

## Clinical results of linezolid in arthroplasty and trauma MRSA related infections

James Joel, Simon Matthew Graham, Adam Peckham-Cooper, Nectarios Korres, Helen Tsouchnica, Eleftherios Tsiridis

James Joel, Adam Peckham-Cooper, Academic Orthopaedic and Trauma Unit, Leeds Teaching Hospitals, Leeds School of Medicine, Leeds LS1 3EX, United Kingdom

Simon Matthew Graham, Royal Liverpool University Hospital, Liverpool L7 8XP, United Kingdom

Nectarios Korres, Helen Tsouchnica, Eleftherios Tsiridis, Academic Orthopaedics and Trauma Unit, Division of Surgery, Aristotle University Medical School, University Campus, 54 124 Thessaloniki, Greece

Author contributions: Joel J, Graham SM and Peckham-Cooper A contributed equally to this work in designing, writing and editing the paper; Korres N and Tsouchnica H assisted with the data collection; Tsiridis E designed the study and oversaw all areas of data collection and writing up of the paper.

Correspondence to: Eleftherios Tsiridis, MD, MSc, DMed, PhD, FRCS, Associate Professor of Orthopaedics and Trauma, Academic Orthopaedic and Trauma Unit, Division of Surgery, Aristotle University Medical School, University Campus, Kiriakidi 1, 54 124 Thessaloniki, Greece. [etsiridis@doctors.org.uk](mailto:etsiridis@doctors.org.uk)  
Telephone: +30-210-3620666 Fax: +30-210-3620666

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**RESULTS:** Infections were classified as post arthroplasty ( $n = 10$ ), post trauma surgery ( $n = 8$ ) or non-trauma related infections ( $n = 4$ ). Twenty patients (91%) underwent surgical intervention as part of their treatment. The number of required surgical procedures ranged from 1 to 6 (mean = 2.56). Mean total length of stay per admission was 28.5 d (range 1-160 d). Furthermore, the mean duration of treatment with linezolid of patients who had resolution of symptoms was 31 d (range 10-84 d). All patients within this group were discharged on oral linezolid. Pathogens isolated included methicillin resistant *Staphylococcus aureus*, coagulase negative staphylococci, coliforms, enterococcus, *Staphylococcus epidermidis*, *Streptococcus viridans*, *Escherichia coli*, group B streptococcus and pseudomonas. An overall 77% of patients demonstrated resolution of infections at follow-up, with mean C-reactive protein reducing from 123 mg/L to 13.2 mg/L.

**CONCLUSION:** This study demonstrates that the use of linezolid offers excellent efficacy in orthopaedic related infections when used alongside appropriate surgical management.

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**Key words:** Antibiotic resistance; Linezolid; Orthopaedic infections; Osteomyelitis; Periprosthetic joint infection

**Core tip:** Our study demonstrates that linezolid delivers excellent oral bioavailability, with good penetration into bone, joints and soft tissue. It exhibits action against gram-positive organisms, including methicillin resistant *Staphylococcus aureus* and vancomycin resistant enterococci, and it is ideally suited for the variety of infections encountered in orthopaedic practice. Used in conjunction with surgical management, excellent results can be achieved in resolving infection.

### Abstract

**AIM:** To analyse the management of patients treated with linezolid for orthopaedic infections.

**METHODS:** Twenty-two patients with orthopaedic related infections receiving a course of linezolid were reviewed retrospectively. Patients were classified into either post trauma, post arthroplasty and non trauma related infections. A diagnosis of infection was based on clinical findings, positive microbiological specimens, and positive signs of infection on radiological imaging and raised inflammatory markers. Pathogens isolated, inflammatory markers both at presentation and at final follow up, length of linezolid treatment, adverse drug reactions, concomitant anti-microbial therapy, length of hospital stay and any surgical interventions were recorded.

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## INTRODUCTION

Infections encountered in trauma surgery and implant related infection in arthroplasty, present a complex therapeutic challenge. Gram-positive organisms, particularly staphylococci and streptococci, are responsible for the majority of these infections encountered in orthopaedic practice in the United Kingdom and United States<sup>[1,2]</sup>. These infections can be notoriously difficult to treat, often requiring lengthy courses of anti-microbial therapy coupled with extensive surgical intervention.

