized and identified at the molecular level than they are now.

In 1976, the mitogenic activity of bacterial cells or cell wall fractions prepared from various *Cutibacterium* species, including *C. avidum* ATCC 25577, was investigated. The results suggested that the cell walls used acted as mitogens on both thymus-derived lymphocytes (T cells) and bone marrow-derived lymphocytes (B cells) (19). This mitogenic potential was suggested to be dose dependent: it was reported to be more active with 100 μ g than with 10 μ g *C. avidum* cell wall preparations (93).

Lymphoreticular stimulatory properties of anaerobic coryneforms may vary remarkably due to cell wall composition, especially the composition of the peptidoglycan. A first comparative study on the cell wall composition of some *Cutibacterium*-related species revealed various lymphoreticular stimulatory activities. The cell wall of *C. granulosum* strains, which is inactive in assays for such activation, was reported to contain a larger amount of alanine than that for most of the *C. avidum* or *C. acnes* strains investigated (94). Accordingly, significantly higher antibody titers toward the acidic polysaccharide fraction are found in severe acne patients than in healthy patients. These antibodies may cross-react with *C. avidum* serotype I or II. These findings suggest that this external bacterial component may participate in the inflammation of acne (95). Nevertheless, no recent studies have reported specificity and antibody titer levels against *C. avidum* or *C. acnes* in acne or other patients.

The key role played by propionibacteria in modulating the immune response has been reported based on different approaches. Indeed, the three main species, including *C. avidum*, were described to be immunomodifiers stimulating the different cell subset populations implicated in nonspecific antibacterial, antiviral, and antitumor resistances (21). The higher activity for *C. avidum* was confirmed in parallel with antitumor activity by Cummins and Linn (23). Later, the Pulverer group demonstrated the ability of *C. avidum* KP-40 (a strain included in Pulverer group patent CA1197798A) to potentially modify and enhance thymocyte/lymphocyte proliferation, maturation, emigration, and activation (21).

Indeed, by using different models, different groups highlighted this ability. Comparing the effect of a killed *C. avidum* preparation to that of lipopolysaccharide on nitric oxide synthase induction kinetics in a rat model, Dhouib et al. confirmed that Kupffer cells were responsible for the uptake of bacteria, like other reticuloendothelial cells, such as specialized macrophages (96). Moreover, several tests (chemiluminescence responses of human leukocytes and mouse peritoneal macrophages, spleen enlargement, and pulmonary tumor colonization) revealed that the *C. avidum* KP-40 isolate displayed clear immunostimulatory and antineoplastic activities (97–99).

Although there have been numerous surveys on the *Cutibacterium* active cell wall element implicated in antitumor activity (see the next section), the active cell wall structure responsible for protecting against viral infections remains unknown. As previously described, *Cutibacterium* can stimulate the reticuloendothelial system, but it can also trigger immune cell modifications, in particular macrophage activation, natural killer cell activation, and interferon induction. In a mouse viral infection model, a protective role of the *Cutibacterium* cell wall fraction in pretreatment was demonstrated (100, 101).

At the veterinary level, using various models, the same groups described the usefulness and probable positive economic impact on farms and animal breeding of the potent granulopoiesis response after *C. avidum* immune stimulation. By use of 10 different test parameters, it was suggested that the role played by this preparation in protection against bacterial and viral infections leads to improved conditions for animal development and growth (faster weight gain) (102, 103). The adjuvant properties of *C. avidum* KP-40 have also been reported for various swine models (104–106).

Thus, *C. avidum* proved to be a potent and sometimes excellent stimulator of the macrophage-monocyte system and an inducer of endogenous interferons (107, 108). This bacterium also seems to be able to act as an adjuvant with vaccines. *C. avidum* and its closest relatives are clearly involved in inflammation (chemokines and cytokines) (109) but can also interact with the immune system (macrophages, dendritic cells, polymorphonuclear cells, and natural killer cells) (110–112). Consequently, different

clinical applications have been proposed. For example, it has been suggested that a 10-mg *per os* administration of *C. avidum* KP-40 (twice a day) for 7 days may restore the downregulated immune response resulting from intense sports activities (113). Lastly, this bacterium can modify the gut microbiota, adhere to intestinal epithelial cells, and produce vitamin B₁₂ as well as inhibiting negative microbiota by fatty acid release and bacteriocin production (114).

These properties are most likely due to specific interactions at the molecular level. Members of the *Cutibacterium* genus interact closely with immune cells via multiple receptors, particularly TLR2, TLR4, and TLR9 (90, 109, 115, 116). These species are triggers for innate immunity and can promote inflammation but can also mediate or modulate the immune system in a complex equilibrium (117). It should be noted that, since 1988, only *C. acnes* has been shown to induce granulocyte activating factor release as a possible mediator of inflammation, a signature of its potential role in the chronic inflammatory disease acne, in which *C. avidum* is less involved (see the information on ecological niches in the earlier sections) (118).

Antitumor Activity

In the 1960s, anaerobic coryneforms were used extensively as antitumor agents following the discovery that, in mice, killed preparations were able to stimulate cells of the reticuloendothelial system (18). A selection of *C. acnes* type I or II strains, *C. granulosum* strains, *C. avidum* strain 4982, and control strains were examined for the ability to inhibit tumor growth. Interestingly, *C. avidum* was marginally more effective than the other strains at high-dose stimulation. In fact, this species stimulated effector cells which were cytotoxic at high effector/target cell ratios. A relatively good correlation between the drop in packed cell volume, splenomegaly, and the antitumor activity of the *C. avidum* strain was observed. In contrast, no correlation was reported with this model between antitumor activity and the extent of the inflammatory peritoneal exudate induced after 4 days. These strains, which have been compared serologically but also in terms of their biological activity, stimulated tumor immunity. This was only an observation, however, especially for the *C. avidum* strain, and it would be premature to speculate on a potential role for the soluble, cell-attaching polysaccharide antigen (18).

Working with a significant panel of anaerobic coryneform strains, Cummins and Linn confirmed the reticulostimulating properties of species (*C. avidum*, *C. acnes*, and *C. granulosum*, but also classical *Propionibacterium* species, such as *Propionibacterium freudenreichii*, *Propionibacterium thoenii*, and *Propionibacterium jensenii*) from a wide variety of both geographic and clinical sources (23). Even though a considerable degree of variation was observed (strain and mouse host variabilities), almost all the vaccines, regardless of origin, produced splenomegaly in the recipient mice. *C. avidum* and *C. acnes* type II were the most active as analyzed by the spleen weight ratio. As reported earlier by McBride et al., the *C. granulosum* strains were either not active or less active (18, 23). These results were later confirmed by Ko et al. by testing of immunostimulatory potency by use of the spleen enlargement responses to different *Cutibacterium* species. They found that 82%, 12%, and 0% of *C. acnes*, *C. avidum*, and *C. granulosum* strains, respectively, displayed stimulatory activity (119). Moreover, the restriction of tumor growth and the prolongation of mean survival time were observed only with strains capable of inducing splenomegaly (>200 mg in a mouse model).

Differences in the immunostimulatory potencies of the species, correlated with various resistances to degradation by macrophages and the prolonged presence of nondisintegrated bacterial membrane elements in these cells, were accountable for the reticulostimulatory effect (119). For vaccines, investigations into the nature of the reticulostimulatory substance by use of different inhibitory treatments (alanine content) also suggested that the cell wall peptidoglycan and lipid fractions are the active material. Nevertheless, a strong adjuvant effect (indirect effect) on B cell responses was noticed, and the primary action was on macrophages (120). The enhancement of *C. avidum* antitumor activity was also confirmed to be macrophage dependent

in the model and depended on the restoration of T cell function in combination with neurotrophin (121). Later, the *C. avidum* KP-40 strain demonstrated immunostimulatory activity, leading to the possible prevention of metastatic lung and liver colonization in a mouse tumor model (122).

Nevertheless, in 1980, Roszkowski et al. revealed the ability of strains of *C. avidum*, *C. acnes*, and *C. granulosum* to stimulate lymphocytes *in vitro* to similar degrees (123). This group demonstrated that the same species injected in multiple doses of 1 mg/mouse appeared effective at retarding the growth of Sarcoma-180 in mice, with a prolonged survival of Sarcoma-180-bearing mice (124). Subsequently, in 1985, Hojo et al. demonstrated a dose effect for limiting BC47 tumor growth in a rat model, leading to cytotoxic lymphocyte action following intraperitoneal injection of the *C. avidum* strain (125).

In summary, *C. avidum*, like other *Cutibacterium* species, not only can stimulate several cells largely involved in the immune system (antitumor activity) but also can modulate this system at both the local level (especially at the skin level) and the systemic level, with involvement of dendritic cells, macrophages, and NK cells.

