Spondylodiscitis by drug-multiresistant bacteria:

a single center experience of 25 cases

Shiban E, Janssen I, Monika Horanim, Wostrack M, Krieg S, Stoffel M

Meyer B, Ringel F

1 Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

2 Department of Neurosurgery, Helios Kliniken, Krefeld Germany

Address for correspondence:
Florian Ringel, MD
Department of Neurosurgery, Klinikum rechts der Isar
Technische Universität München
Ismaninger Str. 22
81675 Munich
Germany

Phone: +49 89 4140 2151
Fax: +49 89 4140 4889
E-mail: florian.ringel@lrz.tum.de

DISCLOSURE
The authors declare that they have no conflict of interest affecting this study. The study was completely financed by the Department of Neurosurgery.
Complete contact information:

Ehab Shiban, MD  ehab.shiban@lrz.tum.de
Insa Janssen, MD  insa.janssen@lrz.tum.de
Florian Ringel, MD  florian.ringel@lrz.tum.de
Maria Wostrack, MD  maria.wostrack@lrz.tum.de
Sandro Krieg, MD  sandro.krieg@lrz.tum.de
Bernhard Meyer, MD  bernhard.meyer@lrz.tum.de

Department of Neurosurgery, Klinikum rechts der Isar
Technische Universität München
Ismanninger Str. 22
81675 Munich
Germany
Phone: +49 89 4140 2151
Fax: +49 89 4140 4889

Michael Stoffel, MD  michael.stoffel@helios-kliniken.de

Department of Neurosurgery
Helios Klinikum Krefeld
Lutherplatz 40
47805 Krefeld
Phone: +49 2151 321320
Fax: +49 2151 322033
Abstract

Introduction

Though the incidence of pyogenic spinal infections is increasing the ideal treatment of spondylodiscitis is still a controversially discussed issue. Furthermore, the proportion of multiresistant bacteria in spondylodiscitis is increasing and treatment recommendations or reported results are missing for this specially difficult subset of patients.

Methods:

We performed a retrospective review of patients treated for a spondylodiscitis from multiresistant bacteria at our department between 2006 and 2011.

Results:

25 patients were identified (15 gram-positive and 10 gram-negative drug-multiresistant bacteria). The mean age at presentation was 66 years, 14 patients were male (56%). All patients presented with pain, a neurological deficit was present in 11 (44%) cases. An epidural abscess was found in 11 (44%) cases. Distribution of the inflammation: lumbar in 12 (48%), thoracic in 6 (24%) and cervical in 4 (16%) cases. 3 patients (12%) had two concomitant non-contiguous spondylodiscitis in different segments of the spine. At admission C-reactive protein (CRP) was elevated in all cases with a mean of 13 ± 9.2 mg/dl. Leukocyte count was elevated in 17 (68%) and fever was present in 9 (36%) cases. The main source of infection was previous spine surgery (44%). All patients in this series underwent surgical debridement of the infection and instrumentation of the spine. Postoperative intravenous antibiotics were administered for 19 ± 8.6 days followed by 3 ± 0.3 months of oral antibiotic therapy. Mean duration of hospital stay was 27 ± 13 days. One patient died three weeks postoperatively due to a fulminant endocarditis. Eradication of the infection was achieved ultimately in all surviving patients as documented by normalization of CRP and clinical
status. Out of 11 patients with neurological deficits, four had a full recovery, four improved incompletely and three remained unchanged after surgery.

**Conclusion:**

Staged surgical immobilization and instrumentation and optimal debridement at the interdiscal space and spinal canal is a reliable approach to achieve complete healing of spinal inflammation with multiresistant bacteria. A period of intravenous antibiotic therapy of 2-3 weeks followed by a three months oral antibiotic therapy seems appropriate for most cases.

**Key words**

Multiresistant bacteria, spondylodiscitis, discitis, surgical management, spinal instrumentation, interbody fusion
**Introduction**

Infections by multidrug resistant bacteria are a major public health problem and treatment options are declining with the emergence of more potent microbial agents (Arias 2009). Among the gram-positive organisms methicillin resistant staphylococcus aureus (MRSA) and glycopeptide resistant enterococci (VRE) represent the largest therapeutic obstacle. After the introduction of penicillin and thereafter methicillin, staphylococcus aureus rapidly developed resistance to the β-lactam compounds and by 2003 more than 50% of Staphylococcus aureus isolates recovered in U.S. hospitals were MRSA (Klevens 2006). The emergence of gram-negative multidrug-resistant organism is even more worrisome, since no new antibiotics are in advanced stages of clinical development.

