

Clinical Audits/Service improvements

A retrospective cohort study of bacterial native vertebral osteomyelitis and its management in the UK

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ABSTRACT

Background: Bacterial native vertebral osteomyelitis (NVO) can present diagnostic and therapeutic challenges leading to high levels of morbidity and mortality. To inform strategies aimed at improving outcomes in these patients, data are needed on the current aetiology, diagnostic interventions, management and risk factors for treatment failure.

Methods: This was a retrospective, multicentre, observational cohort study of adult patients with bacterial NVO across the UK between 1st January 2015 and 31st December 2016. Infectious Disease Society of America (IDSA) guideline standards were selected and used to audit practice relating to the management of these patients.

Results: A total of 286 patients were included from 40 hospitals. An organism was identified in 61% of cases by blood culture or biopsy. Of these, 51% were due to *Staphylococcus aureus* and 12% were due to Gram-negative bacteria. When performed, biopsy obtained a microbiological diagnosis in 50% of cases. Nearly 10% of patients required admission to an Intensive Care Unit, 20% were re-admitted to hospital, 56% experienced complications and 6% died within 90 days. Higher Charlson comorbidity index (CCI) was significantly associated with treatment failure at one month ($p = 0.004$).

Conclusions: This study identified opportunities to improve UK practice in the investigation and management of bacterial NVO. The range of organisms isolated supports the use of diagnostic biopsy where blood cultures are non-diagnostic, to guide antimicrobial therapy and strive to avoid treatment failure or complications. This study shows a clear need for antibiotic guidelines to reflect the current aetiology of NVO and authors support the creation of a formal registry.

Introduction

Native vertebral osteomyelitis (NVO), synonymous with spondylodiscitis, is an important cause of back pain. It is associated with haematogenous seeding or contiguous spread from local infection, but excludes infected implanted metalwork (Nickerson and Sinha, 2016; Zimmerli, 2010; Gasbarrini et al., 2005). Causative agents include bacteria, fungi or mycobacteria (Corrah et al., 2011; Kehrer et al., 2014; Gupta et al., 2014). The incidence (up to 9.8/100,000 per year (Kehrer et al., 2014) has increased over the last 2 decades, possibly reflecting an ageing population (Kehrer et al., 2014; Mylona et al., 2009; Akiyama et al., 2013; Loibl et al., 2014).

The variability of presenting symptoms (Kehrer et al., 2014; Loibl et al., 2014; Gök et al., 2014) and low specificity of inflammatory markers often leads to diagnostic delay (Jean et al., 2017; Marchionni et al., 2019) and higher morbidity from disseminated disease or neurological complications (Widdrington et al., 2018; McHenry et al., 2002; Kim et al., 2019). To optimise patient care, the Infectious Diseases Society of America (IDSA) published guidance, in 2015, which suggest clinicians initiate early investigations to identify causative microorganisms (Chong et al., 2018; Gregori et al., 2019; Gouliouris et al., 2011), give prompt therapy (Gouliouris et al., 2011; Park et al., 2019; Rutges et al., 2016; Bernard et al., 2015) and close follow up, ensuring resolution of symptoms and normalisation of inflammatory markers (Gasbarrini et al., 2005; McHenry et al., 2002).

In this multicentre observational study, we set out to describe the characteristics of UK patients with NVO and established current management measured against selected IDSA standards. These standards are listed in Table 1. Also, we sought to determine which clinical, microbiological and radiological factors were associated with treatment failure.

Methods

Study design

This was a retrospective, multicentre observational cohort study. The study protocol development was supported by the National Infection Trainee Collaborative for Audit and Research (NITCAR), a UK-based network of clinicians training in infection specialties, and adheres to STROBE guidelines (von Elm et al., 2014). The NHS Research Authority approved this study as an audit.

Setting

Sites were recruited in 2017, through promotional events at national and regional infection conferences, via NITCAR members and through the National Student Association for Medical Research. All hospitals in the UK were eligible for inclusion. Data were collected between 1st June 2017 and 31st March 2018.

Participants

The first eight adult patients aged ≥ 16 years with a diagnosis of NVO presenting to participating sites in the two year period between 1st January 2015 and 31st December 2016 were eligible for inclusion. This strategy was chosen as a feasible number for individual sites to recruit based on pilot data collection. Patients with implant-associated vertebral osteomyelitis and patients previously diagnosed with NVO were excluded.