According to *in vitro* and *in vivo* model results obtained during the early 1990s, the Pulverer group in Germany decided to move from the bench to the bedside with prospective randomized studies including patients with gastrointestinal tumors (212). No effect was observed regarding postoperative complications or tumor recurrence rates between the control and treatment groups (212), but after a preoperative intravenous (i.v.) infusion of 10 mg of the whole *C. avidum* KP-40 preparation, they demonstrated enhanced neopterin secretion in urine, with persistence of this biomarker. Indeed, neopterin is considered to be an early signal of the cellular immune response (126). They also highlighted that only a lymphocyte subset population (the natural killer cell population) was statistically increased following infusion of the same preparation (same dose) (110, 111). This immunotherapy approach with the *C. avidum* KP-40 preparation and its therapeutic added value remain debatable according to the type of tumor treated, the strain selected, the route and timing of the administration scheme, and the potential adverse events (127, 128).

DIAGNOSTIC PROCEDURES

Conventional Microbial Cultures

The present section summarizes studies focused on nutritional requirements, especially examining the impacts of amino acids, Tween 80, glucose, pH, and oxygen on *C. avidum* growth in conventional microbial cultures.

In 1978, Ferguson and Cummins developed a basal medium and improved the growth rate of *Cutibacterium* spp. by adding various components (129). The nutritional requirements of the three main *Cutibacterium* species, including *C. avidum* types I and II, were consequently determined. The vitamin requirements for these anaerobic bacteria are consistent with the propionic acid fermentation pathway for carbohydrates found in conventional propionibacteria, leading to propionic acid production.

According to the growth rates observed with numerous modifications of the basal medium used, the nutritional requirements and the products of their metabolic pathways are quite similar. For more details, an excellent summary analyzing the effects of selected nutrients on growth is provided in Table 2 of reference 129. *C. avidum* strains can grow in a glucose-supplemented basal salts medium, pantothenate, biotin, thiamine, and 12 different amino acids. Six more amino acids should be added for *C. granulosum* and *C. acnes* (asparagine, leucine, lysine, proline, threonine, and valine). Nicotinamide had no effect on *C. avidum* growth. Other nutrients that were not absolutely necessary factors, though they greatly enhanced the rate of growth, included purines, sodium L-lactate, pyruvate, α -ketoglutarate, and, to a lesser degree, Tween 80, a potential oleic acid source (129).

A Tween 80 concentration of 0.005% (vol/vol) resulted in the highest growth rate for *C. avidum* strains, whereas 0.1% was better for the other species. This result is consistent with the conditions encountered in their natural habitats (11, 28). Interestingly, this

concentration may play a role in the recovery rate for clinical skin samples, and preincubation of the swab in a 0.1% Tween 20–0.15 M NaCl broth can improve *Cutibacterium* detection, though it decreases the growth of coagulase-negative staphylococci. Moreover, depending on the incubation conditions (anaerobic atmosphere or not), colony growth may vary according to the medium used (blood agar, brucella agar, Schaedler agar, or chocolate agar) and the incubation period (51).

In the 1980s, the effects of glucose concentration were investigated by Cunliffe and coworkers, using different criteria: biomass, maximum specific growth rate, and extracellular enzyme production by *C. avidum* and related species (130). Biomass increased with glucose concentrations of up to 0.3% (wt/vol) for *C. avidum*, and then biomass remained constant or decreased slightly. Under these conditions, lipase activity remained virtually unchanged, while it was higher at 0.4%, and glucose concentrations of up to 0.5% reduced this activity. Under glucose-free conditions, *C. avidum* gave approximately 4-fold higher initial yields than those of *C. granulosum*. Consequently, and unlike *C. granulosum*, *C. avidum* (along with *C. acnes*) displayed the highest maximum specific growth rate when the strains were grown in a medium free of glucose. Therefore, *C. avidum* seems to be the most nutritionally adaptable *Cutibacterium* species. Indeed, this species grew well under glucose-free conditions, and its biomass index in response to glucose supplementation was higher than those for other species.

In contrast, it should be noted that *C. avidum* produced 20-fold less lipase per unit of biomass than that produced by other species. Consequently, in light of their own niches and the protein-rich and moist skin environment, *C. avidum* relies on proteinases to scavenge for amino acids and peptides as a carbon/energy source, whereas *C. granulosum* is dependent on other carbon/energy sources (basically saccharolytic metabolism) (130).

To determine the impact of pH modifications, but also to mimic the reality of microenvironmental skin changes, especially within sebaceous follicles, this variable was similarly investigated. Using *C. avidum*, maximum biomass production was achieved at pH 6.0. The same pH was considered to be optimum for the maximum specific growth rate. According to potential enzyme denaturation (i.e., lipase for *C. avidum*) at low or high pH values (<4.5 and >6.5), lipase production was found to be highest at pH 5.5. With *C. acnes* lipase, lyase, and phosphatase or *C. granulosum* lipase and hyaluronate lyase, the same narrower pH range was reported (131). This pH value is the most frequently encountered on the skin, regardless of location, thus explaining the growth of *Cutibacterium* species in this specific microenvironment. Interestingly, at this pH, lipase can hydrolyze sebum triglycerides produced by the sebaceous glands, which may explain in part how this specific microbial ecology can affect skin homeostasis at different levels, e.g., free fatty acid production, triglyceride degradation, bacterial density, immune system dysregulation, and inflammation (109).

In the same way, oxygen concentration variations were investigated for various *Cutibacterium* species. While the presence of oxygen reduced the maximum specific growth rate for all species, *C. avidum* was unaffected by the presence of oxygen and was the best species at adapting its growth to aerobic conditions (129, 132). This difference is clearly observed with clinical strains in routine laboratory diagnosis. Indeed, *C. avidum* can easily grow aerobically. Consequently, lipase production by *C. avidum* was constant across all oxygen conditions tested, whereas production was dramatically reduced for *C. acnes* and *C. granulosum*. The same observation was made for both species with regard to hyaluronate lyase production (132). These different investigations, with some modifications to growth conditions and their impacts on growth rate (133), show that extracellular enzyme production may constitute an excellent argument due to the role of these species in acne or deep infections, with or without a device. Indeed, bacterial multiplication, but also the role of an enzyme such as lipase or hyaluronate lyase, may be crucial in acne pathogenesis and *Cutibacterium* species device-related infections (134).

To summarize, in daily practice, skin swabs, deep tissues, or biopsy specimens can be used to isolate *Cutibacterium* species. These can be inoculated onto plates containing a medium consisting of 3% tryptone soy broth, 1% yeast extract, 1.2% bacteriological agar, and 0.5% Tween 80 (28). As for *C. acnes* or *C. granulosum*, other media can also be inoculated, such as Schaedler agar or chocolate agar plates or enrichment broth, especially thioglycolate broth for clinical samples. All should be incubated anaerobically for at least 7 to 10 days at 37°C and, depending on the type of infection, for up to 14 days, especially for bone and joint infections (51). Interestingly, *C. avidum* grows faster than *C. acnes*, most likely due to its metabolism (*C. avidum* is more aerobic than *C. acnes*) and to the microenvironment (sebum, skin pH, etc.) (6, 51, 72).

Contamination Issues in Culture

The clinical significance of a culture positive for *Cutibacterium* species in different cases (orthopedic and device-related infections, catheter shunt infections, breast specimens, etc.) remains unclear, both concerning its potential role as a true pathogen (infection), a real contaminant, or a skin invader due to skin incision (commensal presence in deep tissue) and its potential role as a coinfectant (135). There are no available guidelines for culture interpretation. How many media should be used, and how long should the media be incubated? How many colonies are needed to distinguish contamination from infection? In the orthopedic field, Schaedler or thioglycolate broths are usually incubated for up to 14 days (136). Recently, Bossard et al. reported that shortening of the culture incubation time to 7 days would result in a 21.4% increased rate of false-negative diagnosis; thus, they recommend that perioperative samples be incubated for at least 10 days to detect *Cutibacterium* species and to distinguish contamination from true infection (137). This delay of 10 or 11 days was also proposed by Frangiamore et al. to separate early and late growth (138).

C. avidum and *C. acnes* infections are defined as the isolation of *Cutibacterium* species from at least two or more specimens, with the presence of typical perioperative findings and/or local signs of infection (139). Nevertheless, *Cutibacterium* species seem likely to be spread throughout the surgical field from the subdermal layer after the skin incision via soft tissue handling by the surgeon and instruments, even during primary shoulder arthroplasty (140, 141). On the other hand, to assess the *Cutibacterium* species catheter colonization rate, 1,000 vascular catheters were treated by the roll-plate method, but after conventional aerobic incubation, all primary culture plates were reincubated for anaerobe detection. Significant numbers of *C. acnes* cells were detected in these catheter samples (for 39 patients, representing 14.7% of all positive catheters [most likely by contamination of the device, with noninfection or bloodstream infection]). These data suggest that methodological shortcomings impair the proper detection of *Cutibacterium* spp. as a hidden and possible cause of contamination or catheter-related infections (142).

Therefore, to avoid misinterpretation or overinterpretation of positive cultures (contamination), new approaches are necessary to minimize this contact and to reduce the colonization rate (new antibiotic prophylaxis and new strategies for skin preparation). Different risk factors have been pointed out: male sex, previous surgeries, and preoperative corticosteroid injections are associated with a higher likelihood of bacterial growth in culture. More clinical studies are needed to confirm and define the proper role of these risk factors (143, 144). Moreover, the relative risk of obtaining a positive *Cutibacterium* culture was 2-fold greater for the anterolateral approach than for the deltopectoral approach in total shoulder arthroplasty (135). Finally, considering the clinical meaning of unexpected positive *Cutibacterium* cultures, in almost 25% of cases, unexpected culture had no clinical significance, and persistent infection was demonstrated in only 10% of cases (143, 145).

