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Is the Presence of *Actinomyces* spp. in Blood Culture Always Significant?

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The isolation of *Actinomyces* spp. from sterile clinical samples is traditionally regarded as significant. We reviewed the demographic characteristics, clinical risk factors, and outcomes of patients with *Actinomyces* spp. isolated from blood cultures in our NHS Trust and found that this is not necessarily the case.

Actinomyces spp. are Gram-positive anaerobic bacilli found colonizing the human oropharynx, gastrointestinal tract, and urogenital tract (1). Immunosuppression and local tissue damage, allowing entry of *Actinomyces* spp., are recognized risk factors for the development of actinomycosis. Actinomycosis is more common in men, except for pelvic disease associated with contraceptive intrauterine devices (IUDs) (2).

Orocervicofacial actinomycosis related to dental procedures and chronic dental infections represents 50% of cases, with thoracic and abdominal actinomycosis accounting for approximately 40% (3). Central nervous system, bone, and cutaneous infections have been reported (4), but hematogenous spread is rare (1, 5). Treatment of actinomycosis involves the combination of surgical drainage and prolonged courses of antibiotic therapy. *Actinomyces* spp. are susceptible *in vitro* to several antimicrobials, including penicillins, macrolides, and tetracyclines; penicillins are the drugs of choice (2). Recent studies have suggested that, with effective debridement, the course of antibiotic therapy can be reduced without complications (6).

Traditionally, isolation of *Actinomyces* spp. from sterile clinical specimens is always viewed as significant (7). Since the introduction of 16S rRNA gene sequencing and matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) in our laboratory, we have noted an increase in the identification of *Actinomyces* spp. from blood cultures. Although 16S rRNA gene sequencing was used selectively from 2004, it was with the introduction of MALDI-TOF MS in 2009 that all isolates were routinely identified. There was a crossover period in which the results of the technologies were compared. Currently, we use 16S rRNA gene sequencing when MALDI-TOF MS does not provide an answer and there are clinical indications for making an accurate identification. In the current review, only 10 of the 60 patients from whom *Actinomyces* spp. were isolated were considered by the attending physicians to have clinical evidence of actinomycosis requiring treatment. This finding raises questions about the significance of such isolates.

Isolates of *Actinomyces* spp. from blood cultures from patients in our NHS Trust were reviewed. Our NHS Trust is an organization comprising five secondary and tertiary care hospitals providing care to a region of East London. Demographic and outcome information was collected from electronic patient records. Specifically, we looked for evidence of disease attributable to actinomycosis, as well as details of risk factors, investigations, and treatments. Outcomes were reviewed, with particular attention to hospital readmission and death.

The records were reviewed for recognized clinical risk factors for *Actinomyces* infection, i.e., IUD use, diabetes mellitus, immunosuppression, local tissue damage related to trauma (including people who inject drugs [PWID]), inflammatory conditions, surgery, or irradiation (2). Age between 20 and 60 years and male sex are also risk factors; these nonclinical risk factors were not included in the statistical analysis because of the small size of the group and the strong covariance of these risk factors with clinical risk factors.

Fisher's exact test and the Mann-Whitney *U* test were used in the statistical analysis of differences between the groups (treated versus untreated patients). The project was endorsed by the Clinical Effectiveness Department at Barts Health NHS Trust. Ethical approval was not required.

Actinomyces spp. were isolated from 61 blood cultures from 60 patients between October 2009 and December 2014. During this period, 154,573 blood cultures were submitted to the laboratory for processing. A total of 18,984 organisms were isolated, with a number of cultures containing multiple organisms. Patients were separated into two groups on the basis of whether they received treatment as a result of the identification of *Actinomyces* spp. Treatment was defined as documentation of the isolate and recommendation of a prolonged course of appropriate antibiotic therapy and/or surgical intervention.

Patients were between 1 day and 95 years of age. Ten patients, with ages between 35 and 89 years, fulfilled the case definition for treatment of *Actinomyces* spp. There were 33 male patients, 5 of whom received treatment, and 27 female patients, 5 of whom received treatment.