Definitions and variables

NVO is defined as bone infection of the spine not associated with implanted metalwork. It is confirmed by characteristic changes on imaging and a clinically compatible presentation (which may include back pain or discomfort, fevers and malaise) usually accompanied by raised inflammatory markers (ESR, CRP) (Berbari et al., 2015). In this study, investigators included patients diagnosed with NVO by their treating physician and given a corresponding ICD code, using the International Statistical Classification of Diseases and Related Health Problems (ICD) medical classification list by the World Health Organization.

Variables were selected for inclusion based on a literature review of known associations with NVO. Patient variables included demographic, clinical (including Charlson comorbidity index (CCI) (Charlson et al., 1987), microbiological, biochemical and radiological variables. These can be seen in Table 2. Additional hospital-specific data were collected to determine: the type of hospital; relevant services available at the hospital; local guidelines for the management of NVO.

The primary outcome measure was evidence of treatment failure, defined as fever and/or static or rising inflammatory markers and/or death within 28 days after commencing treatment. The presence of pain, although used in some definitions of treatment failure, was not included here as we considered that it often represents previous vertebral damage and not necessarily ongoing infection.

Table 1

Audit standards used in this study, based on the 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults (Berbari et al., 2015).

Study Standard	Corresponding IDSA guideline recommendation	Details of IDSA guideline recommendation
1	7	It is recommended that all patients with suspected native vertebral osteomyelitis (NVO) have a baseline CRP and/or ESR measured, and two sets of blood cultures taken at baseline*
2	8, 9	It is recommended that all patients with suspected NVO undergo MRI spine. If this is not possible it is suggested that patients undergo spine gallium/Tc99 bone scan or computed tomography scan or a positron emission tomography
3	14	It is recommended that all patients with suspected NVO undergo image-guided aspiration biopsy when a microbiologic diagnosis for a known associated organism (<i>Staphylococcus aureus</i> or <i>Staphylococcus lugdunensis</i>) has not been established by blood cultures or serologic tests
4	21, 23	It is suggested that all patients with no microbiological diagnosis undergo a second aspiration biopsy or percutaneous endoscopic discectomy and drainage or open excisional biopsy if the first biopsy is non-diagnostic. This includes specimens with no growth or growth of a presumed skin contaminant such as coagulase-negative staphylococci, (except <i>S. lugdunensis</i>), <i>Propionibacterium</i> species, or diphtheroids
5	26	It is recommended all patients have six weeks of parenteral or highly bioavailable oral antimicrobial therapy for bacterial NVO (with the exceptions of infection caused by <i>Brucella</i> or TB) [^]
6	32	It is suggested all patients have a clinical assessment and CRP and/or ESR monitoring approximately four weeks into treatment
7	36	It is recommended all patients with suspected clinical treatment failure have a follow up MRI scan with emphasis on evolutionary changes in the paraspinal and epidural soft tissue findings
8	37, 38	It is suggested that all patients with suspected clinical treatment failure in combination with suspected radiological treatment failure have further image guided aspiration biopsy or surgical sampling, and consultation with a neurosurgeon and Infection physician

* For the purposes of this study, baseline investigations must have been taken within 96 h pre or post the time a diagnosis of NVO was suspected by the clinical team.

[^] For the purposes of this study, an antimicrobial regime was considered appropriate if it consisted of 6 weeks of parenteral antibiotics, or a minimum of 2 weeks of parenteral antibiotics followed by a course which included oral ciprofloxacin to complete a minimum of 6 weeks of antimicrobial therapy.

Secondary outcome measures included audit standards chosen from the IDSA guideline for the diagnosis and treatment of NVO in adults (Berbari et al., 2015), detailed in Table 1. Standards were chosen by the NITCAR organising committee members based on their applicability and relevance to UK practice.

Data sources, collection and analysis

Participating centres chose their preferred method of identifying patients with NVO from the following list: clinical patient lists such as Outpatient Parenteral Antibiotic Therapy (OPAT) databases, infection team databases; radiology databases or ICD-10 discharge diagnosis codes/procedure codes. Details can be found in Supplementary materials: Table 1. Individual patients' hospital records were examined by investigators to confirm a case of NVO prior to inclusion.