The emergence of antibiotic resistant strains has led to increasing challenges for current management of these infections. In the United States, methicillin resistant *Staphylococcus aureus* (MRSA) now represents 60% of *Staphylococcus aureus* (*S. aureus*) nosocomial infections (CDC 2004)<sup>[3]</sup>. The incidence of MRSA bacteraemia increased from 2% in 1989 to 34% in 1998 in the United Kingdom, but since 2006 there has been a general decline in the incidence of MRSA in the United Kingdom<sup>[4,5]</sup>. Glycopeptide antibiotics, which include vancomycin and teicoplanin, are generally used for treatment in these cases. Use of these agents involves intravenous administration for protracted periods of time usually via a central or a peripherally inserted central catheter (PICC). This factor and the lack of suitable oral alternatives can equate to lengthy inpatient admissions for the treatment of orthopaedic related infections. Additionally, there are increasing concerns over the emergence of glycopeptide resistance in the Gram-positive organisms responsible.

Linezolid is a synthetic antibiotic possessing a novel mode of action, inhibiting bacterial protein synthesis via inhibition of the 50S ribosomal subunit. This blocks the formation of the initiation complex with mRNA and tRNA thus inhibiting bacterial replication<sup>[6]</sup>. Oral administration results in 100% bioavailability and thus, oral and parental administration of the drug are bioequivalent. The drug has a favourable pharmacokinetic profile and has been demonstrated to penetrate in high concentrations in osteo-articular tissues<sup>[7]</sup>. It also has excellent activity against Gram positive bacteria with resistance to beta lactams and glycopeptides<sup>[8]</sup>.

The characteristics of linezolid make it potentially an extremely appealing agent for the treatment of infections encountered in orthopaedic practise. The possibility of an effective oral treatment carries favourable cost saving implications for health care systems. It is estimated that use of outpatient linezolid for prolonged treatment in orthopaedic infection could be considerably less expensive than inpatient glycopeptide therapy<sup>[9]</sup>. Studies support reduction in patient stays of up to 8 d less when treated

with linezolid in comparison to vancomycin. This potentially equates to a cost saving of up to £4800 per patient requiring treatment for orthopaedic related infection.

There are, however, concerns surrounding the tolerability of the drug and particularly in regard to bone marrow suppression. This has been observed with prolonged administration, and requires patients to be carefully monitored whilst undergoing treatment<sup>[10]</sup>.

Although the efficacy of linezolid has been well demonstrated in nosocomial pneumonia, bacteraemia, skin and soft tissue infections there is limited data supporting its use in complex orthopaedic infections. The aims of this study were to identify patients treated with linezolid for orthopaedic infection and evaluate its efficacy and tolerability.

## MATERIALS AND METHODS

This was a retrospective, non-randomised observational study of patients with orthopaedic related infection treated with oral linezolid from April 2005 to June 2007 in a University Hospital covering a population of 1.5 million.

Patients were selected from the hospital data base using clinical coding related to orthopaedic infections, which included infected joint arthroplasty, infection related to fracture fixation, septic arthritis soft tissue or spinal infection. ICD 10 codes used to identify relevant patients included: infection or inflammatory reaction due to other internal prosthetic orthopaedic device/implant graft (T847); infection and or inflammatory reaction due to internal joint prosthesis (T845); infection and or inflammatory reaction due to internal fixation of any device (T846); and the ICD 10 code specific for MRSA infection (B956). In all patients treated with oral linezolid therapy, treatment was initiated following a multi-disciplinary decision and prescribed and monitored with the involvement of medical microbiologist advice. Fifteen patients were initially started with parenteral vancomycin therapy prior to commencement of linezolid when patients were discharged from hospital. The other cases were treated initially with a variety of intravenous antibiotics (rifampicin, cefuroxime and flucloxacillin) based on initial microbiology advice prior to oral linezolid commencement on discharge.

Data regarding patients' concurrent medical history were collected. These included diabetes, nicotine use, alcoholism, vascular disease, systemic inflammatory disease, immunosuppressive drugs and pulmonary disease. Diagnosis of infection was based on a combination of clinical findings, including positive microbiology cultures, and radiographic, biochemical, and haematological signs of infection. Clinical symptoms considered were pain, local warmth, erythema, discharge and tenderness. Objective radiological signs included evidence of osteomyelitis or loosening of the prosthesis on plain X-ray. Laboratory indicators included elevated C-reactive protein (CRP) > 10 mg/L, erythrocyte sedimentation rate (ESR) > 30 mm per hour<sup>[11]</sup>, leucocytosis/leucopenia, and neutrophilia/neutropenia<sup>[11]</sup>. All patients were categorised as having infection following arthroplasty surgery, post trauma

surgery of non trauma bone and/or soft tissue infection. Outcome data collected for review include pathogens isolated, the index procedure, number and nature of surgical interventions required, length of linezolid treatment, use of concomitant antibiotics and duration of treatment, length of hospital stay, adverse reactions to linezolid use, serial biochemical data when available and outcome at follow-up.