Infections with these bacteria are an increasing problem that also involves the spine in form of a spondylodiscitis. The incidence of hematogenous spondylodiscitis including non-multiresistant bugs is increasing (Hadjipavlou 2000). The reason is probably multifactorial: an increasingly ageing population with an increasing incidence of chronic immuno-compromising diseases, more frequent operations of the spine, a greater use of invasive procedures and intravenous lines and the evolution in diagnostics (Jaramillo-de la Torre 2006, Tsiodras 2006). Moreover, the incidence of spondylodiscitis by multidrug-resistant bacteria is increasing which poses an additional treatment challenge. The clinical management of spondylodiscitis – surgical or conservative - varies and is still a controversial issue. To date there are no guidelines for surgical treatment or treatment strategies of pyogenic spinal infections by drug-multiresistant bacteria.
**Material and Methods:**

We performed a retrospective review of patients that underwent surgical treatment for spondylodiscitis by multiresistant bacteria between 2006 and 2011 at our department. 25 consecutive patients were identified and their data were retrospectively examined. Data were gathered through review of patients’ case notes, relevant imaging, and electronic patients’ records. MR imaging of the whole spine including Gd-enhanced T1 sequences were available for all cases. CT scans of the affected regions were available and evaluated for all cases in order to evaluate the extent of bony destruction. Patients were considered to have fever if their temperature was ≥ 38.5 °C. C-reactive protein (CRP) and complete blood cell count was analyzed in all cases using routine laboratory techniques. Neurological deficits were classified according to the ASIA impairment scale. The classification of drug-multiresistant gram-negative bacteria was performed according to the Robert Koch-Institute recommendation (Bundesgesundheitsbl 2012) and is summarized in Table 1.

For patients with neurological deficits the surgical debridement, decompression and stabilization accompanied with antibiotic therapy was strongly recommended. All other patients were advised about treatment options as conservative treatment with bedrest and subsequent mobilization in a brace or surgical debridement and stabilization each accompanied by initially intravenous and following oral antibiotic therapy. However, surgical treatment was recommended for these cases with multiresistant bacteria since outcome was expected to be superior after surgical debridement.

The surgical approach and method of spinal instrumentation was determined for each patient individually according to present comorbidities and extent of bony destruction. Options used were anterior cervical discectomy or corpectomy and fusion with or without dorsal instrumentation or dorsal instrumentation alone for patients with cervical spondylodiscitis. For patients with inflammation in the thoracolumbar spine options used were dorsal
instrumentation with or without interbody fusion. If technically feasible, interbody fusion was performed using a transforaminal approach from posterior and if not feasible then an anterior or anterolateral approach was subsequently selected. Antibiotic treatment included a short period of broad-spectrum intravenous antibiotic therapy followed by oral antibiotics for a period of approximately 3 months. Cure of inflammation was considered to be complete if patients showed no signs or symptoms of active localized infection by clinical examination and inflammatory blood markers after discontinuation of antibiotic treatment. Neurological outcomes mentioned are at a minimum of 3 months postoperative. Additional follow up at a minimum of 12 months was performed by a telephone interview.
Results

Patient characteristics

25 patients have been identified with spondylodiscitis from multiresistant bacteria while during the same period 136 patients with non-multiresistant bacterial spondylodiscitis were treated. Thereby, the proportion of multiresistant bacteria in our spondylodiscitis patients is 15.5% (25/161).

The median age at presentation was 66 years (range 42 - 90). Fourteen patients were male (56%). All patients presented with pain, a neurological deficit was present in 11 patients (44%). Five patients (20%) were referred to our department in a septic condition requiring catecholamines for hemodynamic insufficiency and three patients presented with an accompanying meningitis. Blood C-reactive protein (CRP) was elevated in all patients. Median CRP value upon admission was 12 ± 8.8 mg/dl. White cell count (WCC) was elevated in 17 patients (68%). In this group median WCC value at admission was 10 ± 3.8 G/l. Fever was diagnosed at admission in 9 patients (36%). Localization of the inflammation was lumbar in 12 (48%) and 19, thoracic in 6 (24%) and 6 and cervical in 4 (16%) cases and 5 segments, respectively. Three patients (12%) had two concomitant non-contiguous foci of spondylodiscitis in 8 segments of the spine. An epidural abscess was present in 9 patients (36%). The source of infection was identified in 24 (96%) of all cases. Causes were: prior surgery in 14 (56%) and of those elective spine surgery in 9 (64%) cases, ulcer secondary to diabetes mellitus in 4 (16%) cases and one case each of repetitive cervical injections, transurethral prostate biopsy, CT-guided lumbar biopsy, endocarditis, renal insufficiency and infection, diverticulitis and an anal fissure. In a single case the source of infection remained obscure. I.e. 64% were by direct inoculation, 36% hematogenous infections. While gram-negative bacteria were found in 7 (24%) cases, gram-positive were the cause in 18 (76%)(Tab.2).
Surgical treatment

The surgical approach was chosen for each patient depending on comorbidities, extent of bony destruction and sagittal alignment of the respective segments.