Investigators at each site underwent webinar training, completed case report forms, entered anonymised data into a standardised spreadsheet (Microsoft Excel, 2007) and submitted this securely according to Information Governance protocols. A copy of the case report form is provided in Supplementary materials: Appendix A.

Statistical analysis

Summary and descriptive statistics were reported for demographic details, clinical presentation, outcome and microbiological diagnoses of all patients in the study and for the selected audit standards. Patients with NVO secondary to tuberculosis, brucellosis and fungal infections were excluded from detailed analysis regarding management or outcome, due to different approaches taken in their care, making comparison to those with pyogenic bacterial infection inappropriate. Univariable logistic regression models were used to estimate odds ratios and

Table 2

Demographic and clinical characteristics of individuals with NVO in this study.

Characteristic	Cases (n = 286)
Gender - Female	99 (34.6%)
Age (years) [median(IQR)]	64 (50–73)
Ethnicity	White 233 (81.5%)
	Asian/Asian British 20 (7.0%)
	Black/Black British 9 (3.2%)
	Other 7 (2.5%)
	Not documented 17 (5.9%)
Charlson comorbidity index [median(IQR)]	1 (0–2)
Immunosuppression/ Immunodeficiency	Any 27 (9.4%)
	Asplenia/splenectomy 4/27 (14.8%)
	Chemotherapy 6/27 (22.2%)
	Haemodialysis 2/27 (7.4%)
	Steroids 8/27 (29.6%)
	Rheumatoid arthritis 7/27 (25.9%)
	HIV 2/27 (7.4%)
	Other 4/27 (14.8%)
Other factors	Recent trauma 11 (3.9%)
	Travel outside UK in the previous 12 months 30 (10.5%)
	Intravenous drug use in previous 12 months 27 (9.4%)
Bacteraemia in preceding 12 months	54 (18.9%)

Table 3
Presentation of patients with NVO in this study.

		Number (N = 286)
Route of presentation	ED/clinic	205 (71.7%)
	Transfer from another site	43 (15.0%)
	Ambulatory care	15 (5.2%)
	Other	13 (4.6%)
	Not documented	10 (3.5%)
Symptoms on presentation	Fever (reported or measured)	111/257 (43.2%)
	Pain	260/276 (94.2%)
	Neurological deficit	84/251 (33.5%)
Delay from symptom onset to presentation (days, median (IQR))		17 (5–43) (n = 193)
CRP at presentation (mg/L)	Mean	159 (n = 271) [†]
	Median (IQR)	115 (51–253)
Level of infection	Cervical spine	43 (15.0%)
	Thoracic spine	104 (36.4%)
	Lumbo-sacral spine	170 (59.4%)
	No level documented	6 (2.1%)
	Osteomyelitis	277 (96.9%)
Radiological findings (on MRI)	Associated soft tissue infection (e.g. psoas abscess, sinus tract)	64 (22.4%)
	Paravertebral extension of infection (e.g. paraspinal collection)	86 (30.1%)
	Epidural extension of infection (e.g. epidural collection)	77 (26.9%)
	Suspected source	29 (10.1%)
Suspected source	Skin and soft tissue infections	22 (7.7%)
	Genitourinary tract	16 (5.6%)
	Gastrointestinal sources	16 (5.6%)
	Endocarditis	13 (4.6%)
	Post-operative wounds	11 (3.9%)
	Respiratory tract	11 (3.9%)
	Tuberculosis	8 (2.8%)
	Endovascular infections	4 (1.4%)
	Dental infections	4 (1.4%)
	Intravenous catheter site	18 (6.3%)
	Other*	134 (46.9%)

Denominators <286 reflect the number of patients where data were available.

[†]Nb – 15/271 (5.5%) patients had a CRP < 10 mg/L at presentation.

*Other – current or former IVDU (n = 5), discectomy (n = 5), *Staphylococcus aureus* bacteraemia (n = 2), septic arthritis (n = 2), ablation of renal cell carcinoma, bacterial meningitis, prosthetic joint infection, retropharyngeal abscess (all n = 1).

