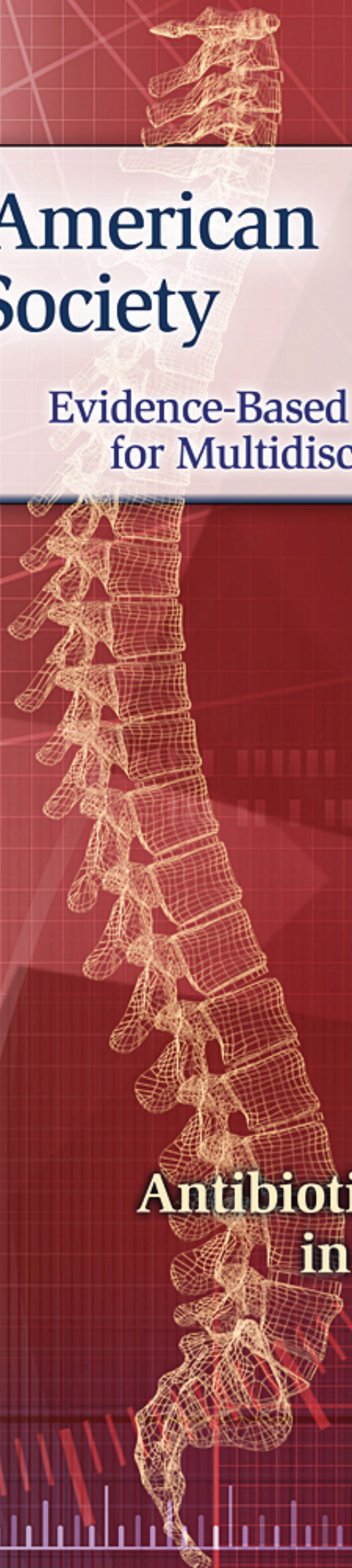
North American Spine Society

Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care



Antibiotic Prophylaxis in Spine Surgery

North American Spine Society
Evidence-Based Clinical Guidelines
for Multidisciplinary Spine Care

Antibiotic Prophylaxis in Spine Surgery
2007

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Financial Statement
This clinical guideline was developed and funded in its entirety by the North American Spine Society (NASS). All participating authors have submitted a disclosure form relative to potential conflicts of interest which is kept on file at NASS.

Comments
Comments regarding the guideline may be submitted to the North American Spine Society and will be considered in development of future revisions of the work.

Special Thanks
The North American Spine Society would like to express its thanks to Dr. Nikolai Bogduk for generating the calculations in Appendix F to explain the prohibitive nature of the sample sizes required to yield Level I data for the efficacy of antibiotic prophylaxis.

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ISBN 1-929988-21-4

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I. INTRODUCTION

Objective

The objective of the North American Spine Society (NASS) Evidence-Based Clinical Guideline on Antibiotic Prophylaxis in Spine Surgery is to provide evidence-based recommendations to address key clinical questions surrounding the use of prophylactic antibiotics in spine surgery. The guideline is intended to address these questions based on the highest quality clinical literature available on this subject as of December 2006. The goals of the guideline recommendations are to assist in delivering optimum, efficacious treatment with the goal of preventing surgical infection.

Scope, Purpose and Intended User

This document was developed by the North American Spine Society Evidence-based Guideline Development Committee as an educational tool to assist spine surgeons in preventing surgical site infections. The NASS Clinical Guideline on Antibiotic Prophylaxis in Spine Surgery addresses the efficacy and appropriate protocol for antibiotic prophylaxis and discusses redosing, discontinuation, wound drains, as well as special considerations related to the potential impact of comorbidities on antibiotic prophylaxis protocol. The recommendations made in this guideline are based on evidence related to open procedures. No evidence was reviewed related to efficacy and protocol for the use of antibiotic prophylaxis in percutaneous procedures.

THIS GUIDELINE DOES NOT REPRESENT A "STANDARD OF CARE," nor is it intended as a fixed treatment protocol. It is anticipated that there will be patients who will require less or more treatment than the average. It is also acknowledged that in atypical cases, treatment falling outside this guideline will sometimes be necessary. This guideline should not be seen as prescribing the type, frequency or duration of intervention. Treatment should be based on the individual patient's need and doctor's professional judgment. This document is designed to function as a guideline and should not be used as the sole reason for denial of treatment and services. This guideline is not intended to expand or restrict a health care provider's scope of practice or to supersede applicable ethical standards or provisions of law.

Patient Population

The patient population for this guideline encompasses adults (18 years or older) undergoing spine surgery.

II. GUIDELINE DEVELOPMENT METHODOLOGY

Through objective evaluation of the evidence and transparency in the process of making recommendations, it is NASS' goal to develop evidence-based clinical practice guidelines for the diagnosis and treatment of adult patients with various spinal conditions. These guidelines are developed for educational purposes to assist practitioners in their clinical decision-making processes. It is anticipated that where evidence is very strong in support of recommendations, these recommendations will be operationalized into performance measures.

Multidisciplinary Collaboration
With the goal of ensuring the best possible care for adult patients suffering with back pain, NASS is committed to multidisciplinary involvement in the process of guideline and performance measure development. To this end, NASS has ensured that representatives from medical, interventional and surgical spine specialties have participated in the development and review of all NASS guidelines. It is also important that primary care providers and musculoskeletal specialists who care for patients with spinal complaints are represented in the development and review of guidelines that address treatment by first contact physicians, and NASS has involved these providers in the development process as well. To ensure broad-based representation, NASS has invited and welcomes input from other societies and specialties.

Evidence Analysis Training of All NASS Guideline Developers
NASS has initiated, in conjunction with the University of Alberta's Centre for Health Evidence, an online training program geared toward educating guideline developers about evidence analysis and guideline development. All participants in guideline development for NASS have completed the training prior to participating in the guideline development program at NASS. This training includes a series of readings and exercises, or interactivities, to prepare guideline developers for systematically evaluating literature and developing evidence-based guidelines. The online course takes approximately 15-30 hours to complete and participants are awarded CME credit upon completion of the course.

Disclosure of Potential Conflicts of Interest
All participants involved in guideline development have disclosed potential conflicts of interest to their colleagues and their potential conflicts have been documented for future reference. They will not be published in any guideline, but kept on file for reference, if needed. Participants have been asked to update their disclosures regularly throughout the guideline development process.

Levels of Evidence and Grades of Recommendation

NASS has adopted standardized levels of evidence (Appendix B) and grades of recommendation (Appendix C) to assist practitioners in easily understanding the strength of the evidence and recommendations within the guidelines. The levels of evidence range from Level I (high quality randomized controlled trial) to Level V (expert consensus). Grades of recommendation indicate the strength of the recommendations made in the guideline based on the quality of the literature.

Grades of Recommendation:

A: Good evidence (Level I studies with consistent finding) for or against recommending intervention.

B: Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention.

C: Poor quality evidence (Level IV or V studies) for or against recommending intervention.

I: Insufficient or conflicting evidence not allowing a recommendation for or against intervention.

The levels of evidence and grades of recommendation implemented in this guideline have also been adopted by the *Journal of Bone and Joint Surgery*, the American Academy of Orthopaedic Surgeons, *Clinical Orthopaedics and Related Research*, the journal *Spine* and the Pediatric Orthopaedic Society of North America.

In evaluating studies as to levels of evidence for this guideline, the study design was interpreted as establishing only a *potential* level of evidence. As an example, a therapeutic study designed as a randomized controlled trial would be considered a *potential* Level I study. The study would then be further analyzed as to how well the study design was implemented and significant short comings in the execution of the study would be used to downgrade the levels of evidence for the study's conclusions. In the example cited previously, reasons to downgrade the results of a potential Level I randomized controlled trial to a Level II study would include, among other possibilities, an underpowered study (patient sample too small, variance too high), inadequate randomization or masking of the group assignments and lack of validated outcome measures.

In addition, a number of studies were reviewed several times in answering different questions within this guideline. How a given question was asked might influence how a study was evaluated and interpreted as to its level of evidence in answering that particular question. For example, a randomized control trial reviewed to evaluate the differences between the outcomes of patients who

received antibiotic prophylaxis with those who did not might be a well designed and implemented Level I therapeutic study. This same study, however, might be classified as giving Level II prognostic evidence if the data for the untreated controls were extracted and evaluated prognostically.

Guideline Development Process

❖ Step 1: Identification of Clinical Questions
Trained guideline participants were asked to submit a list of clinical questions that the guideline should address. The lists were compiled into a master list, which was then circulated to each member with a request that they independently rank the questions in order of importance for consideration in the guideline. The most highly ranked questions, as determined by the participants, served to focus the guideline.

❖ Step 2: Identification of Work Groups
Multidisciplinary teams were assigned to work groups and assigned specific clinical questions to address. Because NASS is comprised of surgical, medical and interventional specialists, it is imperative to the guideline development process that a cross-section of NASS membership is represented on each group whenever feasible. This also helps to ensure that the potential for inadvertent biases in evaluating the literature and formulating recommendations is minimized.

❖ Step 3: Identification of Search Terms and Parameters
One of the most crucial elements of evidence analysis to support development of recommendations for appropriate clinical care is the comprehensive literature search. Thorough assessment of the literature is the basis for the review of existing evidence and the formulation of evidence-based recommendations. In order to ensure a thorough literature search, NASS has instituted a Literature Search Protocol (Appendix D) which has been followed to identify literature for evaluation in guideline development. In keeping with the Literature Search Protocol, work group members have identified appropriate search terms and parameters to direct the literature search.

Specific search strategies, including search terms, parameters and databases searched, are documented in the appendices (Appendix E).

❖ Step 4: Completion of the Literature Search
After each work group identified search terms/parameters, the literature search was implemented by a medical/research librarian, consistent with the Literature Search Protocol.

Following these protocols ensures that NASS recommendations (1) are based on a thorough review of relevant literature; (2) are truly based on a uniform, comprehensive search strategy; and (3) represent the current best research

evidence available. NASS maintains a search history in EndNote,™ for future use or reference.

❖ Step 5: Review of Search Results/Identification of Literature to Review

Work group members reviewed all abstracts yielded from the literature search and identified the literature they would review in order to address the clinical questions, in accordance with the Literature Search Protocol. Members identified the *best research evidence available* to answer the targeted clinical questions. That is, if Level I, II and/or III literature is available to answer specific questions, the work group was not required to review Level IV or V studies.

❖ Step 6: Evidence Analysis

Members of the work group independently developed evidentiary tables summarizing study conclusions, identifying strengths and weaknesses and assigning levels of evidence. In order to systematically control for potential biases, at least two work group members reviewed each article selected and independently assigned levels of evidence to the literature using the NASS levels of evidence. Any discrepancies in scoring have been addressed by two or more reviewers. The consensus level (the level upon which two thirds of reviewers were in agreement) was then assigned to the article.

As a final step in the evidence analysis process, members identified and documented gaps in the evidence to educate guideline readers about where evidence is lacking and help guide further needed research by NASS and other societies.

❖ Step 7: Formulation of Evidence-Based Recommendations and Incorporation of Expert Consensus

Work groups held webcasts to discuss the evidence-based answers to the clinical questions, the grades of recommendations and the incorporation of expert consensus. Expert consensus has been incorporated only where Level I-IV evidence is insufficient and the work group has deemed that a recommendation is warranted. Transparency in the incorporation of consensus is crucial, and all consensus-based recommendations made in this guideline very clearly indicate that Level I-IV evidence is insufficient to support a recommendation and that the recommendation is based only on expert consensus.

