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Surgical Site Infections Caused by Methicillin-resistant *Staphylococcus epidermidis* After Spinal Instrumentation Surgery

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Study Design. Retrospective case series.
Objective. To determine relevant demographics, clinical presentations, and outcomes of surgical site infections (SSIs) after spinal instrumentation (SI) surgery caused by methicillin-resistant *Staphylococcus epidermidis* (MRSE).
Summary of Background Data. This is the first study looking specifically at MRSE-related SSIs after SI surgery.
Methods. We performed a retrospective review of patients with MRSE-related SSIs from 665 consecutive cases of SI surgery performed between 2007 and 2014 at our institution.
Results. During the study period, SSIs occurred in 21 patients. MRSE was isolated from cultures obtained from surgical wounds in nine of the 21 patients (43%). There were four males and five females with a mean age of 63.9 ± 15.1 years. Six patients presented with inflammatory signs, such as wound drainage, pyrexia, erythema, and elevated C-reactive protein. Three patients did not have signs of infection, but had early implant failure, and were diagnosed by positive cultures collected at the time of revision surgery. The mean time from index surgery to the diagnosis of infection was 23.6 days (range, 7–88 days). In one patient, the implant was removed before antibiotic treatment was administered because of implant failure. Eight patients were managed with antibiotics and implant retention. During the follow-up period, MRSE-related SSIs in seven of the eight patients were resolved with implant retention and antibiotics without the need for further surgical intervention. One patient did not complete the antibiotic course because of side effects, and implant removal was required to control the infection.
Conclusion. Early detection, surgical debridement, and administration of appropriate antibiotics for a suitable duration enabled infection control without the need for implant removal in the treatment of MRSE-related SSI after SI surgery.
Key words: methicillin-resistant Staphylococcus epidermidis (MRSE), retrospective study, spinal instrumentation surgery, surgical site infection.
Level of Evidence: 4
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Because of increased longevity, a demand for a better quality of life in aged populations, and advances in surgical technique and perioperative care, spinal instrumentation (SI) surgery is often indicated in elderly patients. Consequently, there are an increasing number of SI surgeries being performed.[1,2] The incidence of surgical site infection (SSI) after SI surgery is also increasing. Previous studies have reported that the incidence of SSI after SI surgery was 2.1% to 8.5%.[3–5]

Treatment for SSI after SI surgery is challenging; it requires a multidisciplinary approach with a definite medical and surgical strategy. SSI can cause patient dissatisfaction with the initial operative procedure because of its negative impact on the overall outcome,[6] and psychological stress to medical personnel because of the absence of an established guideline for the management of SSI after SI surgery. In the treatment of SSI after SI surgery, it is important to control infection and leave the implant *in situ* until bone union is achieved. A delay in diagnosis and treatment may necessitate the removal of the spinal implant to control SSI,[7] resulting in increased morbidity[3,7–9] and healthcare costs;[7,10] therefore, prompt diagnosis and treatment for SSI is imperative.

Staphylococcus epidermidis is the most prevalent bacterium among coagulase-negative staphylococci, and is a common inhabitant of human skin and mucous membranes.[11] Although *S. epidermidis* is considered less virulent than *S. aureus*, it is increasingly recognized as one of the pathogens in implant-associated infections.[11] Recently, *S.*

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epidermidis has become a common cause of SSI after orthopedic implant surgery.[8,12,13] In Japan, 80% of *S. epidermidis* are resistant to antibiotics that were previously effective; they are called methicillin-resistant *S. epidermidis* (MRSE).[14] *S. epidermidis* produces a biofilm, which is considered the most important factor involved in implant-related infection.[15] A biofilm is a microbial derived sessile community characterized by cells that are embedded in a matrix of extracellular polymeric substances.[16,17] The bacteria within biofilms are protected against antibiotics, phagocytes, other cellular and humoral immune responses, and other microbial organisms.[18]

In MRSE-related SSI after SI surgery, treatment and control of infection has been made difficult because of antibiotic resistance and the presence of biofilms; therefore, implants may need to be removed to eradicate the infection.[9] Retaining the implant is important to avoid malalignment or pseudoarthrosis caused by mechanical instability;[3,7,9] therefore, it is imperative to establish a treatment strategy for MRSE-related SSI after SI surgery and to retain the implant if possible. In this study, we retrospectively analyzed nine consecutive cases of MRSE-related SSI after SI surgery and examined which cases could be managed with implant retention.