95% confidence intervals (CI) for any association between independent factors and treatment failure. Statistical analyses were carried out using Stata release 15 (StataCorp. 2017).

Results

Patient cohort and characteristics

In total, 40 hospitals participated in the study. A full list of participating sites is available in Supplementary materials: List of participating sites. On-site infectious diseases services were available in 32 hospitals (80.0%), orthopaedics in 38 (95.0%), neurosurgery in 27 (67.5%) and outpatient parenteral antimicrobial therapy (OPAT) services in 35 hospitals (87.5%). Site-specific guidelines for the management of NVO were available in 20 hospitals (50.0%), with 10 different empiric regimens reported, demonstrating a wide variety of antibiotic choices. This can be seen in Supplementary materials: Tables 2, 3 and 4.

Demographic data for the 286 patients included in the audit is shown in Table 2. The majority were male (n = 187, 65.4%) and white (n = 233, 81.5%), with a median age of 64 years and relatively few comorbidities (median CCI 1). In the year prior to diagnosis intravenous drug use was reported in 27 patients (9.4%) and an episode of bacteraemia in

Table 4
Final microbiological diagnosis of patients with NVO in this study.

Organism ¹	No. of cases (%)
Gram positive	Total number of patients 132 (46.2%)
	<i>Staphylococcus aureus</i> 90 (31.5%)
	Oral streptococci ² 13 (4.5%)
	Enterococci ³ 6 (2.1%)
	<i>Streptococcus dysgalactiae</i> 6 (2.1%)
	<i>Streptococcus agalactiae</i> 5 (1.7%)
	<i>Streptococcus pneumoniae</i> 5 (1.7%)
	<i>Streptococcus pyogenes</i> 3 (1.0%)
	<i>Streptococcus anginosus</i> group 4 (1.4%)
	Other Gram positive organisms ⁴ 3 (1.0%)
Gram negative	Total number of patients 33 (11.5%)
	<i>E. coli</i> 18 (6.3%)
	<i>Pseudomonas</i> species 3 (1.0%)
	Other Enterobacterales ⁵ 6 (2.1%)
	Other Gram negative organisms ⁶ 7 (2.4%)
	<i>Mycobacterium tuberculosis</i> 11 (3.8%)
	Two organisms identified in same patient ⁷ 5 (1.7%)
	No organism identified 111 (38.8%)

All coagulase negative staphylococci (CoNS) (n = 15; 9 cases where CoNS was the only organism isolated on blood culture; 3 cases where CoNS were cultured alongside other, more pathogenic organisms from blood culture; 2 cases where CoNS was the only organism isolated from biopsy and did not grow on blood culture; 1 case where CoNS was cultured alongside other, more pathogenic organisms from biopsy). There were no isolates of *Staphylococcus lugdunensis* in this study.

A *Micrococcus* spp. isolated from blood culture with *Klebsiella* spp. on biopsy.

A *Cutibacterium acnes* which grew from one set of blood cultures, when a *Staphylococcus aureus* grew in the other set.

A “Gram negative coccobacillus” from one set of blood cultures, which did not grow for further identification.

¹ Suspected contaminants excluded from the table above:

² *Streptococcus gallolyticus* (n = 4), *Streptococcus gordonii* (n = 2), *Streptococcus oralis/mitis* (n = 4), *Streptococcus sanguinis* (n = 2), not otherwise specified (n = 1).

³ *Enterococcus faecalis* (n = 5), *Enterococcus* spp. (n = 1).

⁴ Other Gram positive organisms – *Atopobium parvulum*, *Cutibacterium (Propionibacterium) acnes* (grown in both blood cultures and on biopsy) and *Rothia mucilaginosa*.

⁵ Other Enterobacterales – *Enterobacter cloacae*, *Klebsiella aerogenes*, *Klebsiella pneumoniae*, *Klebsiella* spp., *Proteus mirabilis* and *Serratia liquefaciens*.

⁶ Other Gram negative organisms – *Acinetobacter baumannii*, *Aggregatibacter aphrophilus*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Neisseria mucosa/macacae*, *Prevotella buccae* and *Salmonella enterica* serovar Rissen.