Consensus Development Process

Voting on guideline recommendations was conducted using a modification of the nominal group technique in which each work group member independently and anonymously ranked a recommendation on a scale ranging from 1 (“extremely inappropriate”) to 9 (“extremely appropriate”). Consensus was obtained when at least 80% of work group members ranked the recommendation as 7, 8 or 9. When the 80% threshold was not attained, up to three rounds of discussion and

voting were held to resolve disagreements. If disagreements were not resolved after these rounds, no recommendation was adopted.

After the recommendations were established, work group members developed the guideline content, addressing the literature which supports the recommendations.

❖ Step 8: Submission of the Draft Guidelines for Review/Comment
Guidelines were submitted to the full Evidence-based Guideline Development Committee, the Clinical Care Council Director and the Advisory Panel for review and comment. The Advisory Panel is comprised of representatives from physical medicine and rehab, pain medicine/management, orthopedic surgery, neurosurgery, anesthesiology, rheumatology, psychology/psychiatry and family practice. Revisions to recommendations were considered for incorporation only when substantiated by a preponderance of appropriate level evidence.

❖ Step 9: Submission for Board Approval
After any evidence-based revisions were incorporated, the drafts were prepared for NASS Board review and approval. Edits and revisions to recommendations and any other content were considered for incorporation only when substantiated by a preponderance of appropriate level evidence.

❖ Step 10: Submission for Endorsement, Publication and National Guideline Clearinghouse (NGC) Inclusion
Following NASS Board approval, the guidelines were slated for publication, submitted for endorsement to all appropriate societies and submitted for inclusion in the National Guidelines Clearinghouse (NGC). No revisions were made at this point in the process, but comments have been and will be saved for the next iteration.

❖ Step 11: Identification and Development of Performance Measures
The recommendations will be reviewed by a group experienced in performance measure development (eg, the AMA Physician's Consortium for Performance Improvement) to identify those recommendations rigorous enough for measure development. All relevant medical specialties involved in the guideline development and at the Consortium will be invited to collaborate in the development of evidence-based performance measures related to spine care.

This guideline will be pilot-tested among spine care specialists and primary care physicians for one year following publication. Findings of the pilot test will be considered to inform future guideline development.

❖ Step 12: Review and Revision Process

The guideline recommendations will be reviewed every three years by an EBM-trained multidisciplinary team and revised as appropriate based on a thorough review and assessment of relevant literature published since the development of this version of the guideline.

III. Recommendations Regarding Antibiotic Prophylaxis in Spine Surgery

A. Efficacy

For patients undergoing spine surgery, does antibiotic prophylaxis result in decreased infection rates compared to patients who do not receive prophylaxis?

Patients undergoing spine surgery should receive preoperative prophylactic antibiotics.

Grade of Recommendation: B

Barker et al described a meta-analysis based on a systematic review of the literature concerning the efficacy of prophylactic antibiotics on the incidence of postoperative spinal infection.[1] By pooling data from six randomized controlled trials (RCTs), they found a 2.2% (10 of 451) infection rate if antibiotics were given and a 5.9% (23 of 392) infection rate if antibiotics were not administered. Whereas each of the individual studies did not find a statistical difference, the pooled data did ($p<.01$). In critique of this analysis, the individual studies included in the meta-analysis did not show a statistically significant difference in infection rate with antibiotic use. However, the pooled results did show a significantly lower rate of infection with prophylactic antibiotic use. These data offer Level II evidence that antibiotics can lead to lower rates of infection for general spine surgical procedures.

Pavel et al reported a prospective, randomized, control trial comparing the use of antibiotic prophylaxis with cephalozidine with a placebo on the rate of postoperative infection in orthopedic surgical procedures.[18] When separately analyzed, the infection rate after spinal procedures was 9.2% in the placebo group, compared to 3% in the group who received cephalozidine. In critique of this study, the numbers were too small in the spine subgroup to detect a statistically significant difference. While this is a Level I study relative to orthopedic procedures, it provides Level II evidence that the use of perioperative cephalosporin antibiotic can significantly reduce the rate of perioperative infection in the subgroup of patients undergoing orthopedic spinal procedures.

Rubinstein et al conducted a double-masked, randomized, controlled trial comparing the efficacy of cefazolin prophylaxis in 141 patients who underwent "clean" spinal surgery.[27] A 12.7% rate of wound infection occurred in the placebo group and a 4.3% rate was found in the antibiotic group. Details of the two

groups concerning the use of instrumentation were not reported. In critique of this study, the influence of potentially influential covariables, such as the use of instrumentation, was not analyzed. Although the data demonstrate a strong trend in favor of prophylaxis, it did not reach statistical significance indicating that the study was underpowered. Based on the above critique, these data offer Level II evidence that intravenous cefazolin prophylaxis decreases the chance for postoperative infection after spinal surgery.

Primarily retrospective analyses of approximately 3000 patients in a number of Level IV studies demonstrated low postoperative infection rates with the use of prophylactic antibiotics.[5,9,11,16,19,24,28,37] However, these studies were systematically excluded if they lacked a control of patients who did not receive antibiotic prophylaxis. Some of these studies had additional methodological shortcomings that warranted exclusion, such as low sample size or lack of description of the antibiotic protocol. Although these were reasonably executed studies with substantial numbers of patients who underwent instrumented spinal fusion, two additional references were excluded because of nonrepresentative patient populations.[19,31] They predominantly included myelodysplastic and cerebral palsy patients, who are both known to have high postoperative infection rates.

Future Directions for Research

The North American Spine Society believes that deliberately exposing patients to infection and its risk of complications in an appropriately powered study (Appendix F) to satisfy the formality of producing Level I evidence of a trend already evident from the meta-analysis of smaller studies would be unethical. For practical purposes, the North American Spine Society is satisfied to base its recommendations for the use of prophylactic antibiotics on the results of existing data, and does not call for a definitive study to be conducted.

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For patients undergoing spine surgery *without* spinal implants, does antibiotic prophylaxis result in decreased infection rates as compared to patients who do not receive prophylaxis?

Prophylactic antibiotics are recommended to decrease the rate of spinal infections following uninstrumented lumbar spinal surgery.

Grade of Recommendation: B

Luer et al described a retrospective study comparing postoperative infections after laminectomy/microdiscectomy with control cases.[24] The overall incidence of infection after this procedure was 7% (22 of 315 patients). The authors found no difference in the type or frequency of antibiotic agent administered for prophylaxis; however, they did find that a higher percentage of patients in the infected group received antibiotics more than two hours before incision. In critique of this study, it was a retrospective review. However, it included a homogenous group of patients undergoing a single type of uninstrumented procedure. These data provide Level III evidence that antibiotic prophylaxis with cefazolin should be administered preoperatively within two hours of skin incision.

Piotrowski et al performed a retrospective study of 5041 patients, evaluating the rate of postoperative discitis during two time periods: one in which perioperative antibiotics were given, and one in which they were not.[31] During the former, the rate of discitis was 0.6%; during the latter, it was 2.3%. This was statistically significant. There were no other reported differences during these two time periods. In critique of this large study, while it was stated that first or second generation cephalosporins were given, the dosing protocol was not detailed. This study offers Level III evidence that perioperative antibiotics lower the infection rate at the level of the disc after lumbar disc surgery.

In a nonstandardized spinal technique, a study conducted by Rohde et al provides Level III evidence that an intradiscal sponge impregnated with gentamicin decreases the rate of postoperative discitis.[38] However, it should be noted that this study has not been replicated in the spinal literature.

Future Directions for Research
Based on the remarkably low infection rate cited in the Rohde report, further study on the use of collagen or other carriers for local antibiotic treatments could provide useful data.

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For patients undergoing spine surgery *with* spinal implants, does antibiotic prophylaxis result in decreased infection rates as compared to patients who do not receive prophylaxis?

Prophylactic antibiotics are recommended to decrease the rate of infections following instrumented spine fusion.

Grade of Recommendation: C

Beiner et al conducted a review of current treatment recommendations for postoperative wound infections in spine patients.[1] This study contains a good discussion of the epidemiology and risk factors, such as malnutrition. There is a review of prophylactic antibiotic regimens, most of which have also been addressed in the current critical review. There is mention of mechanical treatments such as ingress/egress suction irrigation systems and Vacuum Assisted Closure (VAC) dressing. In critique, this review article is of limited usefulness in addressing the question of efficacy of antibiotics in instrumented patients. This article offers Level V evidence (expert opinion) that prophylactic antibiotics decrease the infection rate in spinal surgery.

Rechtine et al described a retrospective case series of 235 consecutive fracture patients.[6] Of the 235 patients, 117 underwent surgical stabilization. Of the 117 patients, 12 suffered a perioperative infection, two had a staphylococcal infection, and 10 had a polymicrobial infection with gram negative and gram positive organisms. There was a statistically higher infection rate in completely neurologically injured patients compared to those with no deficit or incomplete injuries. In critique, the study was designed to assess the incidence of spinal infection in a spine trauma population. It offers Level IV evidence supporting the efficacy of prophylactic antibiotics in instrumented spinal surgery in patients with incomplete cord injury or in spinal fractures without cord injury. However, in the subgroup with spinal cord injury, infections were more likely a result of multiple organisms including gram negative species. This study raises compelling questions about antibiotic choice for prophylaxis in spinal cord injury patients.

Wimmer et al performed a prospective series detailing antibiotic prophylaxis in an instrumented spinal fusion population.[8] There were 110 patients with Cotrel – Doubassait (CD) or Moss Miami instrumentation. Of the 110 patients, 56 were instrumented for painful spondylolisthesis and 54 for scoliosis. Two grams of cefamandole were given preoperatively followed by three postoperative doses of 2 grams per day for three days. One infection was reported early in the spondylolisthesis group and one late infection was reported in the scoliosis group. The authors concluded that this prophylactic regimen was effective in decreasing the expected infection rate in this instrumented group. This study offers Level IV evidence that perioperative prophylactic antibiotics lowered the

infection rates in instrumented spinal surgery when compared to previously reported infection rates.

Future Directions for Research

Recommendation #1:

A case controlled study is suggested, utilizing available national databases to determine the relative efficacy of antibiotic prophylaxis in single-level, instrumented cases.

Recommendation #2:

A series of randomized, controlled studies is suggested, each dealing with a specific subpopulation defined by diagnosis and procedure.

Efficacy (Instrumented) References

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B. Protocol

For patients receiving antibiotic prophylaxis prior to spine surgery, what are the recommended drugs, their dosages and time of administration resulting in decreased postoperative infection rates?

Patients undergoing spine surgery should receive preoperative prophylactic antibiotics to decrease infection rates. The superiority of one agent or schedule over any other has not been clearly demonstrated.

Grade of Recommendation: B

Pons et al described a prospective, randomized trial comparing perioperative antibiotic protocols that included either 2 g ceftizoxime or 1 g vancomycin plus 80 gentamicin in 826 patients who underwent various clean neurosurgical procedures that included spine surgeries.[30] Wound site infection was reported in 1.18% of patients in the ceftizoxime group and 1.24% in the vancomycin/gentamicin group. Spine procedures had a 2.75% rate of infection overall; 2.8% in the ceftizoxime group and 2.7% in the vancomycin/gentamicin group. Agents were given one hour before skin incision. In critique of this study, spine surgeries were not analyzed independently for the influence of diagnosis, length of surgery and the use of hardware. These data offer Level II evidence that either antibiotic protocol yields similar infection rates after spine surgeries.

