Eur Spine J (2006) 15:1397–1403
DOI 10.1007/s00586-006-0144-6

ORIGINAL ARTICLE

Preventing and treating discitis: cephazolin penetration in ovine lumbar intervertebral disc

Rebecca Walters · Razmi Rahmat · Robert Fraser · Robert Moore

Received: 4 August 2005 / Revised: 22 January 2006 / Accepted: 27 April 2006 / Published online: 8 July 2006

Abstract Infection can occur after any spinal procedure that violates the disc and although it is not common, the potential consequences are serious. Treatment of discitis is not always successful and the key to management is prevention. Intradiscal prophylaxis with antibiotic is routinely used in spinal surgery, but there is a limited understanding of how well antibiotics can enter the avascular disc after intravenous injection. An in vivo ovine study to optimise prophylactic and parenteral treatment of discitis is described to assess the effectiveness of cephazolin in preventing and treating infection. The concentration of cephazolin was measured in disc tissue from normal and degenerate sheep discs to determine if cephazolin can enter the disc and if disc degeneration affects antibiotic uptake. Fourteen sheep were deliberately inoculated with bacteria to induce discitis. Eight sheep (''prophylaxis'' group) were given either a 0, 1, 2 or 3 g dose of prophylactic cephazolin before inoculation while the remaining sheep (''treatment'' group) were treated with cephazolin commencing 7 days after inoculation for 21 days at a dose of 50 mg/kg/day. Histopathology and radiography were used to assess the effect of the different treatments. Cephazolin was given 30 min prior to sacrifice and the intradiscal concentration was measured by biochemistry. In the ''prophylaxis'' group all doses of antibiotic provided some protection against infection, although it was not dose dependent. In the ''treatment'' group discitis was confirmed radiologically and histologically in all animals from 2 weeks onwards. Biochemical assay confirmed that antibiotic is distributed throughout the disc but was present in higher concentration in the anulus fibrosus than the nucleus pulposus. This study demonstrated that whilst the incidence of iatrogenic discitis can be reduced by antibiotic prophylaxis, it could not be abolished in all incidences with a broad-spectrum antibiotic such as cephazolin. Furthermore, antibiotics were ineffective at preventing endplate destruction once an intradiscal inoculum was established.

Keywords Cephazolin · Discitis · Prophylaxis · Treatment · Intervertebral disc

Declaration: The experiments comply with the current laws of Australia including ethics approval for the use of animals in research. Ethical approval was obtained for all animal studies from the Animal Ethics Committee, Veterinary Research Division of the Institute of Medical and Veterinary Science.

R. Walters (✉) · R. Rahmat · R. Moore
Institute of Medical and Veterinary Science,
The Adelaide Centre for Spinal Research,
Adelaide, P.O. Box 14, Rundle Mall, SA 5000, Australia
e-mail: rebecca.walters@adelaide.edu.au

R. Walters · R. Moore
Department of Pathology, The University of Adelaide,
Adelaide, SA, Australia

R. Fraser
Royal Adelaide Hospital, Spinal Unit, Adelaide,
SA, Australia

Introduction

While iatrogenic discitis was once considered to be an aseptic condition there is now evidence that it results from the inadvertent introduction of bacteria during procedures that penetrate the intervertebral disc [2, 17]. Infecting organisms initiate a sequence of inflammatory reactions that eventually lead to

endplate destruction. In most cases the bacteria are eradicated once the endplate is breached, but on some occasions secondary osteomyelitis develops in the vertebral body.

The development in adults of 'spontaneous' discitis is usually secondary to infection of the vertebral body following bacteraemia, which is associated with advanced age, intravenous (IV) drug abuse, IV contamination, urinary tract infection and immunocompromised states. In children, 'spontaneous' primary discitis may result from blood-borne organisms penetrating the vascular immature disc or it may be secondary to infection seeded in the vascular endplate.

