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REVIEW

Actinomyces neuii: review of an unusual infectious agent

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Abstract *Actinomyces neuii*, a species first described in 1994, has proven to be an exception in this genus on account of its aerobic growth, microscopic morphology (no branching), and the types and location of infections. Abscesses and infected atheromas are the most frequent types of infections, followed by infected skin structures, endophthalmitis, and bacteremias, including endocarditis. They are most likely of endogenous origin. To date, approximately 100 cases have been recorded in the literature. Intra-abdominal and intrathoracic infections, however, have not yet been described, and cases of classical actinomycosis seem to be extremely rare. Prognosis has generally been good with antibiotic and/or surgical treatment. Susceptibility to antibiotics has paralleled that of other *Actinomyces* spp.

Keywords Actinomyces

History and taxonomy

Actinomyces spp. are often thought to be the cause of actinomycosis, but they are neither the sole agents of the disease [1] nor do they cause actinomycosis only [2]. In fact, one of the newcomers in this genus, *Actinomyces neuii*, which will be reviewed here, may not cause classical actinomycosis at all. In 1985, Coudron et al. [3] published the characteristics of two aerobically growing coryneform Gram-positive rods isolated from patients with endophthalmitis that resembled organisms earlier called "Coryneform Group A-4" by the Special Bacteriology Reference Laboratory at the Centers for Disease Control (CDC) [4] but differed from this group in several biochemical reactions. Coudron et al. called these and five similar reference strains from the CDC "A-4-like". Two years later, Na'was and CDC researchers [5] published the characteristics of several additional "A-4-like" strains, this time under the term "CDC Fermentative Coryneform Group 1".

In the course of a study aimed at identifying Gram-positive rods isolated in the author's laboratory, more such strains were found and investigated using biochemical and chemotaxonomic [6] as well as molecular biological [7] techniques. The results indicated that the Coryneform Group 1 strains did not belong to any of the hitherto known genera of aerobically growing Gram-positive rods but were close to the genera *Actinomyces* and *Arcanobacterium*, which are known to grow better under anaerobic or capnophilic conditions than under aerobic ones. 16S rRNA sequence analysis and DNA–DNA hybridization studies as well as cellular and metabolic fatty acid profiles placed these strains as a species in the genus *Actinomyces* [6, 7], which we named *Actinomyces neuii* [7] after our colleague Harold Neu, the head of Infectious Disease at Columbia University who had died in 1993. Two subspecies, *A. neuii* subsp. *neuii* and *A. neuii* subsp. *anitratus*, could be distinguished by biochemical tests [7]. In analogy to the sequestration of the genera *Arcanobacterium* and *Actinobaculum* from the genus *Actinomyces*, suggestions have even been made to create a new genus for *A. neuii* since it has turned out to be closer in sequence similarity [8] and chemotaxonomy [9] to the genera *Varibaculum* and *Mobiluncus* than to *A. bovis*, the type species of *Actinomyces*.

For Gaby Pfyffer's birthday on Oct. 30, 2010.

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We were surprised that within a 4.5-year period, we were able to detect 67 strains of *A. neuii* in our routine diagnostic laboratory [10] even using an identification system which is now obsolete [11]. In our as well as in Clarridge's [12] laboratory *A. neuii* was more frequently isolated than *A. odontolyticus*, *A. israelii*, *A.meyeri*, *A. viscosus*, and *A. naeslundii*. At the time this article was being written, a total of 22 reports of *A. neuii* infections covering approximately 100 cases have been published (some isolates have been listed repeatedly in several publications).

These findings required a change in the concept of *Actinomyces* as anaerobic or at best aerotolerant organisms, in their role as causative agents of diseases other than classical actinomycosis, and in the frequency of its species isolated in clinical laboratories. As will be also be shown, *A. neuii* has a microscopic morphology that is unusual for *Actinomyces* spp, and as an infectious agent it seems to prefer special areas of the human body.

Isolation and identification

In direct Gram stained preparations and smears from cultures, *A. neuii* appears as a diphtheroidal and even coccoid organism without branching [5, 13–15]. Only one case has been described in which *A. neuii* (not subspeciated) was found as an agent of classical actinomycosis with characteristic Gram-positive filaments and sulfur granules [16]. The diagnosis was based 16S rRNA sequencing but the catalase reaction was negative, a rare trait [13]. Another report mentioned the presence of multinucleated giant cells [17]; however, in the remaining cases only polymorphonuclear leukocytes were found. The sensitivity of direct Gram stains is only approximately 20% [10]. Biochemical characteristics, among them the positive CAMP reaction, and the identification of *A. neuii* by traditional, semiautomatic ,and molecular techniques have been subjects of several publications [12, 14, 18] and will not be discussed here.