Identification Methods

In the 1970s and 1980s, *C. avidum* strains were identified by colony appearance: glossy, rust colored, and sometimes mucoid on blood agar or Schaedler agar plates

(146). Confirmation was obtained by testing indole production, hemolysin production, and nitrate reduction (28).

Serological and Precipitin Tests for Identification of *Cutibacterium*-Related Species

Before the modern era with MALDI-TOF technology, several teams developed agglutination tests to separate and identify the different species or groups of species within the *Cutibacterium* group (147–149). In 1975, Cummins proposed a serological identification method using trichloroacetic acid extracts. This method was evaluated on 142 human skin strains, including *C. avidum*, *C. acnes*, and *C. granulosum* strains. An excellent agreement between serological results and the fermentation patterns of the strains was reported (150). Serological reactions were generally well developed and easier to interpret under standard conditions for *C. avidum* and *C. acnes* than for *C. granulosum*. The existence of two serotypes was confirmed for both *C. avidum* and *C. acnes* strains, even though investigation of a broad collection of *C. avidum* isolates could not be performed. The majority of the strains provided and analyzed were recovered from suppurative lesions. It was suggested that these microorganisms are not common in the skin microbiota, although they certainly do occur there.

Cell Wall Analysis and Protein Pattern Analysis

Among anaerobic coryneform bacteria, different *Cutibacterium* species were initially defined by DNA homology relationships and cell wall analysis. Cummins confirmed these different species and demonstrated that *C. avidum* and *C. acnes* can be subdivided further into two subtypes (150). Later, the protein patterns obtained after Coomassie brilliant blue staining of polyacrylamide gels proved to be highly distinctive and reproducible. Consequently, including different *C. avidum* strains of various origins (hip sinus, pelvic abscess, inguinal abscess, wound swab earlobe cyst, and normal skin), the protein patterns confirmed the earlier results of DNA homology and immunodiffusion studies, indicating a close relationship between *C. avidum* and *C. acnes*, along with the possibility of distinguishing both serotypes.

Moreover, malate dehydrogenase proteins from the three species had different motilities, with strong, well-defined single bands. Enzymes from *C. avidum* type I and II strains could not be distinguished. This method was distinctive for each species, especially to differentiate subtypes between *C. avidum* and *C. acnes* (22).

Polyacrylamide gel electrophoresis (PAGE) of whole-cell proteins of different *Cutibacterium* isolates of various origins demonstrated no particular protein profile, regardless of origin or patient (healthy skin patient or acne patient). This investigation confirmed the proximity between *C. avidum* and *C. acnes*, with close or identical protein patterns, whereas *C. granulosum* can clearly be distinguished by PAGE (151).

The *C. avidum* ATCC 25577 cell wall polysaccharide composition consists mainly of galactose and mannose, whereas glucose, galactose, and mannose are found for *C. acnes* ATCC 11829, *C. acnes* C7, and *C. granulosum* ATCC 25564 (19). Moreover, the analysis of the cell wall composition of various *Cutibacterium* spp. revealed a new component: 2,3-diamino-2,3-dideoxyglucuronic acid. This component makes up between 3 and 5% of the total cell wall polysaccharides of the closely related species *C. avidum* and *C. acnes*, regardless of type (152). On the other hand, it appears to be present in the *C. granulosum* cell wall, but in much smaller amounts, as also revealed by genomic comparisons (see the section on genomic analysis).

Concerning cell wall composition, all the strains have some combination of galactose, glucose, and mannose as cell wall sugars, and most have alanine, glutamic acid, glycine, and L- α - ϵ -diaminopimelic acid as amino acids of peptidoglycan. However, a few strains that already have some differences in the *C. acnes* and *C. avidum* homology groups have meso-diaminopimelic acid and minimal amounts of glycine (41). These data gave rise to what was probably the first description of *C. acnes* types I and II based on antiserum analysis, leading to the first phylogenetic study of these types. Later, other methods for discriminating both serotypes, based on bacteriophage and fermen-

tation typing as well as immunofluorescence assay with polyclonal antisera, were also reported (34). Unfortunately, to the best of my knowledge, the lack of antisera for *C. avidum* prevented any further investigation with these methods, and now the genomic era will bring deeper information on and new insights into the population diversity of *C. avidum*.

Susceptibility to Free Fatty Acids

As discussed above, *Cutibacterium* species produce lipase, considered to be one of the main virulence factors. A complex mixture of various fatty acids with different chain structures and unsaturation positions can be detected on the human skin surface. These compounds from sebum triglycerides are hydrolyzed by lipase in pilosebaceous follicles. This local chemical reaction may have a significant impact on the physiopathology of inflammatory skin lesions linked to specific interactions with the host immune system (24, 109, 117). Ko et al. focused on differences in the susceptibilities of *C. avidum* and related species to a selection of free fatty acids. MIC values for the different strains tested demonstrated unsaturated acids to be more inhibitory than saturated ones. Octadeca-9,12,15-trienoic acid appeared to be the most inhibitory acid. In contrast, decanoic acid had the lowest bacteriostatic activity. *C. avidum* appeared to be more resistant than the *C. granulosum* strains to octadeca-9,12,15-trienoic acid. Finally, *C. avidum* strains appeared to be more susceptible than *C. granulosum* and *C. acnes* strains to decanoic and dodecanoic acids.

Fatty acid analysis may explain the changes in *Cutibacterium* density and distribution in both healthy and sick patients, especially acne patients. Interestingly, these data can be used for bacterial identification, and their analysis may also serve as an additional characteristic for *Cutibacterium* classification, as recently reported (8, 9).

Although cellular fatty acid composition analysis is restricted to reference laboratories and probably not possible in routine practice, this identification step can be exploited to discriminate between different profiles among closely related species. Thus, *C. avidum* reveals a significant proportion of $C_{i15:0}$ (153), as recently described for the new species *Cutibacterium namnetense* (9).

Biochemical and Enzyme Profiles

As early as 1977, Hoeffler described the production of toxins and enzymes by *Cutibacterium*-related species, including *C. avidum*, *C. acnes*, and *C. granulosum*, to determine whether or not there are differences in their profiles as a means of identification, and possibly as a virulence marker (68).

With a collection of 33 *C. avidum* isolates (from normal human skin), 40 *C. acnes* isolates (from human hair, acne lesions, and nonspecific infections of the cervicofacial region), and 18 *C. granulosum* isolates (from acne lesions and normal human skin), the production of chondroitin sulfatase, hyaluronidase, DNase, phosphatase, and lecithinase was tested.

Chondroitin sulfatase was not detected in most *C. avidum* strains, whereas 68% of *C. acnes* strains were found to be producers. *Cutibacterium* species phosphatase activity was shown to be weakly positive or negative. In contrast, most *C. avidum* strains exhibited DNase and gelatinase activities, but most of them were not producers of hyaluronidase and lecithinase (only 18% and 27% produced these enzymes, respectively) (68).

Looking at the regional distribution of cutaneous *Cutibacterium* strains, McGinley et al. demonstrated that all 52 clinical *C. avidum* strains produced gelatinase and hydrolyzed casein. In contrast, *C. granulosum* strains did not metabolize these compounds, and most *C. acnes* strains produced indole (87%) (11).

In a recent study of the physiological and functional characteristics of *Cutibacterium* strains of the poultry microbiota, the biochemical properties reported to characterize the *C. avidum* isolates studied were as follows: catalase activity, gelatin liquefaction, and esculin hydrolysis. The main substrates used to identify the isolates (100%) by acid formation were as follows: erythritol, D-galactose, N-acetyl-D-glucosamine, maltose,

TABLE 3 Biochemical characteristics of *C. avidum* compared to the other *Propionibacterium* species from the skin environment^a

Characteristic	Result			
	<i>C. avidum</i> CCUG 36754 ^T	<i>C. acnes</i> CCUG 1794 ^T	<i>C. granulosum</i> CCUG 32987 ^T	<i>C. namnetense</i> CCUG66358 ^T
Catalase	+	+	+	+
Beta-hemolysis ^b	+++	++	—	+
Acid produced from:				
Glucose	+	—	+	+
Ribose	+	+	—	+
Xylose	—	—	—	—
Mannitol	—	+	+	—
Maltose	+	—	+	—
Lactose	—	—	—	—
Sucrose	+	—	+	—
Glycogen	—	—	—	—
Raffinose	—	—	+	—
Production of:				
Indole	—	+	—	+
Nitrate reductase	—	+	—	+
α -Galactosidase	+	—	—	—
β -Galactosidase	—	+	—	+
α -Glucosidase	+	—	+	+
β -Glucosidase	+	—	—	—
Arginine arylamidase	+	+	—	—
Proline arylamidase	+	+	+	—
Phenylalanine arylamidase	+	—	—	—
Leucine arylamidase	+	—	—	—
Tyrosine arylamidase	+	—	—	—
Glycine arylamidase	+	+	—	+
Histidine arylamidase	—	—	—	—
Glutamyl glutamic acid arylamidase	+	—	—	—
Hydrolysis of:				
Esculin	+	—	—	—
Gelatin	+	+	—	+

^aCCUG, Culture Collection of the University of Gothenburg (Swedish culture collection). All these strains are type strains. *C. avidum* CCUG 36754 belonged to the Pasteur Institute (unknown origin; Prevot collection), *C. acnes* CCUG 1794 was recovered from an acne lesion in human facial skin, *C. granulosum* CCUG 32987 was isolated from human skin, and *C. namnetense* CCUG 66358 was recovered from a bone infection.