Iatrogenic discitis presents within a few days or weeks of an intradiscal procedure, with back pain that is often severe and accompanied by muscle spasms. The erythrocyte sedimentation rate and creatinine reactive protein (CRP) are usually elevated whilst the white cell count is either normal or marginally elevated. Radiological changes in discitis include narrowing of the disc space, erosion of the endplates and in the later stages vertebral sclerosis. Imaging techniques to identify endplate changes include magnetic resonance imaging (MRI), gallium scanning and helical computerised tomography with sagittal and coronal reformatted images.

The basis for the conservative management of discitis is pain control and an appropriate antibiotic regime. Isolation of the organism (if possible) should be used to guide the choice of antibiotic. Treatment may be prolonged and costly with the possible development of epidural abscess and paralysis. For cases that fail to respond to conservative treatment debridement of necrotic tissue followed by reconstruction should be performed and interbody fusion with a bone graft or posterior stabilisation procedures may be indicated.

At our institution prophylactic antibiotics are routinely administered to reduce the incidence of iatrogenic infection in spinal surgery. Cephazolin sodium is effective against common bacteria such as *Staphylococcus* spp., *Streptococcus* spp. *and Klebsiella* spp. while also providing broad cover against less common organisms. It is given to all patients at the commencement of spinal surgery as a 1–2 g dose depending on body mass. The treatment of established disc and bone infection includes a course of intravenously administered organism-specific antibiotic followed by long-term oral antibiotic. Sometimes cephazolin is used for parenteral treatment of disc and bone infections caused by *Staphylococcus aureus*. In moderate or severe infections the usual adult dosage is 500 mg to 1 g of cephazolin every 6 to 8 h (approximately 50 mg/kg/day). CRP is the most sensitive clinical laboratory marker of treatment response [13].

There are few studies that assess the efficacy of cephazolin in the prevention and treatment of disc space infection. Further there is a lack of information on the ability of cephazolin to enter the disc. Based on our clinical experience and prior animal studies it would seem that if cephazolin were given at an optimum dose it would enter the disc sufficiently to protect the disc from contamination but insufficient to prevent an established infection from progressing to endplate erosion.

The aims of this study were to assess the effectiveness of cephazolin in preventing and treating infection in both normal and artificially degenerated sheep discs; to determine if degeneration of the disc influences antibiotic uptake and; to measure the concentration of cephazolin in non-operated immature and mature discs after a moderate to high dose of cephazolin is given.

Materials and methods

Study one: prophylaxis

With Institutional Animal Ethics Committee approval eight adult Merino wethers (average weight 45 kg) were premedicated with 10 mg of IV xylazine. General anaesthesia was induced by IV injection of 0.5 g pentothal and maintained by endotracheal intubation with 2% halothane and oxygen. Using a left-sided ventrolateral muscle-splitting approach the lumbar spines were exposed. An incision was made using a #11 scalpel blade adjacent to the cranial endplate in each of the two non-adjacent intervertebral discs, no deeper than 5 mm to avoid penetrating the nucleus pulposus (NP). The incisions were made to induce degeneration and to create a vascular granulation tissue response [10]. The incised levels were marked at the time of surgery with a metal suture around the transverse process. A lateral radiograph of the lumbar spine was taken to confirm the operated levels. The wound was closed in layers and the sheep allowed to recover.

Four weeks postoperatively, six sheep were given an IV prophylactic dose of cephazolin (Mayne Pharma Australia Pty Ltd., Australia) under general anaesthesia: two received 1 g, two received 2 g and two received 3 g. Two sheep did not receive prophylactic cephazolin and were controls for the study. Thirty minutes after receiving cephazolin the lumbar spine was exposed on the opposite side.

Under direct vision all sheep underwent discography at the levels that were previously incised and at two previously non-operated levels, using Ultravist 370 radiographic contrast medium (Schering AG, Germany) containing approximately 1,000 organisms/0.1 ml *S. aureus* (ATCC 29213). Approximately 0.1 ml of bacterial suspension containing contrast was injected into each disc. Bacterial cell counts were made before and after inoculation with and without contrast. A lateral plain radiograph of the lumbar spine was taken immediately after discography to confirm the levels of inoculation. The wound was closed in layers and the sheep was allowed to recover. The sheep were observed closely for 3 days following surgery before they were transferred to a farm where they were allowed unrestricted activity in outdoor paddocks. Lateral radiographs of the lumbar spine were taken at 2, 6 and 12 weeks to monitor endplate and vertebral bone changes.

