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Actinomyces and Related Organisms in Human Infections

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SUMMARY

Actinomyces israelii has long been recognized as a causative agent of actinomycosis. During the past 3 decades, a large number of novel *Actinomyces* species have been described. Their detection and identification in clinical microbiology laboratories and recognition as pathogens in clinical settings can be challenging. With the introduction of advanced molecular methods, knowledge about their clinical relevance is gradually increasing, and the spectrum of diseases associated with *Actinomyces* and *Actinomyces*-like organisms is widening accordingly; for example, *Actinomyces meyeri*, *Actinomyces neuii*, and *Actinomyces turicensis* as well as *Actinotignum* (formerly *Actinobaculum*) *schaalii* are emerging as important causes of specific infections at various body sites. In the present review, we have gathered this information to provide a comprehensive and microbiologically consistent overview of the significance of *Actinomyces* and some closely related taxa in human infections.

INTRODUCTION

Human actinomycosis, a chronic, granulomatous infectious disease, has been recognized for a long time (1), and its causative agent, originally named *Streptothrix israeli* (currently *Actinomyces israelii*), was described in 1896 by Kruse (2). It was not until 1951 that another *Actinomyces* species, *Actinomyces naeslundii*, was implicated in actinomycotic lesions in humans (3), while *Actinomyces odontolyticus* and *Actinomyces viscosus* (first named as *Odontomyces viscosus*) were described in 1958 and 1969, respectively (4–6).

It is well established that actinomycosis is an endogenous infection. The causative *Actinomyces* species reside on mucosal surfaces and gain access to deeper tissues via trauma, surgical procedures, or foreign bodies, which disrupt the mucosal barrier. Inside the tissue, these bacteria form masses consisting of aggregates of branching, filamentous bacilli (7–9). Actinomycosis is defined as a hard mass-type lesion with a specific histopathological structure. There are a large number of case reports of actinomycosis in the literature, but in most cases, diagnosis has been based solely on clinical and histopathological findings. In the majority of early reports, microbiological confirmation of diagnosis was lacking. Even when microbiological assessment was included, culture was typically the only method used. If, however, antimicrobial treatment had been started before sample collection, the results of culture may be falsely negative. The increasing introduction of molecular bacterial detection and identification methods is helping to overcome such problems.

A large number of *Actinomyces* species have been described since the description of *A. israelii*, *A. naeslundii*, *A. odontolyticus*, and *A. viscosus*. In addition, reassignments within some species, such as *A. naeslundii* and *A. viscosus*, have occurred (10). However, only some human-associated *Actinomyces* species, including *A. israelii*, *Actinomyces gerencseriae*, and *Actinomyces graevenitzii*, may be involved in classical actinomycosis (11, 12). A wide range of *Actinomyces* species are being increasingly associated with infections at many body sites (11, 13, 14). *Actinomyces meyeri*, *Actinomyces neuii*, and *Actinomyces turicensis* are emerging as important causes of such infections.

Although actinomycosis is relatively rare, at least in Western populations (8), recently reported observations implicating *A. meyeri* in brain abscesses (15) and *Actinobaculum schaalii* (currently *Actinotignum schaalii*) in urosepsis (16) and the introduction of advanced microbiological techniques, which can identify even very fastidious organisms, have resulted in an increased awareness of *Actinomyces* and other Gram-positive, non-spore-forming bacilli in clinical microbiology.

To date, 25 validly published *Actinomyces* species from human material have been described (Table 1). Of these, the descriptions

TABLE 1 Human *Actinomyces* species

Species	Yr of description	Reference(s)
A. israelii	1896	2
A. naeslundii	1951	3
A. odontolyticus	1958	4
A. viscosus	1969	5, 6
A. meyeri	1984	205
A. georgiae	1990	17
A. gerencseriae	1990	17
A. neuii subsp. *neuii* and subsp. *anitratus*	1994	207
A. radingae	1995	288
A. turicensis	1995	288
A. europaeus	1997	202
A. graevenitzii	1997	197
A. radicidentis	2000	188
A. urogenitalis	2000	45
A. funkei	2001	244
A. cardiffensis	2002	65
A. hongkongensis	2003	130
A. nasicola	2003	179
A. oricola	2003	189
A. dentalis	2005	190
A. naeslundii (sensu stricto)[a]	2009	10
A. oris	2009	10
A. johnsonii	2009	10
A. massiliensis	2009	246
A. timonensis	2010	224
A. hominis	2010	214

[a] Emended description of *A. naeslundii*.

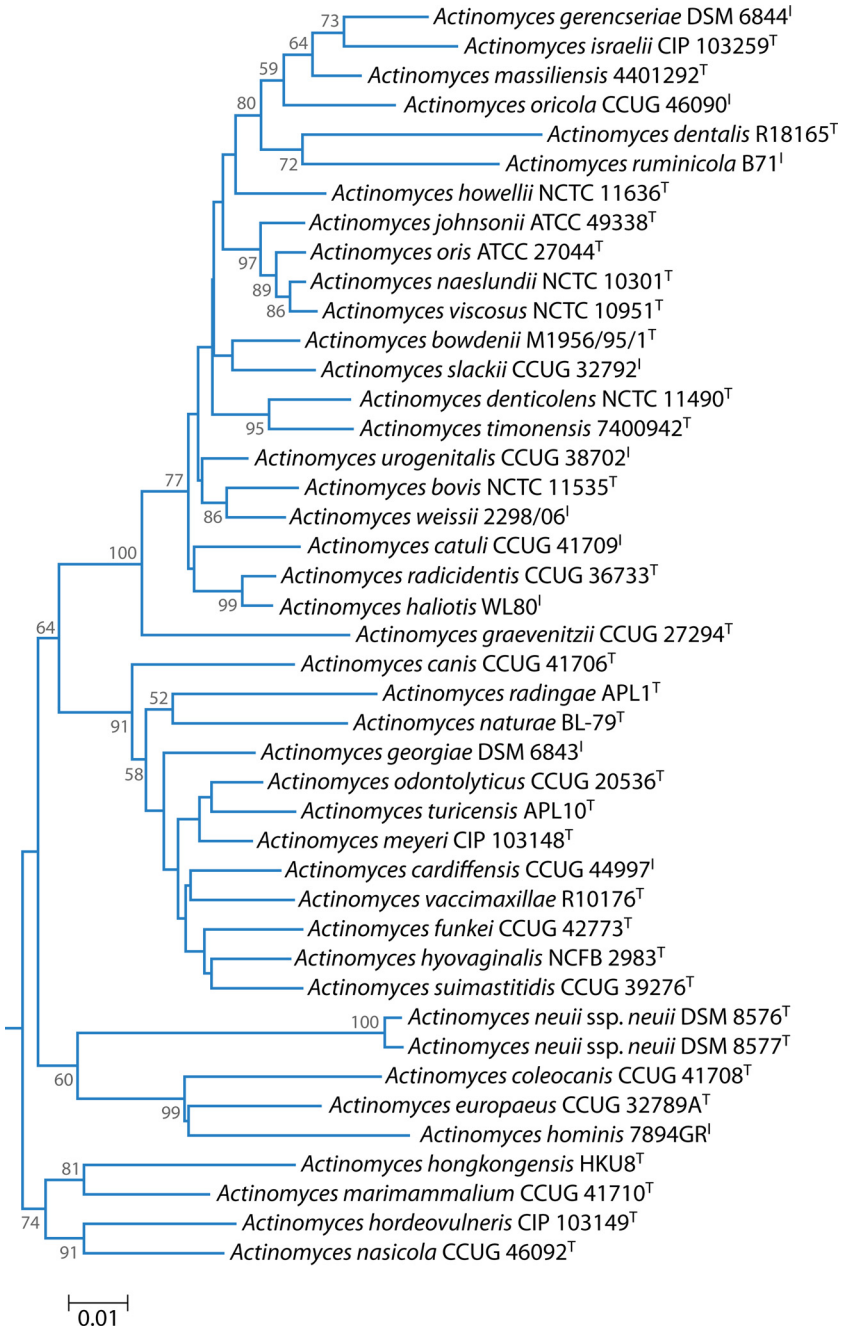

FIG 1 Phylogenetic tree based on 16S rRNA gene sequence comparisons over 1,260 aligned bases showing the relationship between species of the genus *Actinomyces*. The tree was reconstructed by using the neighbor-joining method from a distance matrix constructed from aligned sequences using the Jukes-Cantor correction. Numbers represent bootstrap values for each branch based on data for 1,000 trees.

of 13 species occurred solely during this century. In the present review, we aim to give a comprehensive overview of human *Actinomyces* and closely related organisms and their roles in different types of actinomycoses and other infections.

UPDATE ON TAXONOMY OF *ACTINOMYCES* AND CLOSELY RELATED TAXA

The clinically relevant Gram-positive anaerobic bacilli are found in two phyla: *Actinobacteria* and *Firmicutes*. The genus *Actinomyces* belongs to the *Actinobacteria*, is one of six genera within the family *Actinomycetaceae*, and is currently comprised of 42 validly published species (http://www.bacterio.net/actinomyces.html). The type species is *Actinomyces bovis*. A phylogenetic tree based on 16S rRNA gene sequence comparisons (Fig. 1) shows that there are three principal clusters albeit not particularly strongly supported by bootstrap analysis. The majority of species belong to the cluster that includes *A. bovis*, while the remaining clusters, which include *A. neuii* and *Actinomyces hordeovulneris*, respectively, should be investigated further to determine if they warrant proposal as novel genera.

The *A. naeslundii*/*A. viscosus* group has long been known to be heterogeneous. *A. viscosus* was originally isolated from a hamster (5), but human strains were subsequently isolated with sufficient phenotypic similarity to be assigned to this species. DNA-DNA hybridization studies showed that human *A. viscosus* strains were in fact more closely related to *A. naeslundii* genospecies 2 than *A. viscosus* and that *A. viscosus* includes strains resident in animals only (17). An additional genetic homology group, *A. naeslundii* genospecies WVA963, was also described. Multilocus sequence analysis has further clarified the relationships within this group, leading to a narrowing of the definition of *A. naeslundii* and the proposal of the new species *A. oris* for strains formerly assigned to *A. naeslundii* genospecies 2 and *A. johnsonii* for strains formerly assigned to genospecies WVA963 (10). Despite this work, human strains have continued to be assigned to *A. viscosus*, and it is often difficult to determine the taxon to which they belong in the current scheme. Most of these strains, however, are likely to be members of *A. oris*. For the remainder of this review, "*A. viscosus*" is denoted in quotation marks as a reminder of the taxonomic uncertainty regarding human strains identified as this species.