^bThe number of plus symbols reflects the relative level of hemolysis. For *C. acnes* CCUG 1794^T, the hemolysis level is ++, but for other strains of this species, the level depends on the phylotype (phylotypes II and III are not hemolytic).

mannitol, mannose, sucrose, and trehalose (33). Table 3 provides a summary of the key differences in terms of biochemical characteristics between the *Cutibacterium* species.

In daily practice, routine tests were performed, such as Gram staining of suspected orange colonies with significant beta-hemolysis growing on Schaedler or chocolate blood agar plates and testing for positive reactions for catalase, esculin, and CAMP factor. Moreover, a negative indole spot can distinguish *C. avidum* from other *Cutibacterium* spp. These tests can be oriented toward routine identification (screening tests). Nevertheless, although these parameters were useful at one time, they are now considered obsolete due to the potential risk of reading errors by the operator. Thus, with the advent of MALDI-TOF technology, definitive and accurate identification is achieved quickly, and hence the other methods have been abandoned or restricted to use in reference laboratories.

Molecular Identification

Molecular methods have revolutionized bacterial identification and have highlighted discrepancies, potential discordant results, and errors in phenotypic identifications that, until recently, were the only ones available. Bacterial molecular identification is based on the sequence analysis of a species-specific target gene. The sequence obtained is then run against various publicly available databases via the Internet. Depending on the chosen target, different software applications can be

used, such as the GenBank database (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>), RIDOM (<http://www.ridom.de/seqsphere/>), or the BIBI database (<https://umr5558-bibiserv.univ-lyon1.fr/lebibi/lebibi.cgi>).

In the 1970s, Woese et al. proposed the use of the first molecular clock scale based on 16S rRNA gene analysis as a phylogenetic tool (154). The 16S rRNA gene sequencing method can be performed routinely in microbiology laboratories either for phylogenetic analysis (9) or for the description of species not available in phenotypic or MALDI-TOF databases (see below) (155, 156). However, using this target, multiple cases of probable clinical misidentifications versus conventional culture-based identifications across a wide range of bacteria have been reported (157). Indeed, depending on the species or genus analyzed, 16S rRNA gene sequencing does not warrant an accurate delineation of bacterial species, especially for the *Cutibacterium* or *Propionibacterium* species with bacterial subgroups or complexes (Fig. 5A).

Consequently, the current species definition by molecular identification proposes a 16S rRNA gene divergence of 1.3%, and a genus divergence cutoff of 2% has been validated (about 97% similarity). For more information, see the review by Georgiades and Raoult (158). A second important remark is that regarding the size of the sequence analyzed, the bigger the better. In other words, the more 16S rRNA gene domains are analyzed, the better the resulting species identifications will be.

Finally, before genomic comparison and the revolution of the genomic era, other molecular targets could be used to avoid a misleading species definition. The following targets have been used to identify a broad range of Gram-positive and -negative pathogens: *rpoB*, encoding the β -subunit of RNA polymerase; *gyrB*, encoding the β -subunit of DNA gyrase; *sodA*, encoding superoxide dismutase; *hsp60*, encoding a heat shock protein; *recA*, encoding a bacterial recombination protein; and *tuf*, encoding an elongation factor.

By using *rpoB* and *gyrB* in the routine lab (Fig. 5B and C), my colleagues and I can clearly distinguish all the members of the genus *Cutibacterium* with a greater discriminatory power than that for 16S rRNA gene sequencing (9). Moreover, we have demonstrated the ability of *gyrB* sequencing to distinguish *C. avidum* from *C. namnetense* and the different lineages of the *C. acnes* clinical strains misidentified by the phenotypic method prior to the MALDI-TOF revolution.

Interestingly, as suspected with genomic analysis (see above), we can clearly see two subpopulations of *C. avidum* strains, highlighting the probable existence of two subtypes of *C. avidum* strains by *gyrB* analysis (Fig. 5C), with group 1 comprising the ATCC 25577 and 44067 strains and group 2 comprising the TM16 and DPC6544 strains.

MALDI-TOF Identification

For the past decade, matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has allowed quick and easy bacterial identification (159). This strategy is relevant for both pathogenic and commensal bacteria. It can therefore be performed directly on blood culture bottles, saving time and money by identifying strict pathogens and contaminant bacteria (160). This tool is therefore useful and effective for detection of Gram-positive bacteria, especially *Cutibacterium* spp.

Among the 544 anaerobes identified by MALDI-TOF, La Scola et al. reported an unexpectedly high frequency of *Cutibacterium* spp. in sinus samples, representing 67% of anaerobes recovered during sinusitis. *C. avidum* was the least frequent species, after *C. granulosum* ($n = 2$) and *C. acnes* ($n = 20$) (161). Using another system, called Andromas, clinical *Cutibacterium* strains were correctly identified to the species level, including 18 *C. avidum* strains (162). Finally, only three *C. avidum* strains involved in a prosthetic joint infection were reported by Peel et al., working on the ability of MALDI-TOF to quickly identify and distinguish relevant pathogens versus culture contaminants (163).

Thanks to MALDI-TOF technology, *C. avidum* is increasingly found routinely in laboratories and is probably misidentified by biochemical profile comparison. Regarding the different spectra, several peaks are discriminant for better distinguishing *Cutibacterium* species. Moreover, even though the possibility of identifying slow-growing anaerobes with high accuracy and speed at low cost compared to those of

FIG 5 (A) Neighbor-joining (NJ) tree for the genera *Cutibacterium*, *Propionibacterium*, and *Pseudopropionibacterium* based on 16S rRNA gene sequences, including those for 8 strains of *Cutibacterium avidum*. Twenty-three 16S rRNA gene sequences selected from the GenBank database were aligned by using MEGA6 (www.megasoftware.net). Accession numbers are indicated after strain names. The evolutionary history was inferred using the neighbor-joining method. The

(Continued on next page)

conventional procedures is relevant in daily practice, this tool also has the ability to perform species typing (spectrum analysis and comparison) and to provide information concerning the main phylogenetic groups of a species (164).

Further studies are needed to increase and develop the database of spectra with the different MALDI-TOF systems available and then to investigate the potential diversity in the *C. avidum* population as well as within the *C. granulosum* species. This would indeed be relevant, since the strains are likely different depending on the site of isolation. I provide an example of the four main spectra obtained with Vitek MALDI-TOF MS (bioMérieux) in Fig. 6. Peaks and mass comparisons are also possible with various free software applications, such as Mass. Using Vitek MALDI-TOF MS, one can separate the four main *Cutibacterium* species by using specific peaks and masses. Thus, according to the bioMérieux algorithm, *C. avidum* is characterized by the following 8 masses compared to other *Cutibacterium* spp., with excellent discriminatory power and good to excellent intensity: 3,685.4, 4,762, 5,125.9, 6,526.4, 6,776.6, 6,818.7, 7,369, and 13,045 Da. A detailed analysis is provided in Table 4, with 7, 13, and 11 specific masses with high discriminatory power for *C. acnes*, *C. granulosum*, and *C. namnetense*, respectively, as follows: for *C. acnes*, 3,518.4, 4,984.5, 7,182, 8,668, 8,690.7, 13,576.9, and 15,058.2 Da; for *C. granulosum*, 3,481, 4,421, 4,789.9, 5,258.4, 5,688.8, 6,682.6, 6,709.7, 6,805, 6,985, 7,886, 8,646.3, 8,792, and 9,576.7 Da; and for *C. namnetense*, 3,412.2, 3,472, 3,972, 3,993, 4,767.5, 5,865, 6,766.9, 6,822.7, 7,287, 8,683.5, and 9,530 Da.

CLINICAL PRESENTATION

C. avidum infections may be expected following a skin break or loss of skin integrity. This bacterium can also be recovered after surgery, especially after breast, cardiac, or device-related (e.g., orthopedic) procedures. The prerequisites for these types of infections, in particular infection adjacent to moist areas, increased body mass index (BMI), presence of foreign-body devices, abscess development, etc., have been identified. A detailed review of the specific clinical entities previously reported in the literature is discussed in this section, including treatment options and highlighting the need for debridement in the case of abscess. All *C. avidum* case reports are summarized in Table 5.