Outcome of treatment was classified as successful if no subjective and objective signs of infection were documented at follow up. Cases were considered as unsuccessful if there was evidence of clinical, biochemical or radiological recurrence of infection.

## RESULTS

A total of 22 patients were identified (14 males, 8 females), with an age range of 20 to 86 years (mean age 60.4 years). Infections were classified as post arthroplasty ( $n = 10$ ), post trauma surgery ( $n = 8$ ) or non-trauma related infections ( $n = 4$ ). Non-trauma related infections included infected pre-patella bursitis, 2 cases of L4-5 discitis, L4-5 osteomyelitis, and septic mono-arthritis. 50% of patients were found to have risk factors for infection.

Pathogens identified included MRSA ( $n = 9$ ), coagulase negative staphylococci ( $n = 8$ ), coliforms ( $n = 3$ ) and enterococcus ( $n = 2$ ). Six of the patients had multi-organism infection. In one case no organism was identified despite prolonged culturing of tissue samples and treatment was thus started empirically after discussion with microbiology.

Twenty patients (91%) underwent surgical intervention as part of their treatment. The number of required surgical procedures ranged from 1 to 6 (mean = 2.56) (Table 1). These procedures varied from washout and debridement, removal of metal work and revision surgery.

The mean number of hospital admissions within this group was 1.5 (range 1-6). Mean total length of stay per admission was 28.5 d (range 1-160 d). Mean duration of treatment with linezolid of patients who had resolution of symptoms was 31 d (range 10-84). All patients within this group were discharged on oral linezolid. All previous and concurrent antimicrobial treatment is described in Table 1. Length of follow up for this group ranged from 3 to 57 mo (mean = 28).

Three patients suffered an adverse reaction to linezolid. One patient complained of nausea and vomiting (patient 15), another of visual disturbances (patient 20) and in one instance linezolid treatment was stopped due to thrombocytopenia (patient 16). Two patients died (patient 14, 16) as a sequela of sepsis. Infection resolved in patient 20, but in patients 15, 19 and 21 treatment failed to clear the infection and patients were re-admitted. Their infection subsequently resolved but this was after discontinuing linezolid. The reasons behind these failures are not clear. This resulted in a readmission rate of 13% (3/22).

Resolution of infection was diagnosed clinically by

absence of local and systemic signs and symptoms of infection, alongside radiological and biochemical assessment. Resolution of infection occurred in 17 (77.27%) of all patients at 3-57 mo, with a significant reduction in CRP in all cases. Mean initial CRP was 123 mg/L (range 21-301), with a mean of 13.2 mg/L at resolution of treatment (range < 5-54) (Table 1). The patients were followed up for a mean of 5 years after infection occurred.

## DISCUSSION

Linezolid acts by binding to the 50s ribosomal subunit inhibiting bacterial protein synthesis. It belongs to the oxazolidinone family and demonstrates excellent action against gram-positive bacteria<sup>[6]</sup>. Furthermore, linezolid exhibits excellent penetration into bone and periarticular structures making it suitable for use in orthopaedic related infection<sup>[12]</sup>. Our study clearly demonstrates good results with the use of linezolid to treat orthopaedic related infections, with a resolution of infection in 77% of all patients at 3-57 mo. Additional studies in the literature support our finding, with resolution of infection in up to 90% of patients<sup>[10,13]</sup>.