In cervical cases if the inflammation was located mostly anterior or posterior to the myelon then a ventral or a dorsal approach was used, respectively. If both areas or more than two segments were affected then 360-degree instrumentation was performed. In the thoracic and lumbar cases disc height guided the surgical approach. In cases without any destruction of the endplates and disc height reduction then dorsal instrumentation without interbody fusion was performed. Interbody fusion was performed if the height of the affected disc was normal or increased. If an interbody fusion from posterior was not possible, then interbody fusion was performed through a ventral approach. In the thoracic and lumbar cases, dorsal instrumentation alone was considered sufficient in 6 cases; additional interbody fusion from posterior was performed for 15 levels (9 autologous bone and 6 PEEK cages) in 11 patients and additional interbody fusion from ventral was performed in 9 levels (all titanium cages) in 8 patients. In cervical disease, ventral spondylodesis alone was performed in one cases (autologous bone from the iliac crest) and ventral plating, dorsal instrumentation alone in 3 cases and 360-degree instrumentation with PEEK cage and dorsal instrumentation in one case.

Bacteria identification and antibiotic therapy

After tissue asservation and prior to microbiological identification of the underlying bacteria a calculated antibiotic therapy was intravenously initiated. This therapy varied substantially, according to previous outside therapy initiation, suspected source of infection and
comorbidities. After microbiological identification of the underlying bacteria and results of an antibiogram the intravenous antibiotic treatment was adjusted accordingly.

10 patients were referred to our hospital following failed conservative treatment. 5 were known to harbor drug-multiresistant bacteria as apparent by either positive blood cultures (N=3) or by a biopsy from the source site (N=2). In one case (Num. 8) we performed a CT-guided biopsy initially for bacterial identification because the blood cultures were negative. The patient suffered from multiple comorbidities (>5) and had no abscess, neurological deficit or impending spinal instability. Therefore, surgery would be only recommended in the presents of drug multiresistant bacteria.

Initially most patients (n=12) received a dual antibiotic therapy, 11 a single agent antibiotic therapy and two a triple therapy (Figure 3). Alteration or addition of antibiotic agents during intravenous treatment was necessary in 14 (56%) cases. Most commonly used antibiotic agent was clindamycin (n=19), followed by vancomycin (n=9), linezolid (n=8), meropenem (n=6), 3rd generation cephalosporin (n=5), ciprofloxacin (n=5), and rifampicin (n=4).

Antibiotics were administered intravenously until clear signs of CRP decline as well as significant clinical improvement were seen. Postoperative intravenous antibiotic treatment was administered for a mean duration of 19 ± 8.6 days. It was always followed by an oral continuation of antibiotic treatment with a mean duration of 3 ± 0.2 months were a change of the antibiotic agent to an orally available drug was necessary. In four cases linezolid was the only effective oral antibiotic, therefore, the patients received it for 3 months under a strict follow-up regime including weekly physical examination and blood analysis and were instructed to visit an ophthalmologist if any visual disturbances should become noticeable.

Two of the patients developed diarrhea and linezolid was paused for one week but none of the patients developed any other serious side effects.
Infection resolution and outcome

Median CRP values significantly declined in all cases until discharge to $3.9 \pm 5.1$ mg/dl ($P<0.001$) (Figure 1). WCC was reduced at discharge to a median of $6.6 \pm 2.8$ G/l ($P=0.025$) (Figure 2). Fever resolved in all patients prior to discharge. Pain resolved in all cases. From the four patients with AISA D impairment, one had partial and three had a full recovery. From the four patients with AISA C impairment, two had partial and two had no recovery postoperatively. From the two patients with AISA B impairment, one had a partial recovery and the other was unchanged postoperatively. One Patient (Num. 4) suffered from a high-grade paresis of his left arm involving 3 nerve roots. He recovered fully postoperatively.