⁷ Cases where two organisms were identified in the same patient – *S. aureus* and *E. faecalis* isolated from biopsy; *Streptococcus oralis/mitis* isolated from biopsy; *Pseudomonas aeruginosa* and *Serratia liquefaciens* both isolated from two sets of blood cultures; *S. aureus* and *Streptococcus dysgalactiae* isolated from one set of blood cultures; *E. coli* and *Streptococcus intermedius* isolated from one set of blood cultures.

54 patients (18.9%).

Clinical features on presentation are summarised in Table 3. The majority of patients (n = 260, 94.2%) had back pain, while 43.2% had subjective fever and 33.5% had a neurological deficit. The median duration of symptoms, prior to presentation, was 17 days. An underlying source of infection was not identified in 46.9% of cases. There were no cases of NVO attributable to brucellosis or fungal infection and 11 patients were treated as tuberculosis (TB).

A summary of microbiological findings is shown in Table 4. An organism was identified in 175/286 cases (61.2%). Of these, 90/175 (51.4%) were *Staphylococcus aureus*; methicillin sensitivity data were collected for 68/90 (75.6%) isolates, all were reported as methicillin

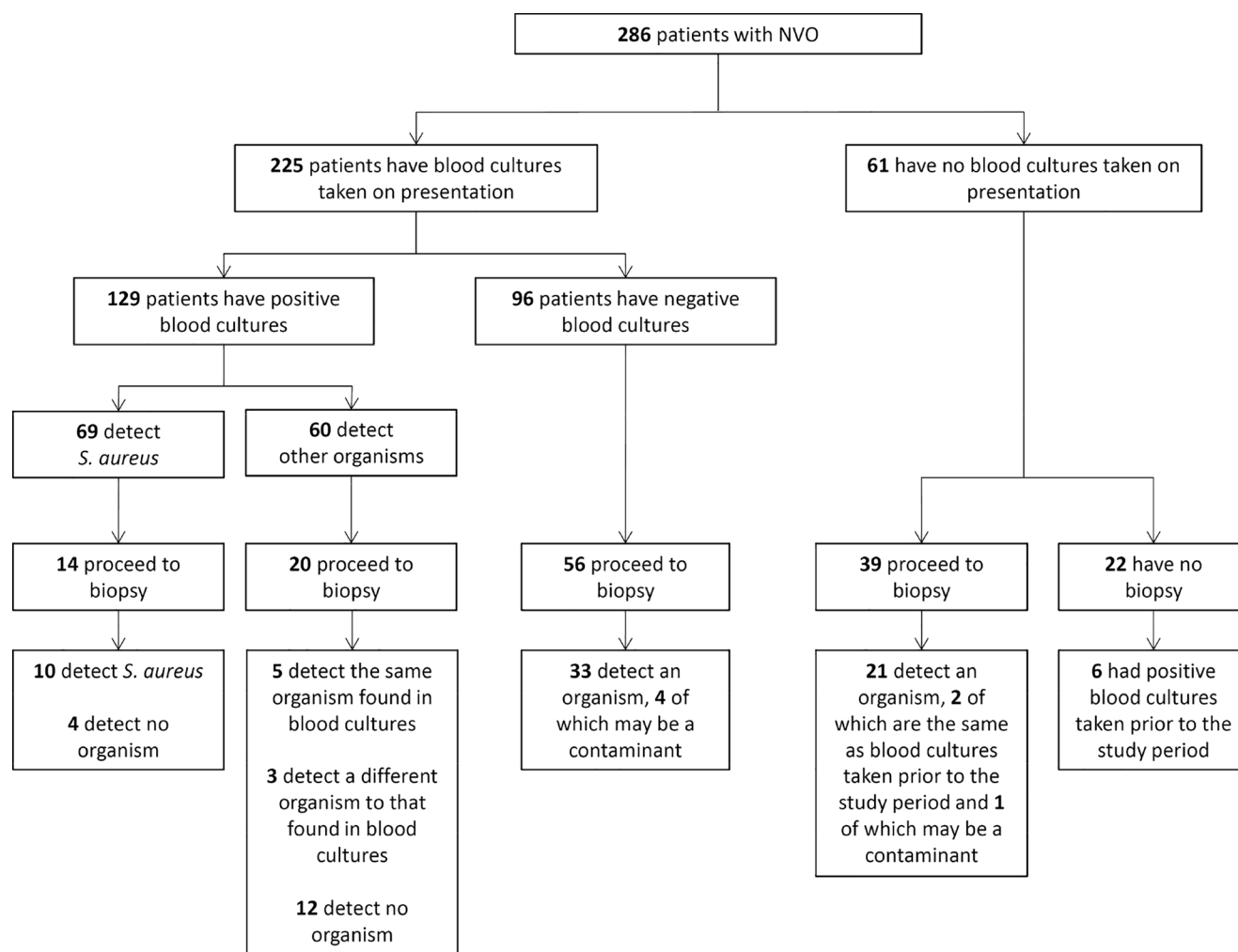


Fig. 1. Flow diagram of the diagnostic pathway for microbiology samples in the 288 NVO patients in this study.

sensitive (i.e. MSSA). Another pathogenic organism was identified in 85/286 cases (29.7%). Gram negative organisms were identified in 33 cases (11.5%). No significant organism was identified in 111/286 cases (38.8%). In three patients an organism was isolated from a distant site that was presumed to be the causative organism in NVO (*Escherichia coli* in urine culture and eye tissue and MSSA and *Streptococcus pyogenes* from a joint). Some cases had multiple organisms isolated.

Patient management

Full results of the audit against IDSA standards can be found in Supplementary materials: Full audit results. A minority of patients (7.6%) had a baseline CRP, ESR and two sets of blood cultures taken at baseline as recommended; however 77.8% had at least a baseline CRP and one set of blood cultures. All 286 patients in this study received appropriate imaging.

