Clinical Infection in Practice 12 (2021) 100101

Contents lists available at ScienceDirect

Clinical Infection in Practice

journal homepage: www.sciencedirect.com/journal/clinical-infection-in-practice

Clinical Audits/Service improvements

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

Rachel Bousfield [a,1,*], Isobel Ramsay [a,1], Ben Warne [a,1], Deevia Kotecha [b], Tamara Mitchell [c], Jonathan Sandoe [d], Elinor Moore [a], Emma Nickerson [a], Andrew Kirby [a,2], David Enoch [e,2], the NITCAR Collaborative[3]

[a] Cambridge University Hospitals NHS Foundation Trust, United Kingdom
[b] University of Leicester, United Kingdom
[c] Sheffield Teaching Hospitals NHS Foundation Trust, United Kingdom
[d] University of Leeds, United Kingdom
[e] Public Health England, United Kingdom

* Corresponding author at: Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, United Kingdom.
E-mail address: rachel.bousfield@addenbrookes.nhs.uk (R. Bousfield).

[1] These authors contributed equally to this work.

[2] These authors contributed equally to this work.

[3] The NITCAR Collaborative includes: Jay Pancholi, University Hospitals of Leicester NHS Trust, Ross John Porter, Aberdeen Royal Infirmary, NHS Grampian, Jennifer Whitley Hutchison, Aberdeen Royal Infirmary, NHS Grampian, Goh Jing Yi, Aberdeen Royal Infirmary, NHS Grampian, James Redmore, Aberdeen Royal Infirmary, NHS Grampian, Dr Aaron Nagar, Antrim, Northern Health and Social Care Trust, Simon Tiberi, Royal London Hospital, Barts Health NHS Trust, Emilia Bober, Barts Health NHS Trust, Callum O'Keeffe, Barts Health NHS Trust, Mr Paul Hegarty, Royal Victoria Hospital, Belfast, Christopher Madden-McKee, Royal Victoria Hospital, Belfast, Mark Rainey, Royal Victoria Hospital, Belfast, Timothy Patterson, Royal Victoria Hospital, Belfast, Arthur Jun Ming Lim, Royal Victoria Hospital, Belfast, Dr Michael Riste, Heartlands Hospital, Birmingham, Dr Steven Laird, Queen Elizabeth Hospital, University Hospitals Birmingham, Adeolu Banjoko, Queen Elizabeth Hospital, University Hospitals Birmingham, Apurva Ashok, Queen Elizabeth Hospital, University Hospitals Birmingham, Dr Phoebe Cross, Bradford Teaching Hospitals NHS Foundation Trust, Dr Razan Saman, Bradford Teaching Hospitals NHS Foundation Trust, Dr Alberto San Francisco, Brighton and Sussex University Hospitals NHS Trust, Faiz Shaikh, Brighton and Sussex University Hospitals NHS Trust, Manahal Mateen, Brighton and Sussex University Hospitals NHS Trust, Dong Eun Lee, Brighton and Sussex University Hospitals NHS Trust, Irena Papapetrou, Brighton and Sussex University Hospitals NHS Trust, Dr Mahableshwar Albur, Southmead Hospital, Bristol, Tejas Netke, Southmead Hospital, Bristol, Sankalp Tandle, Southmead Hospital, Bristol, Lina Alim, University Hospitals Bristol, Magdalene Yin Lin Ting, Cambridge University Hospitals NHS Foundation Trust, Xueying Zheng, Cambridge University Hospitals NHS Foundation Trust, Silvana Talisa Wijaya, Cambridge University Hospitals NHS Foundation Trust, James Lloyd, University Hospital of Wales, Cardiff, Adanna Anomneze-Collins, University Hospital of Wales, Cardiff, Inés Murray, University Hospital of Wales, Cardiff, Paul McNulty, University Hospital of Wales, Cardiff, Jenny Wright, Royal Derby Hospital, Derby Teaching Hospitals Foundation