Rubinstein et al reported a double-blind, randomized, controlled trial comparing the efficacy of cefazolin prophylaxis in 141 patients who underwent “clean” spinal surgery.[36] There was a 12.7% rate of wound infection in the placebo group, while a 4.3% rate was found in the antibiotic group. Details of the two groups concerning the use of instrumentation were not reported. In critique of this study, the influence of potentially influential covariables, such as the use of instrumentation, was not analyzed. While the data demonstrate a strong trend in favor of prophylaxis, it did not reach statistical significance indicating that the study was underpowered. Based on the above critique, these data offer Level II evidence that intravenous cefazolin prophylaxis decreases the chance for postoperative infection after spinal surgery.

Future Directions for Research

Recommendation #1:

Prospective, randomized, clinical trials are suggested to compare the efficacy of cephalosporins to aminoglycocides and other antibiotics.

Recommendation #2:

Prospective, randomized, clinical trials are suggested to compare different timing and dosage protocols, for example, single preoperative dose versus multiple dose protocols.

Protocol (Mixed Groups) References

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For patients receiving antibiotic prophylaxis prior to spine surgery *without* spinal implants, what are the recommended drugs, their dosages and time of administration resulting in decreased postoperative infections rates?

Review of the current literature does not allow recommendation of one specific antibiotic protocol or dosing regimen over another in the prevention of postoperative infections following uninstrumented spinal surgery.

Level of Evidence: II

Dobzyniak et al described the results of a retrospective study comparing the rates of postoperative infections in patients receiving single or multiple dosing regimens.[10] The rate of postoperative infection in patients who underwent uninstrumented laminotomy/discectomy was 1.15% (5 of 435) if they received multiple doses of prophylactic antibiotics whereas it was 1.49% (3 of 201) in those who received only a single dose preoperatively. No statistical difference between these rates was detected. The antibiotic protocol was cephazolin, 1 g in 525 patients, clindamycin, 500 mg in 46 patients, and vancomycin, 1 g in 24 patients.

In critique of this study, the findings are weakened by the absence of data on the exact dosing for the "multiple dose" patients. The investigators did not analyze patient variables that could have potentially influenced the development of infection, such as comorbidities (eg, diabetes). In addition, the study did not compare antibiotic prophylaxis versus no prophylaxis. The current data provides Level III evidence that a single or multiple dose antibiotic regimen results in low (1-1.5%) infection rates.

Klekamp et al performed a retrospective review comparing 35 patients with postoperative methicillin-resistant Staphylococcus aureas (MRSA)infection to 35 uninfected control patients in order to determine risk factors.[20] Regarding antibiotic prophylaxis, 19% of patients in the MRSA infected group received vancomycin at the time of index surgery, while 46% of the control group patients did. The authors found that lymphopenia, history of chronic infections, alcohol abuse, recent hospitalization and prolonged postoperative wound drainage were significant risk factors for MRSA infection. In critique of this study, the authors did not state which prophylaxis regimen was used if vancomycin was not administered; the reader is left to assume that it is cefazolin or a similar agent. There was an equivalent rate of instrumented cases in the infected and noninfected groups; however, conclusions regarding the efficacy of vancomycin prophylaxis based only on the presence of instrumented fusion are difficult to draw. This study offers Level III evidence that vancomycin prophylaxis is more effective than other agents in the presence of the identified risk factors.

Luer et al detailed a retrospective, comparative study evaluating postoperative infections after laminectomy/microdiscectomy.[23] The overall incidence of infection after this procedure was 7% (22 of 315 patients). The authors found no difference in the type or frequency of antibiotic agent administered for prophylaxis; however, they did find that a higher percentage of patients in the infected group received antibiotics more than two hours before incision. One gram of cefazolin was given at the beginning (before) the procedure. No further doses were given. In critique of this study, it was a retrospective review. However, it included a homogenous group of patients undergoing a single type of uninstrumented procedure. These data provide Level III evidence that antibiotic prophylaxis with cefazolin should be administered preoperatively within two hours of skin incision.

Pons et al described a prospective, randomized trial comparing perioperative antibiotic protocols that included either 2 g ceftizoxime or 1 g vancomycin plus 80 mg gentamicin in 826 patients who underwent various clean neurosurgical procedures that included spine surgeries.[30] Wound site infection was reported in 1.18% of patients in the ceftizoxime group and 1.24% in the vancomycin/gentamicin group. Spine procedures had a 2.75% rate of infection overall; 2.8% in the ceftizoxime group and 2.7% in the vancomycin/gentamicin group. Agents were given one hour before skin incision. In critique of this study, spine surgeries were not analyzed independently for the influence of diagnosis, length of surgery and the use of hardware. These data offer Level II evidence that either antibiotic protocol yields similar infection rates after spine surgeries.

In a nonstandardized spinal technique, a study conducted by Rohde, et al. provides Level III evidence that an intradiscal sponge impregnated with gentamicin decreases the rate of postoperative discitis.[36] However, it should be noted that this study has not been replicated in the spinal literature.

Future Directions for Research

Recommendation #1:

Prospective, comparative drug studies are suggested to determine optimal antibiotic prophylaxis regimen.

Recommendation #2:

Prospective, comparative studies are suggested to determine optimal dosing regimens for antibiotic prophylaxis.

Recommendation #3:

A case controlled study is suggested utilizing available national databases to determine the relative efficacy of different antibiotic prophylactic protocols in single-level, uninstrumented cases.

Protocol (Noninstrumented) References

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30. Pons VG, Denlinger SL, Guglielmo BJ, et al. Ceftizoxime versus vancomycin and gentamicin in neurosurgical prophylaxis: a randomized, prospective, blinded clinical study. *Neurosurgery.* 1993;33(3):416-422; discussion 422-423.

31. Quigley KJ, Place HM. The role of debridement and antibiotics in gunshot wounds to the spine. *J Trauma.* 2006;60(4):814-819; discussion 819-820.

32. Rechtine G, Saunders DS. From the operating room... where an old problem is solved by a new technique. *Spine J.* 2006;6(2):214-216.

33. Rhoten RL, Murphy MA, Kalfas IH, Hahn JF, Washington JA. Antibiotic penetration into cervical discs. *Neurosurgery.* 1995;37(3):418-421.

34. Riley LH, 3rd. Prophylactic antibiotics for spine surgery: description of a regimen and its rationale. *J South Orthop Assoc*. 1998;7(3):212-217.

35. Rimoldi RL, Haye W. The use of antibiotics for wound prophylaxis in spinal surgery. *Orthop Clin North Am.* 1996;27(1):47-52.

36. Rohde V, Meyer B, Schaller C, Hassler WE. Spondylodiscitis after lumbar discectomy. Incidence and a proposal for prophylaxis. *Spine.* 1998;23(5):615-620.

37. Rubinstein E, Findler G, Amit P, Shaked I. Perioperative prophylactic cephazolin in spinal surgery. A double-blind placebo-controlled trial. *J Bone Joint Surg Br.* J1994;76(1):99-102.

38. Savitz SI, Lee LV, Goldstein HB. The risk of wound infection in lumbar disk surgery. *Mt Sinai J Med.* 1991;58(2):179-182.

39. Savitz SI, Savitz MH, Goldstein HB, Mouracade CT, Malangone S. Topical irrigation with polymyxin and bacitracin for spinal surgery. *Surg Neurol.* 1998;50(3):208-212.

40. Savitz MH, Malis LI, Savitz SI. Efficacy of prophylactic antibiotic therapy in spinal surgery: a meta-analysis. *Neurosurgery.* 2003;53(1):243-244; author reply 244-245.

41. Schnoring M, Brock M. [Prophylactic antibiotics in lumbar disc surgery: analysis of 1,030 procedures]. *Zentralbl Neurochir.* 2003;64(1):24-29.

42. Swoboda SM, Merz C, Kostuik J, Trentler B, Lipsett PA. Does intraoperative blood loss affect antibiotic serum and tissue concentrations? *Arch Surg.* 1996;131(11):1165-1171; discussion 1171-1162.

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44. Walters R, Rahmat R, Shimamura Y, Fraser R, Moore R. Prophylactic cephazolin to prevent discitis in an ovine model. *Spine.* 2006;31(4):391-396.

45. Warnke JP, Wildfeuer A, Eibel G, Pfaff G, Klammer A. Pharmacokinetics of ampicillin/sulbactam in patients undergoing spinal microneurosurgical procedures. *Int J Clin Pharmacol Ther.* 1998;36(5):253-257.

For patients receiving antibiotic prophylaxis prior to spine surgery *with* spinal implants, what are the recommended drugs, their dosages and time of administration resulting in decreased postoperative infections rates?

A systematic review of the literature did not reveal any high quality comparative studies addressing this specific question. The evidence reviewed does indicate that certain subpopulations are prone to polymicrobial infections. These populations include, but may not be limited to, patients with neuromuscular scoliosis, myelodysplasia and traumatic complete spinal cord injury. Other potential subgroups may exist, but have not yet been identified in the literature.

In patients with risk factors for polymicrobial infection, it is recommended that appropriate broad spectrum antibiotics be considered when instrumented fusion is performed.

Grade of Recommendation: C

Kanafani et al described a case control study comparing risk factors in patients who did or did not develop infections.[5] All patients received antibiotics, although patients with infections more frequently received first generation as opposed to second generation cephalosporins. Also, there was a higher percentage of patients with instrumentation in the infection group. This paper offers Level III evidence that patients who require instrumented fusions have a higher rate of infection than patients who do not require such extensive procedures.

Labbe, et al. conducted a pediatric case control series studying surgical site infections.[6] The authors noted that a significantly higher number of infection patients had not received “optimal” antibiotic prophylaxis. Optimal prophylaxis was defined as being consistent with current CDC Surgical Infection Prevention Project recommendations. The authors concluded that infection rates are higher in patients with myelodysplasia; and gram negative and polymicrobial infections are more common in this subgroup. In critique of this study, the patient population was a pediatric population. This study provides Level IV evidence that, in children, optimal antibiotic administration is associated with lower wound infection rates. Children with myelodysplasia are at risk for polymicrobial infections and may benefit from broader spectrum antibiotics.

Rechtine et al detailed a case series of 235 consecutive fracture patients.[8] Of the 235 patients, 117 underwent surgical stabilization. Of the 117 patients undergoing surgical stabilization, 12 suffered a perioperative infection. Two of the 12 had staph infections, while 10 of the 12 had polymicrobial infections with gram negative organisms. There was a statistically higher infection rate in patients with complete neurological injury compared with those with no deficit or incomplete injuries. Patients with spinal cord injuries are susceptible to polymicrobial

infection following instrumented spinal fusions. This study provides Level IV evidence that the use of broad spectrum antibiotics in this population may be considered.

Sponseller et al described a case series of children with neuromuscular scoliosis, examining risk factors for infection.[9] The effect of antibiotic prophylaxis is not discussed. Authors did note the polymicrobial spectrum and hypothesized that broader spectrum antibiotics may be appropriate in this population. In children with neuromuscular scoliosis, polymicrobial infections occur. This study provides Level IV evidence that broader spectrum antibiotics may be considered in this population.

Future Directions for Research

Recommendation #1:

A case controlled study is suggested utilizing available national databases to determine the relative efficacy of different antibiotic prophylactic protocols in single-level, instrumented cases.