The IDSA recommend that all patients with suspected NVO undergo biopsy unless *S. aureus* or *S. lugdunensis* are isolated in blood cultures. Fig. 1 illustrates the diagnostic pathway for this patient cohort and shows that 69/286 patients had *S. aureus* isolated in blood cultures at presentation (within 96 h.) The remaining 217/286 (75.9%) patients had negative blood cultures, or blood cultures that did not grow *S. aureus* or *S. lugdunensis*. Of these, 115/217 (53.0%) proceeded to biopsy, which was diagnostic in 57/115 cases (49.6%). The most common reason given for not proceeding to biopsy was the isolation of alternate

pathogens in blood cultures (e.g. oral streptococci or *E. coli*.) In patients with a non-diagnostic first biopsy, 10/58 (17.2%) proceeded to a second biopsy; 3/10 (30.0%) isolated an organism from this second biopsy.

A minimum 6 week course of antimicrobial therapy was completed in 200/251 (79.7%) patients (excluding 11 patients with TB, 10 deaths, 5 transfers to other hospitals, 1 lost to follow up and 8 with unknown outcomes). OPAT was utilised for 169/275 patients (61.5%). Between 21 and 28 days of treatment, 89.9% patients received a clinical assessment by a physician and 85.0% had CRP or ESR monitoring. There were 14/40 hospitals with specific antimicrobial guidelines for the treatment of NVO: 7/14 used flucloxacillin as their first line agent. See Supplementary Materials: Table S3 and Table S4.

Patient outcome

The outcome of 275 patients (excluding 11 TB cases) is summarised in Table 5. Nearly 10% (25/268) of patients required ICU admission and 20.2% were re-admitted within 90 days. The majority of patients (145/261, 55.5%) experienced complications. At one month, 9 patients (3.3%) had been lost to follow-up, 9 patients (3.3%) had died and an additional 36 patients (13.4%) met criteria for suspected treatment failure.

Of the 36 patients with suspected treatment failure, at 21–28 days post-initiation of antibiotics, 35 (97.2%) were either referred or already under the care of a specialist team and 17 (47.2%) had repeat imaging.

Table 5
Outcome of patients with NVO in this study, excluding cases of tuberculosis (N = 275).