MATERIALS AND METHODS

Subjects

After local institutional review board approval, we retrospectively reviewed 665 consecutive patients who underwent SI surgery at our institution from January 2007 to December 2014. There were 281 males and 384 females; the mean age was 64.3 ± 11.9 years. The cohort consisted of 608 patients with degenerative disease; nine with a spinal tumor, 48 with spinal trauma, and 100 were undergoing reoperation. The operative site was the cervical spine in 69 patients, the thoracic spine in 27 patients, the thoracolumbar spine in six patients, and the lumbar spine in 563 patients. An anterior approach was used in 51 patients and a posterior approach was used in 614 patients. All patients received intravenous antibiotic prophylaxis before the index operation. The protocol consisted of administering 1 g of cefazolin in patients weighing 80 kg or less and 2 g of cefazolin in patients weighing more than 80 kg and redosing every 3 hours during surgery.

Diagnosis of MRSE-related SSI

Diagnosis for SSI was based on the 1999 Centers for Disease Control and Prevention National Health Safety Network criteria.[19] All suspected cases of SSI underwent surgical irrigation and debridement with implant retention and primary closure of the wound along with the use of suction drains. Antibiotics were not administered until we obtained intraoperative culture samples, to maximize the yield of the cultures. Intraoperative wound culture was routinely performed for patients who underwent early revision surgery owing to implant-related complications, even if the patients did not show signs of infection. Intraoperative samples were cultured for 14 days, and patients with at least two positive intraoperative cultures of MRSE were diagnosed with a MRSE-related SSI. The onset of infection was determined as the date of surgery when the first culture was obtained.

Management of MRSE-related SSI

Postoperative antibiotic treatment consisted of administering intravenous antibiotics: vancomycin (VCM: target trough concentration of 15–20 μg/mL); teicoplanin (TEIC: target trough concentration of 20–30 μg/mL); daptomycin (DAP: 6 mg/kg, once daily); or clindamycin (CLDM: 600 mg, 3 times per day) for 6 weeks. All patients were prescribed oral rifampicin (RFP) together with intravenous antibiotics. Implant removal was indicated if infectious signs persisted after antibiotic treatment, or a recurrence of infection was noted after the completion of antibiotic treatment. We defined successful treatment as both an absence of infectious signs for 6 months after the completion of antibiotic treatment, and imaging findings of bone union. All patients were followed up for at least a year after diagnosis.

RESULTS

Patient Demographics

During the study period, SSIs occurred in 21 patients (3.2%). In nine of the 21 patients, MRSE was isolated from cultures obtained from surgical wounds (Table 1). There were four males and five females with a mean age of 63.9 ± 15.1 years. The lumbar spine was affected in six patients, and the cervical spine was affected in three patients. All patients received autogenous bone grafting. The average operative time of the index surgery was 216.4 ± 32.4 minutes, and the average amount of bleeding was 500.5 ± 382.3 mL. There were four patients with a body mass index greater than 25, one patient with rheumatoid arthritis, and two patients underwent spinal reoperation.

Among the nine patients, three patients presented with wound drainage and two patients had pyrexia. Three patients without signs of infection were diagnosed with SSI from positive cultures at the time of a revision surgery for early implant failure (Cases 1, 3, and 4). There were four patients with reelevated C-reactive protein (CRP) and/or an elevated white blood cell (WBC) count from day 4–7 or day 7–11 after surgery. An average of 2.4 (2 or 3) culture samples were obtained from tissues representing different areas of the surgical field, and at least two intraoperative cultures were positive for MRSE in each case. The average time from index surgery to the diagnosis of SSI was 23.6 days; all SSIs were diagnosed within 3 months of surgery. The cultures of two patients were polymicrobial (Table 2).