Infection following joint arthroplasty is a disastrous complication with treatment notoriously difficult. The development of a glycocalyx biofilm layer on implants confers protection to pathogens and thus requires a two-pronged treatment strategy of chemotherapy and surgery. Studies have demonstrated 80%-100% resolution rates in patients treated for infected hip and knee joint arthroplasty with linezolid<sup>[14,15]</sup>. Ten patients in this series who had infections post arthroplasty insertion, 8 (80%) had resolution of infection. Of the two treatment failures, one individual (patient 21) did not tolerate the drug developing nausea and vomiting. This patient received long-term suppressive flucloxacillin as an alternative. The second treatment failure has ongoing symptoms (patient 16). This patient underwent single stage revision for infection. A two-stage procedure allows for the delivery of local therapeutic levels of antibiotics to the surrounding bone and soft tissues whilst systemic treatment is delivered. This method is thought to represent the most efficacious treatment for clearing infection and allowing for revision of the implant, especially in the presence of resistant organisms<sup>[16,17]</sup>.

Risk factors for infection in post trauma patients are secondary to an inadequate initial debridement, presence of prosthetic material in the wound, degree of devitalisation and contamination of soft tissues, and in chronic situations the length of time infection is present. Furthermore patient risk factors resulting in immunosuppression are significant. Ideally all diseased bone should be removed at the earliest opportunity and a radical debridement should be conducted. Following debridement revascularisation of adult bone takes 3-4 wk and this period of time will adversely affect antibiotic activity<sup>[1]</sup>. 87.5% (7 out of 8) of patients in the post trauma infection group had resolution of infection following treatment with

**Table 1 Summary of patient management**

Patient number	Age, yr	Sex	Organism	Category	CRP (Initial/final)	Surgical intervention	Number of surgical procedures	Linezolid duration (d)	Concurrent antibiotics	Previous antibiotics prior to linezolid	Follow-up (mo)	Resolution
1	43	M	MRSA	Post Trauma	301/< 5	Yes	2	14	Rifampicin	Vancomycin	57	Yes
2	47	F	MRSA	Non Trauma	148/9.8	Yes	2	28	No	Vancomycin Clarithromycin	3	Yes
3	43	M	MRSA	Non Trauma	235/9.8	No	0	84	No	N	14	Yes
4	80	F	Coag neg staph	Arthroplasty	30/< 5	Yes	2	28	No	Vancomycin	33	Yes
5	81	F	Coag Neg staph	Arthroplasty	134/39	Yes	1	42	Rifampicin	Vancomycin	25	Yes
6	20	M	MRSA	Post Trauma	146/< 5	Yes	5	28	No	Flucloxacillin Vancomycin Rifampicin	23	Yes
7	52	F	Staph aureus Pseudomonas	Arthroplasty	133/54	Yes	3	28	No	Vancomycin Clindamycin	41	Yes
8	79	M	Staph epidermidis Coag Neg staph Coliforms	Arthroplasty	153/15.5	Yes	2	28	Rifampicin	Vancomycin	20	Yes
9	73	F	Coag Neg staph	Arthroplasty	106/46	Yes	2	28	No	Vancomycin Rifampicin	24	Yes
10	45	M	None identified	Post Trauma	129/< 5	Yes	2	28	No	Vancomycin	36	Yes
11	48	M	Coag Neg staph Strep viridians Coliforms Acro Xylo	Arthroplasty	79/15	Yes	6	28	No	Vancomycin	41	Yes
12	43	M	MRSA	Post Trauma	72/< 5	Yes	1	28	No	None	24	Yes
13	63	F	Staph aureus	Post Trauma	Sep-63	Yes	1	70	No	Vancomycin	6	Yes
14	47	M	MRSA	Post Trauma	124/12	Yes	4	42	No	Vancomycin	19	No
15	64	F	Staph aureus <i>E. coli</i> Enterococcus	Non Trauma	155/5.5	No	0	8	No	Vancomycin	RIP	No
16	83	F	Enterococcus	Arthroplasty	21/18.6	Yes	1	21	No	Vancomycin	39	No
17	73	M	Coag neg staph	Arthroplasty	68/< 5	Yes	1	28	No	Vancomycin	50	Yes
18	68	M	MRSA Group B strep	Post Trauma	91/< 5	Yes	1	28	No	Vancomycin	18	Yes
19	77	M	MRSA Coliforms Gram negative bacillus	Arthroplasty	65/62	Yes	4	28	No	Vancomycin	47	No
20	86	M	MRSA	Non Trauma	155/26	Yes	2	10	No	Vancomycin Rifampicin	6	Yes
21	79	M	Coag Neg staph	Arthroplasty	29/5	Yes	3	42	No	Vancomycin Rifampicin	22	No
22	35	M	Coag Neg staph	Post Trauma	64/< 5	Yes	3	42	No	Vancomycin	45	Yes