Taxonomic reassessment of members of this genus has led to some species being assigned to other genera, such as *Actinobaculum suis* (previously *Actinomyces suis*) (18), *Cellulomonas humilata* (formerly *Actinomyces humiferus*) (19), *Trueperella bernardiae* (formerly *Actinomyces bernardiae* and *Arcanobacterium bernardiae*) (20), and *Trueperella pyogenes* (formerly *Actinomyces pyogenes* and *Arcanobacterium pyogenes*) (20). In addition to *Actinobaculum suis*, which is of animal origin, three human *Actinomyces*-like species were also described as the novel species *Actinobaculum schaalii* (18), *Actinobaculum massiliae* (later corrected to *A. massiliense*) (21), and *Actinobaculum urinale* (22). Recently, *A. schaalii* and *A. urinale* were assigned to the new genus *Actinotignum*, and a strain from human blood was characterized and described as *Actinotignum sanguinis* (23). In the latter study, the type strain of *Actinobaculum massiliense* obtained from two culture collections was found to be phylogenetically distinct, on the basis of 16S rRNA gene sequence comparisons, from the strain originally described. The *A. massiliense* type strain currently deposited in culture collections appears to be closely related to *A. schaalii* (23). A group of *Actinomyces*-like strains isolated from human infections were found to represent a novel genus, *Varibaculum*, within the family *Actinomycetaceae* (24). The novel species "*Actinomyces lingnae*" and "*Actinomyces houstonensis*" were proposed by Clarridge and Zhang (25), but because the descriptions were incomplete and the strains have not been deposited with culture collections, the proposals have not been validated.

Until recently, all *Actinomyces* species described were isolated from microbiota associated with mammals. Rao et al. (26), however, isolated *Actinomyces naturae* from chlorinated solvent-contaminated groundwater. The optimal temperature for growth of this species, 30°C to 37°C, suggests that the primary source may have been an animal.

Although, as listed above, there have been a number of new *Actinomyces* species proposed in recent years, culture-independent studies directly targeting 16S rRNA genes have revealed sequences representing novel *Actinomyces* taxa. For the human mouth alone, the Human Oral Microbiome Database (http://www.homd.org/) lists 18 as-yet-unnamed species-level *Actinomyces* taxa (27).

NATURAL HABITATS OF *ACTINOMYCES* AND CLOSELY RELATED TAXA

Oral Cavity

Actinomyces is one of the predominant genera in the oral cavity. Indeed, at the age of 2 months, one-third of infants in one study were already colonized with *Actinomyces* (28). On oral mucosal surfaces of these edentulous infants, *A. odontolyticus* was the only representative of the genus found. The diversity of *Actinomyces* populations increased so that >90% of children harbored one or more *Actinomyces* species in their mouths from the age of 1 year onwards. During this 2-year longitudinal study, despite the appearance of *A. naeslundii*, "*A. viscosus*," *A. graevenitzii*, and *A. gerencseriae* in the oral cavity at the time of the eruption of the primary teeth, *A. odontolyticus* clearly remained the most prominent oral *Actinomyces* species recovered from saliva in children (28). *Actinomyces* species play a central role in the initial stages of biofilm formation on teeth (i.e., dental plaque) both above (supragingival) and below (subgingival) the gumline (29). Indeed, *A. odontolyticus*, *A. naeslundii*, *A. oris*, and *A. gerencseriae* have been shown to participate in the formation of supragingival plaque on primary teeth of children aged 3 to 4 years (30). An interesting observation was that *A. israelii*, which is considered the major causative agent of human actinomycosis, is uncommon in the oral cavity of young children (28, 30). In the original description of *A. georgiae* (17), most characterized isolates came from gingival crevice samples from periodontally healthy children. *A. odontolyticus* has been shown to be one of the predominant *Actinomyces* species in developing biofilms on tooth surfaces in subjects of all ages, and the proportions found were not related to periodontal disease status (31). In a study characterizing 195 fresh *Actinomyces* isolates collected from supra- and subgingival plaque samples of five adults with chronic periodontitis, *A. oris* (formerly *A. viscosus* serotype II) was the isolate most commonly identified, followed by *A. gerencseriae*, *A. naeslundii*, *A. georgiae*, and *A. israelii*; *A. meyeri* was not found (32). In general, members of the genus *Actinomyces* are not considered to play a pathogenic role in periodontitis. Although the relative abundance of *Actinomyces* is decreased in diseased sites, its total biomass in subgingival plaque does not differ between periodontally healthy and diseased subjects (33). *A. turicensis* was reported to be the most common *Actinomyces* species on the tongue surface of eight subjects with oral malodor, followed by *A. odontolyticus*, *A. israelii*, and *A. radingae* (34). A recent study on the human oral microbiome, being part of the NIH-supported Human Microbiome Project and using comprehensive molecular tools, revealed *A. georgiae*, *A. gerencseriae*, *A. israelii*, *A. meyeri*, *A. naeslundii*, *A. odontolyticus*, *A. oricola*, *A. radicidentis*, as well as several not-yet-cultivated *Actinomyces* phylotypes as members of the resident microbiota in the human mouth (27).

Pharynx

Relatively few studies have characterized *Actinomyces* populations at nonoral human body sites. In nasopharyngeal specimens collected from infants during their first 2 years of life and examined by culture, *Actinomyces* organisms were common during acute otitis media episodes compared to their occasional presence during periods of health (35). In a recent study of the tonsillar crypt microbiota (36), oral species such as *A. georgiae*, *A. israelii*/*A. gerencseriae*, *A. meyeri*, *A. naeslundii*, *A. odontolyticus*, *A. radicidentis*, and the recently described *A. cardiffensis* and *A. massiliensis* were

found. The bacterial diversity and composition within tonsillar crypts were compared on the one hand between 10 children and 10 adults and on the other hand between 10 subjects with recurrent tonsillitis and 10 corresponding healthy subjects. Interestingly, *A. odontolyticus* colonized all 20 subjects, and *A. naeslundii* colonized half of the subjects regardless of age or disease status, whereas *A. cardiffensis* and *A. massiliensis* were recovered mainly from healthy children (36).

Other Sites of Bacterial Colonization

It is often stated in reviews and case reports that in addition to the mouth, *Actinomyces* organisms are common inhabitants of the gut, genitourinary tract, and skin. It is true that at the phylum level, *Actinobacteria* are frequent colonizers of most ecological niches of the human body (37–39). At the genus level, however, the organisms found may belong to genera other than *Actinomyces*; for instance, until the introduction of accurate molecular methods of identification, many *Bifidobacterium* isolates from urine, cervix/uterus exudates, peritoneal wound, appendix wound, and blood were likely to have been misidentified as *Actinomyces* on the basis of their similarities in Gram stain and culture characteristics (40). Thus, organisms belonging to the phylum *Actinobacteria* may merely represent the genus *Bifidobacterium* in the gut or the genus *Propionibacterium* on skin and hair. The distal human esophagus has been reported to offer a relatively stable environment for bacterial colonization, including some *Actinomyces* species, such as *A. odontolyticus* (in particular), *A. meyeri*, and *A. graevenitzii* (41), although whether this site is truly colonized or whether the bacteria detected there are derived from saliva is unclear. *A. graevenitzii* was identified in biopsy specimens from the proximal small intestine of children with celiac disease, and an unidentified *Actinomyces* sp. was shown to be attached to the epithelial lining (38). Fecal samples were shown to harbor only a few clones identified as *Actinomyces*, with "*A. viscosus*" and *A. odontolyticus* being represented (42). *Actinomyces* species found in the human (female) urogenital tract in the absence of actinomycetal infection include *A. meyeri*, *A. neuii*, *A. radingae*, *A. turicensis*, and *A. urogenitalis* (43–47). After the detection of *Actinobaculum schaalii* (currently *Actinotignum schaalii*), a taxon closely related to the members of the genus *Actinomyces*, in urine, groin swabs, and vaginal swabs (18), it was recently suggested that this organism might be a relatively frequent commensal residing on the skin and mucosae of urogenital sites, but not in the colon, since no detection from feces was made (48).

Actinomyces at Normally Sterile Body Sites

Actinomyces species have been detected at body sites where microbes are not normally found. For example, *Actinomyces* was found to be a core component of the microbiota in sputum samples from 22 tuberculotic patients and 14 controls examined by 16S rRNA gene pyrosequencing (49). This is consistent with a report that *Actinomyces* was among the most prevalent genera in the sputum of cystic fibrosis patients (50). Urine has historically been considered a sterile fluid, but recent data have challenged this. Hilt et al. (51) used a combination of standard and expanded quantitative urine cultures and 16S rRNA gene sequencing to identify bacteria in urine specimens collected from 65 women (41 with overactive bladder and 24 controls). *Actinomyces* proved to be among the most prevalent genera, being found in 7% of the women. *A. neuii*, *A. turicensis*, *A. urogenitalis*, *A. europaeus*, *A. odontolyticus*, *A. graevenitzii*, *A. naeslundii*, and *A. oris* were detected, as were the closely related genus *Actinobaculum* (currently *Actinotignum*) and the species *A. schaalii* and *A. urinale*. Based on their detection of viable bacteria, those authors concluded that there is indeed a resident low-abundance microbiota in the adult female bladder (51). It is usually considered that overactive bladder is not of infectious origin; however, *A. neuii* and *A. schaalii* were recovered from symptomatic women only (11% and 16%, respectively) (52).

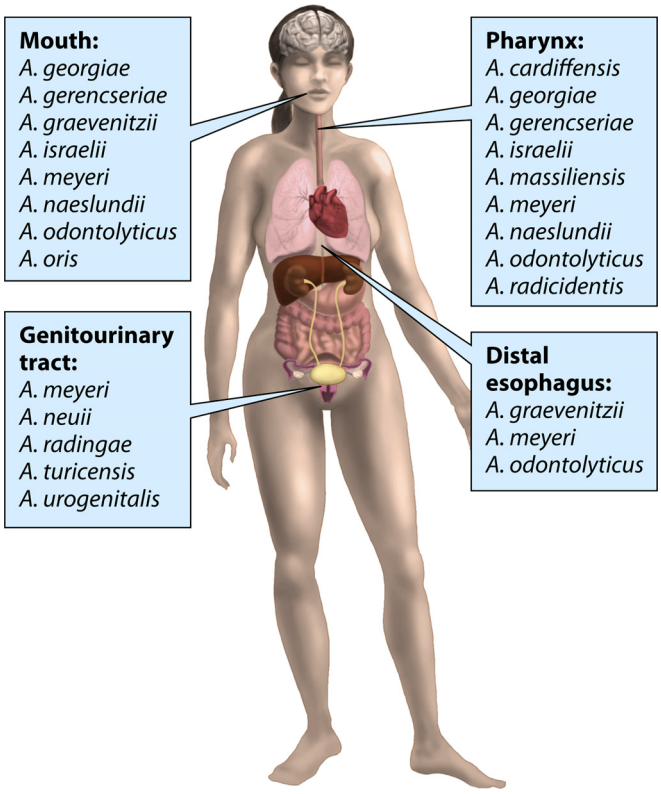

FIG 2 Natural habitats of human *Actinomyces* species.

Figure 2 summarizes the distribution of *Actinomyces* species at various body sites of a healthy subject.

ACTINOMYCOSIS

Actinomycosis is generally considered an uncommon disease; however, current prevalence rates are not available, and furthermore, data from developing countries are incomplete (8). Actinomycosis affects subjects of all ages, although pediatric cases are much less frequent than cases in adults, where the disease is more common in men. The disease can appear in both immunocompetent and immunocompromised individuals (8, 9).