TABLE 1. Demographic Data of Patients

Case	Age (yrs)	Sex	Diagnosis	Level	Approach	Procedure	Implant	Fusion Level	Operation Time (min)	Bleeding (mL)	BMI	Risk Factor
1	42	Male	CDM	C	Anterior	ACCF	Plate	C4-7	242	110	25.6	None
2	80	Female	LDS	L	Posterior	PLIF	cage, screw	L3-5	198	449	18.6	None
3	71	Female	LDS	L	Posterior	PLIF	cage, screw	L3-S1	239	390	24.2	RA
4	75	Female	CDM	C	Anterior	ACCF	plate	C4-7	240	656	22.2	None
5	50	Female	LDS	L	Posterior	PLIF	cage, screw	L3-5	252	554	26.1	None
6	71	Female	Scoliosis	L	Posterior	PLIF	cage, screw	L3-5	231	480	30.0	Reoperation
7	77	Male	CDM	C	Posterior	LMS	screw	C3-4	206	75	26.6	None
8	67	Male	LDS	L	Posterior	PLIF	cage, screw	L2-4	185	1300	24.6	Reoperation
9	42	Male	LDS	L	Posterior	PLIF	cage, screw	L4-5	155	100	21.8	None

ACCF indicates anterior cervical corpectomy and fusion, BMI, body mass index, C, cervical spine; CDM, cervical degenerative myelopathy; L, lumbar spine; LDS, lumbar degenerative spondylolisthesis; LMS, lateral mass screw, PLIF, posterior lumbar interbody fusion, RA, rheumatoid arthritis.

TABLE 2. Perioperative Characteristics of Patients

Case	Fever	Erythema	Drainage	Reelevated WBC	Reelevated CRP	Time from surgery (days)	Culture	Treatment	Follow-up Period (yrs)	Results
1	−	−	−	−	−	35	MRSE	CLDM	8	Removal of implant
2	−	+	−	−	−	10	MRSE, MSSA	CLDM	1	Success
3	−	−	−	−	−	13	MRSE	VCM, TEIC	5.5	Removal of implant
4	−	−	−	−	−	9	MRSE	VCM	4.5	Success
5	−	−	+	−	−	23	MRSE	VCM	2	Success
6	+	−	−	+	+	14	MRSE	VCM	4	Success
7	−	+	+	+	+	7	MRSE, *Pseudomonas aeruginosa*	VCM	2	Success
8	−	−	−	+	+	88	MRSE	VCM	2	Success
9	+	+	+	+	+	13	MRSE	DAP	1.5	Success

CLDM indicates clindamycin; CRP, C-reactive protein; DAP, daptomycin; MRSE, methicillin-resistant Staphylococcus epidermidis; MSSA, methicillin-sensitive Staphylococcus aureus; TEIC, teicoplanin; VCM, vancomycin; WBC, white blood cell.