Recommendation #2:

Case controlled studies are suggested to evaluate rates of polymicrobial infection stratified by comorbidities to identify other high risk populations.

Recommendation #3:

Prospective, randomized studies are suggested to evaluate the effect of broad spectrum antibiotic coverage in reducing infection rates in various high risk populations treated with instrumented fusion.

Protocol (Instrumented) References

1. Beiner JM, Grauer J, Kwon BK, Vaccaro AR. Postoperative wound infections of the spine. *Neurosurg Focus*. 2003;15(3):E14.

2. Christodoulou AG, Givissis P, Symeonidis PD, Karataglis D, Pournaras J. Reduction of postoperative spinal infections based on an etiologic protocol. *Clin Orthop Relat Res.* 2006;444:107-113.

3. Gruenberg MF, Campaner GL, Sola CA, Ortolan EG. Ultraclean air for prevention of postoperative infection after posterior spinal fusion with instrumentation: a comparison between surgeries performed with and without a vertical exponential filtered air-flow system. *Spine*. 2004;29(20):2330-2334.

4. Horwitz NH, Curtin JA. Prophylactic antibiotics and wound infection following laminectomy for lumbar disc herniation. *J Neurosurg*. 1975;43:727-731.

5. Kanafani ZA, Dakdouki GK, El-Dbouni O, Bawwab T, Kanj SS. Surgical site infections following spinal surgery at a tertiary care center in Lebanon: incidence, microbiology, and risk factors. *Scand J Infect Dis.* 2006;38(8):589-592.

6. Labbe AC, Demers AM, Rodrigues R, Arlet V, Tanguay K, Moore DL. Surgical-site infection following spinal fusion: a case-control study in a children's hospital. *Infect Control Hosp Epidemiol.* 2003;24(8):591-595.

7. Massie JB, Heller JG, Abitbol JJ, McPherson D, Garfin SR. Postoperative posterior spinal wound infections. *Clin Orthop Relat Res*. 1992(284):99-108.

8. Rechtine GR, Bono PL, Cahill D, Bolesta MJ, Chrin AM. Postoperative wound infection after instrumentation of thoracic and lumbar fractures. *J Orthop Trauma.* 2001;15(8):566-569.

9. Sponseller PD, LaPorte DM, Hungerford MW, Eck K, Bridwell KH, Lenke LG. Deep wound infections after neuromuscular scoliosis surgery: a multicenter study of risk factors and treatment outcomes. *Spine.* 2000;25(19):2461-2466.

10. Taylor GJ, Bannister GC, Calder S. Perioperative wound infection in elective orthopaedic surgery. *J Hosp Infect*. 1990;16(3):241-247.

C. Redosing

For patients receiving antibiotic prophylaxis prior to spine surgery, what are the intraoperative redosing recommendations for the recommended drugs (including dosages and time of administration) resulting in decreased postoperative infection rates?

Dosing regimens do not appear to affect infection rates. Although no study has shown any significant advantage to intraoperative redosing compared with a single dose, specific clinical situations may dictate additional doses (eg, length of surgery, comorbidities).

Level of Evidence: IV

Dobzyniak et al conducted a retrospective, historical, cohort comparison of roughly comparable groups of patients undergoing spinal surgery.[2] They reviewed a cohort of patients from 1993-1999 with 433 patients in the multiple dose group and 201 patients in the single dose group. No difference in infection rate was detected between the group treated with a single preoperative dose and a group treated with pre- and postoperative antibiotics. In critique of this study, the dosing protocol was changed arbitrarily mid course from multiple dosing to single dosing. The authors, from their retrospective review of the two cohort groups, recommend a single preoperative dose as redosing postoperatively did not have any effect. This study provides Level IV evidence that redosing may not be useful or effective in preventing postoperative infections.

Mastronardi et al performed a retrospective, cohort study of 973 clean neurosurgical cases, including cervical, thoracolumbar, instrumented and noninstrumented cases.[4] Patients received a single dose of ampicillin, 1 g and sublactam, 500 mg unless they had instrumentation or surgery was longer than 120 minutes. If surgery extended beyond 120 minutes, patients received teicoplanin, 400 mg. A second dose of teicoplanin, 400 mg was given to patients in surgeries of greater than four hours duration and procedures with blood loss greater than 1500 cc. No postoperative antibiotics were administered. Infection was defined by any one of the following: purulent discharge, serous discharge with positive culture, deep/superficial abscess or spondylodiscitis. Nine cases of infection were reported, of which four were staph coag negative, two were routine staph, one was kleibsiella and one was pseudomonas. Two cases meeting criteria for infection remained culture negative. In critique of this Level IV study, the authors admit that to make a meaningful determination, a much larger cohort would be needed to draw conclusions regarding the efficacy of redosing, since the difference in infection rates in “clean” cases is low to begin with.

Riley et al described a retrospective study of one year's patients (40) who had either simple discectomy or instrumented procedures.[6] Patients received 1.5 g cefuroxime preoperatively and every four hours for a 48-hour duration. Intravenous gentamycin (80 mg) was administered preoperatively, with redosing every six hours intraoperatively and every eight hours postoperatively for a 48-hour duration. No infections occurred in the 40 patients. The study provides a good discussion of the basic science behind the use of cefuroxime and gentamicin as readily disc eluting antibiotics as compared with cephazolin as a less disc eluting antibiotic. In critique of this study, it was a retrospective, chart review evaluating postoperative infection in an extremely small cohort of patients. With such a small sample size, no conclusions regarding efficacy of a specific regimen can be drawn. This is an extension of a basic science study looking at the penetration of cephazolin, gentamicin and cefuroxime into disc tissue. It provides Level IV evidence that redosing in a small cohort resulted in no infections.

Future Directions for Research

Recommendation #1:

A case controlled study is suggested utilizing available national databases to determine the relative efficacy of redosing antibiotic prophylaxis in specific patient populations undergoing spine surgery.

Recommendation #2:

A series of randomized controlled studies evaluating dosing regimens is recommended; each study could address a specific subpopulation defined by diagnosis, procedure and comorbidity.

Redosing References

1. Barker FG, 2nd. Efficacy of prophylactic antibiotic therapy in spinal surgery: a meta-analysis. *Neurosurgery.* 2002;51(2):391-400; discussion 400-391.

2. Dobzyniak MA, Fischgrund JS, Hankins S, Herkowitz HN. Single versus multiple dose antibiotic prophylaxis in lumbar disc surgery. *Spine.* 2003;28(21):E453-455.

3. Horwitz NH, Curtin JA. Prophylactic antibiotics and wound infection following laminectomy for lumbar disc herniation. *J Neurosurg.* 1975;43:727-731.

4. Mastronardi L, Tatta C. Intraoperative antibiotic prophylaxis in clean spinal surgery: a retrospective analysis in a consecutive series of 973 cases. *Surg Neurol.* 2004;61(2):129-135; discussion 135.

5. Pons VG, Denlinger SL, Guglielmo BJ, et al. Ceftizoxime versus vancomycin and gentamicin in neurosurgical prophylaxis: a randomized, prospective, blinded clinical study. *Neurosurgery*. 1993;33(3):416-422; discussion 422-413.

6. Riley LH, 3rd. Prophylactic antibiotics for spine surgery: description of a regimen and its rationale. *J South Orthop Assoc.* 1998;7(3):212-217.

7. Rohde V, Meyer B, Schaller C, Hassler WE. Spondylodiscitis after lumbar discectomy. Incidence and a proposal for prophylaxis. *Spine.* 1998;23(5):615-620.

8. Savitz SI, Savitz MH, Goldstein HB, Mouracade CT, Malangone S. Topical irrigation with polymyxin and bacitracin for spinal surgery. *Surg Neurol.* 1998;50(3):208-212.

D. Discontinuation

For patients receiving antibiotic prophylaxis prior to spine surgery, does discontinuation of prophylaxis at 24 hours result in decreased or increased postoperative infection rates as compared to longer periods of administration?

A comprehensive review of the spine literature did not yield evidence to address the question related to the effect on postoperative infection rates of discontinuation of prophylaxis at 24 hours compared with longer periods of administration.

Future Directions for Research

Controlled studies are suggested comparing infection rates in spinal surgical patients who received antibiotics which were discontinued at 24 hours as compared with groups who received antibiotics for a longer period of time.

Discontinuation References

1. Beiner JM, Grauer J, Kwon BK, Vaccaro AR. Postoperative wound infections of the spine. *Neurosurg Focus.* 2003;15(3):E14.

2. Christodoulou AG, Givissis P, Symeonidis PD, Karataglis D, Pournaras J. Reduction of postoperative spinal infections based on an etiologic protocol. *Clin Orthop Relat Res.* 2006;444:107-113.

3. Ehrenkranz NJ, Richter EI, Phillips PM, Shultz JM. An apparent excess of operative site infections: analyses to evaluate false-positive diagnoses. *Infect Control Hosp Epidemiol.* 1995;16(12):712-716.

E. Wound Drains

For patients receiving antibiotic prophylaxis prior to spine surgery and who receive placement of wound drains at wound closure, does discontinuation of prophylaxis at 24 hours result in decreased or increased postoperative infection rates as compared to discontinuation of antibiotics at time of drain removal?

A comprehensive review of the literature did not yield evidence to address the question related to the effect on postoperative infection rates of the duration of prophylaxis in the presence of a wound drain.

The use of drains is not recommended as a means to reduce infection rates following single level surgical procedures.

Grade of Recommendation: I (Insufficient Evidence)

Payne et al described a randomized controlled trial of drain use in 205 patients undergoing a single level laminectomy without fusion. The patients were randomized to determine whether they would receive a wound drain. There was no difference between the groups in terms of infection rates. In critique, this study appears on the surface to provide Level I evidence. However, it was downgraded to Level II because it was substantially underpowered. It provides Level II evidence that drains have no effect on infection rates. For a single level nonfusion spine procedure a drain neither decreases nor increases the infection rate.

Future Directions for Research

Recommendation #1:

Controlled studies are suggested comparing infection rates in nonfusion and nonimplanted spinal surgical patients with drains and discontinuation at 24 hours as compared with longer duration prophylaxis.

Recommendation #2:

Controlled studies are suggested comparing infection rates in spinal surgical patients receiving spinal implants with drains and discontinuation at 24 hours as compared with longer duration prophylaxis.

Wound Drains References

1. Barker FG, 2nd. Efficacy of prophylactic antibiotic therapy in spinal surgery: a meta-analysis. *Neurosurgery.* 2002;51(2):391-400; discussion 400-391.

3. Bullock R, Van Dellen JR, Ketelbey W, et al. A double-blind placebo controlled trial of perioperative prophylactic antibiotics for elective surgery. *J Neurosurgery.* 1988;69:687-691.

4. Djinjian M, Lespresle E, Homs JB. Antibiotic prophylaxis during prolonged clean neurosurgery: result of a randomized double blind study using oxacillin. *J Neurosurgery.* 1990;73:383-386.

5. Geraghty J, Felly M. Antibiotic prophylaxis in neurosurgery: a randomized controlled trial. *J Neurosurgery.* 1984;60:724-726.

6. Guiboux JP, Ahlgren B, Patti JE, Bernhard M, Zervos M, Herkowitz HN. The role of prophylactic antibiotics in spinal instrumentation. A rabbit model. *Spine.* 1998;23(6):653-656.