Typical actinomycosis is an indolent, slowly progressing granulomatous disease, which can be categorized, according to the body site, as orocervicofacial, thoracic, and abdominopelvic forms (7–9). The disease can also appear as cutaneous actinomycosis, musculoskeletal disease, pericarditis, infection of the central nervous system (CNS), or disseminated disease. Moreover, some actinomycosis cases have been linked to specific conditions, such as osteoradionecrosis or bisphosphonate-related osteonecrosis of the jaws (53, 54), the use of anti-inflammatory drugs (55, 56), or some hereditary diseases (57, 58). Also, unusual presentations of

human actinomycosis have been reported, which presents a diagnostic challenge (59). Conversely, it is important to remember that *Actinomyces* species are found in a variety of polymicrobial infections, particularly associated with the head and neck, and only a minority of these are classical actinomycoses.

Early diagnosis of slowly progressing actinomycosis is difficult due to the nonspecific nature of the signs and symptoms of the disease, such as swelling, cough, low-grade fever, and weight loss, which leads to delays in patients seeking medical care. An additional diagnostic challenge is that a growing fibrotic mass, spreading through tissue planes, can resemble a malignant tumor (9). For example, in a recent case series of 94 thoracic actinomycosis cases (60), one-third of the cases were initially diagnosed as lung cancer, and only 6% were diagnosed as actinomycosis. Radiographic imaging techniques, such as computed tomography, and magnetic resonance imaging are valuable diagnostic tools for recognizing the location and size of the lesion(s) (61–63). Characteristic features of actinomycosis include chronic manifestations, abscess formation with sinus tracts, and purulent discharge (9). Hard macroscopic grains, "sulfur granules," in pus have been considered among the confirmatory characteristics of actinomycotic lesions; however, they are not always present in pus samples (7, 12). When available, sulfur granules are of diagnostic value; in a histopathological examination, the granules are crushed, Gram stained, and viewed under a microscope, revealing typical Gram-positive branching filaments forming segment-like structures and being surrounded by inflammatory cells, mainly polymorphonuclear neutrophils (9, 14).

Orocervicofacial Actinomycosis

Orocervicofacial actinomycosis is the most common form of actinomycosis, consisting of more than half of all actinomycosis cases (7–9). According to the experience of Schaal and Lee (13) in Germany over a period of 25 years, cervicofacial actinomycosis cases were common, making up ~25% of the odontogenic infections examined in their laboratory. This may not be surprising, since the mouth, particularly dental plaque, is the primary habitat of *Actinomyces* species. Indeed, poor oral hygiene is seen as an important predisposing factor for actinomycosis, as are smoking and heavy use of alcohol, reflecting the health behavior of the host. *Actinomyces* can easily gain access to oral tissues via invasive dental procedures such as tooth extraction (8).

To date, the most comprehensive data on the bacteriology of this form of actinomycosis come from a study conducted in two reference laboratories in Germany (12). Altogether, 12,253 specimens, collected between 1972 and 1999 from patients having cervicofacial inflammatory processes, were examined thoroughly by using culture-based techniques with a wide variety of growth media and incubation times of up to 14 days. Of these, 1,997 specimens yielded growth of filamentous bacteria, consisting primarily of *A. israelii* (42%) and *A. gerencseriae* (26.7%). In addition, *A. naeslundii*/"*A. viscosus*" was found in ~9% of the specimens, while *A. odontolyticus*, *A. meyeri*, *A. georgiae*, and *A. neuii* subsp. *neuii* were occasionally recovered. Those authors suggested, however, that the latter *Actinomyces* findings could be due to these species being part of a polymicrobial infection rather than indicating their potential to cause true actinomycotic lesions, and the absence of real causative organisms may be explained by missing them in culture. Furthermore, 20% of *Actinomyces* isolates could not be identified to the species level, which is not surprising if the number of recently described novel species and the number of known unnamed species are considered. Noteworthy is that ~90% of the 1,997 specimens also contained other bacterial species. In a reference laboratory in the United Kingdom, 88 clinical strains from unspecified infections of the neck-face area were identified; *A. israelii*, *A. naeslundii*, *A. odontolyticus*, and *A. gerencseriae* proved to be the main *Actinomyces* species, with each of them having a prevalence of ~10% (64). Among the strain collection, several *A. graevenitzii*, *A. meyeri*, and *A. turicensis* as well as sporadic *A. europaeus*, *A. georgiae*, *A. neuii*, *A. cardiffensis*, and *A. funkei* strains were also identified (64, 65).

A recent report (66) reviewed 17 cases of pediatric cervicofacial actinomycosis, defined as a culture positive for *Actinomyces* or a biopsy specimen with "sulfur granules." Of the 13 cases with a culture positive for *Actinomyces*, five isolates were identified as *A. israelii*, and three isolates each were identified as *A. odontolyticus*, "*A. viscosus*," or *A. bovis*. It is not uncommon, however, that there are uncertainties in identifications in sporadic case reports. For instance, as nonhuman species, *A. bovis* and "*A. viscosus*" have probably been misidentified. Bacterial masses similar to those seen in actinomycosis, and from which *A. israelii* has been isolated, have also been recognized in pediatric osteomyelitis, and in the majority of cases, their location is the mandible (67).

Within the oral cavity, the hard palate is an uncommon site for actinomycosis, since only four cases have been described in the literature; in one of these cases, *A. naeslundii* was isolated from a diabetic patient (68). Another report described an ulcer-type actinomycotic lesion with *A. odontolyticus* on the oral mucosa of a patient with diabetes (69). Other locations for actinomycotic lesions categorized as cervicofacial actinomycosis include, for instance, the nasal and sinus region (70–72); pharynx (73, 74); larynx/tonsillae (75–78); middle ear, mastoid, and/or temporal bone (79–81); and skull base with the craniovertebral junction (82). A somewhat more distant location is the esophagus, from where actinomycotic lesions have also been recovered in both immunocompetent and immunocompromised individuals (83, 84). Except for actinomycotic cases with *A. meyeri* in the middle ear and mastoid (79) and *A. israelii* in the mastoid (81) and in the skull base (82), identified by molecular methods, as well as *A. odontolyticus* in the larynx (77), diagnoses were not based on microbiology but on clinical manifestations and histopathology with or without a presentation of sulfur granules. In some cases, culture was performed, resulting in "no growth," or the species identification was not defined. Therefore, which specific *Actinomyces* species could have been involved in these actinomycotic lesions remains unclear.

Thoracic Actinomycosis

The main source of thoracic actinomycosis is considered to be the aspiration of oropharyngeal secretions, although hematogenous spread or direct spread from local infections can result in actinomycotic lesions at pulmonary sites (7, 8). Alternative causes to be considered in differential diagnoses include lung cancer, pneumonia, and tuberculosis (60). Since the spread of an actinomycotic lesion occurs despite anatomic barriers, invasion into the pleura or the chest wall can result in empyema or actinomycosis in the chest wall and surrounding bone structures (7, 9).

A. graevenitzii appears to have a predilection for respiratory sites (25, 64). Indeed, *A. graevenitzii* has been reported to be a causative organism in thoracic actinomycosis (56, 85, 86), multi-

ple lung abscesses mimicking coccidioidomycosis (87), and organizing pneumonia with microabscesses (88). These observations are credible due to the possibility of aspiration, since *A. graevenitzii* colonizes the oral cavity in particular (28). *A. meyeri* (89–94), *A. israelii* (95, 96), *A. odontolyticus* (97, 98), and *A. cardiffensis* (99) have been recovered from actinomycotic lesions at pulmonary sites. *A. cardiffensis* has also been isolated from the blood of a patient with multiple lung abscesses and septicemia (100). Sporadic findings of *A. naeslundii* and "*A. viscosus*" from pediatric actinomycosis cases have been reported (95). Interestingly, a variety of typical oral species were present as concomitant bacteria in most specimens. Rarely, a progressing thoracic lesion extends to extrathoracic tissues, with abscess formation on the thoracic wall and pus eroding through the chest wall, causing "empyema necessitatis." This is a severe condition, where *A. odontolyticus*, *A. israelii*, *A. gerencseriae*, and unspecified *Actinomyces* species have been detected as causative organisms besides mycobacteria and staphylococci (101–103). There are reports of cases where thoracic actinomycosis was found together with tuberculosis (85). In most of these cases, actinomycosis was due to *A. israelii*, while in one case, *A. graevenitzii* was identified as the causative organism.

Other *Actinomyces* species isolated from thorax specimens, collected in routine clinical laboratories and identified in a reference laboratory, were mainly *A. meyeri* and *A. odontolyticus*, but one isolate each of *A. turicensis*, *A. cardiffensis*, and *A. funkei* were also detected (64). Since there was no further clinical/histopathological information, it is not possible to confirm their connection specifically to actinomycosis.

Abdominal/Pelvic Actinomycosis

Abdominal actinomycosis is mainly a consequence of invasive procedures or abdominal infection such as appendicitis (8). Laparoscopic cholecystectomy with a lost gallstone(s) has been reported to be a potential complication leading to actinomycosis; *A. naeslundii* and an unspecified *Actinomyces* sp. were detected in two cases of abdominal abscesses (104), while *A. meyeri* was found in a case of abdominal actinomycosis extending from the kidney up to the thorax (105) and in an actinomycotic subphrenic abscess (106). *A. israelii* and *A. meyeri* have been identified in pus specimens from periappendical abscesses (107). *A. meyeri* was also implicated in splenic abscesses in a young girl with autoimmune hepatitis (108). In some abdominal actinomycosis cases arising from an abdominal source or even from the mouth, *Actinomyces* can result in pericarditis or the involvement of the liver; several *Actinomyces* species, particularly *A. israelii* (109–112) and *A. meyeri* (92, 113) but also *A. funkei* (114), *A. odontolyticus* (115), and *A. turicensis* (116), have been detected in liver abscesses. *A. neuii* has been detected in pericardial effusion samples of patients with chronic pericarditis (117). It is notable, however, that *A. neuii* is not considered to be involved in classical actinomycosis (118, 119).