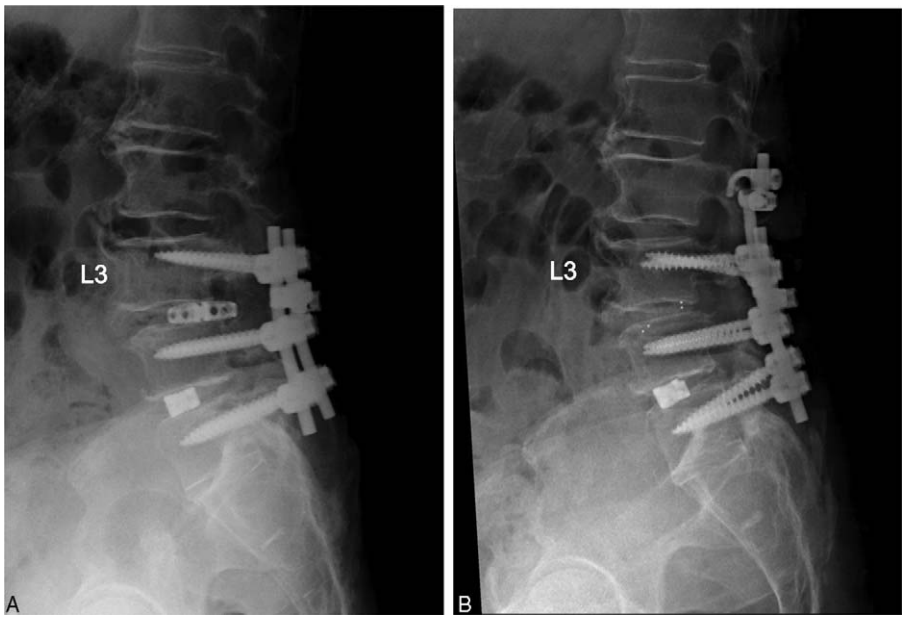

Figure 1. Lateral plain radiographs of the lumbar spine taken before (**A**) and after (**B**) a revision surgery.

Treatment of MRSE-related SSI

There were no cases of sepsis, and antibiotic treatment was started after positive cultures of MRSE in all cases. Two patients were treated with CLDM, six patients with VCM, one patient with TEIC, and one patient with DAP. There were no patients requiring more than one debridement surgery. During the follow-up period, SSIs were controlled with implant retention in seven patients, whereas implants were removed in two patients. In Case 1, the loosened anterior cervical plate and screws were removed, and posterior screw stabilization was used at a revision surgery before antibiotic treatment was started. In Case 3, we could not continue antibiotic treatment for 6 weeks caused by the side effects experienced by the patient.

Case Presentation (Case 3)

A 71-year-old female underwent a 2-level posterior lumbar interbody fusion for lumbar degenerative spondylolisthesis. Seven days post surgery, a lateral radiograph showed back-out of the implanted cage at the L3-4 level into the spinal canal (Figure 1A). She had no clinical signs of infection. Thirteen days after surgery, she underwent reoperation to replace the boomerang type cage with two box-type cages (Figure 1B). Although there were no abnormal findings in the surgical field, MRSE was cultured from intraoperative wound samples. After the revision surgery, she was treated with 750 mg of VCM intravenously every 12 hours and 450 mg of RFP orally. She developed linear IgA dermatosis after 12 days of VCM administration, so she was switched to 400 mg of TEIC intravenously every 24 hours. She developed pancytopenia 17 days after starting treatment with TEIC, which is a possible side effect of this antibiotic. Administration of TEIC was stopped and replaced with oral minocycline. Laboratory data returned to normal levels (WBC count: 4500/μL, CRP: 0.2 mg/dL) 3 months after the revision surgery; however, after this they started to gradually increase. Magnetic resonance imaging demonstrated decreased signal intensity at the L3-4 disc and adjacent vertebral bodies (Figure 2A), where gadolinium-enhancement was noted (Figure 2B). We diagnosed a recurrence of SSI, and a second revision surgery was performed 9 months after the index surgery. The patient had no clinical signs, and a WBC count and CRP levels within the normal range 5.5 years after the second revision surgery (Figure 3).

DISCUSSION

Our treatment protocol for SSI after SI surgery is to perform surgical intervention with wound irrigation and debridement as early as possible. After obtaining intraoperative culture samples, an antibiotic course is initiated. To maximize the yield of the intraoperative cultures, we do not administer antibiotics before obtaining culture samples. In this study period, we did not experience a late-onset (diagnosed more than 3 months after surgery) SSI using this protocol. The rate of MRSE-related SSI was 42.8%, which was a relatively high percentage compared with the other studies.[8,20] Some surgeons might start antibiotic therapy before taking culture samples when they suspect a patient of having an SSI. A number of those patients might be cleared of infection before being diagnosed as having a MRSE-related SSI, and therefore the incidence of MRSE-related SSIs might be under reported.