Trust, Alexander Light, East Kent University Hospitals NHS Foundation Trust, Dr Rebecca Sutherland, Western General Hospital, Edinburgh, NHS Lothian, Dr Oliver Koch, Consultant & Honorary Senior Clinical Lecturer in Infectious Diseases, Western General Hospital, Edinburgh, NHS Lothian, David Henshall, Western General Hospital, Edinburgh, NHS Lothian, Savva Pronin, Western General Hospital, Edinburgh, NHS Lothian, Alexander Christides, Western General Hospital, Edinburgh, NHS Lothian, Nicole Lau, Western General Hospital, Edinburgh, NHS Lothian, Rebecca Murphy Lonergan, Western General Hospital, Edinburgh, NHS Lothian, Nikitha Rajaraman, Queen Elizabeth University Hospital, Glasgow, Olivia Mansfield, Queen Elizabeth University Hospital, Glasgow, Dr Carolyn Hemsley, Guy's & St Thomas' NHS Foundation Trust, Madura Nandakumar, Guy's & St Thomas' NHS Foundation Trust, Amal Boulbadaoui, Medical student, Guy's & St Thomas' NHS Foundation Trust, Dr Gavin Barlow, Hull York Medical School, University of York, Angus McMillan, Castle Hill Hospital, Hull and East Yorkshire Hospitals, Mohit Patel, Castle Hill Hospital, Hull and East Yorkshire Hospitals, James Hatcher, Imperial College Healthcare NHS Trust, Abena Kufuor, Imperial College Healthcare NHS Trust, Amer Al-Balah, Imperial College Healthcare NHS Trust, Dr Janine Carter, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Vladislav Kutuzov, University Hospitals of Leicester NHS Foundation Trust, Dr Chris Parry, University of Liverpool, Dr Fiona McGill, University of Liverpool, Natasha Varshney, Royal Liverpool University Hospital, Mr Martyn Lovell, University Hospital Of South Manchester NHS Foundation Trust, Bernardo Brandao, University Hospital Of South Manchester NHS Foundation Trust, Mr Andrew Bowey, Royal Victoria Infirmary, Newcastle, Daniel Matterson, Royal Victoria Infirmary, Newcastle, Dr Hamish Houston, North Middlesex University Hospital NHS Trust, Dr Vivienne Weston, Queens Medical Centre, Nottingham University Hospitals Trust, Rachel Thavayogan, Nottingham University Hospitals Trust, Kelsey Aimar, Nottingham University Hospitals Trust, Nnedi Ojukwu, Nottingham University Hospitals Trust, Dr Maria Dudareva, Nuffield Orthopaedic Centre, Oxford, Jade Kinton, Nuffield Orthopaedic Centre, Oxford, Mr Peter Whitfield, University Hospitals Plymouth NHS Trust, Fatima Adamu-Biu, University Hospitals Plymouth NHS Trust, Antony Lam, University Hospitals Plymouth NHS Trust, Temidayo Osunronbi, University Hospitals Plymouth NHS Trust, Ebrahiem Tumi, Medical student, University Hospitals Plymouth NHS Trust, Dr Janet Purcell, Lancashire Teaching Hospitals NHS Foundation Trust, Miss Leila White, Lancashire Teaching Hospitals NHS Foundation Trust, Yin Ern Chua, Lancashire Teaching Hospitals NHS Foundation Trust, Sophia Vieira, Royal Free London NHS Foundation Trust, Claudia Lee, Royal Free London NHS Foundation Trust, Guan Hui Tricia Lim, Royal Free London NHS Foundation Trust, Dr Samira Mohd Afzal, Royal Stoke University Hospital, Stoke-on-Trent, Arushi Sharma, Royal Stoke University Hospital, Stoke-on-Trent, Dr Jonathan Underwood, University College London Hospitals Trust, Dr Sarah Logan, University College London Hospitals Trust, Dr Victoria Ward, University College London Hospitals Trust, Mirella Ling, Worcestershire Royal Hospital.