F: Female; M: male; MRSA: Methicillin resistant Staphylococcus aureus; CRP: C-reactive protein.

linezolid. All patients within this group underwent surgical intervention as part of their management. The single patient within this group (patient 14), who failed treatment, had initial resolution of symptoms but returned 9 months later with recurrence and thus was regarded as a treatment failure. Surgical debridement in prosthetic related orthopaedic infection is of paramount importance in trying to eradicate infection. The production of the glycocalyx biofilm can act as a protective colony for MRSA thus increasing difficulty in eradication where orthopaedic implants may be *in-situ*<sup>[18]</sup>. This therefore ne-

cessitates the use of debridement and implant removal<sup>[18]</sup>. Studies have demonstrated that debridement alone with retention of prosthetic material in MRSA infection following total knee arthroplasty has a high failure rate<sup>[19]</sup>. Ninety one percent of patients in our cohort underwent at least one surgical procedure alongside combined chemotherapy in an attempt to eradicate the infection. All of these patients using the outlined strategy were successful. The use of combined surgical and chemotherapeutic regimens as demonstrated in this study should be used in combination for the highest chance of success.

The final group reviewed were the patients with non-trauma related infection. The use of linezolid in spinal surgery is less well documented. A study evaluating antibiotic penetration in a rabbit spine model suggests that linezolid is inadequate for the treatment of spinal infection limited to the intervertebral disc, but may be effective for the treatment of infection extending into the muscle and bone marrow, such as in vertebral osteomyelitis, iliopsoas abscess, and postsurgical infection. Three cases (75%) in this series were successfully treated with linezolid<sup>[20]</sup>. The patient with treatment failure in this group (patient 15) developed an L4/5 osteomyelitis with associated psoas abscess and died related to a sequelae of sepsis.

Linezolid has 100% oral bioavailability<sup>[21]</sup>. Oral administration avoids the morbidity associated with intravenous access and line sepsis and the cost of insertion and monitoring of these devices. This may aid in shortening patient stay, as traditionally these patients have required lengthy admissions for parenteral antibiotics. This potentially has major cost implications for health care systems. However, this must be offset by the need to undertake more outpatient follow-up appointments and the fact regular blood tests need to be undertaken to monitor for myelosuppression. Welshman *et al*<sup>[22]</sup> demonstrated statistically significant reduction in length of in-patient stay with MRSA soft tissue infection in patients treated with linezolid as opposed to vancomycin. Further studies have also demonstrated reduction of length of hospital stay in patients with MRSA treated with linezolid<sup>[19,23]</sup>.

*Staphylococcus aureus* is the single most common organism causing osteomyelitis secondary to trauma, surgery or insertion of a joint<sup>[24]</sup>. Chronic infection is notoriously difficult to treat. The relatively high failure rate of antibiotic treatment alone in bone infection is well documented<sup>[25]</sup>. Use of linezolid, along with appropriate surgical management, has been shown to be efficacious. Vercillo *et al*<sup>[26]</sup> demonstrated no recurrence of infection at a minimum of 6 mo follow up in a group of 14 patients with implant related chronic osteomyelitis. Similarly, Rao *et al*<sup>[27]</sup> prospectively monitored 11 patients who received linezolid for osteomyelitis for a mean 27 mo. The entire group had remission demonstrated by clinical, biochemical and radiographic markers<sup>[27]</sup>. The most common causative organisms encountered in this study were predominantly gram-positive organisms, the most common being MRSA.

Only 3 of the patients in our study group were treated with an additional antibiotic as well as linezolid. In all cases this was oral rifampicin. Resistance rates to linezolid have been reported to be low<sup>[28]</sup>. Linezolid resistance occurred in < 1% of *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci isolates from the US between 2002 and 2009<sup>[29]</sup>. Resistance usually develops after prolonged therapy with linezolid for serious infection although nosocomial acquisition of both resistant enterococci has been reported, including cases in patients with no prior treatment with linezolid<sup>[30-32]</sup>. It has been proposed that a combination with a second antibacterial

agent, particularly rifampicin or fusidic acid, may delay the emergence of linezolid resistance in *Staphylococcus aureus*<sup>[33]</sup>.

Adverse reactions to linezolid treatment are documented. Treatment has been associated with myelosuppression, with reports of anaemia, leucopenia and thrombocytopenia<sup>[15,34,35]</sup>. The side effects of treatment can be detected by close monitoring of blood with myelosuppression being reversible on stopping treatment<sup>[34]</sup>. In this series myelosuppression was observed in one case. The patient developed multi-organ dysfunction syndrome related to sepsis.