One 90-year-old female patient (Num. 9) died 3 weeks postoperatively due to a fulminant endocarditis. Spinal surgery was a prerequisite for further urgent cardiac surgery.

Eradication of the infection was achieved ultimately in all surviving patients as documented by normalization of CRP, clinical findings as a recurrence free course after discontinuation of the antibiotic treatment for all except one of the surviving patients. This patient (Num. 24) had a relapse of the inflammation at a different site one month following his first surgery. He underwent a second surgery and subsequent antibiotic treatment.

Ehab Shiban 11/10/13 21:02
Supprimé: posterior instrumentation, only. Therefore, this was followed by an anterior debridement and interbody fusion upon relapse and the patient finally recovered infection free.
Discussion

Spondylodiscitis by drug-multiresistant bacteria is hardly rare any more, MRSA spondylodiscitis accounts for 10-30% of all staphylococcus aureus spinal infections (Hadjipavlou 2000, Al-Nammari 2007) and more recently few case reports of gram-negative drug-multiresistant bacteria have also been published (Barton 2008, Neumayer 2009).

Similar to previous studies, the patient population in this study was mostly elderly and male. The association with the elderly is believed to be due to the higher incidence of comorbidities and compromised host defenses in this age group (Dufour 2005, Hopkinson 2001). Also in accordance to the literature, the distribution of the inflammation was mostly seen in the lumbar spine followed by the thoracic and cervical spine (Dufour 2005, Hopkinson 2001)

Amongst the inflammatory markers CRP was the most reliable in affirmation of the diagnosis as well as for monitoring response to treatment. CRP was elevated in all patients. Median CRP value upon admission was 12 ± 8.8 mg/dl and it significantly declined in all cases upon discharge to a mean of 3.9 ± 5.1 mg/dl (P<0.0001). WCC was not very reliable as it was elevated in only 11 patients (44%) with a mean of 10 ± 3.8 G/l and declined at discharge to a median of 6.6 ± 2.8 G/l (P=0.025). Immunocompromised patients and those over 60 years are more likely to have normal WCC (Carragee 1997). Erythrocyte blood sedimentation rates were not assessed in this cohort of patients which certainly is a limitation.

Clinical findings of spondylodiscitis are often very vague. However, back or neck pain is very common but could be absent in up to 15% of cases (Sakkas 2009). Fever is not frequently experienced and occurs in only 20-50% of cases (Mylona 2009). In this series 24 patients (96%) presented with pain, fever was diagnosed at admission in 7 patients (28%) and resolved in all cases prior to discharge. Similar to other studies neurological deficits were found in 36% of cases and were more likely to be present with epidural abscess or delayed diagnosis (Pigrau 2005).
To date there are no guidelines for the best treatment modality for spondylodiszitis. The traditional conservative method includes external immobilization by orthosis or bed rest with a long duration of intravenous antibiotic administration and analgesics (Krodel 1989, Sindern 1993, Quinones-Hinojoa 2004). However, prolonged immobilization by bed rest could lead to complications like deep vein thrombosis, pulmonary embolism, muscle atrophy and hypostatic pneumonia. Also prolonged immobilization obviously leads to extended hospital stay and significant loss of productivity. Clinical success does not occur in all patients following conservative treatment (Przybylski 2001, Hanaoka 2006) and might leads to spinal instability, progressive kyphotic deformity, instability related chronic pain and neurologic deficit (Przybylski 2001).

The surgical approach and method of spinal instrumentation was determined for each patient individually according to present comorbidities and extent of bony destruction. In cervical cases the location of the inflammation dictated the surgical approach. If the inflammation was located mostly anterior or posterior to the myelon then an anterior or posterior approach was used, respectively. If both areas or more than two segments were affected a 360-degree instrumentation was applied. In cases of thoracic or lumbar infections without any destruction of the endplates with a disc height reduction posterior stabilization without interbody fusion was performed. Interbody fusion was performed if the height of the affected disc was normal or increased. If an interbody fusion from posterior was not possible due to massive destruction of the bony structures, an anterior interbody fusion was performed either through an extreme lateral or an anterior approach. Staged surgery was needed in 28% and 25% in the thoracolumbar and cervical cases, respectively.

Satisfactory clearance of the infected disc tissue addresses the key issue of spinal infection. Tissue samples obtained for culture enables identification of the causative organism so that organism specific antibiotics can be initiated. Furthermore, early surgical debridement is
recommended to reduce the bacterial load and thereby increase the antibiotic efficacy and reduces the risk of drug-resistant formation (van Hal 2011).