Outcome		Number (N = 275)	
Patient Care	Inpatient only	103 (37.5%)	
	OPAT only	15 (5.5%)	
	Both inpatient and OPAT	154 (56.0%)	
	Unspecified	3 (1.1%)	
ICU Admission		25/268 (9.3%)	
Symptoms at 90 days	Pain	115/186 (61.8%)	
	Neurological symptoms	32/186 (17.2%)	
Readmission within 90 days	All cause	49/243 (20.2%)	
	Due to NVO	30/243 (12.3%)	
Complications	Any	145/261 (55.5%)	
	Spinal abscess	97/261 (37.2%)	
	Distant abscess	21/261 (8.0%)	
	Stroke	5/261 (1.9%)	
	Endocarditis	18/261 (6.9%)	
	Surgical drainage of abscess	24/261 (9.2%)	
	Surgical fixation	16/261 (6.1%)	
	Death at 90 days	16/271 (5.9%)	
	Treatment failure at one month	Clinical failure*	36/269 (13.4%)
		Death	9/269 (3.4%)
Combined		45/269 (16.7%)	

*Clinical treatment failure defined as persistent fever and/or rising inflammatory markers 21–28 days after commencing treatment.

This demonstrated radiological evidence of worsening infection in 5 cases (3 showed worsening osteomyelitis/discitis, 1 showed worsening epidural extension, 1 showed worsening soft tissue infection). None of these patients had further biopsies.

Risk factors for treatment failure

The results of a univariable logistic regression analysis undertaken to assess potential risk factors for treatment failure is summarised in Table 6. A higher CCI was the only risk factor for treatment failure that was statistically significant with a *p*-value of < 0.05, increasing the odds of treatment failure by 1.24 (95% CI 1.07–1.42) for each additional unit of the CCI.

Discussion

To our knowledge this is the largest retrospective multicentre cohort study of UK patients with NVO. Practice deviated from IDSA recommendations in several areas. There were low rates of diagnostic biopsy and few patients underwent repeat biopsy where the first had been non-diagnostic. This may stem from uncertainty in the approach to patients with bacteraemia with organisms other than *S. aureus* or *S. lugdenensis*. IDSA guidance suggests that pursuing a biopsy in this situation is left to clinical discretion and, in this study, clinicians were often sufficiently convinced that they had isolated the causative agent on blood culture that biopsy was not felt warranted. This approach is supported by our finding that lack of microbiological diagnosis was not found to be a significant contributor to treatment failure.

There was a concerning minority of patients (6/102) who did not undergo a biopsy due to lack of access to this procedure. Anecdotally, a lack of robust referral pathways for centres without on-site surgeons or interventional radiologists may account for this. As only 10% of the included patients were from non-teaching hospitals, our study may underestimate this issue.

The management of suspected treatment failure also differed from IDSA guidelines, with few patients undergoing repeat imaging or biopsy. This may reflect variability in the definition of treatment failure used in practice. The time period of follow up (21–28 days) was chosen as it

aligned to the follow up recommended by the IDSA guidelines and was judged useful clinically. Although 21% of patients with repeat imaging had worsening appearances, only a quarter of these met our definitions for clinical failure. This illustrates a distinction between clinical and imaging findings and the complexities in identifying patients who have truly failed therapy.

CCI was the only factor independently associated with clinical treatment failure. Due to the small size of the treatment failure group, other smaller effects may have been missed. Comorbidities are commonly associated with NVO and are associated with poor outcome (Mylona et al., 2009; Akiyama et al., 2013; Widdrington et al., 2018). The only other variable approaching statistical significance was the borderline protective effect of an epidural abscess identified on baseline imaging. However, previous studies have identified this as a risk factor for treatment failure (Skaf et al., 2010; D'Agostino et al., 2010).

The patient characteristics and microbiology in this cohort reflect previous studies (Zimmerli, 2010; Gasbarrini et al., 2005; Kehrer et al., 2014; Mylona et al., 2009; Gouliouris et al., 2011). Diagnostic delay in NVO is often several months (Gasbarrini et al., 2005; Gök et al., 2014); the shorter time identified here may reflect lower incidence of TB and brucellosis in the UK or easier access to imaging (Jean et al., 2017).

Monomicrobial infection with *S. aureus* or streptococcal species was most common with a smaller but significant number of Gram negative infections. Previous cohorts have reported *S. aureus* as a causative organism in 32–67% cases (Nickerson and Sinha, 2016; Mylona et al., 2009) and ours reported 31.5%. No MRSA was detected, reflecting current low rates of MRSA carriage and invasive disease in the UK in comparison to the US (Dudareva et al., 2019). We acknowledge methicillin sensitivity data were limited (in 68/90 isolates) as the initial data collection did not capture this information and sites were asked to conduct a secondary data collection where possible. These findings highlight the need for national guidelines to support best prescribing practice.