Breast Infections

Aesthetic (reduction mammoplasty) or reconstructive breast implant surgeries after

FIG 5 Legend (Continued)

figure shows the optimal tree, for which the sum of the branch lengths for 16S rRNA genes was 0.54511947. The percentages of replicate trees in which the associated taxa clustered together in the bootstrap test (1,000 replicates) are shown next to the branches. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Kimura 2-parameter method and expressed as numbers of base substitutions per site. Codon positions included were 1st, 2nd, 3rd, and noncoding positions. All ambiguous positions were removed for each sequence pair. There were a total of 1,302 positions in the final data set. Evolutionary analyses were conducted in MEGA6. (B) Neighbor-joining tree for the genera *Cutibacterium*, *Propionibacterium*, and *Pseudopropionibacterium* based on *rpoB* gene sequences, including those for 6 strains of *Cutibacterium avidum*. Thirteen *rpoB* gene sequences selected from the GenBank database were aligned by using MEGA6 (www.megasoftware.net). Accession numbers are indicated after strain names. The evolutionary history was inferred using the neighbor-joining method. The figure shows the optimal tree, for which the sum of the branch lengths for *rpoB* genes was 0.60848730. The percentages of replicate trees in which the associated taxa clustered together in the bootstrap test (1,000 replicates) are shown next to the branches. The tree is drawn to scale, with branch lengths in the same units as those for the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Kimura 2-parameter method and expressed as numbers of base substitutions per site. Codon positions included were 1st, 2nd, 3rd, and noncoding positions. All ambiguous positions were removed for each sequence pair. There were a total of 3,264 positions in the final data set. Evolutionary analyses were conducted in MEGA6. (C) Neighbor-joining tree for the genera *Cutibacterium*, *Propionibacterium*, and *Pseudopropionibacterium* based on *gyrB* gene sequences, including those for 4 strains of *Cutibacterium avidum*. Fourteen *gyrB* gene sequences selected from the GenBank database were aligned by using MEGA6 (www.megasoftware.net). Accession numbers are indicated after strain names. The evolutionary history was inferred using the neighbor-joining method. The figure shows the optimal tree, for which the sum of the branch lengths for *gyrB* genes was 1.76236673. The percentages of replicate trees in which the associated taxa clustered together in the bootstrap test (1,000 replicates) are shown next to the branches. The tree is drawn to scale, with branch lengths in the same units as those for the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Kimura 2-parameter method and expressed as numbers of base substitutions per site. Codon positions included were 1st, 2nd, 3rd, and noncoding positions. All ambiguous positions were removed for each sequence pair. There were a total of 2,214 positions in the final data set. Evolutionary analyses were conducted in MEGA6.

FIG 6 Main spectra obtained by Vitek MALDI-TOF MS for *C. avidum*, *C. granulorum*, *C. acnes*, and *C. namnetense*. The abscissa axis corresponds to the mass m/z (Da) and the ordinate axis to the peak intensity (arbitrary units).

TABLE 4 *Cutibacterium* species identification by Vitek MALDI-TOF MS, with measured masses and their discriminating powers and intensities according to bioMérieux algorithms

Species	Measured mass (Da)	Discriminating power	Intensity
<i>C. avidum</i>	3,143.3	+++	+
	3,404	---	—
	3,460	---	+
	3,685.4	+++	++
	4,021	+	+
	4,329	---	+
	4,374	—	++
	4,485.1	+	+
	4,762	+++	++
	5,125.9	+++	++
	5,679	+++	+
	5,733	+	++
	5,792	---	+
	6,380	+	+
	6,490	+++	—
	6,526.4	+++	++
	6,659.7	+++	—
	6,776.6	+++	++
	6,918.7	+++	++
	6,937	---	—
	7,369	+++	+++
	11,622	+++	+
	13,045	+++	++
<i>C. acnes</i>	3,290	---	+
	3,404	+	+
	3,424	---	+
	3,519.4	+++	++
	4,023	---	+
	4,077	---	++
	4,346	---	+
	4,374	---	+++
	4,396	---	+
	4,484	---	+
	4,694.4	+++	+
	4,779	---	+
	4,984.5	+++	++
	5,172	---	+++
	5,191	---	+
	6,377	---	—
	6,787	---	++
	7,182	+++	+++
	8,668	+++	++
	8,690.7	+++	++
	9,964	+	+++
	13,576.9	+++	+
	15,058.2	+++	+++
<i>C. granulosum</i>	3,231.4	+++	+
	3,341	+++	+
	3,355.5	+++	+
	3,481	+++	+++
	3,500.2	+	+
	4,324	+	++
	4,397.3	+	++
	4,421	+++	++
	4,789.9	+++	++
	4,849.3	+++	+
	5,067.6	+++	+
	5,113	+++	+
	5,212.9	+++	+
	5,258.4	+++	++
	5,688.8	+++	++

(Continued on next page)

TABLE 4 (Continued)

Species	Measured mass (Da)	Discriminating power	Intensity
	5,794.2	+	—
	6,462	+++	++
	6,682.6	+++	++
	6,709.7	+++	++
	6,781.5	+	+
	6,805	+++	++
	6,962	---	+++
	6,985	+++	++
	7,886	+++	+++
	8,266	+	+
	8,646.3	+++	++
	8,792	+++	++
	9,222.4	+++	+
	9,257.9	+++	+
	9,576.7	+++	++
	10,133	+++	+
	10,220	+++	—
<i>C. namnetense</i>	3,177.7	+++	+
	3,247	+++	+
	3,290.2	+	++
	3,412.2	+++	++
	3,425.6	+	++
	3,462.8	+	+
	3,472	+++	++
	3,501	---	+
	3,957.9	+++	+
	3,972	+++	+++
	3,993	+++	++
	4,010	+++	+
	4,079	+	++
	4,343	+	++
	4,376	---	+++
	4,513	+++	+
	4,767.5	+++	++
	4,781.6	+	++
	5,172	+	++
	5,193.1	+	++
	5,733	---	+
	5,865	+++	++
	6,405	+++	+
	6,766.9	+++	+++
	6,822.7	+++	++
	6,943	+	+++
	6,965.6	+	++
	7,287	+++	+++
	8,260	---	—
	8,683.5	+++	++
	8,721.4	+++	+
	9,322	+++	+
	9,530	+++	++
	9,556	+++	+
	9,964	---	—
	10,067.6	+++	+
	10,383	+++	+
	12,801	+++	—

carcinoma are potentially vulnerable to infections, in particular *S. aureus*, anaerobe, and *Cutibacterium* infections, despite the increase in standardized preventive measures. An initial case of breast infection due to *C. avidum* was reported in 2005 by Panagea et al. following a breast reduction surgery (32). Several studies revealed predisposing conditions or risk factors for the occurrence of *Cutibacterium* infection but no specific characteristic correlates for *C. avidum* infection. In the first case, the only predisposing factor was surgery (165).

TABLE 5 Clinical characteristics of the main *C. avidum* infections described in the literature^a

Reference	Patient no.	Age (yr)	Sex	<i>C. avidum</i> samples	Diagnosis	Presence of fever (°C)	Signs and symptoms of infected site/joint	BMI
72	1 to 12	Median, 61 (45–81)	7 F, 5 M	Synovial fluid, tissue cultures 3 to 8, and sonication fluid culture	10 hip and 2 shoulder prosthesis infection	4 of 12 patients	Pain (<i>n</i> = 12), wound secretion or sinus tract (<i>n</i> = 6)	Median, 34 (27.9–40.6)
178	13	85	F	3 sets of blood culture bottles	Infective endocarditis	Yes (38.3)	Aortic stenosis	NA
14	14	87	F	Synovial fluid and 5 tissue biopsy specimens	Abscess formation anterior to the left hip	No	Redness, intense pain	38
14	15	75	M	Superficial wound culture and 6 biopsy specimens plus synovial fluid	Hip prosthesis infection	NA	Loosening of the cup	37
14	15	75	M	Synovial fluid and 7 tissue biopsy specimens	Hip prosthesis infection and abscess formation below the acetabulum floor	NA	Increase of pain and discomfort	37
17	16	37	F	1 purulent fluid sample	Liponecrosis, breast abscess	No	No	
15	16	36	F	1 purulent fluid sample	Liponecrosis, breast abscess	No	No inflammatory syndrome	
175	17	26	M	Drainage fluid	Skin inguinal abscess	No	No	NA
167	17	46	F	1 purulent fluid sample	Abdominal parietoplasty	No	Pain	30.1
16	18	56	F	2 deep swabs	Skin necrosis	No	Generalized induration and erythema	NA
16	18	56	F	Repeat swabs	Wound deterioration	NA	Generalized induration and erythema	NA
185	19	78	F	Joint purulent fluid and blood culture bottle	Hip septic arthritis	No	Pain	30.5
32	20	40	F	Pus samples	Breast abscess	No	Induration and erythematous breasts	NA
168	21	70	M	Abscess pus	Perianal abscess	NA	Painful left buttock mass and ruptured epidermal cyst with abscess formation	NA
173	22	79	M	Splenic abscess	Cardiac infarction	Yes (38.5)	Pain	NA
184 ^b	23	67	M	Different bone samples and biopsy specimens plus blood	Sacroiliitis, psoas abscess, and osteomyelitis	Yes (38.4)	Chronic lumbago and sciatica	NA
169 ^c	24	61	M	Collection of fluid under sonographic guidance	Splenic abscess	Yes (39.1)	No	NA

^aM, male; F, female; NA, not available; DAIR, debridement-antibiotics-irrigation-retention; WBC, white blood cell; AMC, amoxicillin-clavulanate; AMX, amoxicillin; CEF, cephalothin; CIP, ciprofloxacin; CLI, clindamycin; MEM, meropenem; MTR, metronidazole; MXF, moxifloxacin; RIF, rifampin; SXT, trimethoprim-sulfamethoxazole; TZP, piperacillin-tazobactam; VAN, vancomycin.