After 12 weeks all sheep were administered another IV dose of cephazolin as 1, 2, 3 or 4 g (two sheep per dose). Thirty minutes after antibiotic administration the sheep were killed by IV injection of 7 g sodium pentobarbitone (Virbac, Australia). The lumbar spines were excised and prepared for biochemistry and light microscopy. Fresh samples of anulus fibrosus (AF) and NP from non-operated (non-discitis) levels were prepared for high-performance liquid chromatography to measure cephazolin concentration [8]. Samples from inoculated levels were not collected because of the potential for blood contamination and loss of identifiable structures. Discitis had changed the anatomy of the disc to such an extent that ensuring pure samples of NP and AF were collected was not possible. Representative 4 mm thick mid-sagittal slices of the remaining discs with adjacent vertebral bone were fixed in 10% neutral buffered formalin, decalcified in nitric acid/EDTA and processed into paraffin wax.

Haematoxylin and eosin stained sections of the discs were assessed histologically for evidence of discitis [4]. Infection of the disc was confirmed if the following histologic criteria of discitis were met: an inflammatory response, breaching of the endplate, granulation tissue and vascularisation of the disc. Radiographs were assessed with particular emphasis on endplate erosion and disc thinning. Successful prophylaxis was judged by lack of progression of discitis compared with the control discs. Data from disc cephazolin concentration (mean ± SD) were analysed using the Student–Newman–Keuls test for difference between AF and NP samples with dose. Statistical significance was set at $P < 0.05$.

Study two: treatment

With Institutional Animal Ethics Committee approval the lumbar spines of three Merino lambs aged 12 weeks (average weight 30 kg) and three 24-month sheep (average weight 42 kg) were exposed by the left-sided approach previously described. Using a #11 scalpel blade an incision was made adjacent to the cranial endplate in two non-adjacent discs, no deeper than 4 mm in lambs and 5 mm in adult sheep to avoid penetrating the NP. The incised levels were marked by placing a wire suture through and around the transverse process and a lateral radiograph of the lumbar spine was taken to confirm the operated levels.

Four weeks later all sheep underwent intradiscal injections of contrast to which bacteria had been added (previously described). Approximately 0.1 ml of infected contrast was injected into sheep discs and 0.05 ml was injected into the lamb discs. One week after inoculation 5 ml of venous blood was collected for blood culture.

Seven days after inoculation two lambs and two sheep began antibiotic treatment. Cephazolin was administered IV for 21 consecutive days at a dose of 50 mg/kg/day, as two equal doses 12 h apart. This dose is recommended for a moderately severe infection (*S. aureus*). The duration of the antibiotic was based on veterinary advice. Pilot studies concluded that sheep cannot tolerate more than 21 days of cephazolin at this dose, the sheep developed side effects from the drug (predominantly diarrhoea). One lamb and one sheep did not receive treatment and acted as the controls for the study.

Lateral radiographs of the lumbar spines were taken at 2, 6 and 12 weeks. Twelve weeks after discography the sheep were killed by IV injection of 7 g sodium pentobarbitone. Aspirates were taken from the inoculated discs either directly or after injection of 0.1 ml saline for microbiological culture. Disc tissue was prepared for light microscopy as previously described. Successful treatment was judged by lack of progression of histopathologic parameters and radiographic findings compared with the control discs.

Results

Study one: prophylaxis

Radiography and histology

Discitis was detected radiographically in all discs from the control sheep (n=8) that did not receive cephazolin

and in 7/24 discs from the sheep that received a prophylactic dose (Table 1). There was endplate erosion and disc thinning in sheep with discitis from 2 weeks after inoculation. At 12 weeks these erosions had extended through the endplate and approximately half had extended into the adjoining vertebral body. Histologically, these lesions were characterised by an extensive chronic inflammatory reaction. Disc tissue, granulation tissue and extensive vascularisation breached the endplates of the levels with discitis and approximately half of the lesions extended through the epiphysial growth plate into the main vertebral body. Histologically the lesions were consistent regardless of the antibiotic dose. In the sheep that received a prophylactic dose of cephazolin and developed discitis, two discs were initially incised. Incision of the AF initiated a vascular granulation tissue response in the peripheral layers but this did not affect the incidence of discitis.