7. Payne DH, Fischgrund JS, Herkowitz HN, Barry RL, Kurz LT, Montgomery DM. Efficacy of closed wound suction drainage after single-level lumbar laminectomy. *J Spinal Disord.* 1996;9(5):401-403.

8. Raves JJ, Slifkin M, Diamond DL. A bacteriological study comparing closed suction and simple conduit drainage. *Am J Surg.* 1984;148:618-620.

9. Rubinstein E, Findler G, Amit P, Shaked I. Perioperative prophylactic cephazolin in spinal surgery. A double-blind placebo-controlled trial. *J Bone Joint Surg Br.* 1994;76(1):99-102.

10. Young RG, Lawner PM. Perioperative antibiotic prophylaxis for prevention of postoperative neurosurgical infections: a randomized clinical trial. *J Neurosurgery.* 1987;66:701-705.

F. Body Habitus

For patients receiving antibiotic prophylaxis prior to spine surgery, should the recommended protocol differ based upon body habitus (eg, body mass index)?

Obese patients are at higher risk for postoperative infection, when given a standardized dose of antibiotic prophylaxis. In spite of this conclusion, the literature search did not yield sufficient evidence to recommend any specific modifications to antibiotic protocols for this specific population.

Level of Evidence: III

Olsen et al described a retrospective, case-control study, in which 41 patients with an infection after spinal surgery were compared to 178 without infection in order to determine potential risk factors.[7] The investigators' identified postoperative urinary incontinence, posterior approach, surgery for tumor and morbid obesity (BMI >35) as independent risk factors for postoperative wound infection. All patients received one or more doses of prophylactic cefazolin with or without an aminoglycoside or vancomycin with an aminoglycoside. Fusion or the use of instrumentation was not found to be a risk for infection. In critique of this study, it was a retrospective review of a limited number of patients. In addition, the specific antibiotic regimens given to obese and nonobese patients were not analyzed. However, these data offer Level III evidence that morbid obesity defined as a BMI greater than 35 is an independent risk factor for infection despite the use of a standardized antibiotic prophylaxis regimen. This study does not offer any evidence concerning specific antibiotic prophylaxis for obese patients.

Wimmer et al performed a retrospective study of 850 spinal procedures, in which all patients received 2 gm of cefazolin IV perioperatively and a single additional injection if the surgery lasted more than three hours.[10] In an analysis of the 22 patients who developed an infection, six were obese. Analyzed as a subgroup, obesity was found to be a risk factor with a p-value <0.04. In critique of this study, there was no analysis of adjustments made to the antibiotic regimen in relation to the patients' BMI. While other risk factors were considered more important, obesity was found to be an independent risk factor for postoperative infection in this retrospective review despite the use of prophylactic antibiotics. This study offers Level IV evidence that obesity is a risk factor for perioperative infection, but does not offer clear evidence for a specific adjustment of antibiotic prophylaxis in obese patients.

Future Directions for Research

Prospective, randomized clinical trials are suggested to evaluate the effect of antibiotic choice and altered dosing on infection rates in obese patients.

Body Habitus References

1. Andreshak TG, An HS, Hall J, Stein B. Lumbar spine surgery in the obese patient. *J Spinal Disord.* 1997;10(5):376-379.
2. Capen DA, Calderone RR, Green A. Perioperative risk factors for wound infections after lower back fusions. *Orthop Clin North Am.* 1996;27(1):83-86.
3. Kardaun JW, White LR, Shaffer WO. Acute complications in patients with surgical treatment of lumbar herniated disc. *J Spinal Disord.* 1990;3(1):30-38.
4. Lang R, Folman Y, Ravid M, Bental T, Gepstein R. Penetration of ceftriaxone into the intervertebral disc. *J Bone Joint Surg Am.* 1994;76(5):689-691.
5. Luer MS, Hatton J. Appropriateness of antibiotic selection and use in laminectomy and microdiskectomy. *Am J Hosp Pharm.* 1993;50(4):667-670.
6. Marmor L. Surgery for osteoarthritis. *Geriatrics.* 1972;27(2):89-95.
7. Olsen MA, Mayfield J, Lauryssen C, et al. Risk factors for surgical site infection in spinal surgery. *J Neurosurg.* 2003;98(2 Suppl):149-155.
8. Telfeian AE, Reiter GT, Durham SR, Marcotte P. Spine surgery in morbidly obese patients. *J Neurosurg.* 2002;97(1 Suppl):20-24.
9. Walters R, Rahmat R, Shimamura Y, Fraser R, Moore R. Prophylactic cephazolin to prevent discitis in an ovine model. *Spine.* 2006;31(4):391-396.
10. Wimmer C, Gluch H, Franzreb M, Ogon M. Predisposing factors for infection in spine surgery: a survey of 850 spinal procedures. *J Spinal Disord.* 1998;11(2):124-128.

G. Comorbidities

For patients receiving antibiotic prophylaxis prior to spine surgery, do comorbidities (other than obesity) such as diabetes, smoking, nutritional depletion and immunodeficiencies alter the recommendations for antibiotic prophylaxis?

Based on the literature reviewed to address this question, information was only available on patients with diabetes, older age or instrumentation. While this information suggests that these three groups are at higher risk for postoperative infection when given a standardized dose of antibiotic prophylaxis, the literature search did not yield sufficient evidence to recommend any specific modifications to antibiotic protocols for this specific population.

Level of Evidence: III

Kanafani et al described a case control study comparing risk factors in patients who did or did not develop infections.[4] This study reported the incidence of postoperative infection after spinal surgeries at a single institution. They also compared infected cases with control samples from the same population in order to identify risk factors. The presence of diabetes, older age, and implants (spinal hardware) were the only three variables that were significantly higher in the infected group. Both cases and controls received preoperative antibiotic prophylaxis, but infected cases received a first generation cephalosporin more often. The authors documented infection rates for patients who received first generation cephalosporin, second generation, third generation cephalosporin, or a glycopeptide. The average duration of antibiotic administration was 2.2 days in infected cases and 1.5 hours in controls. In critique of this study, the efficacy of antibiotic prophylaxis could not be analyzed for instrumented versus noninstrumented cases. The study offers Level III evidence that diabetes, older age and the use of instrumentation are risk factors for postoperative wound infection despite the use of perioperative antibiotic prophylaxis. This study does not offer any evidence suggesting alterations in antibiotic prophylaxis in the presence of specific co-morbidities.

Piotrowski et al performed a retrospective study of 5041 patients evaluating the rate of postoperative discitis during two time periods: one in which perioperative antibiotics were given, and one in which they were not.[6] During the former, the rate of discitis was 0.6%; during the latter, it was 2.3%. This was statistically significant. There were not other reported differences during these two time periods. In critique of this study, “lumbar disc surgery” was not defined as either

discectomies. While it was stated that first or second generation cephalosporins were given, the dosing protocol was not detailed. This study offers Level III evidence that perioperative antibiotics lower the infection rate after lumbar disc surgery. It does not offer any evidence regarding the influence of comorbidities on the efficacy of specific antibiotic prophylaxis regimen.

Future Directions for Research

Recommendation #1:

Prospective, randomized clinical trials are suggested to evaluate the effect of antibiotic choice and altered dosing on infection rates in potentially high risk patients.

Recommendation #2:

A case controlled study is suggested to help identify other potential comorbidities leading to higher infection rates in patients undergoing spine surgery.

Comorbidities References

1. Beiner JM, Grauer J, Kwon BK, Vaccaro AR. Postoperative wound infections of the spine. Neurosurg Focus. Sep 15 2003;15(3):E14.
2. Capen DA, Calderone RR, Green A. Perioperative risk factors for wound infections after lower back fusions. *Orthop Clin North Am.* 1996;27(1):83-86.
3. Honan M, White GW, Eisenberg GM. Spontaneous infectious discitis in adults. *Am J Med.* 1996;100(1):85-89.
4. Kanafani ZA, Dakdouki GK, El-Dbouni O, Bawwab T, Kanj SS. Surgical site infections following spinal surgery at a tertiary care center in Lebanon: incidence, microbiology, and risk factors. *Scand J Infect Dis.* 2006;38(8):589-592.
5. Pigrau C, Almirante B, Flores X, et al. Spontaneous pyogenic vertebral osteomyelitis and endocarditis: incidence, risk factors, and outcome. *Am J Med*. 2005;118(11):1287.
6. Piotrowski WP, Krombholz MA, Muhl B. Spondylodiscitis after lumbar disk surgery. *Neurosurg Rev.* 1994;17(3):189-193.
7. Schnoring M, Brock M. [Prophylactic antibiotics in lumbar disc surgery: analysis of 1,030 procedures]. *Zentralbl Neurochir.* 2003;64(1):24-29.
8. Stambough JL, Beringer D. Postoperative wound infections complicating adult spine surgery. *J Spinal Disord.* 1992;5(3):277-285.

Special Note about Exclusion of Pharmokinetic Studies

Our literature search provided several references to the studies concerned with the pharmacokinetics of various antibiotics used in surgical prophylaxis. Several studies were concerned with the measuring concentration of antibiotic in the blood and into various soft tissue compartments in the operative field, including the intervertebral disc and cerebrospinal fluid. (Warnke et al, Lang et al, Tai et al, Klekner et al, Boscardin et al.) Other reports added the effect of intraoperative blood loss on serum antibiotic levels (Swoboda et al). Clearly such studies are valuable contributions to our understanding and improving the process of reducing perisurgical infection rates. These studies did not, however, provide direct evidence, specifically concerning observed clinical infection rates. These studies are, therefore, not included in the evidentiary tables, nor in the guideline text.

IV. APPENDICES

APPENDIX A:
Levels of Evidence for Primary Research Question[1]

	Types of Studies			
	Therapeutic Studies – Investigating the results of treatment	Prognostic Studies – Investigating the effect of a patient characteristic on the outcome of disease	Diagnostic Studies – Investigating a diagnostic test	Economic and Decision Analyses – Developing an economic or decision model
Level I	• High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic Review[2] of Level I RCTs (and study results were homogenous[3])	• High quality prospective study[4] (all patients were enrolled at the same point in their disease with ≥ 80% follow-up of enrolled patients) • Systematic review[2] of Level I studies	• Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) • Systematic review[2] of Level I studies	• Sensible costs and alternatives; values obtained from many studies; with multiway sensitivity analyses • Systematic review[2] of Level I studies
Level II	• Lesser quality RCT (eg, < 80% follow-up, no blinding, or improper randomization) • Prospective[4] comparative study[5] • Systematic review[2] of Level II studies or Level 1 studies with inconsistent results	• Retrospective[6] study • Untreated controls from an RCT • Lesser quality prospective study (eg, patients enrolled at different points in their disease or <80% follow-up.) • Systematic review[2] of Level II studies	• Development of diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) • Systematic review[2] of Level II studies	• Sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity analyses • Systematic review[2] of Level II studies
Level III	• Case control study[7] • Retrospective[6] comparative study[5] • Systematic review[2] of Level III studies	• Case control study[7]	• Study of non-consecutive patients; without consistently applied reference "gold" standard • Systematic review[2] of Level III studies	• Analyses based on limited alternatives and costs; and poor estimates • Systematic review[2] of Level III studies
Level IV	Case series[8]	Case series	• Case-control study • Poor reference standard	• Analyses with no sensitivity analyses
Level V	Expert Opinion	Expert Opinion	Expert Opinion	Expert Opinion

1. A complete assessment of quality of individual studies requires critical appraisal of all aspects of the study design.
2. A combination of results from two or more prior studies.
3. Studies provided consistent results.
4. Study was started before the first patient enrolled.
5. Patients treated one way (eg, cemented hip arthroplasty) compared with a group of patients treated in another way (eg, uncemented hip arthroplasty) at the same institution.
6. The study was started after the first patient enrolled.
7. Patients identified for the study based on their outcome, called "cases"; eg, failed total arthroplasty, are compared to those who did not have outcome, called "controls"; eg, successful total hip arthroplasty.
8. Patients treated one way with no comparison group of patients treated in another way.