^bFor this study (surgical repair of an inguinal hernia), the resulting erythrocyte sedimentation rate (ESR) was 60 mm/h.

^cFor this study (coronary artery bypass surgery), the resulting ESR was 90 mm/h.

Later, the same case was described by two teams, from Switzerland and Austria, revealing the role of this common skin colonizer, which is well known as a resident of the pilosebaceous follicle unit (15, 17). The strain was the only etiology of an ulceration of the inframammary region with induration and putrid secretion. In this case, the proximity of the axillary region may have played a role in wound contamination

TABLE 5 (Continued)

Predisposing conditions and risk factors	WBC concn (g/liter)	CRP concn (mg/liter)	Resistance	Surgical treatment	Treatment	Outcome
Degenerative joint disorder (<i>n</i> = 9), trauma (<i>n</i> = 2), head necrosis (<i>n</i> = 1)	NA	50 (4.6–200)	None except one isolate resistant to clindamycin and later to rifampin plus a fluoroquinolone	DAIR (<i>n</i> = 5), one-stage exchange (<i>n</i> = 2), two-stage exchange (<i>n</i> = 4), only medical treatment (<i>n</i> = 1)	CLI (<i>n</i> = 1), levofloxacin plus RIF (<i>n</i> = 4), ciprofloxacin plus RIF (<i>n</i> = 2), clindamycin plus RIF (<i>n</i> = 2)	Good outcome except for DAIR strategy
Hypertension diabetes mellitus	NA	86	None	Delayed cardiac surgery	Daptomycin plus ampicillin plus ceftriaxone	Death
Surgeries, corticoid treatment, obesity	16.3	155	None	Moore dorsolateral approach	3 doses of cloxacillin at 2 g i.v., then CLI (300 mg 3 times per day) plus RIF (600 mg per day) (1 mo), then phenoxymethylpenicillin at 2 g 3 times per day (2 mo)	Favorable
Surgery, obesity	NA	64	None	Muscle-sparing Watson-Jones approach (anteriorly curved skin incision)	CLI at 600 mg 3 times per day (1 wk) and then CLI at 300 mg 3 times per day (5 wk)	Failure
Surgery, obesity	47.2 in synovial fluid	180	None	Revision two-stage exchange	TZP 3 times per day (1 wk) plus benzylpenicillin at 1 g i.v. 3 times per day (3 wk); TZP at 4 g 3 times per day plus VAN at 1.5 g twice a day and then SXT at 800 mg 3 times daily plus AMX at 1 g 3 times daily	Favorable
Surgery	9.1	16	Clindamycin	Abscess drainage	i.v. AMC at 2.2 g 3 times per day (15 days) and p.o. AMC at 750 mg 3 times per day (1 mo)	Favorable
Surgery, smoker	11	6	Clindamycin	Abscess drainage	i.v. AMC at 2.2 g 3 times per day (15 days) and p.o. AMC at 750 mg 3 times per day (1 mo)	Favorable
Seborrheic dermatitis skin alteration	11.1	26	None	Abscess drainage	i.v. CEF at 1 g 6 times daily plus MTR at 500 mg 3 times daily (5 days) and then oral cephalixin (7 days)	Favorable
Prosthetic abdominal surgery, overweight	13	162	None	Surgical evacuation with abscess drainage	p.o. AMC at 3 g per day	Favorable
Surgery	10.3	7.1	NA	Necrosis debridement	i.v. MEM plus p.o. MXF (2 wk)	Failure
Surgery	NA	NA	NA	Further fat debridements	MXF (2 wk) and then AMC (4 wk)	Favorable
Intra-articular glucocorticoid treatment, overweight, permanent humidity of the inguinal folds	6.5	185	None	Arthrotomy plus lavage	i.v. CEF (6 g per day) plus RIF (1,800 mg per day)	Favorable
Surgery	22.5	135	None	Purulent aspiration	i.v. flucloxacillin plus penicillin G and p.o. AMC (1 mo)	Favorable
Cirrhotic patient hemorrhoidectomy	7.5	NA	NA	Abscess drainage	Ampicillin plus cloxacillin (1 wk)	Favorable
Cardiac catheterization, diabetes, hypertension	13.1	NA	NA	Laparotomy with abscess resection	NA	NA
Surgical repair of an inguinal hernia	16.6	NA	NA	Bone biopsy and psoas abscess debridement	i.v. AMC at 8.8 g per day followed by CIP at 1 g per day for 6 mo	Favorable but sacroiliitis sequela
Coronary artery bypass surgery	5.6	NA	None	Laparotomy and spleen resection	NA	NA

(representing a difference from bone and joint infections [see below]). In this context, and despite the absence of foreign-body material, the development of *C. avidum* led to severe infection by virtue of its ability to adhere but also to grow and create abscesses, as reported previously (Table 5).

Moreover, the decrease in inoculum by excellent debridement and a prolonged course of antibiotics may play a crucial role in the successful treatment of severe breast infections following reduction mammoplasty (16). Persistence and biofilm production ability were suspected by Mak et al. on comparing the genomes of several *Cutibacterium* species and were later confirmed by Wildeman et al. by specific and extended genomic analysis of *C. avidum* genomes (13, 14).

Abdominal Infections

Acute abdominal infections are usually caused by *Enterobacteriaceae*, enterococci, and anaerobes, such as *Bacteroides fragilis* (166). In 2013, Janvier et al. reported an abdominal wall and intraperitoneal abscess by *C. avidum* as a complication of abdominal parietoplasty (167). In this case, I can hypothesize that the microorganism was hidden in skin folds and that infection began due to contiguity with the scar. Lastly, and again in this case, the authors specified the presence of an abscess requiring debridement surgery, which is quite often reported for the different deep infection cases published (Table 5). A perianal abscess caused by *C. avidum* in a cirrhotic patient was also reported and had a favorable outcome after surgical drainage (168).

Splenic Abscesses

C. avidum was first reported as the causative agent of a splenic abscess in 1986 (169). This disease remains rare, involving mainly *S. aureus* or *Enterobacteriaceae*. In the 1980s, *C. acnes* was also described as a potential etiologic agent (170, 171), and more recently, a new case was reported, involving multiple splenic nodules with fever in an immunocompromised patient with chronic lymphocytic leukemia (172). Despite the absence of hyperleukocytosis, the splenic abscess was positive only for *C. avidum*. This species should therefore be taken into account, especially after surgical explorations. Thus, *C. avidum* can be responsible for serious deep infectious diseases, including abscesses, most likely linked to its ability to develop inflammation and to recruit immune cells leading locally to a cytokine storm.

A second case of a *C. avidum* splenic abscess was reported after a cardiac catheterization complication. This disease remains uncommon but may occur in patients with sickle hemoglobinopathies, trauma, bacteremia, splenic infarction, hematoma, or intravenous drug use. For the second patient, the etiology of the splenic abscess was unclear, with different potential hypotheses, including undetected *C. avidum* endocarditis (a recent case was published [see below]) or a predisposing splenic lesion (hematoma, infarction, or cyst) (173). In both cases, debridement surgery was the key to success.

Skin Abscesses

Only one case of skin abscess, without any risk factors in a young immunocompetent subject, has been reported, especially without previous surgery. Interestingly, a recurrence of this abscess was noticed despite a 7-day course of ciprofloxacin treatment, but the emergence of fluoroquinolone resistance in *Cutibacterium* spp. was recently reported (174). A lavage drainage was performed during surgery to reduce the inoculum, and the patient was treated for 2 weeks with antibiotics, with a favorable clinical outcome. The inguinal localization may explain the infection, which had a purulent aspect. Nevertheless, no obvious cause except for broken skin integrity can explain the occurrence of such an infection (175).

Infective Endocarditis

There have been several reports of infective endocarditis (IE) due to *C. avidum*. In 2001, an initial case of *C. avidum* IE was reported for a patient with a history of aortic valve prosthesis. Blood cultures were positive in 7.8 days, with a clinical diagnosis of vegetation regarding the transesophageal echocardiography (TEE) investigation and an abscess of the aortic ring (176). A second IE case report revealed an elevated C-reactive protein (CRP) level (up to 200 mg/liter) with a positive *C. avidum* blood culture (unknown time to positivity) in a 70-year-old woman who had undergone biological aortic valve replacement surgery 3 months previously. TEE showed multiple vegetations on the biological aortic valve and a perivascular abscess (177). The last case of *C. avidum* IE was recently reported by a Spanish group. An elderly woman with a permanent pacemaker implantation underwent bioprosthetic aortic valve replacement due to aortic stenosis. Eighteen months later, a perivalvular abscess was diagnosed, and three sets of blood culture bottles were positive. Following a complicated postopera-

tive course, the patient died 48 h after surgery, highlighting the fact that *C. avidum* can lead to host tissue damage (178).