Other notable side effects include peripheral neuropathy<sup>[36]</sup>. A single patient within this study group developed a visual disturbance. Optic neuropathy secondary to linezolid has been described<sup>[14]</sup> and there are concerns that linezolid induced peripheral neuropathy may be an irreversible event<sup>[34,36]</sup>. Furthermore, there are several documented case reports of serotonin toxicity when linezolid is used with selective serotonin reuptake inhibitors<sup>[37]</sup>. The symptoms of serotonin syndrome are alteration of mental state, autonomic dysfunction, and neuromuscular disorders. None of our patients developed such symptoms; however it is important that surgeons and physicians are aware of the nonspecific presentation of serotonin symptoms and the treatment when using linezolid. Additionally, contraindications to commencing linezolid include patients taking any medicine which inhibits monoamine oxidases A or B (*e.g.*, phenelzine, isocarboxazid) or within two weeks of taking any such medicinal product. Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (*e.g.*, pseudoephedrine), vasopressive agents (*e.g.*, epinephrine, norepinephrine), dopaminergic agents (*e.g.*, dopamine, dobutamine).

Our study has a number of limitations. The patient group was highly heterogeneous and the numbers, as with many other studies, were relatively small. The lack of randomisation and a control further limits definitive conclusions. However, it does lend weight to the growing evidence of linezolid use in this group of patients with joint, bone and implant related infection.

In conclusion, linezolid delivers excellent oral bioavailability, with good penetration into bone, joints and soft tissue. It exhibits action against gram-positive organisms, including MRSA and vancomycin resistant enterococci, and it is ideally suited for the variety of infections encountered in orthopaedic practice. Used in conjunction with surgical management, excellent results can be achieved in resolving infection. It is generally well tolerated but regular monitoring of blood parameters is advisable. While haematological disturbance have been documented, these are generally shown to be transient and reversible in nature on cessation of treatment. Oral administration facilitates earlier hospital discharge, with

associated cost savings to health care systems. Prospective randomised controlled trials are required to further ascertain the role of linezolid in the treatment of orthopaedic related infection.

## COMMENTS

### Background

Infections encountered in trauma surgery and implant related infection in arthroplasty present a complex therapeutic challenge, often requiring lengthy courses of anti-microbial therapy coupled with extensive surgical intervention. Furthermore, the emergence of antibiotic resistant strains has led to increasing challenges for current management of these infections.

### Research frontiers

Linezolid is a synthetic antibiotic that when orally administered results in 100% bioavailability. The drug has a favourable pharmacokinetic profile and been demonstrated to penetrate in high concentrations in osteo-articular tissues. The characteristics of linezolid make it potentially an extremely appealing agent for the treatment of infections encountered in orthopaedic practice.

### Innovations and breakthroughs

Although the efficacy of linezolid has been well demonstrated in nosocomial pneumonia, bacteraemia, skin and soft tissue infections there is limited data supporting its use in complex orthopaedic infections.

### Applications

This study demonstrates that linezolid delivers excellent oral bioavailability, with good penetration into bone, joints and soft tissue. It exhibits action against gram-positive organisms, including methicillin resistant *Staphylococcus aureus* and vancomycin resistant enterococci, and it is ideally suited for the variety of infections encountered in orthopaedic practice. Used in conjunction with surgical management, excellent results can be achieved in resolving orthopaedic infections.

### Terminology

Arthroplasty is the insertion of a prosthetic joint into a patient. Following arthroplasty surgery and bone related injuries, people can potentially develop infections which are very difficult to treat. This study demonstrates that by using the antibiotic linezolid, these infections can be treated effectively. Since linezolid can be given as an oral tablet this results in a patient potentially spending less time in hospital being treated for these types of infections, which results in health care savings and is more convenient for patients

### Peer review

According to the authors "the aim of the present investigation was to identify patients treated with linezolid for orthopaedic infection and evaluate efficacy and tolerability". The authors state that "the results of this study support the use of linezolid, with a 77% resolution at 3-57 mo across all patient groups". It was concluded that the study demonstrates that use of linezolid offers excellent efficacy in orthopaedic related infections when used alongside appropriate surgical management. This is an interesting and important case series.

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