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Mini-review

Actinomyces—Gathering evidence of human colonization and infection

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Abstract

The roles of the 'classical' *Actinomyces* spp. as colonizers of oral cavities of man and animals, in development of intra-oral infections and as agents of actinomycosis have been well documented. This mini-review focuses on perceptions of human colonization and infection that have emerged in the past decade, largely as a result of advances in classification, identification and direct detection from clinical material. Arguably, of the greatest importance is the recognition of actinomycosis as a major factor and indicator of poor prognosis in both infected osteoradionecrosis and bisphosphonate-associated osteonecrosis of the jaws. Among recently described species, *Actinomyces graevenitzii* has been isolated almost exclusively from oral and respiratory sites and may be a causative agent of actinomycosis. Conversely, several other *Actinomyces* spp. are isolated commonly from superficial soft tissue infections.

Members of the genus *Actinobaculum*, which is closely related to *Actinomyces*, are strongly associated with urosepsis. Isolation and identification of *Actinomyces* and related genera by conventional methods remain difficult. Diagnosis is commonly belated and based solely upon histological findings. Development of direct detection methods may aid patient management and further elucidate clinical associations.

Keywords: Actinomyces; Actinomycosis; Osteoradionecrosis; *Actinobaculum*

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1. Introduction

The roles of the 'classical' *Actinomyces* spp. as colonizers of oral cavities of man and animals, in development of intra-oral infections and as agents of actinomycosis have

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been well documented elsewhere [1–3]. This mini-review focuses on perceptions of human colonization and infection that have emerged in the past decade, largely as a result of advances in classification, identification and direct detection from clinical material.

2. Taxonomic changes

Since the 1990s, classification of the genus *Actinomyces* and related genera has changed dramatically, principally due to the application of 16S rDNA sequencing and supported by other taxonomic tools [3]. Since 1997 some 18 novel species of *Actinomyces* have been described and a few former members have been transferred to the genera *Arcanobacterium*, *Actinobaculum* or *Cellulomonas*. Also, the closely related genus *Varibaculum* has been described [4]. At the time of writing 34 *Actinomyces* spp. are recognized, 20 of which have been reported from human sources. Others have been isolated from cattle, dogs, cats, pigs and marine mammals. The apparent host–mammal specificity of most *Actinomyces* spp. is consistent with bacterial evolution within individual host species and suggests that additional taxa may yet be discovered in other mammalian species.

Sub-species variation occurs in several *Actinomyces* spp. and is most pronounced in *Actinomyces naeslundii* and *Actinomyces viscosus* wherein a wide diversity in phenotypic, genotypic and physiological characteristics is found [1,5–9]. This group of organisms represents a challenge to current concepts of distinct species; it is not easily divisible into discrete taxa and, at present, is probably best referred to as the '*A. naeslundii*/*A. viscosus* complex'. Such diversity has implications for the validity of any research carried out on only one or very few strains representing this complex.

As the number of *Actinomyces* spp. has grown, divisions at the genus level have become apparent. In 1999, Schaal et al. suggested several subgroups based upon composition of cell-wall components and found that these clusters correlated well with those seen in contemporary phylogenetic trees [10]. Subgroup 1 comprised only *Actinomyces neuii* and phylogenetically this species is more closely related to the genera *Varibaculum* and *Mobiluncus* than it is to *Actinomyces*. Subgroup 2 comprised *Actinomyces hordeovulneris* alone. Subgroup 3 contained *Actinomyces odontolyticus*, *Actinomyces meyeri*, *Actinomyces georgiae*, *Actinomyces turicensis*, *Actinomyces radingae* and *Actinomyces hyovaginalis*. Subgroup 4 demonstrated some heterogeneity and may prove to be further divisible. This group included the type species, *Actinomyces bovis* with *Actinomyces israelii*, *Actinomyces gerencseriae*, *A. naeslundii*, *A. viscosus*, *Actinomyces slackii*, *Actinomyces howellii* and *Actinomyces denticolens*. Phylogenetic trees compiled from 16S rDNA sequence data allow the tentative assignment of more recently described species as follows: *Actinomyces nasicola*, *Actinomyces hongkongensis* and *Actinomyces marimammalium* join subgroup 2; *Actinomyces funkei*, *Actinomyces cardiffensis*, *Actinomyces suimastitidis*, *Actinomyces canis* and *Actinomyces vaccimaxillae* clearly cluster in subgroup 3; while *Actinomyces europaeus* and *Actinomyces coleocanis* are outliers of this subgroup. *Actinomyces graevenitzii*, *Actinomyces urogenitalis*, *Actinomyces radicidentis* and *Actinomyces catuli* cluster in subgroup 4 with *A. bovis*, while *Actinomyces oricola*, *Actinomyces dentalis*, *Actinomyces bowdenii* and *Actinomyces ruminicola* cluster more closely with the other members of this subgroup [11,12]. However, the chemotaxonomic markers of some species are unknown and divisions based upon sequence data are open to interpretation hence no formal proposal to divide the genus *Actinomyces* has been made to date.

3. Advances in identification

The description of so many novel species has made the previously problematic task of identifying *Actinomyces* by phenotypic tests almost impossible. The textbooks and databases used to interpret results of conventional tests and commercial kit-based systems, respectively, have been rendered obsolete.

Serological, immunodiffusion and immunofluorescent techniques have been used to identify some of the classical *Actinomyces* spp. but problems with sensitivity, specificity and availability of reagents have prevented their widespread usage [1]. With the benefit of modern *Actinomyces* taxonomy, it seems unsurprising that specificity and sensitivity were problematic in antisera developed at a time when only five species were recognized.

SDS–PAGE analysis of whole-cell proteins has proved useful to demonstrate distinct taxa [13–15]. This technique can be a valuable aid to the identification of unknown isolates where relevant expertise and sufficient well-characterized strains are available.

More recently, highly discriminatory genotypic methods have been utilized to great effect. At the UK Anaerobe Reference Unit (ARU), amplified rDNA restriction analysis has been used to identify more than 1000 clinical isolates of *Actinomyces* spp. ([16,17]; ARU unpublished data). While this remains a reference laboratory method, the use of DNA sequencing has become increasingly widespread in clinical laboratories. However, as most public-domain databases are largely unregulated, some experience is necessary in interpretation of results.

For clinical microbiologists, the many novel species and changes of names have often caused confusion and may seem unhelpful to patient management as little or nothing is known of natural habitats or clinical significance of most new species. However, the robust classification system and accurate identification of many isolates is gradually elucidating the natural habitats and clinical entities associated with specific *Actinomyces* spp.

4. Direct detection from clinical material

The traditional tools: detection of 'sulfur' granules and Gram's and histological staining, remain the principal