Therefore, *C. avidum* IE should be suspected in patients with a history of prosthetic heart valves, even if unspecific symptoms are present. Even though the incidence of *Cutibacterium* IE remains rare (approximately 1%), it should not be disregarded, as it can be linked to abscess formation, as noticed for breast infections. Lastly, although *Cutibacterium* species, which are constituents of the skin microbiota, are too often considered nonvirulent microorganisms, the overall mortality rate is relatively high, at almost 20 to 25% (179). In the three recent *C. granulosum* IE reports, it was also systematically noticed that extensive decalcification, abscess formation, and valvular destruction are in fact trends of *Cutibacterium* species IE (180, 181).

More recently, the same observation was reported for 24 cases of *C. acnes* IE. The authors highlighted that *C. acnes* remains an underrecognized cause of prosthetic valve IE. Among the 24 cases, almost exclusively prosthetic valves were affected. Surgery was required in most cases, and only males with advanced heart disease were found to have IE due to *C. acnes*. Moreover, it was almost systematically associated with high rates of local invasion and embolic complications, as reported for *C. avidum* and *C. granulosum* (182). Therefore, as previously written, and even though this *Cutibacterium* infectious episode remains rare, it constitutes a serious medical entity, and valve DNA sequencing (with careful sample handling) identifies *Cutibacterium* spp. as the cause of the aortic endocarditis in most cases, whereas otherwise these cases would have been categorized as culture negative. Routine use of extended-duration incubation of blood cultures should be recommended (i.e., more than 7 days) when *Cutibacterium* IE is suspected and can be expected to identify *C. avidum* in patients whose IE would otherwise have been misdiagnosed.

The increasing reports of infections associated with this bacterium may be explained by improvements in diagnostic microbiology techniques and by the increased number of foreign-body devices implanted in patients.

Bone and Joint Infections

Due to its conventional niche, *C. avidum* is an unusual player in bone and joint infections, particularly in hip prostheses. Nevertheless, in the event of a high BMI with skin folds, the growth and development of *C. avidum* near the surgical wound can lead to contiguous inoculation of this uncommon bacterium. A potential association with the anterior surgical approach, which has been performed in recent years, has been mentioned (183). This observation was also reported by Achermann et al., but without any proof (72).

Estoppey et al. reported a case of *C. avidum* sacroiliitis and osteomyelitis, highlighting the fact that this species may act as a potential etiology of septic arthritis and osteomyelitis, although *C. acnes* remains the leader of such anaerobic infections (184). In this case, the bacterium was recovered not only from several bone samples and biopsy specimens but also from blood. This severe *C. avidum* infection did not reveal any specific risk factors (prosthesis, iatrogenic immunosuppression, or surgery), as noted by Brook and Frazier (165).

In 2008, Million et al. reported a case of septic arthritis of the hip with *C. avidum* bacteremia following intra-articular treatment for hip osteoarthritis (185). Although *C. avidum* is considered a contaminant or colonizer, note that in these last two cases the deep infection was accompanied by bacteremia. Even though the potential pathogenic properties of *C. avidum* (see the virulence factor section) are not fully understood, this microorganism appears to be capable of causing severe deep infections, even with a delay in disease expression as often described for *Cutibacterium* (6, 51, 75, 186). More recently, Wildeman et al. reported *C. avidum* as a new etiological agent of prosthetic hip joint infection (14).

Several cases in the literature have revealed the ability of this microorganism to cause clinically relevant infections, including abscess formation (72). In the cases described above, the BMI was circa 38 and 37. This raises the following initial question:

how can we be sure about the antiseptic process with chlorhexidine? Another hypothesis may consider the impact of the anteriorly curved skin incision approach. Indeed, this strategy can be considered a risk factor, since the incision is closer to the groin than in other approaches. Nevertheless, Ilchmann et al. demonstrated no increased risk factors for the direct anterior approach performed by two highly experienced surgeons (187). Moreover, perioperative antibiotic prophylaxis should be taken into account in the prevention of infections due to *Cutibacterium* spp. No consensus guidelines exist at this time, especially for total shoulder arthroplasties, for which there have been a number of *Cutibacterium*-related publications in recent years (188–190).

Finally, what about monotherapy treatment and the pharmacokinetics/pharmacodynamics (PK/PD) approach (mode of administration, dose, and frequency but also absorption, distribution, metabolism, and elimination) to be sure about penetration into bone tissue and the ability to eradicate bacteria growing in a biofilm? Indeed, genomic analysis revealed specific sequences compared to those of other *Cutibacterium* species and the ability to produce a biofilm structure according to the description of a gene cluster encoding exopolysaccharide production, suspected to be involved in strong adherence, as previously described for *C. acnes* (74). Interestingly, and recently in my experience, it has been observed that *C. avidum* can be involved in shoulder prosthesis infection, probably leading to a chronic status (years) according to its ability to resist antibiotics and to evade the immune system. Henceforth, *C. avidum* should clearly be considered a virulent pathogen causing, in particular, hip prosthesis infection (after hip arthroplasty surgery using an anterior surgical approach) in obese patients (risk factor), with pain and wound secretion (183). Treatment combining one-stage exchange with prolonged antibiotic therapy allows a favorable outcome. In contrast, for all patients treated with either an initial debridement-antibiotics-irrigation-retention (DAIR) procedure or antibiotic alone, treatment failed, necessitating a two-stage revision of the prosthesis, with a final good clinical outcome (72).

Prostate Infections

Though *Cutibacterium* spp. have clearly been reported and associated with inflammation, their role in several diseases besides acne (see below), such as prostate carcinoma or sarcoidosis, has also been highlighted in various studies. *C. acnes* was the organism most frequently recovered from radical prostatectomy specimens, reaching rates of 23% to 60% in cases of prostate carcinoma (191). Nevertheless, *C. avidum* was represented in 7% of prostate tissue samples (192). From an experimental point of view, these species may contribute to prostate carcinogenesis by locally inducing high-level inflammation (193). Indeed, using the HACAT or RWPE1 prostate epithelial cell line, cytokine secretion was upregulated using the TLR2–NF- κ B signaling pathway. Coculture with *C. acnes* also revealed different pathways (STAT3, COX2-prostaglandin, and plasminogen-matrix metalloproteinase pathways) (194).

According to updated knowledge with the next-generation approach, it would be interesting to investigate the roles of the various *C. avidum* clusters recently described for other infections, such as bone and joint infections (14). Indeed, one may hypothesize that different clusters of *C. avidum* are associated with different localizations and/or infections. More studies are required to better characterize the numerous *C. avidum* strains in order to reveal any specificities or a possible tropism as described for *C. acnes*. No overlap was observed between *C. acnes* lineages involved in acne (CC18, CC3, and CC28) and strains isolated from opportunistic infections belonging to other clusters (CC53 and CC60) (13, 192).

Acne Lesions

Compared to the significant amount of literature on the involvement of *C. acnes* in acne, *C. avidum* remains a rare or exceptional player in this skin disease. Its presence has nevertheless been reported in combination with *C. acnes* and *C. granulosum*. This species should therefore not be forgotten during discussions and should be included as a potential etiological factor for acne (195). More recently, an investigation of bacterial colonization and

keratinocyte proliferation in hair follicles from control ($n = 117$) and acne ($n = 26$) skin patients revealed that none of the samples were positive for *C. avidum* (30). In fact, as previously suggested, *C. avidum* is more probably detected in the wet body areas (196). Its ecological niche may explain the behavior observed when skin innate immunity is explored *in vitro*, which is different from those of different *C. acnes* types, such as phylotypes III, II, IC, IA1, and IB. Therefore, *C. avidum* has much less inflammatory potential, inducing only tissue inhibitor metalloproteinase 2 (TIMP-2) and matrix metalloproteinase 13 (MMP-13) expression, according to a recent study by my group (109). Importantly, and unlike the *C. acnes* strains, *C. avidum* decreased TLR2 expression, downregulated anti-inflammatory transforming growth factor beta (TGF- β) expression, and had no effect on proinflammatory tumor necrosis factor alpha (TNF- α) expression.

Caries-Like Lesions

Because the pH in the mouth is near 6, the best pH for *C. avidum* growth, plaque pH can lead to *C. avidum* development, especially after a sugar challenge or exposure. Cell-to-cell interaction with various bacterial species, such as *Streptococcus mutans*, can lead to caries. Consequently, repeated exposure to high-starch and carbohydrate diets gives rise to metabolically active plaque, leading to distinct lesions. The fermentation of sucrose, sorbitol, or xylitol by *C. avidum* can result in the formation of caries-like lesions in enamel (197). Although plaque acidogenicity does not necessarily reflect cariogenicity, food components, and especially sugar retention, may account for increased cariogenicity at plaque retention sites in the mouth.