Patients with SSIs initially present with inflammatory signs, such as pyrexia, local pain, periincisional erythema, and wound drainage.[21] One of the inflammatory markers, CRP, which is a sensitive marker for infection, is also helpful to detect early SSIs. After SI surgery, CRP levels generally peak on day 3 and decrease to normal baseline levels between days 10 and 14. Reelevated CRP levels from day 3 to 7 or from day 7 onwards is reported to be an important

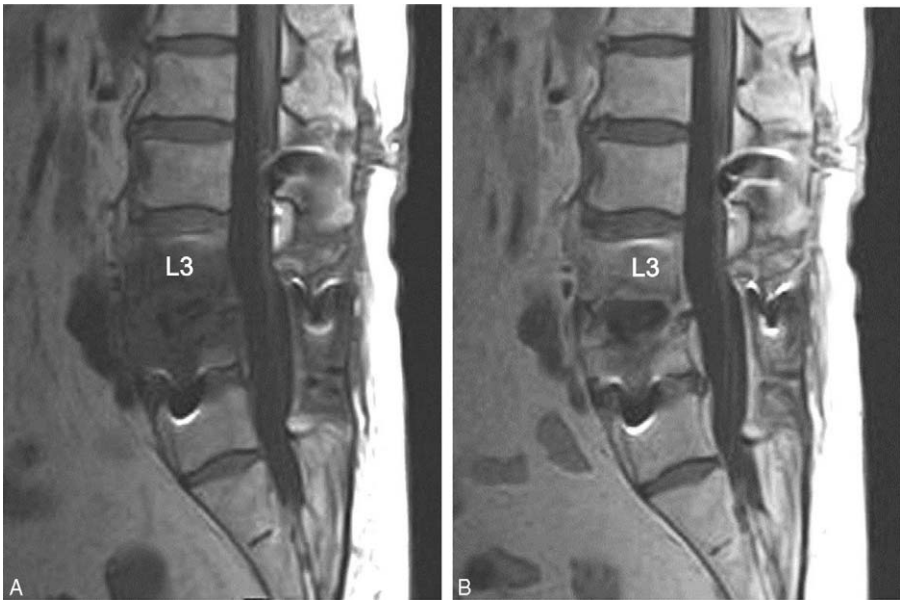

Figure 2. Magnetic resonance imaging of the lumbar spine before a second revision surgery. **A**, Sagittal T1-weighted image. Decreased signal intensity at the L3-4 disc space and adjacent vertebral bodies was noted. **B**, Contrast-enhanced sagittal T1-weighted image. Enhancement of the L3-4 disc space around cages and L3 and L4 vertebrae was noted.

indicator of SSI.[22,23] A blood test was routinely performed every 4 days for 2 weeks post surgery. If reelevation of CRP levels were noted, we suspected an SSI. In this study, three patients were suspected as having an SSI because of the presence of inflammatory signs and reelevated CRP levels, two patients had inflammatory signs without reelevated CRP levels, and one patient had reelevated CRP levels without inflammatory signs. An SSI was diagnosed at revision surgery in three patients who did not present with inflammatory signs. Inflammatory signs may be less likely in MRSE infection because of the low virulence potential of *S. epidermidis*; therefore, it is important to pay close attention to the patient's condition in the early postoperative period to ensure MRSE-related SSIs are not missed.

Recently, methicillin-resistant *S. aureus* (MRSA) has been an increasing cause of SSI.[8,20,24] On the other hand, MRSE has not attracted much attention and there are no universal protocols for the management of MRSE-related SSIs after SI surgery, for example, recommendations for the duration of antimicrobial therapy and whether implants should be removed. In MRSE-related SSI, our treatment protocol involves surgical irrigation, debridement, and implant retention followed by a 6-week course of intravenous antibiotics, according to the antibiotic sensitivity of MRSE. In addition, patients receive RFP as an adjuvant agent against biofilm-embedded bacteria.[24,25] The drug dosage was based on the guideline for MRSA infections.[24] Successful implant salvage was achieved in seven out of nine patients (78%). None of the patients required surgical debridement more than once and there was no recurrence of infection during the follow-up period. Treatment for MRSA-related SSIs using surgical irrigation and debridement, implant retention, and antibiotics are unlikely to resolve the infection.[26,27] In contrast, our study showed that MRSE-related SSIs were controlled in almost all patients managed with a 6-week antibiotic course and implant retention. The key to successful treatment of MRSE-related SSIs is early diagnosis and the administration of appropriate antibiotics for a suitable duration.[7,28]

One issue in the clinical setting is determining whether MRSE cultured from a sample is a contaminant or a