APPENDIX B:

Grades of Recommendation for Summaries or Reviews of Studies

A: Good evidence (Level I studies with consistent finding) for or against recommending intervention.

B: Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention.

C: Poor quality evidence (Level IV or V studies) for or against recommending intervention.

I: Insufficient or conflicting evidence not allowing a recommendation for or against intervention.

APPENDIX C:

Protocol for NASS Literature Searches

One of the most crucial elements of evidence analysis to support development of recommendations for appropriate clinical care or use of new technologies is the comprehensive literature search. Thorough assessment of the literature is the basis for the review of existing evidence, which will be instrumental to these activities.

Background

It has become apparent that the number of literature searches being conducted at NASS is increasing and that they are not necessarily conducted in a consistent manner between committees/projects. Because the quality of a literature search directly affects the quality of recommendations made, a comparative literature search was undertaken to help NASS refine the process and make recommendations about how to conduct future literature searches on a NASS-wide basis.

In November-December 2004, NASS conducted a trial run at new technology assessment. As part of the analysis of that pilot process, the same literature searches were conducted by both an experienced NASS member and a medical librarian for comparison purposes. After reviewing the results of that experiment and the different strategies employed for both searches, it was the recommendation of NASS Research staff that a protocol be developed to ensure that all future NASS searches be conducted consistently to yield the most comprehensive results. While it is recognized that some searches occur outside the Research and Clinical Care Councils, it is important that all searches conducted at NASS employ a solid search strategy, regardless of the source of the request. To this end, this protocol has been developed and NASS-wide implementation is recommended.

Protocol for NASS Literature Searches

The NASS Research Department has a relationship with Northwestern University's Galter Health Sciences Library. When it is determined that a literature search is needed, NASS research staff will work with the requesting parties and Galter to run a comprehensive search employing *at a minimum* the following search techniques:

1. A preliminary search of the evidence will be conducted using the following clearly defined search parameters (as determined by the content experts). The following parameters are to be provided to research staff to facilitate this search.

- Time frames for search
- Foreign and/or English language
- Order of results (chronological, by journal, etc.)
- Key search terms and connectors, with or without MeSH terms to be employed
- Age range
- Answers to the following questions:
  - Should duplicates be eliminated between searches?
  - Should searches be separated by term or as one large package?
  - Should human studies, animal studies or cadaver studies be included?

This preliminary search should encompass a search of the Cochrane database when access is available.

2. Search results with abstracts will be compiled by Galter in EndNote™ software. Galter typically responds to requests and completes the searches within two to five days. Results will be forwarded to the research staff, who will share it with the appropriate NASS staff member or requesting party(ies). (Research staff have access to EndNote™ software and will maintain a database of search results for future use/documentation.)

3. NASS staff shares the search results with an appropriate content expert (NASS Committee member or other) to assess relevance of articles and identify appropriate articles to review and on which to run a "related articles" search.

4. Based on content expert's review, NASS research staff will then coordinate with the Galter medical librarian the second level searching to identify relevant "related articles."

5. Galter will forward results to research staff to share with appropriate NASS staff member.

6. NASS staff share related articles search results with an appropriate content expert (NASS Committee member or other) to assess relevance of this second set of articles, and identify appropriate articles to review and on which to run a second "related articles" search.

7. NASS research staff will work with Galter library to obtain the 2nd related articles search results and any necessary full-text articles for review.

8. NASS members reviewing full-text articles should also review the references at the end of each article to identify additional articles which should be reviewed, but may have been missed in the search.

Protocol for Expedited Searches

At a minimum, numbers 1, 2 and 3 should be followed for any necessary expedited search. Following #3, depending on the time frame allowed, deeper searching may be conducted as described by the full protocol or request of full-text articles may occur. If full-text articles are requested, #8 should also be included. Use of the expedited protocol or any deviation from the full protocol should be documented with explanation.

Following these protocols will help ensure that NASS recommendations are (1) based on a thorough review of relevant literature; (2) are truly based on a uniform, comprehensive search strategy; and (3) represent the current best research evidence available. Research staff will maintain a search history in EndNote,™ for future use or reference.

APPENDIX D:

Literature Search Parameters

Antibiotic Prophylaxis in Spine Surgery
Key Clinical Questions and Search Terms/Parameters

SEARCH PARAMETERS:

- Time frames for search: 1990-PRESENT
- Foreign and/or English language: ENGLISH ONLY
- Order of results (chronological, by journal, etc.): CHRONOLOGICAL
- Key search terms and connectors, with or without MeSH terms to be employed: LISTED WITH EACH QUESTION
- Age range: 18+
- Should duplicates be eliminated between searches? NO
- Should searches be separated by term or as one large package? ONE PACKAGE PER QUESTION
- Should human studies, animal studies or cadaver studies be included? HUMAN STUDIES ONLY

Question 1: For patients undergoing spine surgery, does antibiotic prophylaxis result in decreased infection rates as compared to patients who do not receive prophylaxis?
Search terms: (spine surgery AND antibiotic prophylaxis AND infection). See Key MeSH document for actual terms used.

Question 2: For patients undergoing spine surgery without spinal implants, does antibiotic prophylaxis result in decreased infection rates as compared to patients who do not receive prophylaxis?
Search terms: (spine surgery AND antibiotic prophylaxis AND infection) NOT (implants concept). These general concepts were used. See Key MeSH document for actual terms used.

Question 3: For patients undergoing spine surgery with spinal implants, does antibiotic prophylaxis result in decreased infection rates as compared to patients who do not receive prophylaxis?
Search terms: (spine surgery AND antibiotic prophylaxis AND infection AND implants concept). These general concepts were used. See Key MeSH document for actual terms used.

Question 4: For patients receiving antibiotic prophylaxis prior to spine surgery, what are the recommended drugs, their dosages and time of administration resulting in decreased postoperative infections rates?

Search terms: (spine surgery AND antibiotic prophylaxis AND infection) AND (drug therapy concept). These general concepts were used. See Key MeSH document for actual terms used.

Question 5: For patients receiving antibiotic prophylaxis prior to spine surgery without spinal implants, what are the recommended drugs, their dosages and time of administration resulting in decreased postoperative infections rates?
Search terms: (spine surgery AND antibiotic prophylaxis AND infection) AND (drug therapy concept) NOT (implants concept). These general concepts were used. See Key MeSH document for actual terms used.

Question 6: For patients receiving antibiotic prophylaxis prior to spine surgery with spinal implants, what are the recommended drugs, their dosages and time of administration resulting in decreased postoperative infections rates?
Search terms: (spine surgery AND antibiotic prophylaxis AND infection AND implants concept AND Drug therapy concept). These general concepts were used. See Key MeSH document for actual terms used.

Question 7: For patients receiving antibiotic prophylaxis prior to spine surgery, what are the intraoperative redosing recommendations for the recommended drugs (including dosages and time of administration) resulting in decreased postoperative infections rates?
Search terms: (spine surgery AND antibiotic prophylaxis AND infection AND Drug therapy concept) AND (dos* OR redos*) AND intraoperativ*. These general concepts were used. See Key MeSH document for actual terms used. The * is the truncation symbol used in PubMed, so in this case it picks up dose, dosage, redose, redosing, intraoperative, intraoperatively.

Question 8: For patients receiving antibiotic prophylaxis prior to spine surgery, does discontinuation of prophylaxis at 24 hours result in decreased or increased postoperative infection rates as compared to longer periods of administration?
Search terms: (spine surgery AND antibiotic prophylaxis AND infection) AND (discontinu* OR duration OR timing OR length). These general concepts were used. See Key MeSH document for actual terms used.

Question 9: For patients receiving antibiotic prophylaxis prior to spine surgery and who receive placement of wound drains at wound closure, does discontinuation of prophylaxis at 24 hours result in decreased or increased postoperative infection rates as compared to discontinuation of antibiotics at time of drain removal?

Search terms: (spine surgery AND antibiotic prophylaxis AND infection AND drainage concept). These general concepts were used. See Key MeSH document for actual terms used.

Question 10: For patients receiving antibiotic prophylaxis prior to spine surgery, how does the recommended protocol differ based upon body habitus (eg, body mass index)?
Search terms: (spine surgery AND antibiotic prophylaxis AND infection) AND Body Size concept. These general concepts were used. See Key MeSH document for actual terms used.

Question 11: For patients receiving antibiotic prophylaxis prior to spine surgery, do comorbidities such as diabetes, smoking, nutritional depletion and immunodeficiencies alter the recommendations for antibiotic prophylaxis?
Search terms: (spine surgery AND antibiotic prophylaxis AND infection) AND comorbidities concept. These general concepts were used. See Key MeSH document for actual terms used.

Antibiotic Prophylaxis in Spine Surgery: Key MeSH

Spine Surgery concept
Conditions/Areas of body – explode and use with surgery subheading
Spine – includes Thoracic Vertebrae, Cervical Vertebrae, Lumbar vertebrae, Invertebral Disk
Spinal Injuries – includes Spinal Fractures
Spinal Diseases – includes Spinal Curvatures, Spinal Osteophytosis, Kyphosis, Scoliosis, Spondylolisthesis, Intervertebral Disk Displacement, Spinal Stenosis,
Spinal Cord
Spinal Cord Diseases – includes Spinal Cord Compression, Spinal Neoplasms, Spinal Cord Injuries
Low Back Pain

Surgical Procedures of the Spine – explode and do not restrict by subheading
Spinal Fusion
Laminectomy
Diskectomy
Vertebroplasty – search as textword
Kyphoplasty – search as textword

Text Words to add

Spinal Surgery [All Fields]
Spine Surgery [All Fields]

Antibiotic Prophylaxis concept

Antibiotic Prophylaxis 1996 –
Antibiotics aka **Antibacterial Agents** 1966-1995
Antibacterial Agents [Pharmacological Action]
Antibiotic prophylaxis [Title]

Infection concept

Surgical Wound Infection
Postoperative Complications
Bacterial Infections
Intraoperative Period
Intraoperative Complications
Infection [Title]

Spinal Implants concept

Prostheses and Implants – includes Bone Screws, Bone Nails
Prosthesis Implantation
Instrumentation [subheading]
Instrumentation [title]
Orthopedic Fixation Devices – includes Internal Fixators
Vertebroplasty – search as textword
Kyphoplasty – search as textword

Drug administration and dosage concept

Administration and Dosage [subheading]
Drug Administration Schedule – includes Pulse Therapy, Drug
Drug Therapy
Drug Therapy [subheading]

Wound drain concept

Drainage – includes Suction

Body habitus concept

Body Mass Index
Body Size – includes Body Weight, Overweight, Obesity

Comorbidity concept

Comorbidity
Diabetes Mellitus
Smoking
Nutrition Disorders – includes Malnutrition, Deficiency Diseases
Immunologic Deficiency Syndromes
Immunocompromised Host

APPENDIX E:
Evidentiary Tables

Antibiotic Prophylaxis
- Efficacy (Mixed Groups)-

Question 1:
For patients undergoing spine surgery, does antibiotic prophylaxis result in decreased infection rates as compared to patients who do not receive prophylaxis?