A. neuii grows within 48 h on aerobically and anaerobically incubated blood agar plates; very few reports mention poorer [19, 20] or better [21] growth under anaerobic conditions. Colonies are indistinguishable from those of other *Actinomyces* spp., although most resemble the smooth variety of other *Actinomyces* spp.

Habitat and transmission

Several *Actinomyces* spp. are known as colonizers of the human body [22] but to date only one study has shown that *A. neuii* can be part of the normal flora: DNA–DNA hybridization showed that it was present in larger numbers in patients with gingivitis than in orally healthy individuals [23]. No studies have investigated the presence of *A. neuii* in the environment, but based on the types of infections it must be assumed that it is endogenous. Transmission from patient to patient has also not been observed, with the exception of a case of maternal chorioamnionitis in which *A. neuii* caused neonatal septicemia (see below).

Infections

Abscesses and infected atheromas Abscesses and infected atheromas have been, overall, the most frequent infections from which *A. neuii* has been cultured [10, 12, 13, 15, 17]. Abscesses were mostly localized in the mammary, axillar, and inguinal areas, similar to other *Actinomyces* spp. [22]. In a minority of abscesses and atheromas, *A. neuii* was found in pure culture, with the majority yielding a mixed anaerobic, occasionally also aerobic flora. These mixtures are also not unusual in similar *Actinomyces* spp. infections [24]. In our own cases, community acquisition was the rule, immunosuppression was rare, and treatment with systemic antimicrobials alone yielded poor results or relapses. The outcome was satisfactory if the infected focus was removed by surgery [10].

Infected skin lesions Infected skin lesions, such as community-acquired diabetic ulcers, were second in frequency in our own collection [10] but have been published elsewhere in single cases only [5, 21]. Mixtures with coagulase-negative staphylococci were the rule.

Endophthalmitis Endophthalmitis following phacoemulsification and lens implantation has been reported in three publications [25–27], although more isolates of *A. neuii* from eyes have been recorded without details [5, 8]. Intraocular, topical, and systemic application of antibiotics led to successful outcomes in two cases [26, 27], while one patient developed a central vein occlusion [25]. Endophthalmitis due to other *Actinomyces* spp. has been known for some time [28].

Endocarditis Endocarditis has been reported in two patients, one on a prosthetic valve [19] and one complicated by an aortic abscess [29]. The former was cured by antibiotic treatment (penicillin) alone, while the second one required combined medical (ampicillin)–surgical treatment. Other *Actinomyces* spp. have been known as agents of endocarditis as well [30].

Bacteremia Blood cultures positive for *A. neuii* as the only organism have been reported in 12 patients [5, 10, 14, 31, 32], excluding those with endocarditis (the Abstract of reference [19] erroneously lists 14 patients with endocarditis). Of the bacteremias whose histories were detailed,

two originated from the urinary tract [14], one was septicemia in a newborn that had its origin in a maternal chorioamnionitis [31], and one originated from either a urinary tract or a joint infection [10]. All of these were healthcare-associated. With the exception of the latter case, antibiotic treatment was successful. Bacteremias with other *Actinomyces* spp. have recently been published [33].

Other infections Single cases of pericarditis [34], osteomyelitis (with a mixed culture; [35]), and chorioamnionitis [31] as well as infections of a periprosthetic joint [36], a ventriculo-peritoneal shunt [20], and a penile prosthesis reservoir [37] have been published. We have also observed cases of urinary tract infection and of prostatitis [10]. Similar infections have been caused by other *Actinomyces* spp. [1, 12, 14, 22, 24]. Removal of prosthetic devices and antibiotics led to successful outcomes.

Of note, no isolates of *A. neuii* have been reported from intra-abdominal and -thoracic sources, which figure prominently in other *Actinomyces* spp. infections [1, 24]. Of those isolates that were subspeciated, subsp. *neuii* prevailed over subsp. *anitratus*. There was no preference for age or sex; and immunocompromised individuals were more frequent only among those with systemic disease and skin lesions. Potential virulence factors have not been investigated thus far.

Antimicrobial susceptibility

The antimicrobial susceptibility of *A. neuii* corresponds to that of other *Actinomyces* spp. [38]. To date, all strains have been susceptible to penicillin, ampicillin, the cephalosporins, imipenem, rifampicin, vancomycin, erythromycin, and clindamycin [3, 10, 13, 19–21, 25, 27, 29, 31, 35, 36]. A few were resistant to tetracycline [6, 10]. Susceptibility to aminoglycosides and ciprofloxacin has varied [10, 15, 21, 25, 27, 29]. For treatment, beta-lactam antibiotics and vancomycin have been preferentially used. Development of resistance to the above listed antibiotics has not been observed so far.

Conflict of interest None.

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