Patients were under the care of a wide range of specialties at the time of blood culture sampling. Eighteen of the positive blood cultures were sent from accident and emergency, 11 from pediatrics and neonatology, 6 from intensive care, 20 from a range of

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TABLE 1 *Actinomyces* spp. isolated, by group

Species	No.		
	Total cohort	Treated group	Untreated group
Actinomyces odontolyticus	14	2	12
Actinomyces oris	8[a,b]	1	7[a,b]
Actinomyces naeslundii	8[a,c]	1[c]	7[a]
Actinomyces sp. undifferentiated	8	1	7
Actinomyces neuii	7	1	6
Actinomyces turicensis	6	2	4[d]
Actinomyces viscosus	6[b,c]	3[c]	3[b]
Actinomyces europaeus	2	1	1

[a] One isolate was identified to a high percentage as either *A. oris* or *A. naeslundii*.
[b] One isolate was identified to a high percentage as either *A. oris* or *A. viscosus*.
[c] One isolate was identified to a high percentage as either *A. naeslundii* or *A. viscosus*.
[d] Includes two separate isolates from the same patient.

TABLE 2 Clinical risk factors, by group

Risk factor	No.	
	Treated group	Untreated group
Diabetes mellitus	0	3
Local tissue trauma (including PWID)	3	2
Recent surgery	1	1
Inflammatory condition	1	6
Chronic infection	1	1
Immunosuppression		
HIV	2	0
Leukemia and chemotherapy	1	2
Transplant	0	2
Alcohol excess	0	2
More than one risk factor	2	4

medical specialties, including elderly care, hematology, and renal medicine, and 6 from surgical specialties, including maxillofacial surgery, obstetrics, and orthopedics. A broad range of comorbidities, including cognitive impairment, hypertension, hepatitis C, and stroke, were documented. It was clear for all except one patient that blood cultures were taken at a time of acute changes that could be attributed to infection.

A total of 87% of isolates (53/61 isolates) were identified to the species level. Eight of those identifications were made by 16S rRNA PCR. All of those samples were also subjected to MALDI-TOF MS, which confirmed the 16S rRNA PCR results for all except two samples, for which there was no reliable identification from MALDI-TOF MS. The remaining samples were identified by MALDI-TOF MS alone. Four isolates gave two possible *Actinomyces* sp. identifications, i.e., one *Actinomyces viscosus* or *Actinomyces naeslundii*, one *A. naeslundii* or *Actinomyces oris*, and two *A. viscosus* or *A. oris*. The MALDI-TOF MS scores are no longer available for analysis. No particular distribution of species between the groups was identified (Table 1).

There was a difference in the median time to positivity in the treated and untreated groups (36.5 h [range, 18 to 72 h] and 46 h [range, 26 to 120 h], respectively), but this difference did not reach statistical significance (two-tailed Mann-Whitney *U* test, $P = 0.11$).

A second isolate was identified in 4 of the 10 cultures (40%) in the treated group that were positive for *Actinomyces* spp., compared with 15 of the 51 cultures (29%) from the 50 patients in the untreated group. A wide range of organisms were identified, including *Corynebacterium* spp., oral *Streptococcus* spp., and coagulase-negative staphylococci. In addition to those organisms, which are classically seen as contaminants in blood cultures, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Escherichia coli* were identified with the *Actinomyces* isolates; in all of those cases, the patients were treated for those organisms even if no action was taken with respect to the *Actinomyces* spp.

Seven of the 10 patients who received treatment had recognized clinical risk factors (Table 2). Two patients had two risk factors, i.e., HIV and PWID. In the untreated group, 14 patients had risk factors and 4 patients had more than one risk factor, i.e., PWID with alcohol excess, leukemia and chemotherapy with a transplant and an inflammatory condition, a renal transplant with leukemia and chemotherapy, and an inflammatory condition and surgery. Statistical analysis using Fisher's exact test demonstrated a significant difference in the presence of risk factors between the two groups (two-tailed $P = 0.0116$).

The 10 patients who received treatment had their disease categorized as follows: pulmonary actinomycosis, 3; abdominal actinomycosis, 1; dental actinomycosis, 1; multiple sites, 1; soft tissue disease, 3; not categorized, 1. One patient was not investigated for a source of infection because of the life-limiting nature of his comorbidities and prioritization of palliative care input. Six patients received a combination of antibiotic therapy and drainage/debridement, and the remaining four received antibiotic therapy alone.