Pelvic actinomycosis has usually been connected to *Actinomyces* present on an intrauterine contraceptive device (IUCD) after its prolonged use (8, 9). In a study conducted in Singapore, cervical smears of 1,108 women with IUCDs were screened for *Actinomyces*-like organisms by two cytologists (120). The prevalence of smears positive for target organisms was nearly 14%; however, no connection between positive smears and the duration of placement of the IUCD was found, contrary to most reports (121). Moreover, nearly all women, despite the presence of *Actinomyces*-like organisms, were asymptomatic (120, 121). When considering the frequency of use of IUCDs, the recovery of <100 actinomycotic specimens, most of those being tubo-ovarian abscesses, between 1926 and 1995 indicated that the risk of pelvic actinomycosis in relation to the use of IUCDs is very low (122). Among 130 *Actinomyces* isolates from clinical material associated with IUCDs sent to a reference laboratory for identification to the species level, one-third were identified as *A. israelii*, with its prevalence being double those of *A. turicensis*, *A. naeslundii*, *A. odontolyticus*, and *A. gerencseriae*, which were the next most common species (64). In an *in vitro* study, *A. israelii* grown in synthetic intrauterine medium was demonstrated to attach to and form spiderlike colonies and porous biofilm structures on copper plates, where the presence of sulfur was also confirmed (123). *A. israelii* has been found in IUCD users with pelvic manifestations (124, 125). Furthermore, *A. odontolyticus* (126) and some of the more recently isolated *Actinomyces* species, including *A. urogenitalis* (127, 128), *A. hongkongensis* (129, 130), *A. cardiffensis* (65), and *A. turicensis* (131, 132), appear to play a role in IUCD-associated pelvic actinomycosis. Certain gynecologic procedures may predispose an individual to complications with *Actinomyces* organisms; a case of bacteremia from a tubo-ovarian abscess caused by *A. urogenitalis* in a non-IUCD user exposed to a transvaginal oocyte retrieval procedure was reported (128), while in IUCD users, a similar procedure resulted in an infectious complication with *A. israelii* (124), and another gynecologic procedure, hysterectomy and salpingectomy, resulted in pelvic actinomycosis due to *A. hongkongensis* (129). In fact, the type strain of *A. hongkongensis* originates from a pus specimen from a pelvic actinomycosis case where ovarian tubes were described as being filled with pus (130).

The spread of causative organisms from pelvic sites to the abdominal region or vice versa can lead to abdominopelvic actinomycosis (7).

Other Types of Actinomycosis

Cutaneous actinomycosis. Cutaneous actinomycosis is usually a secondary infectious process with an underlying focus at deeper tissues, or it appears as a result of hematogenous spread from actinomycotic lesion elsewhere in the body. Manifestations with a single or multiple draining sinuses can occur at various body sites, including the face, chest, midriff, hip, as well as upper and lower extremities. Primary cutaneous actinomycosis with multiple lesions has been described to be a first sign of a patient's HIV infection (133). *A. meyeri* and "*A. viscosus*" have been reported to be causative organisms of cutaneous actinomycosis (92, 133–135).

Musculoskeletal actinomycosis. Musculoskeletal actinomycotic disease has been associated mainly with *A. israelii*. Typically, the patients' dentition and oral hygiene are poor, which are predisposing factors for the disease to occur. A recent report described an actinomycotic case with an involvement of the cervical spine, where *A. meyeri* was isolated from prevertebral pus samples and blood (136). Among 15 actinomycotic cases with an involvement of thoracic vertebral bone, however, *A. israelii* was detected in 9 of the cases, and *A. meyeri* was detected in 1 (137). In one *A. israelii* case, no signs of osteomyelitis in the spinal column were observed; the organism was detected in cerebrospinal fluid, and the entire spinal cord was involved, leaving the patient with severe neurological symptoms (138). Furthermore, *A. israelii* has been isolated from actinomycotic tissue biopsy specimens taken from the spine, together with *Fusobacterium nucleatum* and *Aggregati-*

bacter actinomycetemcomitans (139); iliac bone (140); and bones of a hand with extensive deformities (141). The latter was a most unusual case, initiated during the invasion of Normandy Beach in 1944, due to the persistence of the lesion despite long-term therapeutic interventions.

Cerebral actinomycosis. Actinomycotic lesions in the CNS cause the most severe form of actinomycosis (7, 8). *Actinomyces* organisms usually gain access to this area either by hematogenous spread from remote sites or directly from local actinomycotic lesions of the head, and the disease usually appears as a single or multiple brain abscesses; among 70 cases of actinomycosis in the CNS, two-thirds proved to be brain abscesses (142). *Actinomyces* species isolated from cerebrospinal fluid include *A. israelii*, from a patient with meningitis (107), and *A. naeslundii* (sensu stricto) (10). Clinicians should be aware of the possibility of actinomycosis in the CNS, especially in patients with neurological symptoms who have a history of actinomycosis elsewhere in the body (143). Pediatric cerebral actinomycosis cases are very rare; *A. israelii* was detected in a 10-year-old boy with congenital heart disease (144), and "*A. viscosus*" together with *Streptococcus constellatus* were detected in an immunocompetent 7-year-old girl, who died due to subdural empyema (145). In the latter case, again, poor dental health was suspected to be a predisposing factor.

Disseminated actinomycosis. Disseminated actinomycosis exhibits multiorgan involvement (9) and usually also has a polymicrobial nature; *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans* is often among the coinfecting organisms (89, 146, 147). *A. meyeri* in particular has a tendency to be involved in disseminated infections (89, 146, 148). Despite the severity of disseminated infection, it can have clinically mild manifestations. For example, a patient with longstanding shoulder pain with gradual spread to the chest area was finally diagnosed with pericarditis and pneumonia, after many challenges. This infection was caused by *Actinomyces* and *Actinobacillus* (*Aggregatibacter*) *actinomycetemcomitans*, and 6 months later, the patient also developed a brain abscess (147). Notably, the patient's poor dentition was seen as a predisposing factor.

Actinomycosis Occurring in a Specific Context

Bisphosphonate-related osteonecrosis of the jaw. Bisphosphonates are commonly used drugs in oncology. Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is widely considered a specific disease entity where *Actinomyces* organisms may play an important role (54, 149). In three case series on BRONJ including a total of 96 patients, the rate of detection of *Actinomyces* varied between 53% and 86% (54, 150, 151). As known for most actinomycosis cases, concomitant or coinfecting organisms are usually present; therefore, it is conceivable that multiple bacterial morphotypes, located on active sites of bone resorption, were seen in BRONJ lesions examined by scanning electron microscopy (152).

Osteoradionecrosis. Another type of therapy used in oncology, namely, irradiation of the head and neck area, can lead to devitalization and necrosis of the jaw bone. Out of 50 patients examined, 12% were diagnosed as having an actinomycotic bone lesion (150). It is notable that, already in the early 1980s, *A. israelii* was suggested to be an associated organism on the basis of immunocytological findings (153), but this was ignored at that time. Later, the impact of *Actinomyces* as an infectious organism under this condition was reinforced when *Actinomyces*, identified as *A. israelii*, was found prominently colonizing necrotic bone in the majority of 31 patients with osteoradionecrosis (53). Furthermore, it was shown that patients with bone biopsy specimens positive for *Actinomyces* were more susceptible to treatment failures than those with *Actinomyces*-negative biopsy specimens (154). In a study using sequencing of the 16S rRNA gene, however, only one *A. israelii*-positive specimen from osteoradionecrotic bone was found among six specimens examined (155), whereas the use of a DNA-DNA checkerboard method with targeted probes revealed the presence of *Actinomyces* species in all 12 resected jaw bone specimens examined (156). Ten specimens consisting of deep medullar bone of the jaw were positive for *A. israelii*, six for were positive "*A. viscosus*," and five were positive for *A. gerencseriae*. These discrepancies in bacterial findings may be explained by different methodologies used in these studies.

Anti-tumor necrosis factor alpha drugs. Anti-tumor necrosis factor alpha (TNF-α) drugs, which are increasingly used in the treatment of inflammatory diseases such as rheumatoid arthritis and Crohn's disease, have been linked to an increased susceptibility to bacterial infections. The most common infections resulting in hospitalization are pneumonia, skin/soft tissue infections, urinary tract infections, and bacteremia/sepsis (157). Sporadic actinomycosis cases have also been reported in this context, including thoracic actinomycosis due to *A. graevenitzii* (56), rapidly progressing pneumonia due to *A. meyeri* (93), as well as cutaneous actinomycosis, with one case due to *A. neuii* subsp. *anitratus* and another case due to coinfection with *A. turicensis* and *A. urogenitalis* (55).

Hereditary hemorrhagic telangiectasia. Hereditary hemorrhagic telangiectasia is a vascular dysplasia with multiple-organ involvement. Recently, a case of multiple brain abscesses caused by *A. israelii* in a patient with hereditary hemorrhagic telangiectasia was described, and a review of such cases was conducted (57). Individuals with this syndrome are especially predisposed to brain abscesses, which are found in 75% of these individuals. In the literature between 1953 and 2013, ~10 actinomycosis cases in telangiectasia patients are known, where *A. israelii*, *A. meyeri*, *A. odontolyticus*, and *A. bovis* were implicated (57, 158). Other bacteria were also present in half of the cases; for example, organisms isolated concomitantly with *A. meyeri* were *Streptococcus intermedius*, *Fusobacterium nucleatum*, *Capnocytophaga* spp., and *Staphylococcus epidermidis* (159), and in another case, organisms isolated concomitantly with *A. odontolyticus* included *Haemophilus aphrophilus* (now *Aggregatibacter aphrophilus*), peptostreptococci, and *Bacteroides* sp. (160). These findings suggest an oral source of these polymicrobial brain abscesses.

Chronic granulomatous disease. The rare hereditary condition chronic granulomatous disease, which affects the clearance of phagocytosed microorganisms, can lead to severe infections, especially in the lungs, skin, lymph nodes, gastrointestinal tract, and liver, caused by fungi (e.g., *Aspergillus*) or aerobic bacteria (e.g., *Staphylococcus aureus*) (161). Interestingly, *Actinomyces* was detected in two pulmonary specimens from a total of 684 infectious episodes in 284 patients. Indeed, it was recently reported that patients suffering from chronic granulomatous disease could be especially vulnerable to actinomycosis (58). This case series of 10 patients consisted mainly of abscess specimens collected from the upper part of the body (submandibular region, neck, liver, and lung). Typically, recurrent infections in these patients are connected to catalase-producing bacteria and fungi (162), but here mainly catalase-negative *Actinomyces* species, including *A.*

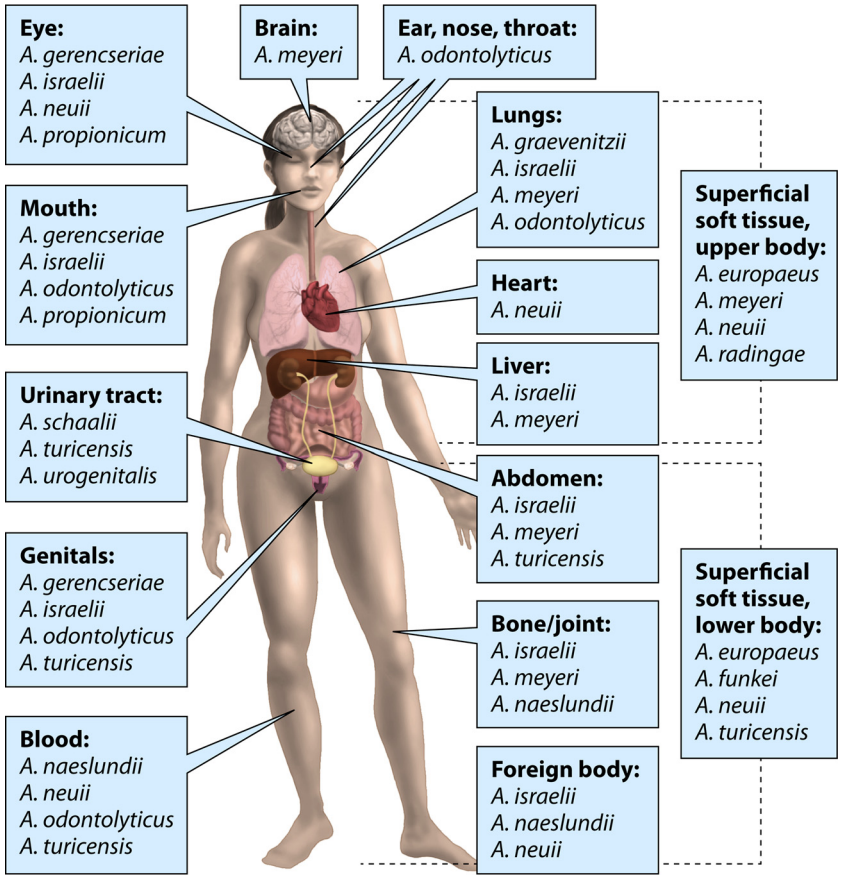

FIG 3 Major *Actinomyces* findings in human infections at different body sites.

naeslundii ($n = 5$), *A. gerencseriae* ($n = 1$), *A. meyeri* ($n = 1$), an unspecified *Actinomyces* sp. ($n = 1$), and two cases specified as "actinomycosis," were suggested to be causative organisms of chronic granulomatous disease-related actinomycosis (58). However, whether the described cases represented typical actinomycosis or another type of *Actinomyces*-associated infection remained unclear.