Biochemistry

Biochemical analysis confirmed that cephazolin diffused throughout the disc. The concentration of cephazolin was measured in the discs of sheep that received 1, 2, 3 and 4 g doses. As the dose increased the concentration of cephazolin in the disc increased in a linear fashion. When the data were separated into AF and NP this relationship held only for the AF. The concentration in the NP reached a plateau from 2 g and was significantly lower ($P < 0.05$) than in the AF (Fig. 1). There was no significant difference between cephazolin concentration in the NP for a 2, 3 or 4 g dose (Table 2). The extent of disc degeneration did not alter antibiotic concentration in the disc.

Bacterial count

Prior to inoculation the bacterial cell count was approximately 1,050 CFU/0.1 ml. Three hours after injection the count dropped to approximately 560 CFU/0.1 ml. Suspending the bacteria in radiographic contrast did not affect the count significantly compared to the postoperative count (approximately 400 CFU/0.1 ml). From these results it is concluded that all discs were inoculated with viable bacteria.

Table 1 Incidence of discitis at 12 weeks after an IV dose of cephazolin prior to inoculation of four lumbar discs per animal (two non-operated and two incised discs)

Cephazolin dose (g)	Non-operated disc	Incised disc
0	4/4	4/4
1	2/4	1/4
2	2/4	0/4
3	1/4	1/4

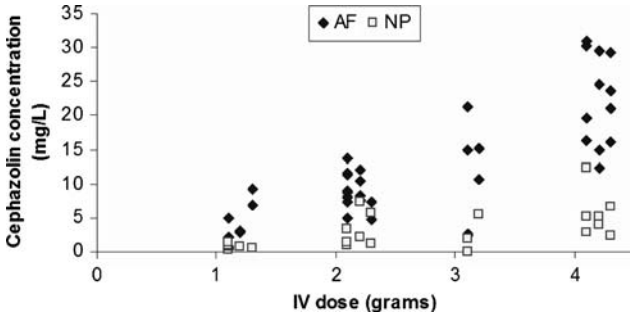

Fig. 1 Cephazolin concentration of AF and NP samples after 1, 2, 3 or 4 g IV doses of cephazolin. A linear distribution was apparent for AF samples while NP levels were significantly lower for all doses

Study two: treatment

Radiography and histology

Regardless of age all sheep showed radiographic evidence of discitis in all inoculated discs from 2 weeks (Fig. 2). After 12 weeks erosive lesions were present macroscopically in all inoculated discs (Fig. 3). Microscopic changes consistent with discitis with additional haemorrhagic encapsulated granulation tissue response surrounding necrotic debris was observed in all control and treated sheep. Approximately half of the lesions breached the epiphysial growth plate (Fig. 4). The histological appearance was the same with or without antibiotic treatment.

Table 2 Cephazolin concentration (mean ± SD) in samples of the anulus fibrosus (AF) and nucleus pulposus (NP) collected 30 min after 1, 2, 3 or 4 g IV doses of cephazolin

Cephazolin dose (g)	Concentration of cephazolin (mg/l)	
	AF	NP
1	3.7±3.1[a]	0.7±0.3
2	8.9±2.6[a]	3.1±2.5[b]
3	11.1±7.6[a]	2.4±2.8[b]
4	22.3±6.8[a]	5.3±3.1[b]

Cephazolin concentration in AF was significantly higher than in the NP for all doses. There was no significant difference between cephazolin concentrations in the NP for a 2, 3 or 4 g dose

[a]Cephazolin concentration was significantly different for 1, 2, 3 and 4 g ($\alpha < 0.05$).

[b]Cephazolin concentration was significantly higher than 1 g ($\alpha < 0.05$).