A microbiological diagnosis was obtained in 61.2% of patients. This is lower than previously reported (Gupta et al., 2014; Mylona et al., 2009) and may be partly explained by low biopsy rates. Biopsy or aspiration yielded a microbiological diagnosis in 49.6%, but a microbiological diagnosis was not obtained in 38.8% patients. As lack of microbiological confirmation has previously been associated with a higher likelihood of attributable readmission and death (Chong et al., 2018), this is a key area for improvement.

The key strength of this study is the large number and variety of patients included from multiple sites over a comparably short timeframe (Corrah et al., 2011; McHenry et al., 2002) made possible using a national multicentre collaborative and novel recruitment strategies through trainee and student networks. The results should be applicable to most sites within the UK and are likely to be generalisable to other centres in high income settings with similar rates of TB and antimicrobial resistance. However, the retrospective design brings risk of bias. Sites chose their method of case ascertainment, so there may be heterogeneity between cases submitted by different sites. Also sites were asked to recruit the first 8 patients presenting to their trust over a 2 year period. This strategy was chosen as a feasible number for individual sites to recruit based on pilot data collection and to avoid overrepresentation of tertiary centres. We acknowledge that this may have introduced sampling bias.

To study larger prospective cohorts of those with NVO would require greater collaborative networks, such as the recently developed European Endocarditis registry (Habib et al., 2019), a comparable infectious disease in terms of its relatively low incidence, high morbidity and multi-disciplinary management. In conclusion, this retrospective study has explored the differing management and outcomes of UK patients with NVO and shown that causative organisms vary in prevalence compared to the US, confirming the urgent need for guidelines reflecting local epidemiology and best practice.

Table 6
Risk factors for treatment failure at 28 days of treatment (N = 269*).

Variable	Category	No treatment failure (n = 224)	Treatment failure (n = 45)	OR (95% CI)	p-value
Gender	Female	79	15	1.08 (0.55–2.15)	0.80
	Male	145	30		
Age (years), median (IQR)		64 (50–73)	69 (57–78)	1.02 (1.00–1.04)	0.077
Ethnicity	White	186	41	-	-
	Asian/Asian British	12	2	0.76 (0.16–3.51)	0.72
	Black/Black British	6	0	1	-
	Other	5	1	1.24 (1.07–1.42)	0.93
Charlson comorbidity index, median (IQR)		1 (0–2)	2 (1–3)	1.24 (1.07–1.42)	0.004
Immuno-compromise	No	203	40	1.21 (0.43–3.39)	0.72
	Yes	21	5		
Previous bacteraemia	No	178	37	0.84 (0.36–1.92)	0.67
	Yes	46	8		
Fever at 28 days	Absent	111	23	0.92 (0.46–1.83)	0.82
	Present	89	17		
Pain at 28 days	Absent	12	4	0.36 (0.18–1.87)	0.21
	Present	204	39		
Neurological deficit at 28 days	Absent	131	28	0.79 (0.38–1.64)	0.52
	Present	63	12		
CRP (mg/L), median (IQR)		112 (53–259)	157 (97.5–277)	1.00 (1.00–1.00)	0.39
Radiological findings (on MRI) at presentation	Soft tissue infection	51	10	0.94 (0.45–2.09)	0.94
	Paravertebral extension	67	13	0.95 (0.47–1.93)	0.89
	Epidural collection	66	7	0.43 (0.18–1.02)	0.054
Organism	<i>Staphylococcus aureus</i>	73	16	1.14 (0.58–2.23)	0.70
	None identified	90	15	0.74 (0.38–1.46)	0.39
ICU admission	No	197	41	0.88 (0.30–2.81)	0.88
	Yes	21	4		
Complications	No	103	18	1.25 (0.65–2.43)	0.50
	Yes	114	25		
Time from symptom onset to first dose of antibiotics (days), median (IQR) (n)		22.5 (7–63.5) (n = 152)	14 (4–42) (n = 22)	0.99 (0.98–1.00)	0.26

*Exclusions: 11 patients with TB; 5 patients who were transferred to a different care setting prior to 28 days of treatment; 1 patient lost to follow up.

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