-Evidentiary Table-

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Barker FG II. Efficacy of prophylactic antibiotic therapy in spinal surgery: a meta-analysis. *Neurosurgery.* 2002;51(2):391-400; discussion 400-391.	II	This study was a meta-analysis based on a systematic review of the literature concerning the efficacy of prophylactic antibiotics on the incidence of postoperative spinal infection. By pooling data from six RCTs, they found a 2.2% (10 of 451) infection rate if antibiotics were given and a 5.9% (23 of 392) infection rate if they were not given. Although each of the individual studies did not find a statistical difference, the pooled data did ($p<.01$).	In critique of this analysis, the individual studies included in the meta-analysis did not show a statistically significant difference in infection rate with antibiotic use. However, the pooled results did show a significantly lower rate of infection with prophylactic antibiotic use. These data offer Level II evidence that antibiotics can lead to lower rates of infection for general spine surgical procedures.
Pavel A, Smith RL, Ballard A. Larson IJ. Prophylactic antibiotics in elective orthopedic surgery: a prospective study of 1591 cases. *South Med J*. 1977;Suppl 1:50-55.	II	Prospective randomized control trial comparing the use of antibiotic prophylaxis with cephalozidine with a placebo on the rate of postoperative infection in orthopedic surgical procedures when separately analyzed the infection rate after spinal procedures was 9.2% in the placebo group, compared to 3% in the group who received cephalozidine.	In critique of this study, the numbers were too small in the spine subgroup to detect a statistically significant difference. While this is a Level I study relative to orthopedic procedures, it provides Level II evidence that the use of perioperative Cephalosporin antibiotic can significantly reduce the rate of perioperative infection in the subgroup of patients undergoing orthopedic

			spinal procedures.
Rubinstein E, Findler G, Amit P, Shaked I. Perioperative prophylactic cephazolin in spinal surgery. A double-blind placebo-controlled trial. J Bone Joint Surg Br. Jan 1994;76(1):99-102.	II	This study was a double-blind, randomized controlled trial comparing the efficacy of cefazolin prophylaxis in 141 patients who underwent “clean” spinal surgery. There was a 12.7% rate of wound infection in the placebo group, while a 4.3 %t rate was found in the antibiotic group. Details of the two groups concerning the use of instrumentation were not reported.	In critique of this study, the influence of potentially influential covariables, such as the use of instrumentation, was not analyzed. Although the data demonstrate a strong trend in favor of prophylaxis, it did not reach statistical significance indicating that the study was underpowered. Based on the above critique, these data offer Level II evidence that intravenous cefazolin prophylaxis decreases the chance for postoperative infection after spinal surgery.

Antibiotic Prophylaxis
- Efficacy (uninstrumented)-

Question 2:
For patients undergoing spine surgery without spinal implants, does antibiotic prophylaxis result in decreased infection rates as compared to patients who do not receive prophylaxis?

-Evidentiary Table-

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Luer MS, Hatton J. Appropriate-ness of antibiotic selection and use in laminectomy and microdisk-ectomy. *Am J Hosp Pharm*. 1993;50(4):667-670.	III	In this retrospective study, postoperative infections after laminectomy/microdiscectomy were compared to control cases. The overall incidence of infection after this procedure was 7% (22 of 315 patients). The authors found no difference in the type or frequency of antibiotic agent administered for prophylaxis; however, they did find a higher percentage of patients in the infected group received antibiotics more than two hours before incision.	In critique of this study, it was a retrospective review. However, it included a homogenous group of patients undergoing a single type of uninstrumented procedure. These data provide Level III evidence that antibiotic prophylaxis with cefazolin should be administered preoperatively within two hours of skin incision.
Piotrowski WP, Krombholz MA, Muhl B. Spondylodisc itis after lumbar disk surgery. Neurosurg Rev. 1994;17(3):189-193.	III	In this retrospective study of 5041 patients, the rate of postoperative discitis was evaluated during two time periods: one in which perioperative antibiotics were given, and one in which they were not. During the former, the rate of discitis was 0.6 percent; during the latter, it was 2.3 percent. This was statistically significant. There were no other reported differences during these two time periods.	In critique of this large study, whereas it was stated that 1st or 2nd generation cephalosporins were given, the dosing protocol was not detailed. This study offers Level III evidence that perioperative antibiotics lower the infection rate at the level of the disc after lumbar disc surgery.

Antibiotic Prophylaxis
- Efficacy (with Implants) -

Question 3:
For patients undergoing spine surgery with spinal implants, does antibiotic prophylaxis result in decreased infection rates as compared to patients who do not receive prophylaxis?

-Evidentiary Table-

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Beiner JM, Grauer J, Kwon BK, Vaccaro AR. Postopera-tive wound infections of the spine. *Neurosurg Focus.* 15 2003;15(3):E 14.	V	This study is a review article describing the current treatment recommendations for treating a postoperative wound infection in spine patients. It includes a good discussion of the epidemiology and risk factors, such as malnutrition. It also includes a review of prophylactic antibiotic regimens, most of which have been addressed in this critical review.Mmechanical treatments such as ingress/egress suction irrigation systems and VAC dressing are mentioned.	This review article is of limited usefulness in addressing the question of efficacy of antibiotics in instrumented patients. This article offers Level V evidence (expert opinion) that prophylactic antibiotics decrease the infection rate in spinal surgery.
Rechtine GR, Bono PL, Cahill D, Bolesta MJ, Chrin AM. Postopera-tive wound infection after instrumentati on of thoracic and lumbar fractures. *J Orthop Trauma.*	IV	This study is a retrospective case series of 235 consecutive fracture patients. Of the 235 patients, 117 underwent surgical stabilization. Of the 117 patients, 12 suffered a perioperative infection, two had a staphylococcal infection, and 10 had a polymicrobial infection with gram negative and gram positive organisms. There was a statistically higher infection rate in completely neurologically injured patients compared to those with no deficit or incomplete injuries.	The study was designed to assess the incidence of spinal infection in a spine trauma population. It offers Level IV evidence supporting the efficacy of prophylactic antibiotics in instrumented spinal surgery in patients with incomplete cord injury or in spinal fractures without cord injury. However, in the subgroup with spinal cord injury, infections were more likely a result of multiple organisms including gram negative species. This study

2001;15(8):566-569.			raises compelling questions about antibiotic choice for prophylaxis in spinal cord injury patients.
Wimmer C, Nogler M, Frischut B. Influence of antibiotics on infection in spinal surgery: A prospective study of 110 patients *J Spinal Disord.* 1998: 11;498-500	IV	This study is a prospective series detailing antibiotic prophylaxis in an instrumented spinal fusion population. Specifically, 110 patients received either Cotrel – Doubassait (CD) or Moss Miami instrumentation. Of the 110 patients, 56 were instrumented for painful spondylolisthesis and 54 for scoliosis. Two grams of cefamandole were given preoperatively followed by three postoperative doses of 2 grams per day for three days. One infection early in the spondylolisthesis group and one late infection in the scoliosis group. The authors concluded that this prophylactic regimen was effective in decreasing the expected infection rate in this instrumented group.	This study offers Level IV evidence that perioperative prophylactic antibiotics lowered the infection rates in instrumented spine surgery when compared to previously reported infection rates.

Antibiotic Prophylaxis
- Protocol (Mixed Groups)-

Question 4:
For patients receiving antibiotic prophylaxis prior to spine surgery, what are the recommended drugs, their dosages and time of administration resulting in decreased postoperative infection rates?

-Evidentiary Table-

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Pons VG, Denlinger SL, Guglielmo BJ, et al. Ceftizoxime versus vancomycin and gentamicin in neurosurgical prophylaxis: a randomized, prospective, blinded clinical study. *Neurosurgery.* 1993;33(3):416-422; discussion 422-423.	II	This study was a prospective randomized trial comparing perioperative antibiotic protocols that included either 2 g ceftizoxime or 1 g vancomycin plus 80 gentamicin in 826 patients who underwent various clean neurosurgical procedures that included spine surgeries. Wound site infection was reported in 1.18% of patients in the ceftizoxime group and 1.24% in the vancomycin/gentamicin group. Spine procedures had a 2.75% rate of infection overall; 2.8% in the ceftizoxime group and 2.7% t in the vancomycin/gentamicin group. Agents were given one hour before skin incision.	In critique of this study, spine surgeries were not analyzed independently for the influence of diagnosis, length of surgery, and the use of hardware. These data offer Level II evidence that either antibiotic protocol yields similar infection rates after spine surgeries.
Rubinstein E, Findler G, Amit P, Shaked I. Perioperative prophylactic cephazolin in spinal	II	This study was a double-blind, randomized controlled trial comparing the efficacy of cefazolin prophylaxis in 141 patients who underwent “clean” spinal surgery. The placebo group experienced a 12.7%rate of wound infection and the antibiotic group a 4.3% rate.	In critique of this study, the influence of potentially influential covariables, such as the use of instrumentation, was not analyzed. While the data demonstrate a strong trend in favor of prophylaxis, it did not reach statistical significance

surgery. A double-blind placebo-controlled trial. *J Bone Joint Surg Br.* 1994;76(1):99-102.		Details of the two groups concerning the use of instrumentation were not reported.	indicating that the study was underpowered. Based on the above critique, these data offer Level II evidence that intravenous cefazolin prophylaxis decreases the chance for postoperative infection after spinal surgery.

Antibiotic Prophylaxis
- Protocol (Uninstrumented)-

Question 5:
For patients receiving antibiotic prophylaxis prior to spine surgery without spinal implants, what are the recommended drugs, their dosages and time of administration resulting in decreased postoperative infection rates?

-Evidentiary Table-

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Dobzyniak MA, Fischgrund JS, Hankins S, Herkowitz HN. Single versus multiple dose antibiotic prophylaxis in lumbar disc surgery. *Spine.* 2003;28(21): E453-455.	III	In this retrospective study, the rate of postoperative infection in patients who underwent uninstrumented laminotomy/discectomy was 1.15% (5 of 435) if they received multiple doses of prophylactic antibiotics and it was 1.49% (3 of 201) in those who received only a single dose preoperatively. No statistical difference between these rates was detected. The antibiotic protocol was cephazolin 1 g in 525 patients, clindamycin 500 mg in 46 patients, and vancomycin 1 g in 24 patients.	In critique of this study, the findings are weakened by the absence of data on the exact dosing for the "multiple dose" patients. The investigators did not analyze patient variables that could have potentially influenced the development of infection, such as comorbidities (eg diabetes). In addition, the study did not compare antibiotic prophylaxis versus no prophylaxis. The current data provides Level III evidence that a single or multiple dose antibiotic regimen results in low (1-1.5%) infection rates.
Klekamp J, Spengler DM, McNamara MJ, Haas DW. Risk factors associated with methicillin-resistant staphylococcal wound	III	This retrospective review compared 35 patients with postoperative MRSA infection to 35 uninfected control patients in order to determine risk factors. Regarding antibiotic prophylaxis, 19% of patients in the MRSA infected group received vancomycin at the time of index surgery, whereas 46% of the control group patients did. The authors found that lymphopenia, history of chronic infections,	In critique of this study, the authors did not state what prophylaxis regimen was used if vancomycin was not administered; the reader is left to assume that it is cefazolin or a similar agent. There was an equivalent rate of instrumented cases in the infected and noninfected groups; however, conclusions regarding the efficacy of vancomycin prophylaxis based only the

infection after spinal surgery. *J Spinal Disord.* 1999;12(3):187-191.		alcohol abuse, recent hospitalization, and prolonged postoperative wound drainage were significant risk factors for MRSA infection.	presence of instrumented fusion are difficult to draw. This study offers Level III evidence that vancomycin prophylaxis is more effective than other agents in the presence of the identified risk factors.
Luer MS, Hatton J. Appropriate-ness of antibiotic selection and use in laminectomy and microdisk-ectomy. *Am J Hosp Pharm.* 1993;50(4):667-670.	III	In this retrospective comparative study, postoperative infections after laminectomy/microdiscectomy were compared to control cases. The overall incidence of infection after this procedure was 7% (22 of 315 patients). The authors found no difference in the type or frequency of antibiotic agent administered for prophylaxis; however, they did find a higher percentage of patient in the infected group received antibiotics more than two hours before incision. 1 gm of cefazolin was given at the beginning (before) the procedure. No further doses were given.	In critique of this study, it was a retrospective review. However, it included a homogenous group of patients undergoing a single type of uninstrumented procedure. These data provide Level III evidence that antibiotic prophylaxis with cefazolin should be administered preoperatively within two hours of skin incision.