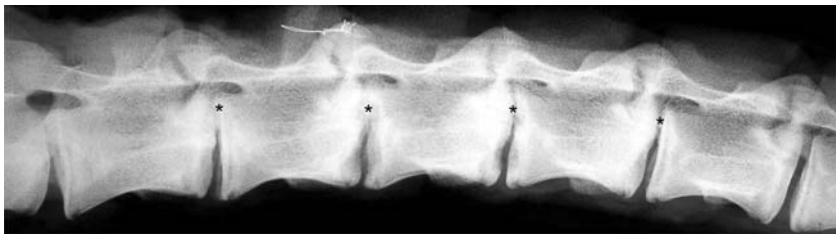

Fig. 2 Radiograph taken 2 weeks after four level disc inoculation of *S. aureus*. Discitis is evident in all inoculated discs (*asterisk*) demonstrated by endplate erosion and disc thinning comparable to adjacent non-inoculated levels

Microbiology

Blood cultures at 7 days were negative suggesting that bacteria from the inoculum were not spreading across adjacent discs via the vessels in the highly vascular immature discs or the vessels surrounding the mature disc.

There was no bacterial growth from the disc aspirates collected at 12 weeks suggesting that the bacteria were removed once the endplates were breached either by the immune system of the sheep or by subsequent antibiotic treatment administered over 21 days.

Discussion

An earlier animal study [3] concluded that 1 g of intravenous cephazolin to be highly effective for prophylaxis against bacterial contamination during discography and chemonucleolysis. In that study, there were no instances of discitis in 46 discs inoculated with *S. epidermidis*, in contrast with the current study in which discitis developed in 7 of 24 discs despite the use of higher doses of cephazolin. This difference would seem to be due to the use of the organism (*S. aureus*) in the current study that was less sensitive to cephazolin. This study highlights that whilst the incidence of iatrogenic discitis can be diminished by antibiotic prophylaxis it cannot be eliminated with a broad-spectrum antibiotic such as cephazolin.

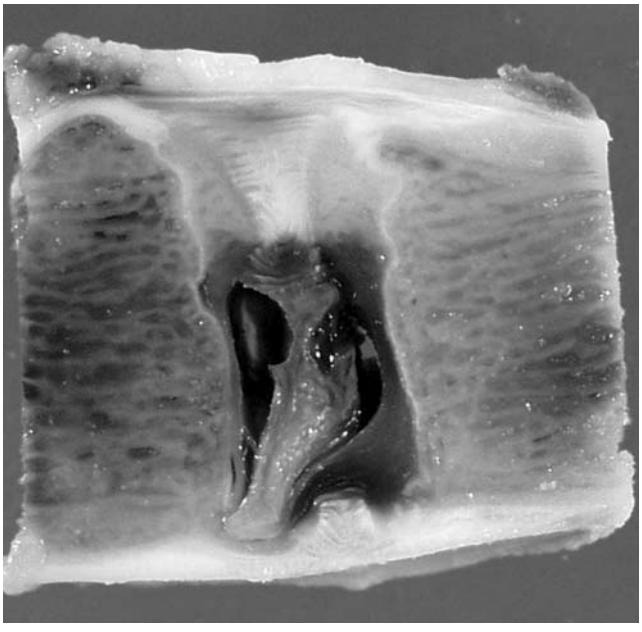

Fig. 3 Representative mid sagittal slice of a disc with discitis at 12 weeks after inoculation. Discitis is evident macroscopically with irregular haemorrhagic lesions breaching the cartilage endplate. The epiphysial growth plate contains the lesion but there is extensive tissue destruction of the disc

This study, as with others, [1, 3, 11] shows that cephazolin can diffuse through the disc. However, since it was present in higher concentration in the AF than in the NP it is possible that the levels in the NP are not therapeutic, particularly against more virulent organisms.

It has been postulated that certain antibiotic groups are not able to penetrate the disc due to their molecular charge[5]. Discs contain abundant proteoglycans that are negatively charged and control the internal distribution of charged molecules [15]. Previous studies have described the penetration of negatively charged antibiotics into the disc when adequate serum concentrations are maintained [1, 3]. When antibiotic levels are measured in different regions of the disc (AF and NP) however, the results have not been equivalent. It has been suggested that negatively charged penicillin is able to penetrate the AF but is less likely to penetrate the negatively charged NP, while positively charged gentamicin penetrates both regions readily [12]. This current study also supports the view that charge influences the delivery of molecules to their target sites. Although the IV dose of cephazolin was four times that of the standard dose, the concentration in the NP barely changed, in contrast to the AF which steadily increased. Therefore no single dose given was more effective at increasing the concentration in the NP.