OTHER INFECTIONS WITH INVOLVEMENT OF *ACTINOMYCES*

The range of clinical infections with an involvement of *Actinomyces* species is widening due to the introduction of novel species that have been described during this century. Figure 3 presents infectious sites and major *Actinomyces* recoveries from human infections besides classical actinomycosis.

Brain Abscesses

In a recent comprehensive nationwide study conducted in Norway, the bacteriology of brain abscess specimens collected over a 2-year period was examined by culture and direct 16S rRNA gene sequencing, and positive specimens ($n = 52$) were reanalyzed by using massive parallel sequencing (15). Of these specimens, 37 came from spontaneous brain abscesses, 3 were from spontaneous subdural infections, and 12 were from postoperative infections. That study revealed a bacterial detection rate by massive parallel sequencing that was three times higher than that obtained by standard culture-based routine diagnostics. The vast majority of abscess specimens yielded polymicrobial growth, where *Aggregatibacter aphrophilus*, *Fusobacterium nucleatum*, *Streptococcus intermedius*, and *Actinomyces* were among the predominant organisms. A very interesting observation was that nearly all *Actinomyces* isolates recovered from 37 spontaneous brain abscesses were identified as *A. meyeri* ($n = 12$), while other findings included *A. georgiae* ($n = 2$), *A. israelii* ($n = 1$), and *Actinomyces* sp. ($n = 1$) (15). Indeed, there are several reported cases of the involvement of *A. meyeri* in brain abscesses and/or other types of CNS infections (64, 92, 163), indicating the predilection of this organism for severe infections in the human CNS.

Eye Infections

Actinomyces species have been isolated from cases of endophthalmitis, keratitis, and canaliculitis. Of these, the most common infection is postoperative endophthalmitis after an ocular procedure, where *A. neuii* (164–166), *A. meyeri* (167), and "*A. viscosus*" (168) have been detected, while in cases of endogenous endophthalmitis, which is far less common, *A. neuii* (169) and *A. israelii* (170) have been detected. *A. israelii* has also been isolated from cases of postoperative keratitis (171) and primary infections of the lacrimal duct, i.e., canaliculitis (172–174). In addition, *A. meyeri* and *A. georgiae* have been found in specimens from cases of canaliculitis (172, 175), while *A. naeslundii* was identified in a swab specimen taken from a cornea after trauma leading to keratitis (107). Of 59 eye secretions/tear fluid examined in a reference laboratory in Germany, 22% were positive for "*A. viscosus*," 19% were positive for *A. israelii*, 14% were positive for *A. naeslundii*,

and 10% were positive for *A. gerencseriae* and *A. odontolyticus* each; *A. israelii* and *A. gerencseriae* were isolated from canaliculitis cases, whereas "*A. viscosus*," *A. naeslundii*, and *A. odontolyticus* were more common in cases of conjunctivitis (13). Among 15 clinical strains collected from eye infections (infection not specified) and sent to a reference laboratory in the United Kingdom for identification, *A. gerencseriae*, *A. israelii*, *A. odontolyticus*, *A. naeslundii*, and *A. georgiae*, in descending order, were detected (64).

Ear, Nose, and Throat Infections

Actinomyces has been detected at increased frequencies in the nasopharynx of children suffering from recurrent otitis media during their first 2 years of life (35). In nasopharyngeal aspirates collected during acute otitis media episodes, one-quarter were colonized by *A. odontolyticus*, but *A. gerencseriae* was also found (176). In a culture-based study of peritonsillar abscesses, *A. odontolyticus* was found in one-quarter of 124 pus aspirates collected from young adults (177). *A. turicensis* has been detected in chronic otitis media and mastoiditis cases (47, 178), while one *A. cardiffensis* strain was found in pus collected from temporal, large, and small parietal and ear abscesses in a patient after mastoidectomy (65). Moreover, another *A. cardiffensis* strain was obtained from an antral washout specimen of a patient with sinusitis (65), and a novel *A. nasicola* strain was obtained from pus collected from the nasal antrum (179).

Oral Infections

Actinomyces species are involved in infectious processes of the mouth, including a wide variety of diseases induced by polymicrobial consortia living in biofilms.

Dental caries. The role of *Actinomyces* in dental caries is well known; in this context, the most important species are *A. gerencseriae* and *A. israelii* (30, 180, 181). *A. gerencseriae* in particular is among the most active species in dental plaque of children suffering from severe early childhood caries, which is a chronic disease causing extensive destruction of the primary dentition (181). Elderly subjects with exposed root surfaces (usually due to treated or untreated advanced periodontitis) are susceptible to root caries, where certain *Actinomyces* species are considered important causative organisms, particularly *A. israelii* and *A. gerencseriae*, but *A. naeslundii*, *A. odontolyticus*, and *A. georgiae* have also been isolated (180). Both *A. naeslundii* genospecies 1 (*A. naeslundii* sensu stricto) and genospecies 2 (now *A. oris*) colonize active root caries lesions (182).

Endodontic infections. The primary cause of endodontic infection is dental caries, which, when untreated, progresses into the pulp cavum and root canal, infecting the pulp and eventually causing necrosis of the pulpal tissue. Since the infectious process can be asymptomatic, if no root canal treatment is given, microorganisms may gain access to even periapical sites. *Actinomyces* species are rarely involved in early stages of endodontic infections but are typically found in persistent infections and extraradicular lesions (183–187). Rates of detection of *Actinomyces* in clinical endodontic samples varied from 9% among 53 specimens examined by DNA-DNA checkerboard analysis (185) to 56% among 129 specimens examined by PCR (187). There were also obvious differences in the species distribution: *A. gerencseriae* and *A. israelii* (185) on the one hand and "*A. viscosus*" and *A. israelii* (187) on the other hand were reported as major *Actinomyces* species in teeth with abscesses, whereas *A. naeslundii* was either absent (185) or present at low levels (187). In a culture-based study of refractory periapical infections, sulfur granules were found in 9 of 36 periapical lesions (186); five of the seven culture-positive granules grew *Actinomyces*, including *A. israelii*, "*A. viscosus*," *A. naeslundii*, and *A. meyeri*. Also, *A. radicidentis* isolates have been recovered sporadically from endodontic specimens (184, 188). Most, if not all, endodontic infections are polymicrobial (183–187). Two novel *Actinomyces* species, *A. oricola* and *A. dentalis*, with one strain each, have been isolated from dental abscesses (189, 190).

Oral infections in tissues surrounding teeth/implants. *Actinomyces* organisms, particularly *A. naeslundii* and *A. oris*, are common in dental plaque (10). Indeed, *A. naeslundii* has been found in cases of dental plaque-induced gingivitis, although *A. naeslundii* and *A. gerencseriae* were also reported to be associated with periodontal health (191). Somewhat surprising was the detection of *A. gerencseriae* as one of the dominant species of the microbiota at the gingival margin in relation to a severe form of gingival disease, necrotizing ulcerative gingivitis (192). Typically, Gram-negative anaerobes, such as fusobacteria, *Prevotella intermedia*, and spirochetes, are considered the etiologic organisms of this acute and painful disease, which destroys soft tissues around affected teeth, especially interdental gingival papillae. Elevated levels of *A. neuii* in subgingival sites of women with gingivitis were reported in a study where the DNA-DNA checkerboard technique was used as a detection method (193). Otherwise, *A. neuii* is seldom detected in oral biofilms. The known cross-reactivity of the checkerboard method may explain this unusual finding. Furthermore, *A. odontolyticus*, *A. israelii*, *A. naeslundii*/"*A. viscosus*," *A. meyeri*, and *A. gerencseriae*, in descending order, have been recovered from a case of pericoronitis of wisdom teeth (194), while *A. odontolyticus*, *A. naeslundii*, "*A. viscosus*," *A. israelii*, *A. georgiae*, *A. gerencseriae*, and *A. graevenitzii*, in descending order, were recovered from 33 failed dental implant fixtures, which had been removed due to infection (195). When bone was harvested from jawbone(s) for augmentation procedures, which may occasionally be needed for successful implantation of dental implant fixtures, *A. odontolyticus* was found to be among the most frequent contaminants of bone debris (196).

Pulmonary Infections

On the basis of the literature, it is unclear whether reported pneumonia or other disease cases with an involvement of *Actinomyces* represent thoracic actinomycosis or lung infection without specific actinomycotic lesions. For instance, in the original description of *A. graevenitzii*, three out of four strains characterized came from respiratory material, including bronchus brush, bronchial secretion, and sputum samples; however, no information on the clinical situation regarding these strains was given (197). This was also the case in another study, where four *A. graevenitzii* isolates were obtained from similar pulmonary sources (25). In a recent epidemiological investigation, *A. graevenitzii* proved to be the predominant species identified in *Actinomyces*-positive bronchoscopy cultures (198). The 18 case patients had abnormalities on chest radiography but no biopsy findings typical of pulmonary actinomycosis; 12 of the patients were positive for *A. graevenitzii*, 3 were positive for *A. odontolyticus*, 1 was positive for both *A. graevenitzii* and *A. odontolyticus*, and 2 were positive for unspecified *Actinomyces* species. An interesting observation was the significant increase in the number of *Actinomyces*-positive pulmo-

nary specimens after the culture protocol was modified (198). Previously, *A. israelii* had been identified as the main *Actinomyces* species recovered in bronchial secretions (13). *A. meyeri* was isolated from a pus specimen related to an empyema that developed after pneumonia (107). Indeed, several *A. meyeri* cases in connection to pneumonia have been reported (92). Besides *A. meyeri*, *A. odontolyticus*, *A. turicensis*, *A. cardiffensis*, and *A. funkei* were among thorax specimens that were identified in a reference laboratory in the United Kingdom (64); due to the lack of other information, it was not possible to estimate whether they were associated with thoracic actinomycosis or other pulmonary infections.