https://doi.org/10.1016/j.clinpr.2021.100101
Received 2 June 2021; Received in revised form 1 September 2021; Accepted 14 September 2021
Available online 20 September 2021

ARTICLE INFO

Keywords:
Discitis
Osteomyelitis

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., 20142014). 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 $\geq$ 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 (*Staphylococcus aureus* or *Staphylococcus lugdunensis*) 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 *S. lugdunensis*), *Propionibacterium* 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 Brucella 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%)
	Asplenism/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)ˆ
	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%)
Radiological findings (on MRI)	Osteomyelitis	277 (96.9%)
	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	Skin and soft tissue infections	29 (10.1%)
	Genitourinary tract	22 (7.7%)
	Gastrointestinal sources	16 (5.6%)
	Endocarditis	16 (5.6%)
	Post-operative wounds	13 (4.6%)
	Respiratory tract	11 (3.9%)
	Tuberculosis	11 (3.9%)
	Endovascular infections	8 (2.8%)
	Dental infections	4 (1.4%)
	Intravenous catheter site	4 (1.4%)
	Other*	18 (6.3%)
	None identified	134 (46.9%)

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

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%)
	Staphylococcus aureus	90 (31.5%)
	Oral streptococci[2]	13 (4.5%)
	Enterococci[3]	6 (2.1%)
	Streptococcus dysgalactiae	6 (2.1%)
	Streptococcus agalactiae	5 (1.7%)
	Streptococcus pneumoniae	5 (1.7%)
	Streptococcus pyogenes	3 (1.0%)
	Streptococcus anginosus group	4 (1.4%)
	Other Gram positive organisms[4]	3 (1.0%)
Gram negative	Total number of patients	33 (11.5%)
	E. coli	18 (6.3%)
	Pseudomonas species	3 (1.0%)
	Other Enterobacterales[5]	6 (2.1%)
	Other Gram negative organisms[6]	7 (2.4%)
Mycobacterium tuberculosis		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 cocco-bacillus" 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.

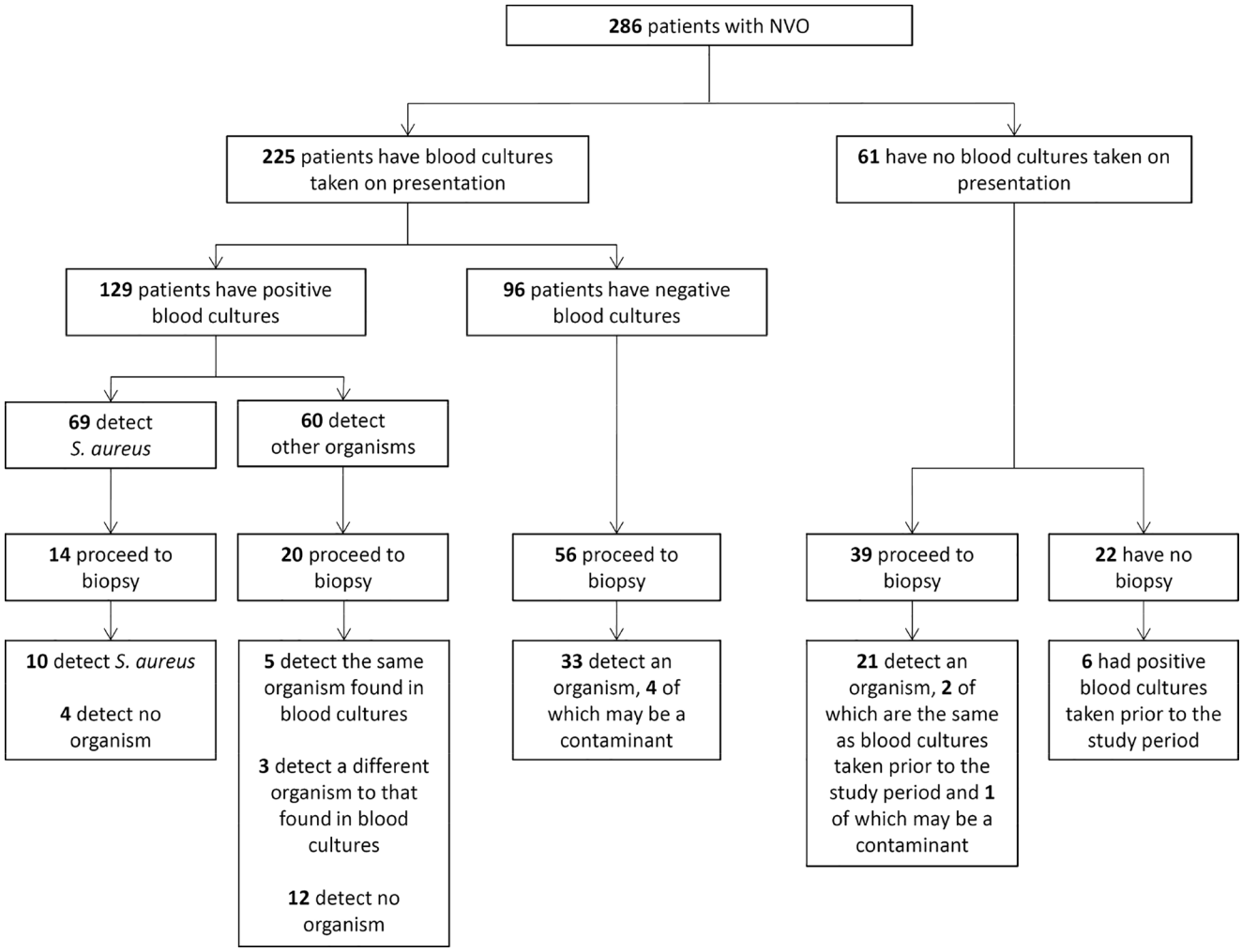

Fig. 1. Flow diagram of the diagnostic pathway for microbiology samples in the 288 NVO patients in this study.