ANTIMICROBIAL SUSCEPTIBILITY OF *C. AVIDUM* AND RELATED SPECIES

In 1976, Hoeffler et al. reported the first major study focusing on the antimicrobial susceptibility of *Cutibacterium avidum* and related species, especially *C. acnes*, *C. granulosum*, and *Corynebacterium minutissimum* (198). Seventy-three strains were tested against 32 antimicrobial components from different families. No acquired resistance was observed, regardless of the species, and the lowest MICs were reported for β -lactams, rifampin, erythromycin, clindamycin, and minocycline (198, 199). Nevertheless, among the aminoglycosides, kanamycin was the least active, and most *C. avidum* strains were (naturally) resistant to metronidazole and colistin.

One point should be highlighted: the European guidelines for antibiotic susceptibility testing do not provide any rules or critical breakpoints for interpreting anaerobe testing in the latest version (http://www.eucast.org/clinical_breakpoints/). Conversely, the CLSI guidelines propose various critical breakpoints, as summarized in Table 6.

However, as early as 1989, erythromycin-resistant *Cutibacterium* species in antibiotic-treated acne patients were investigated, and a potential association with therapeutic failure was discussed (200). Among the strains isolated from the 52 subjects enrolled in the study, 63 strains were resistant to erythromycin, including five *C. avidum* strains (8% versus 66.6% for *C. acnes* and 25.4% for *C. granulosum*). At that time, no molecular investigation was conducted to characterize the genetic support of the resistance compared to that of *C. acnes*. Later, numerous studies, especially on *C. acnes*, revealed that erythromycin resistance is usually due to methylation of the 23S ribosomal subunit (mutation in the 23S rRNA gene, usually at position 2058 or 2059), with a high- or low-level resistance pattern.

In contrast, and to the best of my knowledge, among *C. avidum* isolates recovered in different contexts (from skin, blood, tissue, prostate, or abdomen) (201), macrolide resistance due to point mutations remains rare compared to that in *C. acnes* clinical strains, and no *ermX* gene has yet been described (51). Interestingly, the strains from the various published case reports (Table 5) were fully susceptible to antibiotics, except for clindamycin in two cases (15, 17) with high-level resistance to clindamycin, as previously reported (51, 202). The same observation was reported for clinical strains isolated during bone and joint infections (203). Consequently, one recommendation is that clindamycin should be tested when used in clinical treatment to avoid treatment failure.

TABLE 6 CLSI anaerobe breakpoints of interest for treatment of *Cutibacterium avidum* infections

Drug class	Antimicrobial agent	MIC interpretative breakpoint (mg/liter)		
		Susceptible	Intermediate	Resistant
Penicillins	Penicillin	≤0.5	1	≥2
	Ampicillin	≤0.5	1	≥2
β-Lactam–β-lactam inhibitor combinations	Amoxicillin-clavulanate	≤4/2	8/4	≥16/8
	Piperacillin-tazobactam	≤32/4	64/4	≥128/4
Cephems	Cefotetan	≤16	32	≥64
	Cefoxitin	≤16	32	≥64
	Ceftriaxone	≤16	32	≥64
	Cefotaxime	≤16	32	≥64
Carbapenems	Ertapenem	≤4	8	≥16
	Imipenem	≤4	8	≥16
	Meropenem	≤4	8	≥16
Tetracyclines	Tetracycline	≤4	8	≥16
Fluoroquinolones	Moxifloxacin	≤2	4	≥8
Lincosamides	Clindamycin	≤2	4	≥8
Phenicol	Chloramphenicol	≤8	16	≥32

To limit the emergence of antibiotic resistance due to resistant mutant selection, various alternative treatments have been proposed. Whether or not tetracyclines are still used, this bacteriostatic antibiotic family remains active against *Cutibacterium* species (less than 10 to 15% resistance) (204). Even in the acne field, low-dose tetracyclines are still used for their anti-inflammatory properties (205), but the *C. avidum* clinical strains (from various origins) remain susceptible to this family. Based on experience with *Cutibacterium* species over 8 years in the microbiology laboratory, more than 1,900 *Cutibacterium* strains have been isolated, and all *C. avidum* strains were fully susceptible to all the antibiotics tested, with the exception of one macrolide-resistant strain recovered from a healthy skin patient. Otherwise, tetracycline can also have a slight effect on the extracellular lipase produced by *C. avidum*. Lipase production is twice as sensitive to tetracycline as that of total cellular and extracellular proteins (206).

Another component, benzoyl peroxide, seems to be quite active and bactericidal, without resistance (207). This compound displayed excellent activity *in vitro* when tested on *C. avidum* PF77. This powerful oxidizing agent is active because it releases highly reactive oxygen species that can disrupt the bacterial cell wall (132). Recently, to optimize the surgical process and reduce the local *Cutibacterium* sp. burden, especially in cases of total shoulder arthroplasty, local antibiotic treatment and combination with benzoyl peroxide demonstrated an excellent effect in reducing the risk of delayed and biofilm-associated *Cutibacterium* infections, which are frequent in males during the posterolateral surgery approach (208, 209).

ANTIBIOTIC TREATMENT

To date, there is no gold standard in terms of treatment of *Cutibacterium* infections (85). Various strategies have been developed, though the therapeutic approaches proposed are usually based on tradition and guided by personal and expert experience. Although daily routine practices vary, some consensus can be reported in light of the knowledge base for *C. acnes* infections. Recently, Shah et al. proposed different therapeutic schemes for cases of prosthetic joint infection (i.e., device-related infection), as follows: first-line therapy, penicillin at 20 to 24 million units given i.v. daily, either as a continuous infusion or in 6 divided doses, or ceftriaxone at 2 g given i.v. daily; and

second-line therapy, clindamycin at 600 to 900 mg given i.v. every 8 h or vancomycin at 15 mg/kg of body weight given i.v. every 12 h. The recommended duration of therapy is 4 to 6 weeks (210). Interestingly, different groups of experts usually recommend prolonged treatment with different antibiotics, in particular combinations including rifampin (75, 211), with excellent bone distribution and diffusion through biofilms, along with a fluoroquinolone, amoxicillin, or clindamycin. In case of abscesses, initial surgery with excellent debridement should be performed, and a course of 2 to 4 weeks seems to be linked to a favorable outcome. Nevertheless, as far as the literature (Table 5) is concerned, there again appears to be no consensus. Therefore, like the case for *C. acnes* infection, further studies are clearly needed to optimize *C. avidum* infection treatment, and even though this microorganism remains rare, it is most likely underestimated (85).

Indeed, with respect to device-related infection or abscess infection (high inoculum), new *in vitro* and especially *in vivo* (animal models) investigations are required to allow proposal of an optimal regimen and its duration. Recently, Achermann et al. reported on 12 hip prosthetic infection treatments. Following surgical debridement or prosthesis exchange, all patients were treated intravenously for approximately 2 weeks with a β -lactam (or vancomycin in the event of allergies), followed by oral therapy including either clindamycin, clindamycin plus rifampin, or a fluoroquinolone plus rifampin. Oral treatment and its duration were determined according to MIC values and the surgical approach adopted, respectively. Thus, antibiotics were given for 3 months for the DAIR approach as well as one-stage exchange and for 6 weeks for two-stage exchange (72). Zeller et al. reported a similar approach with either clindamycin or cefazolin combined with rifampin administered for 12 weeks after a one-stage exchange for 11 chronic *C. avidum* hip infections (183). According to these experiences, the DAIR approach seems to be linked to poor outcomes, whereas combining a one-stage surgical approach with prolonged antibiotic treatment allows favorable outcomes.

In my opinion, and based on my experience, rifampin, amoxicillin, ceftriaxone, levofloxacin, and maybe moxifloxacin, as well as daptomycin or linezolid (in cases of mixed infection with multidrug-resistant coagulase-negative staphylococci), remain the drugs of choice, in combination for 3 months, to eradicate *Cutibacterium* biofilm- or device-related infection.

In any event, based on my experience, although *C. avidum* is clearly encountered less frequently in daily routine, these strains are more susceptible to all antibiotics than potentially occurring *C. acnes* strains resistant to fluoroquinolones, macrolides, tetracyclines, co-trimoxazole, and rifampin (51).

CONCLUSIONS

This review focused on *C. avidum* infections, which are an emergent medical issue due to the increased use of implants, especially orthopedic implants but also breast implants, and depending on the ecological niche of wet areas of human skin. Numerous clinical cases have been detailed reporting different features. This underrecognized species, and most likely its various subtypes suggested by molecular identification methods, may cause more infections in the future and will require closer attention, especially after surgery or in the presence of a skin abscess.

Over the past few years, focus has been placed on improved diagnostic procedures and accurate identification methods (molecular or spectral). With the genomic era, new insights will be investigated in terms of pathogenesis and host-bacterium interactions, which might explain how this bacterium was able to be used as an immunomodulator several decades ago.

To better understand *C. avidum* physiopathogenesis and virulence, its bacterial adherence, invasiveness, and biofilm formation ability, along with phage and mobile genetic element (e.g., plasmid) acquisition and gene transfer, should be investigated further to determine their roles.

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