Superficial Infections

The upper body. Many *Actinomyces* species have been identified in soft tissue abscesses of the body above the waistline. Breast tissue is a site commonly affected by actinomycosis, with *A. neuii* especially being identified as a causative organism (11, 64, 119, 175, 199–201). Also, *A. europaeus* (25, 64, 202, 203), *A. radingae* (25, 64, 204), *A. meyeri* (92, 205), and *A. turicensis* (25, 204, 206) have been recovered. In one breast abscess case, *A. turicensis* was isolated in pure culture (25). Nipple piercing was suggested to be a predisposing factor for *Actinomyces* infection of the breast in two patients, one due to *A. radingae* (204) and another due to *A. turicensis* together with a Gram-positive anaerobic coccus, *Peptoniphilus harei* (206). Other sites of the upper body with abscesses with an involvement of *Actinomyces* organisms include the face, neck, axilla, armpit, chest, and/or back, with *A. europaeus*, *A. georgiae*, *A. meyeri*, *A. neuii* (both subspecies), and *A. radingae* being the identified species (25, 64, 92, 107, 175, 205). In addition, *A. turicensis* has been isolated from necrotic tissue associated with cervicofacial fasciitis (107), and *A. neuii* has been isolated from a mammary hematoma (207).

The lower body. The majority of skin-related infections caused by *Actinomyces* below the waistline are due to *A. turicensis* (25, 64, 107, 178, 208, 209). Abscesses are typically found in the groin, buttock, rectal area, and skin of the genitals. Other *Actinomyces* species commonly detected include *A. europaeus*, *A. funkei*, *A. neuii* (both subspecies), and *A. radingae* (25, 47, 64, 107, 114, 175, 178, 202, 209). It has been suggested that lipid-rich areas are favorable for the growth of these *Actinomyces* species (178). Furthermore, *A. europaeus*, *A. funkei*, and *A. turicensis* have been isolated from decubitus ulcers (25, 114, 202); *A. neuii* and *A. radingae* have been isolated from diabetic ulcers (118, 175); and *A. europaeus*, *A. turicensis*, and *A. odontolyticus* have been isolated from skin-related infections in lower extremities (25, 202, 210). It was suggested that the latter species, isolated from an intravenous drug abuser, originated from the oral cavity due to licking of an injection needle (210). This is consistent with the results of a study comparing bacterial recoveries from soft tissue abscesses of intravenous drug abusers and nonusers (211). Oral-type bacteria, including *A. odontolyticus*, dominated in the majority of abscesses of drug abusers but not nonusers. In another case, *A. odontolyticus* together with *Eikenella corrodens*, both oral species, caused infection in a foot due to trauma by toothpick puncture (212). A coinfection by two *Actinomyces* species, *A. europaeus* and *A. turicensis*, resulting in subcutaneous fistulae in association with an irritative exoprosthesis of a leg was reported (213). Sporadic *Actinomyces* findings include *A. neuii* and *A. europaeus* in infected atheromas (118, 202) and an *A. hominis* strain in a wound specimen (214), but their location was not specified. A case with a large vulvar lesion was connected to *A. israelii*, present together with *Propionibacterium acnes* and *Peptostreptococcus* sp. (215). Recently, a polymicrobial case of Fournier's gangrene affecting an immunocompetent elderly man was analyzed by using 16S rRNA gene sequencing, which revealed the presence of *A. funkei* together with *Fusobacterium gonidiaformans* and *Clostridium hathewayi* as etiologic organisms (216). Seven cases of *A. funkei* infection were also detected recently in Spain by using sequencing-based isolate identification. Positive specimens included specimens from three abscesses, three wounds, and one bronchial aspirate (216).

Genitourinary Infections

Genital tract. The most common infections due to *Actinomyces* species in the genital tract are associated with the use of an IUCD. Among 130 isolates from IUCD-related infections, *A. israelii* in particular as well as *A. turicensis*, the *A. naeslundii*-"*A. viscosus*" complex, *A. odontolyticus*, and *A. gerencseriae* were identified as the main species in a reference laboratory in the United Kingdom, but *A. cardiffensis* and *A. funkei* were also not uncommon (64, 65). According to data from a reference laboratory in Germany (13), *A. israelii* was the most frequently detected isolate from IUCDs and cervical secretions. Also "*A. viscosus*" was frequently found, whereas *A. gerencseriae*, *A. naeslundii*, and *A. odontolyticus* were identified in only 5% of 82 specimens. In addition, *A. urogenitalis* and *A. radingae* have been isolated from IUCDs and vaginal secretions (11, 45, 175). *A. urogenitalis* has also been detected in high numbers in vaginal samples from patients with bacterial vaginosis (45). *A. turicensis* can be detected in a variety of infections of the female genital tract, such as adnexitis, endometritis, cervicitis, vaginitis, and vulvitis (178). In pregnancy, *A. neuii* has been found in infected amniotic fluid (118) and in severe cases of chorioamnionitis, leading to sepsis of the neonate (217). *A. meyeri* has been found to cause chorioamnionitis, leading to necrotizing funisitis and preterm birth (218). In infections of the genital tract in males, *A. neuii* has been detected in prostatitis cases (118), and *A. turicensis* has been detected in balanitis, penile abscess, and prostatitis cases (64, 175, 178).

Urinary tract. In both males and females, *A. turicensis* has been detected in connection with urethritis and cystitis (25, 107, 178). Other *Actinomyces* organisms found in the urinary tract include *A. urogenitalis* from urethra and urine (45), *A. neuii* in urinary tract infection (118), and *A. europaeus* in patients with cystitis or purulent urethritis (178). There are often other bacteria present, and only slightly elevated levels of leukocytes are observed in urine (178).

Bone/Joint Infections

Actinomyces species have been recovered from infections affecting bone, including osteomyelitis with an involvement of *A. meyeri* in the jaw, symphysis pubis, leg (tibia), and foot (92); *A. israelii* in osteomyelitis of the sternum (219); *A. naeslundii* in chronic osteomyelitis with thickening of the periosteum in the lower leg (220); and *A. graevenitzii* in an osteitis lesion of the jaw (197). There are also reports where two causative organisms of chronic osteomyelitis have been described, including *A. meyeri* together with *Fusobacterium nucleatum* in the leg (fibula) (221) and *A. neuii* subsp. *neuii* together with *Dermabacter hominis* in the calcaneus (222). Spondylodiscitis can rarely be due to *Actinomyces* organisms, such as *A. meyeri* (92) and *A. israelii* (223). A strain representing the novel *Actinomyces* species *A. timonensis* was isolated from an os-

teoarticular specimen of a 13-year-old girl suffering from chronic sacroiliitis (224).

Foreign-Body Infections

Different types of devices and materials are increasingly used in modern medicine to support defective or lost functions of the human body. According to recent reports, *A. neuii*, especially *A. neuii* subsp. *neuii*, seems to be the most frequently detected *Actinomyces* species in infected tissues around different types of prostheses, including mammary prostheses (225), penile prostheses (226), prosthetic valves (227), and hip prostheses (228), but also in connection to medical devices such as ventriculoperitoneal shunts (229, 230) and peritoneal dialysis catheters (231). In addition, *A. israelii* and *A. naeslundii* have been identified as causative agents of periprosthetic infections of the hip or knee joints (232–234). Moreover, *A. odontolyticus* was isolated from a subcutaneous abscess connected to an exit site of a catheter in a patient treated with continuous ambulatory peritoneal dialysis (235). Recently, *A. meyeri* was found to be the cause of a disseminated infection resulting in fatal mediastinitis after an esophageal stent operation (236).

Infective Endocarditis

Although *Actinomyces* species are rarely considered causative organisms in cases of endocarditis, isolation of *A. neuii* (119, 227, 237), *A. funkei* (238), *A. israelii* (239, 240), "*A. viscosus*" (240–242), and *A. meyeri* (92, 243) has been reported. One reason for the rarity of reports of *Actinomyces* in blood specimens could be due to considering the finding to be insignificant or, if an organism is isolated, to the difficulty of identification of members of this group. Methodological improvements in identification and the availability of these methods in clinical microbiology laboratories, e.g., matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry and 16S rRNA gene sequencing, may allow more definitive data to be collected.

Bacteremia/Sepsis

Several *Actinomyces* species have been detected in blood, including *A. funkei* (244), *A. georgiae* (64, 175), *A. graevenitzii* (245), *A. massiliensis* (246), *A. naeslundii* (10, 64, 247), *A. neuii* (107, 119, 207), *A. odontolyticus* (25, 64, 97, 107), *A. turicensis* (64, 175, 178), and "*A. viscosus*" (107). An important source of *Actinomyces* bacteremias is the mouth in particular. Since bacteremia is common after invasive dental procedures and after tooth brushing in subjects with gingivitis and periodontitis, who typically have inflamed bleeding gums, oral actinobacteria can easily gain access to the bloodstream; *A. georgiae*, *A. meyeri*, *A. odontolyticus*, *A. cardiffensis*, and a number of unnamed *Actinomyces* phylotypes were detected in blood samples particularly following the extraction of a tooth without antibiotic prophylaxis (248).

INFECTIOUS ROLE OF SOME *ACTINOMYCES*-RELATED ORGANISMS

Actinotignum (Formerly *Actinobaculum*) Species in the Urogenital Tract

Five *Actinomyces*-like strains characterized as *A. schaalii* were isolated from either human blood or urine in the original description of the novel genus *Actinobaculum* (18). Subsequently, two novel *Actinobaculum* strains were detected in urine samples from women with urinary tract infections, namely, *A. massiliae* (*A. massiliense*) and *A. urinale* (21, 22). Following these reports, it remained unclear as to whether these species played a significant role as human pathogens. This may have been because routine aerobic culture of urine samples, with an incubation time of 18 to 24 h, was not adequate for the detection of these fastidious and slow-growing species. In addition, if they had been cultivated, they may have been regarded as being insignificant commensals. Therefore, the first reports on their involvement in infections of the urinary tract came from laboratories with a special interest in unusual organisms and expertise in molecular detection methods. Among these organisms, *A. schaalii* was found to be a causative organism in several cystitis cases (249) and, more significantly, in patients with disseminated infection (249–252). The first described pediatric case of *A. schaalii* infection was that of a child with purulent pyelonephritis (253). Sporadic findings of *A. urinale* and *A. massiliense* were also reported (250, 252, 254). Before the 2010s, there were a total of ~30 cases caused by human *Actinobaculum* (currently *Actinotignum*) species in the literature. Since then, an extensive number of reports, especially on *A. schaalii* as an important uropathogen, have been published.