Use of instrumentation in treating spinal infections has been a subject of intense debate. Several authors have expressed concern over the use of foreign body implant at the site of active infection (Eysel 1997, Faraj 2000, Fang 1994, McGuire 1994, Carragee 1997). Bacteria tend to heavily colonize stainless steel and polymethyl-methacylate, thereby reducing antibiotic effectiveness. However titanium is less prone to bacterial adherence (Chang 1994). Also, recent studies showed excellent result with PEEK Cages (Pee YH 2008, Mondorf Y 2009, Brase A 2010, Walter J 2010). The material used for fusion seems to be less important as there are no differences in clinical (pain, functional disability) or imaging outcome (correction of segmental lordosis and fusion rate) (Pee 2008).

There are no standard guidelines or recommendations on the duration of intravenous antibiotic administration or on the total duration of antibiotic therapy. Duration of intravenous antibiotics administered varied from two to eight weeks in different series (Mann 2004, Deininger 2009, Hanaoka 2006, Przybylski 2001, Pee 2008, Priest 2005, Jensen 1998). The duration of oral antibiotics administered ranges from 6 weeks to 3 months (Pee 2008, Deininger 2009, Hanaoka 2006, Mann 2004). There is a general consensus on discontinuing long term oral antibiotics only after normalisation of ESR, CRP and leucocyte count (Mann 2004, Pee 2008, Heyde 2006, Hanaoka 2006). In this study postoperative intravenous antibiotics were administered for a relatively short period of 16 ± 8 days followed by 3 ± 0.7 months of oral antibiotics. Oral antibiotics were administered as soon as CRP significantly declined and clinical symptoms started to resolve. Prolonged oral antibiotic administration harbors risks of substantial complications. Within the maximum allowed treatment duration
of 28 days (as presently recommended), linezolid has a favorable safety profile (Moellering 2003, Bressler 2004). However, when linezolid treatment is prolonged anemia and thrombocytopenia are common. Sparse cases of neuritis (including optic nerve neuritis) and lactic acidosis were also anecdotally reported (Nasrawy 2003, Kopterides 2005, Moellering 2003, Bressler 2004). In this study linezolid was the only effective oral antibiotic in four cases, therefore, the patients received it further for 3 months but were under strict supervision with weekly physical examination and blood analysis and were instructed to visit an ophthalmologist if any visual disturbances should become noticeable. Two of the patients developed diarrhea and linezolid was paused for one week but none of the patients developed any serious side effects.

Using such an algorithm of staged surgical approach if needed and short-term postoperative intravenous antibiotics followed by 3 months of oral antibiotics, complete healing of the inflammation was ultimately achieved in all surviving patients. One patient had a relapse of the inflammation at a different site one month after the initial surgery. At one year, none of the patients suffered from a recurrence. This is much lower than in other series that report recurrence rates of 2% - 10% in spondylodiscitis overall and up to 29% in drug-multiresistant spondylodiscitis (Al-Nammari 2007). The reasons for absence of recurrence in our series even in drug-multiresistant bacteria cannot be fully explained by this retrospective and non-comparative study. However, the duration of antibiotics administration in our series is much longer than in other studies with a postoperative obligatory 3 months antibiotics administration.
Conclusion

Our results show that the surgical treatment of spondylodiscitis with a staged surgical approach and a short period of intravenous antibiotics of 2-3 weeks is followed by 3 months of oral antibiotics is appropriate in most cases of infections with multiresistant bacteria. Early surgery avoids the complications of prolonged immobilization and shortens the duration of intravenous antibiotic therapy thereby avoiding the complications of prolonged antibiotic therapy and may reduce drug-resistant formation. The choice of fusion material (autologous bone, Titanium, PEEK) seems less important. Rapid immobilization leads to shorter hospital stay and early return to productive activity.
References


Figure Legend:

Figure 1
Diagram showing C-reactive protein (CRP) levels throughout the hospital stay. CRP was elevated in all cases. Median CRP value upon admission was 14.5 ± 8.8 mg/dl and it significantly declined in all cases upon discharge to a median of 6.4 ± 5.1 mg/dl (P<0.0001)

Figure 2
Diagram showing white cell count (WCC) levels throughout the hospital stay. WCC was elevated in 11 patients (44%). Median WCC value of those patients at admission was 12 ± 2.4 G/l and it was reduced at discharge to a median of 8.3 ± 2.6 G/l (P=0.025)

Figure 3
Summary of antibiotics used.