In the treated group, five patients were discharged either during or following a prolonged antibiotic course. One patient declined long-term antibiotic therapy, having received 10 days of therapy following debridement of a dental abscess. She did not re-present with any complications. Three patients were readmitted, one within 30 days and two within 6 months. Two of those readmissions were due to ongoing infection issues attributable to actinomycosis. One patient died as a result of chest sepsis during admission. Another patient died as a result of complications related to a different underlying condition.

In the untreated group, 43 patients were discharged following the positive blood culture results, without apparent complications related to actinomycosis. Two patients were recalled and two had their admissions prolonged for assessment. Following clinical review, those patients were deemed to have no evidence of actinomycosis and were discharged without treatment.

Four patients from the untreated group had another hospital admission within 30 days and an additional nine patients in the subsequent 6 months. None of those admissions could be clearly attributed to untreated actinomycosis. Seven deaths occurred in the untreated group. Five patients died during the same episode as the positive blood culture results, as a result of progression of an underlying disease, and one died 11 months later as a result of urosepsis, having been well in the interim. For one patient, there was no documentation related to the death.

In this retrospective analysis of clinical correlates associated with the isolation of *Actinomyces* spp. from blood cultures, the majority of patients were not treated for actinomycosis, with no apparent negative impact on clinical outcomes. We hypothesize that, prior to the introduction of MALDI-TOF MS and 16S rRNA

PCR techniques for identifying organisms to the species level directly from cultures, such organisms would have been dismissed as contaminants such as *Corynebacterium* spp. or *Propionibacterium* spp. MALDI-TOF MS has been shown to perform well for identification to the genus level, providing reassurance that these results accurately represent the organisms present (8).

The isolation of *Actinomyces* spp. from blood cultures from patients for whom there is no evidence of clinical disease raises the question of whether these organisms are blood culture contaminants or represent transitory bacteremia caused by translocation from commensal sites. Blood culture collection procedures are standardized in our NHS Trust, which has seen a decrease in the number of blood cultures growing organisms that are classically viewed as skin contaminants (9). Historically, *Actinomyces* spp. have not been considered part of the human cutaneous flora. However, the application of recent molecular methods suggests that the flora may be more diverse than previously recognized and *Actinomyces* spp. may be components at sites such as the antecubital fossa in some individuals (10). The susceptibility of these potential cutaneous *Actinomyces* spp. to topical antibacterial washes used prior to procedures remains undetermined.

Alternatively, we may be detecting transient bacteremia associated with periods of translocation from the oropharyngeal or bowel mucosa. This phenomenon is seen with multiple mucosal organisms in teething children and is associated with procedures such as colonoscopy (11). Such bacteremia, although transient, can cause significant morbidity through the sepsis response and seeding. Classically, *Actinomyces* spp. cause infection at sites of local tissue invasion; hematogenous spread and disseminated disease are rare (1, 2).

In our study of 60 patients from whom *Actinomyces* spp. were isolated, only 10 received treatment for actinomycosis. The main difference between the patients who received treatment and those who did not was the presence of clinically recognized risk factors. This finding supports the use of such risk factors as part of the clinical assessment to establish the significance of *Actinomyces* spp. isolated from blood cultures. It also highlights the importance of interpreting results in the context of the patient's clinical situation and background.

One of the strengths of our study is the fact that our laboratory performs unbiased identification of isolates, as the system to identify organisms grown from cultures is not influenced by clinical findings. A weakness is the fact that our data on the progress of the patients during and after hospital admission are based on information in the electronic health records, which may not be complete. In addition, only repeat attendances within the NHS Trust could be recorded, unless admission to another NHS Trust was documented in the records. Studies related to the analysis of blood culture isolates suffer from an inherent sampling bias; blood cultures are, and should be, performed only for patients for whom there are concerns regarding systemic infection.

In this era of rapid development and application of diagnostic techniques, we are identifying a multitude of organisms from a variety of patient sample types (12). This expansion in diagnostics needs to be matched with an understanding of the clinical significance, to ensure appropriate therapy for patients. Further research to look more closely at *Actinomyces* spp. isolated from other culture types will help to elucidate the true significance of these isolates.

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