This may explain why discitis occurred in some of the sheep from the ‘‘prophylaxis’’ group and all in the ‘‘treated’’ group. Perhaps cephazolin was not present in the NP at a level that is required to combat the inoculum.

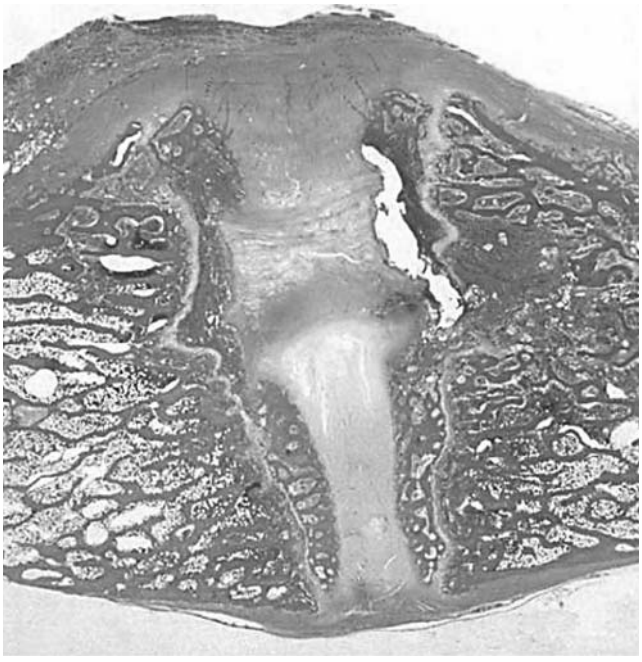

Fig. 4 Haematoxylin and eosin stained section of an inoculated disc after treatment with IV cephazolin for 21 days at a dose of 50 mg/kg/day. Histological changes consistent with discitis (breaching of the cartilage endplate by disc tissue) with additional haemorrhagic encapsulated granulation tissue response surrounding necrotic tissue are observed

It is clear from this study that cephazolin enters the disc. Thus, the failure to treat established infection was due to the organism, which was less sensitive to cephazolin, the ability of the antibiotic to diffuse into the NP or inappropriate timing. If treatment begins after the infection has breached the endplate, the disc is already damaged. Paradoxically the subsequent inflammatory response causes damage to the surrounding tissues. In this study, as with childhood discitis, the outcome after inoculation may be the same regardless of the antibiotic treatment [7, 14, 16]. Treatment of established discitis with antibiotics is rarely successful at preventing endplate destruction [3] and adults (more so than children) are still at risk of developing complications, such as abscess formation, spinal fusion, neurological compromise and recurrent infection [6, 9, 13]. The treatment of discitis is complicated by late detection, poor vascular supply to the infected area and unsuccessful culture and susceptibility studies.

In healthy immature discs, the vascular supply is prominent and theoretically facilitates antibiotic diffusion, whereas the diminished vascularity seen with age may impede diffusion. Disc degeneration, however, is often accompanied by vascular granulation tissue, particularly at the site of injury, thereby facilitating the penetration of antibiotic into the disc. Although, annular incision in this study led to the development of granulation tissue, the concentration of cephazolin in these discs was not different from non-incised discs. It would appear therefore that granulation tissue had no significant effect on the delivery of antibiotics in the disc.

We relied on the radiological changes such as narrowing of the disc space, vertebral bony sclerosis and erosion of the endplates to identify discitis. MRI would have identified endplate changes earlier and enabled close monitoring, but was not feasible for this animal study.