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., 20142014; 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 multidisciplinary 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		
	Male	145	30	1.08 (0.55–2.15)	0.80
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	0.72
	Black/Black British	6	0	(0.16–3.51)	-
	Other	5	1	1	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		
	Yes	21	5	1.21 (0.43–3.39)	0.72
Previous bacteraemia	No	178	37		
	Yes	46	8	0.84 (0.36–1.92)	0.67
Fever at 28 days	Absent	111	23		
	Present	89	17	0.92 (0.46–1.83)	0.82
Pain at 28 days	Absent	12	4		
	Present	204	39	0.36 (0.18–1.87)	0.21
Neurological deficit at 28 days	Absent	131	28		
	Present	63	12	0.79 (0.38–1.64)	0.52
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	*Staphylococcus aureus*	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		
	Yes	21	4	0.88 (0.30–2.81)	0.88
Complications	No	103	18		
	Yes	114	25	1.25 (0.65–2.43)	0.50
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.

Funding

Isobel Ramsay is an academic clinical fellow supported by the National Institute for Health Research.

Ben Warne is supported by a clinical research fellowship from Addenbrooke's Charitable Trust.

Rachel Bousfield is supported by Public Health England.

This research did not receive any additional specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work used data from patients collected by the NHS staff and medical students listed below. Without their contributions this work would not have been possible.

Aberdeen – Aberdeen Royal Infirmary.

Mr George Patrick Ashcroft, Consultant Orthopaedic Surgeon.

Dr Vhairi Bateman, Consultant in Infectious Diseases and Medical Microbiology.

Zheng Siying Cindy, Medical student.

Niti Athavle, Medical student.

Barts Health NHS Trust.

Kathryn O'Brien, Medical student.

Matthew Barrett, Medical student.

Florence Wilkinson, Medical student.

Belfast – Royal Victoria Hospital.

Mr Niall Eames, Orthopaedic Surgeon.

Mr Rakesh Dhokia, Specialty Registrar in Trauma and Orthopaedics.

Birmingham – Heart of England NHS Trust.

Dr Angela Minassian, Consultant in Infectious Diseases.

University Hospitals Birmingham NHS Trust.

Dr Paul McWhinney, Consultant in Infectious Diseases.

Bristol – University Hospital Bristol.

Dr Martin Williams, Consultant in Infection and Microbiology.

Omdesola Awokoya, Medical student.
Leona Richards, Medical student.
Cardiff – University Hospital Wales.
Dr Anil Kumar, Consultant in Acute Medicine.
Claudia Zeicu, Medical student.
Derby – Derby Teaching Hospitals Foundation Trust.
Mr Rajendra Bommireddy, Consultant Orthopaedic spinal surgeon.
East Kent Hospitals University NHS Foundation Trust.
Dr Srinivasulu Reddy, Consultant Microbiologist, East Kent University Hospitals NHS Foundation Trust.
Edinburgh – Western General Hospital.
William Broadhurst, Medical student.
Glasgow – Queen Elizabeth University Hospital.
Mr Nassir Hussain, Consultant Orthopaedic Surgeon.
Andrew Croall, Medical student.
Andrew Wilkinson, Medical student.
Jacob Mewse, Medical student.
James Irvine, Medical student.
Imperial College Healthcare NHS Trust.
Imogen John, Medical student.
Jake Symington, Medical student.
Lancaster – Royal Lancaster Infirmary.
Dr Monika Pasztor, Consultant.
Auday Marwaha, Medical student.
Zuzanna Nowinka, Medical student.
Ege Arioglu, Medical student.
Dominic Beith, Medical student.
Aditi Ranjan, Medical student.
Leeds – Leeds Teaching Hospitals NHS Trust.
Aimee Lloyd, Medical student.
Leicester – University Hospitals Leicester.
Mr Jason Braybrooke, Consultant Orthopaedic Spinal Surgeon.
Elsie Hunter, Medical student.
Abina Dharmaratnam, Medical student.
Chris Wilkinson, Medical student.
National Student Association of Medical Research.
Eloisa MacLachlan, Medical student.
Kathryn O'Brien, Medical student.
Reem Abdelgalil, Medical student.
Serena Banh, Medical student.
Newcastle – Royal Victoria Infirmary.
Lauren Medwell, Medical student.
North Middlesex University Hospital.
Dr Daniel Bell, Consultant.
Nottingham – Queens Medical Centre.
Mr Guiseppe Morassi, Consultant Spinal Surgeon.
Adam Graham, Medical student.
Delan Sivandarajah, Medical student.
Oxford – Oxford University Hospitals NHS Trust.
Dr Matthew Scarborough, Consultant in Infectious Diseases and Microbiology.
Plymouth – Plymouth Hospitals NHS Trust.
Dr James Greig, Consultant Microbiologist.
Royal Free Hospital.
Dr Susan Hopkins, Consultant in Infectious Diseases and Microbiology.
Stephanie Harris, Medical student.
Sheffield – Sheffield Teaching Hospitals.
Dr Katharine Cartwright, Consultant in Infectious Diseases.
Shrewsbury and Telford.
Dr Yasar Hussain, Consultant Clinical Scientist in Medical Microbiology.
Worcestershire -Worcestershire Royal Hospital.
Sophie Turton, Medical student.