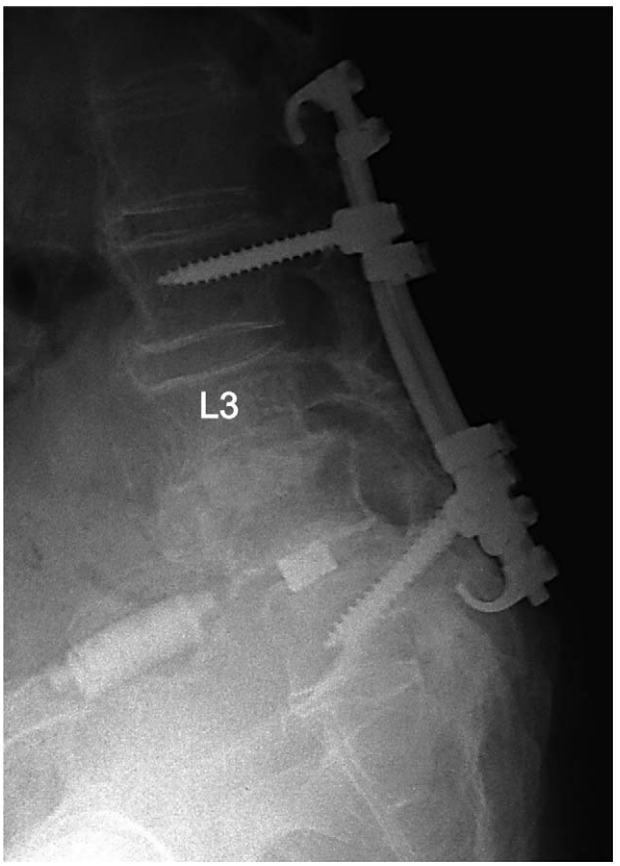

Figure 3. Lateral plain radiograph of the lumbar spine taken 5.5 years after a second revision surgery.

pathogen. In our study, MRSE was detected in cultures from three patients who were not showing inflammatory signs at the time of revision surgery. In Case 3, removal of the implanted cages and screws was required because of septic loosening. Therefore, antibiotic treatment should be started in MRSE-positive patients whether or not they are showing inflammatory signs.[20,29]

The main limitation of our study was the retrospective collection of data from medical records, which may have introduced bias. In addition, our study was a case series with a small sample size and no comparison groups. During the study period, no patients were diagnosed with a late-onset SSI; therefore, we cannot comment on whether our treatment strategy would be effective in cases of late-onset MRSE-related SSIs.

CONCLUSION

A MRSE-related SSI is a challenging complication in patients undergoing SI surgery. Our experience indicates that early detection, surgical debridement, and the administration of appropriate antibiotics for a suitable duration enable successful infection control without the need for implant removal.

➢ Key Points

- ❑ Among 21 patients with SSI after spinal instrument (SI) surgery, MRSE was isolated from cultures obtained from surgical wounds of 9 patients (43%).
- ❑ During the follow-up period, SSIs in seven patients were controlled with implant retention without the need for a revision surgery, whereas implants were removed in two patients.
- ❑ In the treatment of MRSE-related SSI after SI surgery, the key to control infection with implant retention is early diagnosis and the administration of appropriate antibiotics for a suitable duration.