Administration of prophylactic antibiotics at the time of surgery appears to be effective and advisable since treatment of discitis is often difficult, costly and time consuming. Although the most appropriate dose to be given remains arguable a 2 g prophylactic dose appears to be as effective as a 4 g dose. Alternatively, a single IV dose could be administered in combination with an intradiscal dose if applicable for the type of surgery, however giving intradiscal injections as a treatment option would be inappropriate. A positively charged antibiotic such as clindamycin or gentamicin could be used, although the efficacy of these antibiotics is also unclear.

Conclusion

This study demonstrates that whilst the incidence of iatrogenic discitis can be diminished by antibiotic prophylaxis discitis cannot be eliminated with a broad-spectrum antibiotic such as cephazolin. Furthermore, cephazolin appears to be ineffective at preventing endplate destruction once discitis has become established.

Acknowledgments Mayne Pharma Australia Pte Ltd. supplied antibiotic and the Department of Biochemistry, Royal Perth Hospital conducted the antibiotic assay. The staff of the Veterinary Services Division, IMVS assisted with the animal study and staff from Infectious Diseases Laboratories, IMVS provided bacterial suspensions.

References

1. Boscardin JB, Ringus JC, Feingold DJ, Ruda SC (1992) Human intradiscal levels with cefazolin. Spine 17:S145–S148
2. Fraser RD, Osti OL, Vernon-Roberts B (1986) Discitis following chemonucleolysis. An experimental study. Spine 11:679–687

3. Fraser RD, Osti OL, Vernon-Roberts B (1989) Iatrogenic discitis: the role of intravenous antibiotics in prevention and treatment. An experimental study. Spine 14:1025–1032
4. Fraser RD, Moore RJ (2003) Iatrogenic Discitis. In: Govender S, Leong JCY (eds) Inflammatory Diseases of the Spine. TTG Asia Media Pte Ltd., Singapore pp 1–9
5. Gibson MJ, Karpinski MR, Slack RC, Cowlishaw WA, Webb JK (1987) The penetration of antibiotics into the normal intervertebral disc. J Bone Joint Surg (Br) 69:784–786
6. Hadjipavlou AG, Mader JT, Necessary JT, Muffoletto AJ (2000) Hematogenous pyogenic spinal infections and their surgical management. Spine 25:1668–1679
7. Jansen BR, Hart W, Schreuder O (1993) Discitis in childhood. 12–35-year follow-up of 35 patients. Acta Orthop Scand 64:33–36
8. McAteer JA, Hiltke MF, Silber BM, Faulkner RD (1987) Liquid-chromatographic determination of five orally active cephalosporins—cefixime, cefaclor, cefadroxil, cephalexin, and cephradine—in human serum. Clin Chem 33:1788–1790
9. Muckley T, Schutz T, Kirschner M, Potulski M, Hofmann G, Buhren V (2003) Psoas abscess: the spine as a primary source of infection. Spine 28:E106–E113
10. Osti OL, Vernon-Roberts B, Fraser RD (1990) 1990 Volvo Award in experimental studies. Anulus tears and intervertebral disc degeneration. An experimental study using an animal model. Spine 15:762–767
11. Rhoten RL, Murphy MA, Kalfas IH, Hahn JF, Washington JA (1995) Antibiotic penetration into cervical discs. Neurosurgery 37:418–421
12. Riley L, Banovac K, Martinez O, Eismont F (1994) Tissue distribution of antibiotics in the intervertebral disc. Spine 19:2619–2625
13. Silber JS, Anderson DG, Vaccaro AR, Anderson PA, McCormick P (2002) Management of postprocedural discitis. Spine 2:279–287
14. Spiegel PG, Kengla KW, Isaacson AS, Wilson JC Jr (1972) Intervertebral disc-space inflammation in children. J Bone Joint Surg (Am) 54:284–296
15. Urban J (1996) Disc biochemistry in relation to function. 2nd WB Saunders, Philadelphia
16. Ventura N, Gonzalez E, Terricabras L, Salvador A, Cabrera M (1996) Intervertebral discitis in children: a review of 12 cases. Int Orthop 20:32–34
17. Walters RM, Smith SHE, Hutchinson JH, Dolan AM, Fraser RD, Moore RJ (2005) Effects of intervertebral disc infection on the developing ovine spine. Spine 30:1252–1257