References

Nickerson, E.K., Sinha, R., 2016. Vertebral osteomyelitis in adults: an update. Br. Med. Bull. 117 (1), 121–138.
Zimmerli, W., 2010. Vertebral Osteomyelitis. N. Engl. J. Med. 362 (11), 1022–1029.
Gasbarrini, A., Bertoldi, E., Mazzetti, M., et al., 2005. Clinical features, diagnostic and therapeutic approaches to haematogenous vertebral osteomyelitis. Eur. Rev. Med. Pharmacol. Sci.
Corrah, T.W., Enoch, D.A., Aliyu, S.H., Lever, A.M., 2011. Bacteraemia and subsequent vertebral osteomyelitis: a retrospective review of 125 patients. QJM 104 (3), 201–207.
Kehrer, M., Pedersen, C., Jensen, T.G., Lassen, A.T., 2014. Increasing incidence of pyogenic spondylodiscitis: A 14-year population-based study. J. Infect. 68 (4), 313–320.
Gupta, A., Kowalski, T.J., Osmon, D.R., et al. Long-Term Outcome of Pyogenic Vertebral Osteomyelitis: A Cohort Study of 260 Patients. Open Forum. Infect. Dis. 2014; 1: ofu107–ofu107.
Mylona, E., Samarkos, M., Kakalou, E., Fanourgiakis, P., Skoutelis, A., 2009. Pyogenic Vertebral Osteomyelitis: A Systematic Review of Clinical Characteristics. Semin. Arthritis Rheum. 39 (1), 10–17.
Akiyama, T., Chikuda, H., Yasunaga, H., Horiguchi, H., Fushimi, K., Saita, K., 2013. Incidence and risk factors for mortality of vertebral osteomyelitis: a retrospective analysis using the Japanese diagnosis procedure combination database. BMJ Open 3 (3), e002412. https://doi.org/10.1136/bmjopen-2012-002412.
Loibl, M., Stoyanov, L., Doenitz, C., Brawanski, A., Wiggermann, P., Krutsch, W., Nerlich, M., Oszwald, M., Neumann, C., Salzberger, B., Hanses, F., 2014. Outcome-related co-factors in 105 cases of vertebral osteomyelitis in a tertiary care hospital. Infection 42 (3), 503–510.
GÖk, Ş.E., Kaptanoğlu, E., Çelikbaş, A., ErgÖnül, Ö., Baykam, N., Eroğlu, M., Dokuzoğuz, B., 2014. Vertebral osteomyelitis: clinical features and diagnosis. Clin. Microbiol. Infect. 20 (10), 1055–1060.
Jean, M., Irisson, J.-O., Gras, G., Bouchand, F., Simo, D., Duran, C., Perronne, C., Mulleman, D., Bernard, L., Dinh, A., 2017. Diagnostic delay of pyogenic vertebral osteomyelitis and its associated factors. Scand. J. Rheumatol. 46 (1), 64–68.
Marchionni, E., Marconi, L., Ruinato, D., Zamparini, E., Gasbarrini, A., Viale, P., 2019. Spondylodiscitis: is really all well defined? Eur. Rev. Med. Pharmacol. Sci. 23, 201–209.
Widdrington, J., Emmerson, I., Cullinan, M., Narayanan, M., Klejnow, E., Watson, A., Ong, E., Schmid, M., Price, D., Schwab, U., Duncan, C., 2018. Pyogenic Spondylodiscitis: Risk Factors for Adverse Clinical Outcome in Routine Clinical Practice. Med. Sci. 6 (4), 96. https://doi.org/10.3390/medsci6040096.
McHenry, M.C., Easley, K.A., Locker, G.A., 2002. Vertebral Osteomyelitis: Long-Term Outcome for 253 Patients from 7 Cleveland-Area Hospitals. Clin. Infect. Dis. 34 (10), 1342–1350.
Kim, J., Lee, J.H., Kim, S.W., Oh, J.-K., Kim, Y.-W., Kim, T.-H., 2019. Outcomes of additional instrumentation in elderly patients with pyogenic vertebral osteomyelitis and previous spinal instrumentation. Spine J. 19 (9), 1498–1511.