References

1. Deyo RA, Nachemson A, Mirza SK. Spinal-fusion surgery—the case for restraint. *N Engl J Med* 2004;350:722–6.
2. Deyo RA, Mirza SK, Martin BI, et al. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. *JAMA* 2010;303:1259–65.
3. Collins I, Wilson-MacDonald J, Chami G, et al. The diagnosis and management of infection following instrumented spinal fusion. *Eur Spine J* 2008;17:445–50.
4. Smith JS, Shaffrey CI, Sansur CA, et al. Rates of infection after spine surgery based on 108,419 procedures: a report from the Scoliosis Research Society Morbidity and Mortality Committee. *Spine (Phila Pa 1976)* 2011;36:556–63.
5. Gerometta A, Rodriguez Olaverri JC, Bitan F. Infections in spinal instrumentation. *Int Orthop* 2012;36:457–64.
6. Petilon JM, Glassman SD, Dimar JR, et al. Clinical outcomes after lumbar fusion complicated by deep wound infection: a case-control study. *Spine (Phila Pa 1976)* 2012;37:1370–4.
7. Hedequist D, Haugen A, Hresko T, et al. Failure of attempted implant retention in spinal deformity delayed surgical site infections. *Spine (Phila Pa 1976)* 2009;34:60–4.
8. Mok JM, Guillaume TJ, Talu U, et al. Clinical outcome of deep wound infection after instrumented posterior spinal fusion: a matched cohort analysis. *Spine (Phila Pa 1976)* 2009;34:578–83.
9. Kim JI, Suh KT, Kim SJ, et al. Implant removal for the management of infection after instrumented spinal fusion. *J Spinal Disord Tech* 2010;23:258–65.
10. Whitmore RG, Stephen J, Stein SC, et al. Patient comorbidities and complications after spinal surgery: a societal-based cost analysis. *Spine (Phila Pa 1976)* 2012;37:1065–71.
11. Otto M. Staphylococcus epidermidis—the 'accidental' pathogen. *Nat Rev Microbiol* 2009;7:555–67.
12. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med* 2004;351:1645–54.
13. Ho C, Skaggs DL, Weiss JM, et al. Management of infection after instrumented posterior spine fusion in pediatric scoliosis. *Spine (Phila Pa 1976)* 2007;32:2739–44.
14. Yoshida I, Yamaguchi T, Kudo R, et al. Antimicrobial susceptibility of clinical isolates of aerobic gram-positive cocci and anaerobic bacteria in 2008. *Jpn J Antibiot* 2012;65:49–72.
15. Fey PD, Olson ME. Current concepts in biofilm formation of *Staphylococcus epidermidis*. *Future Microbiol* 2010;5:917–33.
16. Donlan RM. Biofilm formation: a clinically relevant microbiological process. *Clin Infect Dis* 2001;33:1387–92.
17. Costerton JW. Biofilm theory can guide the treatment of device-related orthopaedic infections. *Clin Orthop Relat Res* 2005;7–11.
18. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science* 1999;284:1318–22.
19. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1999;20:250–78; quiz 279-80.
20. Abdul-Jabbar A, Berven SH, Hu SS, et al. Surgical site infections in spine surgery: identification of microbiologic and surgical characteristics in 239 cases. *Spine (Phila Pa 1976)* 2013;38:E1425–31.
21. Weinstein MA, McCabe JP, Cammisa FP Jr. Postoperative spinal wound infection: a review of 2391 consecutive index procedures. *J Spinal Disord* 2000;13:422–6.
22. Takahashi J, Ebara S, Kamimura M, et al. Early-phase enhanced inflammatory reaction after spinal instrumentation surgery. *Spine (Phila Pa 1976)* 2001;26:1698–704.
23. Mok JM, Pekmezci M, Piper SL, et al. Use of C-reactive protein after spinal surgery: comparison with erythrocyte sedimentation rate as predictor of early postoperative infectious complications. *Spine (Phila Pa 1976)* 2008;33:415–21.
24. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52:e18–55.
25. Widmer AF, Frei R, Rajacic Z, et al. Correlation between *in vivo* and *in vitro* efficacy of antimicrobial agents against foreign body infections. *J Infect Dis* 1990;162:96–102.
26. Dipaola CP, Saravanja DD, Boriani L, et al. Postoperative infection treatment score for the spine (PITSS): construction and validation of a predictive model to define need for single versus multiple irrigation and debridement for spinal surgical site infection. *Spine J* 2012;12:218–30.
27. Ploumis A, Mehbod AA, Dressel TD, et al. Therapy of spinal wound infections using vacuum-assisted wound closure: risk factors leading to resistance to treatment. *J Spinal Disord Tech* 2008;21:320–3.
28. Hong HS, Chang MC, Liu CL, et al. Is aggressive surgery necessary for acute postoperative deep spinal wound infection? *Spine (Phila Pa 1976)* 2008;33:2473–8.
29. Haque N, Bari MS, Haque N, et al. Methicillin resistant *Staphylococcus epidermidis*. *Mymensingh Med J* 2011;20:326–31.