Typically, individuals affected by *A. schaalii* have an underlying condition in the urinary tract and are >60 years of age (255–257). Interestingly, considerable proportions of individuals without symptoms can also be positive for this organism; urine specimens from 13% of 38 healthy controls (aged between 63 and 81 years) proved to be positive by real-time PCR (255), and 22% of 55 culture-positive elderly subjects were characterized as having asymptomatic bacteriuria (256). *A. schaalii* is thus considered a uropathogen in the elderly, but the significance of this species in children is receiving attention (258, 259). Cystitis, pyelonephritis, and urosepsis are the major forms of *Actinotignum* (formerly *Actinobaculum*)-associated infections; however, other types of infections, especially with *A. schaalii*, are increasingly being reported, including bacteremia, abscesses, cellulitis, spondylodiscitis, bladder necrosis, epididymitis, and endocarditis (16, 260–264). In a case of Fournier's gangrene, only *A. schaalii* was detected by 16S rRNA gene sequencing (265). Despite improved techniques and targeted searches for *Actinotignum* (formerly *Actinobaculum*) species in urine specimens, only single findings of *A. massiliense* and *A. urinale* in urine or blood have been made (256, 261, 266), differing from the obvious involvement of *A. schaalii* in infections in, and occasionally outside, the urogenital tract.

Varibaculum cambriense as a Soft Tissue Pathogen

Fifteen *Actinomyces*-like strains from infections at a variety of body sites in 14 subjects were characterized and described as belonging to the genus *Varibaculum*, including one species, *V. cambriensis* (later corrected to *V. cambriense*) (24). Most cases were abscesses, including sites such as brain, ear, cheek, jaw, breast, and the ischiorectal area, but were also infections of the female genital tract with or without an IUCD. In addition, a study performed in Hong Kong in 2006 reported four cases caused by *V. cambriense* (267). All four subjects suffered from superficial abscesses, with the pus specimens originating from a recurrent umbilical scar with abscess formation on the skin, an abscess in the groin, a persistent lump in the groin, and an abscess on the back. Taken together, *V. cambriense* was proven to be a pathogen involved in superficial soft tissue infections.

Propionibacterium propionicum Infections

Propionibacterium propionicum is an organism resembling *Actinomyces* (formerly *Actinomyces propionicus* and then *Arachnia propionica*), but it differs from *Actinomyces* by producing large amounts of propionic acid as its metabolic end product in glucose fermentation (14). The morphological and biochemical resemblance to *A. israelii* is particularly striking. *P. propionicum* can cause infections similar to those with an involvement of *Actinomyces* organisms, such as actinomycotic lesions and abscesses (12, 13). In addition, this organism has been associated mainly with infections of the eye (13, 172, 268) and various endodontic infections (183, 184, 269, 270). In a German reference laboratory, 22% of 59 specimens from eye secretions/tear fluid and 12% of 43 bronchial secretion specimens were found to be positive for *P. propionicum* (13). Of 26 *P. propionicum* isolates recovered from patients with eye infections by a United Kingdom reference laboratory, the majority originated from cases of canaliculitis in the elderly (268). A study using a nested-PCR assay targeted to *P. propionicum* and *A. radicidentis* revealed high rates of detection of *P. propionicum* in primary endodontic infections: 50% in teeth with acute apical periodontitis, 37% in teeth with periradicular abscesses, and 29% in teeth with chronic periradicular lesions (184). Moreover, a different disease pattern was observed for *A. radicidentis*. *P. propionicum* was also among the species related to endodontic treatment failures (270). A pulmonary infection with multiple microabscesses in a 7-year-old child with chronic granulomatous disease (271) and a brain abscess in a young male with congenital cyanotic heart disease (272) due to *P. propionicum* have been described. The involvement of *P. propionicum* in brain abscesses is very rare, with only two reports in the current literature (272, 273). The first case of pelvic actinomycosis caused by *P. propionicum* was that of a woman who had long-term use of an IUCD as a predisposing factor (274). In addition to *P. propionicum*, two peptostreptococcal organisms were isolated from a pus specimen from the right ovary, and their identification was confirmed by 16S rRNA gene sequencing. Although three different microorganisms were present, of those, *P. propionicum* was considered the most significant (274). Recently, a psoas abscess caused by *P. propionicum* in a woman with no history of IUCD, other foreign bodies, or previous surgery was reported (275).

VIRULENCE PROPERTIES OF *ACTINOMYCES*

Little is known regarding virulence factors of *Actinomyces* species. They do not produce classical exotoxins, and the virulence determinants that allow *A. israelii*, *A. gerencseriae*, and others to cause actinomycosis are unknown. Presumably, they possess the ability to evade clearance by the host immune system and, thus, cause a chronic lesion. An *A. israelii* strain that was able to cause infection in an animal model was rapidly phagocytosed *in vitro*, and it was hypothesized that the ability of this organism to form a dense mass of interlinked branched chains of bacilli inhibited phagocytic clearance *in vivo* (276).

The virulence factors involved in polymicrobial soft tissue infections are also poorly characterized, but it is thought that multispecies communities can work together to evade the host, for example, by the production of a capsule (277) and serially degrade host tissues to provide nutrients for the whole community (278). Since *Actinomyces* species are frequently isolated from polymicrobial infections, they must be assumed to contribute to the pathogenetic processes involved in such situations.

A. oris and *A. naeslundii* play an important role in dental plaque (biofilm) formation. They are early colonizers and produce fimbriae that bind to saliva proline-rich proteins and statherin, which adsorb onto the tooth surface (279, 280). They also interact with a range of other dental plaque bacteria, including representatives of the genera *Fusobacterium*, *Prevotella*, and *Veillonella*, by coaggregation (281), which provides structural integrity to the plaque (282). Once a biofilm has formed, and in the presence of a fermentable carbohydrate, many plaque bacteria, such as *Actinomyces* species, can produce acid, which may lead to dental caries (182, 283).

CONCOMITANT/COINFECTING MICROBES

It is noteworthy that the vast majority of actinomycotic lesions as well as other *Actinomyces*-associated infections are polymicrobial, with the rate of occurrence of concomitants varying between 75 and 95% (12, 13, 178). The role of concomitant organisms is considered to synergistically enhance the infectious process. Bacteria frequently occurring together with *Actinomyces* species include strict anaerobes, such as *Fusobacterium* spp.; members of the family *Bacteroidaceae*; and Gram-positive anaerobic cocci (GPAC), especially *Parvimonas micra*, microaerophilic anginosus group streptococci (formerly "*Streptococcus milleri*"), and the capnophilic *Aggregatibacter* species *A. actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*) and *A. aphrophilus* (formerly *Haemophilus paraphrophilus*), and aerobic coagulase-negative staphylococci.

Analysis of material from sulfur granules and/or pus of 1,997 specimens from cervicofacial actinomycotic lesions, collected by incision or needle aspiration and thoroughly examined under various culture conditions and with prolonged incubation, revealed that 95.5% of specimens were positive for not only fermentative actinomycetes, mainly *A. israelii* and *A. gerencseriae*, but also aerobic and/or anaerobic companions (12). "Microaerophilic and anaerobic streptococci" were identified in 49.7% of the specimens. Based on previously reported data from the same laboratories in Germany, it can be estimated that 60% of these organisms were anginosus group streptococci and that 40% were GPAC (13). Other common findings, in descending order, were coagulase-negative staphylococci (39.1%); *Fusobacterium* spp. (37.7%); *Propionibacterium* spp. other than *P. propionicum* (27.5%); pigmented and nonpigmented *Prevotella-Porphyromonas* spp. (25.1% and 21%, respectively); corroding Gram-negative rods (18.5%), including *Campylobacter gracilis*, *Capnocytophaga* spp., and *Eikenella corrodens*; and *Aggregatibacter actinomycetemcomitans* (14.2%) (12).

Data on pediatric cases include data from 10 case reports of cervicofacial actinomycosis, 8 of which reported the presence of concomitant organisms (66), and 14 case reports of thoracic actinomycosis, with all specimens being positive for concomitants (95). In cases of cervicofacial actinomycosis, except for a recent report of concomitants representing the genera *Capnocytophaga*, *Prevotella*, *Enterococcus*, and *Streptococcus*, only a few, poorly defined bacterial taxa have been identified (66). Among 14 thoracic actinomycosis cases involving children, *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum* were the most commonly detected organisms, being detected in 9 and 5 cases, respectively (95).

Brain abscesses with an involvement of *A. meyeri* seem to harbor striking similarities in the compositions of their concomitant and/or coinfecting microbiota. Based on data reported recently by

TABLE 2 Concomitant/coinfecting organisms in 12 brain abscess cases with an involvement of *Actinomyces meyeri*[a]

Case	Concomitant/coinfecting organism							
	Aggregatibacter	*Campylobacter*	*Eikenella*	*Eubacterium*	*Fusobacterium*	*Parvimonas*	*Streptococcus*	Other
A	*A. aphrophilus*	*C. gracilis* *C. rectus*	*E. corrodens*		*F. nucleatum*	*Parvimonas* sp.		
B	*A. aphrophilus*	*C. gracilis*		*E. brachy*	*Fusobacterium* sp.	*P. micra* *Parvimonas* sp.	*S. intermedius*	*Actinomyces georgiae*
C	*A. aphrophilus*				*F. nucleatum*	*P. micra* *Parvimonas* sp.	*S. constellatus*	*Anaeroglobus geminatus*
D	*A. aphrophilus*						*S. intermedius*	*Actinomyces georgiae* *Capnocytophaga*
E	*A. aphrophilus*	*C. gracilis*	*E. corrodens*	*E. brachy* *E. yurii*	*F. nucleatum*	*P. micra*	*S. intermedius*	*Capnocytophaga* *Tannerella forsythia*
F					*Fusobacterium* sp.	*Parvimonas* sp.	*S. intermedius*	
G		*C. gracilis*	*E. corrodens*		*F. nucleatum*	*P. micra* *Parvimonas* sp.	*S. intermedius*	*Gemella morbillorum*
H				*E. brachy*	*F. nucleatum*	*P. micra*	*S. intermedius*	
I		*C. gracilis*	*E. corrodens*	*E. brachy* *E. yurii*	*F. nucleatum*	*P. micra*	*S. intermedius*	*Prevotella oris* *Prevotella timonensis* *Tannerella forsythia*
J		*C. gracilis*	*E. corrodens*		*F. nucleatum* *Fusobacterium* sp.	*P. micra*	*S. intermedius*	*Prevotella* sp.
K		*C. rectus*		*E. brachy*	*F. nucleatum*	*P. micra*	*S. intermedius*	
L	*A. aphrophilus*	*C. gracilis*	*E. corrodens*	*E. brachy*	*Fusobacterium* sp.	*Parvimonas* sp.	*S. intermedius*	*Johnsonella ignava*

[a] Data adapted from reference 15.