Chong, B.S.W., Brereton, C.J., Gordon, A., Epidemiology, D.JS., 2018. Microbiological Diagnosis, and Clinical Outcomes in Pyogenic Vertebral Osteomyelitis: A 10-year Retrospective Cohort Study. Open Forum. Infect. Dis. 5 (ofy037).
Gregori, F., Grasso, G., Iaiani, G., Marotta, N., Torregrossa, F., Landi, A., 2019. Treatment algorithm for spontaneous spinal infections: A review of the literature. J. craniovertebral junction spine 10 (1), 3. https://doi.org/10.4103/jcvjs.JCVJS_115_18.
Gouliouris, T., Aliyu, S.H., Brown, N.M., 2011. Spondylodiscitis: update on diagnosis and management–authors' responses. J. Antimicrob. Chemother. 66 (5), 1200–1202.
Park, K.-H., Kim, D.Y., Lee, Y.-M., Lee, M.S., Kang, K.-C., Lee, J.-H., Park, S.Y., Moon, C., Chong, Y.P., Kim, S.-H., Lee, S.-O., Choi, S.-H., Kim, Y.S., Woo, J.H., Ryu, B.-H., Bae, I.-G., Cho, O.-H., Smyth, D.S., 2019. Selection of an appropriate empiric antibiotic regimen in hematogenous vertebral osteomyelitis. PLoS One 14 (2), e0211888. https://doi.org/10.1371/journal.pone.021188810.1371/journal.pone.0211888.t00110.1371/journal.pone.0211888.t00210.1371/journal.pone.0211888.t003.
Rutges, J.P.H.J., Kempen, D.H., van Dijk, M., Oner, F.C., 2016. Outcome of conservative and surgical treatment of pyogenic spondylodiscitis: a systematic literature review. Eur. Spine J. 25 (4), 983–999.
Bernard, L., Dinh, A., Ghout, I., Simo, D., Zeller, V., Issartel, B., Le Moing, V., Belmatoug, N., Lesprit, P., Bru, J.-P., Therby, A., Bouhour, D., Dénes, E., Debard, A., Chirouze, C., Fèvre, K., Dupon, M., Aegerter, P., Mulleman, D., 2015. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. Lancet 385 (9971), 875–882.
von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., 2014. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. Int. J. Surg. 12 (12), 1495–1499.
Berbari, E.F., Kanj, S.S., Kowalski, T.J., et al., 2015. 2015 IDSA Clinical Practice Guidelines Native Vertebral Osteomyelitis in Adults. Clin. Infect. Dis. 61, e26–e46.
Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R., 1987. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J. Chronic Dis. 40 (5), 373–383.
Skaf, G.S., Domloj, N.T., Fehlings, M.G., Bouclaous, C.H., Sabbagh, A.S., Kanafani, Z.A., Kanj, S.S., 2010. Pyogenic spondylodiscitis: An overview. J. Infect. Public Health 3 (1), 5–16.

D'Agostino, C., Scorzolini, L., Massetti, A.P., Carnevalini, M., d'Ettorre, G., Venditti, M., Vullo, V., Orsi, G.B., 2010. A Seven-Year Prospective Study on Spondylodiscitis: Epidemiological and Microbiological Features. Infection 38 (2), 102–107.

Dudareva, M., Hotchen, A.J., Ferguson, J., Hodgson, S., Scarborough, M., Atkins, B.L., McNally, M.A., 2019. The microbiology of chronic osteomyelitis: Changes over ten years. J. Infect. 79 (3), 189–198.

Habib, G., Lancellotti, P., Erba, P.-A., et al. The ESC-EORP EURO-ENDO (European Infective Endocarditis) registry. Eur. Hear. J. – Qual. Care Clin. Outcomes 2019; 5: 202–207.