Kommedal et al. (15) (Table 2), 4 to 10 species were found in specimens from 12 spontaneous brain abscesses with an involvement of *A. meyeri*. In these specimens, *Fusobacterium nucleatum*, *Parvimonas micra*, and *Streptococcus intermedius* were the major concomitants, but also, *Aggregatibacter aphrophilus*, *Campylobacter gracilis*, *Eikenella corrodens*, and *Eubacterium brachy* were each detected in at least half of the specimens (15). All these organisms are inhabitants of the oral cavity. Interestingly, *Aggregatibacter aphrophilus* has been linked to invasive infections of the CNS, and its frequency in brain abscesses was considered disproportional to its presence in its natural habitat, the oropharynx (284). Among 26 various types of actinomycosis cases caused by *A. meyeri* identified from 1960 to 1995, 17 cases involved concomitants; of these, *Aggregatibacter actinomycetemcomitans* was the most common (89). This is, however, contradictory to the assumption that *Aggregatibacter actinomycetemcomitans* acts as a concomitant solely for *A. israelii* (25).

In a case report of a polybacterial brain abscess, *Capnocytophaga* spp. and *Streptococcus intermedius* were found together with *Actinomyces*, i.e., all typical inhabitants of the mouth, thus indicating an oral source, since the 25-year-old patient had severe gingivitis and three infected wisdom teeth (285). The authors of that report underlined the importance of prolonged incubation in detection of these fastidious organisms. In another case, after 14 days of incubation, nonpigmented *A. odontolyticus* was isolated together with *Haemophilus paraphrophilus* (i.e., *Aggregatibacter aphrophilus*), *Fusobacterium nucleatum*, and *Peptostreptococcus micros* (now *Parvimonas micra*) (286). A case of a cerebellar abscess where *Actinomyces* ("non-*israelii*" *Actinomyces*) was found among other oral-type bacteria, namely, alpha-hemolytic streptococci, *Eikenella corrodens*, and *P. micros* (i.e., *P. micra*), was suggested to be linked to tongue piercing (287). On the other hand, according to a report on five intracranial cases of *Actinomyces* infection in immunocompetent individuals, three cases were coinfected with another bacterium, including *Escherichia coli*, *Pseudomonas aeruginosa*, or *Staphylococcus warneri* (61). These findings obviously reflect an origin other than the oral cavity. *Aggregatibacter* species have not been detected together with *A. funkei*, *A. radingae*, or *A. turicensis*. Instead, their typical concomitants are, for example, *Bacteroides* spp., especially *B. fragilis*; enterococci; and coagulase-negative staphylococci but also GPAC (25, 114, 288). Together with *A. europaeus*, coagulase-negative staphylococci and corynebacteria, commonly found on the skin, are typical (25).

Similar to infections with *Actinomyces*, those with *P. propionicum* and *A. schaalii* are often polymicrobial (13, 257). For example, together with *A. schaalii*, other bacteria were isolated from 5 of 12 (42%) urine and 5 of 21 (24%) blood specimens examined, while polymicrobial infection was detected in all 7 abscess specimens (257). In polybacterial blood cultures, *Pseudomonas aerugi-*

nosa, *Finegoldia magna*, *Clostridium clostridioforme*, *Bacteroides fragilis*, and/or *Veillonella* spp. were identified.

IDENTIFICATION IN CLINICAL LABORATORIES

Direct microscopic examination of samples collected from suspected cases of actinomycosis should be performed. The presence of masses of Gram-positive branching filaments is characteristic of the disease, as are sulfur granules visible with the naked eye, although, as discussed above, these may not always be present. The presence of branching Gram-positive organisms in cervical smear specimens from women with an IUCD suggests an infection with *Actinomyces* (122). Results of microscopy of samples from superficial infections at mucosal surfaces where *Actinomyces* and other Gram-positive bacilli are commonly found should be interpreted with caution. It is important not to imply a diagnosis of actinomycosis in the absence of a relevant clinical history, signs, and symptoms.

Identification of presumptive *Actinomyces* species using conventional biochemical tests is possible for most species but challenging (14). Strains frequently exhibit indifferent growth in test media, leading to false-negative results and poor reproducibility. Recent taxonomic changes have compounded these problems. Many species descriptions have been based on a single strain, so the natural variation of test results within species is unknown. Furthermore, the taxonomy of some species, e.g., members of the *A. naeslundii* group, have been clarified on the basis of multilocus gene sequence analysis, and there are no phenotypic characteristics that differentiate certain species (10).

Commercially available identification kits that test for preformed enzymes can be used to identify the members of this group. Although kits offer a convenient method for isolate identification, they are typically supported by databases, which are incomplete in that either representatives of recently described species are not included or profiles for named species are inaccurate (175, 289).

Because it is now recognized that the use of conventional and biochemical tests may result in misidentification of clinical isolates of *Actinomyces* and related taxa, alternative methods with greater precision are increasingly being used. 16S rRNA gene sequence analysis, which was originally used to reconstruct phylogenetic relationships between organisms, is now frequently used for isolate identification. Far more precise identifications can be obtained by 16S rRNA gene sequence analysis (290). Genomic DNA can be extracted easily from isolates by using commercially available kits and the 16S rRNA gene amplified with "universal" primers that amplify all members of the domain *Bacteria* (291). A partial sequence of ~500 bp will allow the identification of most *Actinomyces* species. Sequences can be submitted via the Internet to databases such as the Ribosomal Database Project (292) for identification. Although this method is extremely powerful and can be relied upon for genus-level identification, some validly published species have highly similar 16S rRNA sequences, and there has been extensive recombination in the genomes, including the 16S rRNA gene, among certain groups of organisms, notably those that are naturally competent, such as the genus *Neisseria* (293). The *A. naeslundii* group presents similar problems, and 16S rRNA gene sequence analysis does not allow unequivocal identification of some of the recently described members of this group (10).

A bacterial identification method based on MALDI-TOF mass spectrometry is being widely adopted by clinical laboratories (294). Evaluations of its use with *Actinomyces* species have yielded positive results. In a comparative study, MALDI-TOF mass spectrometry correctly identified 97% of 32 strains to the species level, while a commercially available biochemical kit achieved only 33% success (209). This method was also shown to correctly identify five clinical isolates of *A. neuii* (295).

CLINICAL ANTIMICROBIAL SUSCEPTIBILITY TESTING

Susceptibility testing of anaerobes is seldom performed in clinical microbiology laboratories. In general, this may not be an important issue with *Actinomyces* species, since they are rarely, if ever, resistant to beta-lactam agents (14). As Gram-positive organisms, they are also susceptible to vancomycin. Whenever isolates originate from serious invasive infections, however, antimicrobial susceptibility testing is indicated. Standard methods and interpretations, as for other anaerobic Gram-positive nonsporing rods, can be used. Recently, an excellent review on susceptibility testing of anaerobic bacteria was reported, describing the methods to be used and their challenges (296). For testing of single clinical isolates, a commercially available MIC gradient diffusion method, which gives results equivalent to those generated by using the Clinical and Laboratory Standards Institute (CLSI) agar dilution method (296), is the most appropriate choice.

CONCEPTS OF TREATMENT

An appropriate diagnosis is the cornerstone to be able to choose a proper treatment modality and, conceivably, to have a successful treatment outcome. In the case of actinomycosis, it has been considered that a long duration of antimicrobial therapy with high doses is necessary, with treatment extending up to 1 year (or even longer). This concept is changing, and medications are now adjusted on the basis of individual treatment needs (8). The same is valid for surgery, which was previously used routinely for treatment of actinomycotic lesions; however, the current trend is to limit invasive procedures and to rely on a targeted antibiotic regimen instead (8, 9). Treatment of abscesses usually requires drainage, whereas resective surgery may be indicated only in cases with extensive necrotic lesions or when antimicrobial therapy fails.

In general, *Actinomyces* species are susceptible to penicillin and other beta-lactam antibiotics as well as to most agents used against Gram-positive anaerobic rods; however, it must be noted that they are intrinsically resistant to metronidazole (14). In a recent survey on antimicrobial susceptibilities of anaerobic bacteria conducted in laboratories in Ontario, Canada, nearly 400 *Actinomyces* and 30 *Actinobaculum* (currently *Actinotignum*) strains were tested against six antimicrobial agents, including penicillin, piperacillin-tazobactam, meropenem, cefoxitin, clindamycin, and metronidazole (297). Except for high rates of resistance to metronidazole (>80% for both genera) and clindamycin (18% for *Actinomyces* and 53% for *Actinobaculum*), the strains were fully susceptible to the other antimicrobial agents examined. Moreover, it is noteworthy that there are considerable differences in MICs among *Actinomyces* species, with *A. europaeus* and *A. turicensis* being the most resistant (298). *A. turicensis* strains showed resistance to clindamycin, tetracyclines (doxycycline and tetracycline), macrolides (clarithromycin and erythromycin), ciprofloxacin, and/or linezolid, whereas *A. europaeus* strains showed resistance to ceftriaxone, clindamycin, macrolides (clarithromycin and erythromycin), ciprofloxacin, and/or tazobactam (298).

In addition, sporadic strains with increased MIC values to tested antimicrobial agents have been observed for other *Actinomyces* species, such as *A. funkei* (tetracycline), *A. graevenitzii* (doxycycline and tetracycline), *A. israelii* (linezolid), *A. odontolyticus* (clindamycin), and "*A. viscosus*" (clindamycin) (298–301).

For the treatment of *A. schaalii* infections of the urinary tract, beta-lactam antibiotics are recommended (16). In contrast, fluoroquinolones are considered ineffective despite their relatively good (except for ciprofloxacin) *in vitro* activities. Indeed, *A. schaalii* is resistant to typical antibiotics used for the treatment of urinary tract infections (262). Although there are no clear guidelines for the length of antimicrobial therapy of *A. schaalii*-associated infections, it has been suggested that the duration should be 2 weeks or more (16).

The impact of concomitant/coinfecting organisms is not well known. Despite the lack of data, it is generally accepted that targeted therapy against *Actinomyces* organisms, *P. propionicum*, or *A. schaalii* will result in the expected outcome.

FUTURE CONSIDERATIONS

It is clear from this review that there are still a number of uncertainties regarding the role of *Actinomyces* and related organisms in human infections. On the one hand, actinomycosis is relatively rare and often diagnosed by clinical and histopathological means, with accurate microbiological analysis not being performed. Multicenter studies should be performed in order to be able to include a sufficiently high number of cases. At the very least, major centers should store the strains isolated from confirmed cases of actinomycosis so that detailed microbiological investigations can be performed later. On the other hand, there needs to be enhanced educational efforts to make health care professionals aware that *Actinomyces* species are members of the healthy core microbiome, particularly in the mouth, and are thus frequently isolated from samples collected from mucous membranes. Whether these organisms can or do play a pathogenic role in these circumstances should also be the focus of research. As discussed above, little is known regarding the virulence properties of *A. israelii* and other disease-associated *Actinomyces* species. The increasing availability of genome sequences of strains representing many *Actinomyces* species should be exploited, in order to better understand their pathogenesis in human infection and to enable the development of new methods of treatment.

Recent taxonomic advances, including the naming of a number of novel *Actinomyces* species, have led to interesting and specific disease associations. This demonstrates the value of and need for taxonomic studies; the high number of known unnamed *Actinomyces* species-level taxa suggests that this genus should be a priority.

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