Antibiotic Prophylaxis
- Protocol (with Implants) -

Question 6:

For patients receiving antibiotic prophylaxis prior to spine surgery with spinal implants, what are the recommended drugs, their dosages and time of administration resulting in decreased postoperative infections rates?

-Evidentiary Table-

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Kanafani ZA, Dakdouki GK, El-Dbouni O, Bawwab T, Kanj SS. Surgical site infections following spinal surgery at a tertiary care center in Lebanon: incidence, microbiology, and risk factors. *Scand J Infect Dis.* 2006;38(8):589-592.	III	This study is a case control study comparing risk factors in patients who did or did not develop infections. All patients received antibiotics, although patients with infection more frequently received first generation as opposed to second generation cephalosporins. Also, there was a higher percentage of patients with instrumentation in the infection group.	This paper offers Level III evidence that patients who require instrumented fusions have a higher rate of infection than patients who do not require such extensive procedures.
Labbe AC, Demers AM, Rodrigues R, Arlet V, Tanguay K, Moore DL. Surgical-site	IV	This study is a pediatric case control series regarding surgical site infections. The authors noted that a significantly higher number of infection patients had not received “optimal” antibiotic prophylaxis. Optimal prophylaxis	In critique of this study, the patient population was a pediatric population. This study provides Level IV evidence that, in children, optimal antibiotic administration is associated with lower wound

infection following spinal fusion: a case-control study in a children's hospital. *Infect Control Hosp Epidemiol.* 2003;24(8):591-595.		was defined as being consistent with current CDC Surgical Infection Prevention Project recommendations. The authors concluded that infection rates are higher in myelodysplasia, and gram negative and polymicrobial infections are more common in this subgroup.	infection rates. Children with myelodysplasia are at risk for polymicrobial infections and may benefit from broader spectrum antibiotics.
Rechtine GR, Bono PL, Cahill D, Bolesta MJ, Chrin AM. Postoperative wound infection after instrumentation of thoracic and lumbar fractures. J Orthop Trauma. Nov 2001;15(8):566-569.	IV	This study is a case series of 235 consecutive fracture patients. Of the 235 patients, 117 underwent surgical stabilization. Of the 117 patients undergoing surgical stabilization, 12 suffered a perioperative infection. Two of the 12 had a staph infection, while ten of the 12 had a polymicrobial infection with gram negative organisms. There was a statistically higher infection rate in patients with complete neurological injury compared with those with no deficit or incomplete injuries.	Patients with spinal cord injuries are susceptible to polymicrobial infection following instrumented spinal fusions. This study provides Level IV evidence that the use of broad spectrum antibiotics in this population may be considered.
Sponseller PD, LaPorte DM, Hungerford MW, Eck K, Bridwell KH, Lenke LG. Deep wound infections after neuromuscu-lar scoliosis surgery: a multicenter	IV	This study is a case series of children with neuromuscular scoliosis examining risk factors for infection. The effect of antibiotic prophylaxis is not discussed. Authors did note the polymicrobial spectrum and hypothesized that broader spectrum antibiotics may be appropriate in this population.	In children with neuromuscular scoliosis, polymicrobial infections occur. This study provides Level IV evidence that broader spectrum antibiotics may be considered in this population.

study of risk factors and treatment outcomes. *Spine.* 2000;25(19): 2461-2466.			

Antibiotic Prophylaxis
- Redosing -

Question 7:

For patients receiving antibiotic prophylaxis prior to spine surgery, what are the intraoperative redosing recommendations for the recommended drugs (including dosages and time of administration) resulting in decreased postoperative infection rates?

-Evidentiary Table-

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Dobzyniak MA, Fischgrund JS, Hankins S, Herkowitz HN. Single versus multiple dose antibiotic prophylaxis in lumbar disc surgery. *Spine.* 2003;28(21):E 453-455.	IV	Retrospective historical cohort comparison between roughly comparable groups of patients undergoing spinal surgery. Four hundred thirty-three patients in the multiple dose group and 201 in the single dose group were reviewed from a cohort from 1993-1999. No difference in infection rate was detected between a group treated with a single pre-operative dose and a group treated with pre- and postoperative antibiotics.	In critique of this study, the dosing protocol was changed arbitrarily in mid course from multi dosing to single dosing. The authors, from their retrospective review of the two cohort groups, recommend single preop dose as re-dosing postop did not have any effect. This study does offer Level IV evidence that redosing may not be useful or effective in preventing post op infections.
Mastronardi L, Tatta C. Intraoperative antibiotic prophylaxis in clean spinal	IV	This is a retrospective cohort study of 973 clean neurosurgical cases, including cervical, thoracolumbar, instrumented and non-	In critique of this study, the authors admit that to make a meaningful determination, a much greater cohort

surgery: a retrospective analysis in a consecutive series of 973 cases. *Surg Neurol.* 2004;61(2):129-135; discussion 135.		instrumented cases. Patients <120 min received single dose ampicillin 1 g and sulbactam 500 mg unless they had instrumentation or surgery was >120min, then they also had teicoplanin 400 mg . A second dose was given in operations >4hrs and procedures >1500cc. No postop prophylaxis was administered. Infection was defined by purulent discharge, or serous discharge with culture, or deep/superficial abscess, or spondylodiscitis. Nine cases of infection were reported: staph = 4, coag – staph=2, kleibsiella=1 and pseudomonas=1. Two cases cultured negative.	would be needed to draw conclusions regarding the efficacy of re-dosing, as the difference in infection rates in "clean" cases is low to begin with, This study is Level IV evidence.
Riley LH III.. Prophylactic antibiotics for spine surgery: description of a regimen and its rationale. *J South Orthop Assoc.* 1998;7(3):212-217.	IV	This is a retrospective study of one year's patients (40) who had either 'simple discectomy' or instrumented procedures. Cefuroxime 1.5 g was given preop and q4h for 48h. Gentamycin 80 mg iv preop and q6h intraop and q8h postop for 48h. No infections occurred in the 40 patients. This paper includes a good discussion of the basic science behind the use of cefurozime and gentamicin as readily	As a retrospective study, chart review for evidence of post op infection (and finding none) in an extremely small cohort (40), no conclusions regarding efficacy of specific regimen can be drawn. This is an extension of a basic science study looking at the penetration of cephazolin, gentamicin and cefuroxime into disc tissue. The only

		disc-eluting antibiotics v. cephazolin as a less disc-eluting antibiotic.	thing it shows for our needs is that redosing in a small cohort over one year led to no infections. As such it is Level IV evidence.

Antibiotic Prophylaxis
- Discontinuation -

Question 8:

For patients receiving antibiotic prophylaxis prior to spine surgery, does discontinuation of prophylaxis at 24 hours result in decreased or increased postoperative infection rates as compared to longer periods of administration?

-Evidentiary Table-

A comprehensive review of the literature did not yield evidence to address the question related to the effect of discontinuation of prophylaxis at 24 hours compared with longer periods of administration on postoperative infection rates.

Antibiotic Prophylaxis
- Wound Drains -

Question 9:

For patients receiving antibiotic prophylaxis prior to spine surgery and who receive placement of wound drains at wound closure, does discontinuation of prophylaxis at 24 hours result in decreased or increased postoperative infection rates as compared to discontinuation of antibiotics at time of drain removal?

-Evidentiary Table-

A comprehensive review of the literature did not yield evidence to address the question related to the effect on postoperative infection rates of the duration of prophylaxis in the presence of a wound drain.

The study below suggests that drains do not influence infection rates in patients with single level decompressive procedures.

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Payne DH, Fischgrund JS, Herkowitz HN, Barry RL, Kurz LT, Montgomery DM. Efficacy of closed wound suction drainage after single-level lumbar laminectomy. *J Spinal Disord.* 1996;9(5):401-403.	II	This is a randomized controlled trial of drain use in 205 patients undergoing a single level laminectomy without fusion. The patients were randomized to drain vs. no drain. There was no difference between the groups in terms of infection rates.	This study appears on the surface as Level I evidence. However, it was downgraded to Level II because it was substantially underpowered. It provides Level II evidence that drains have no effect on infection rates. For a single level nonfusion spine procedure a drain does not decrease nor increase the infection rate.

Antibiotic Prophylaxis
- Body Habitus -

Question 10:
For patients receiving antibiotic prophylaxis prior to spine surgery, should the recommended protocol differ based upon body habitus (eg, body mass index)?

-Evidentiary Table-

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Olsen MA, Mayfield J, Lauryssen C, et al. Risk factors for surgical site infection in spinal surgery. *J Neurosurg.* 2003;98(2 Suppl):149-155.	III	In this retrospective case-control study, 41 patients with an infection after spinal surgery were compared to 178 without infection in order to determine potential risk factors. As identified by investigators ,postoperative urinary incontinence, posterior approach, surgery for tumor, and morbid obesity (BMI >35) were independent risk factors for postoperative wound infection. All patients received one or more doses of prophylactic cefazolin with or without an aminoglycoside or vancomycin with an aminoglycoside. Fusion or the use of instrumentation was not found to be a risk for infection.	In critique of this study, it was a retrospective review of a limited number of patients. In addition, the specific antibiotic regimens given to obese and non-obese patients was not analyzed. However, these data offer Level III evidence that morbid obesity defined as a BMI more than 35 is an independent risk factor for infection despite the use of a standardized antibiotic prophylaxis regimen. This study does not offer any evidence concerning specific antibiotic prophylaxis for obese patients.
Wimmer C, Gluch H, Franzreb M, Ogon M. Predisposing factors for infection in spine surgery: a survey of 850 spinal procedures.	IV	In this retrospective study of 850 spinal procedures, all patients received 2 gm of cefazolin IV perioperatively and a single additional injection if the surgery lasted more than three hours. In an analysis of the 22 patients who developed an infection, six were obese. Analyzed as a subgroup, obesity was found to be a risk factor with a p-value <0.04.	In critique of this study, there was no analysis of adjustments made to the antibiotic regimen in relation to the patients' BMI. Although other risk factors were considered more important, obesity was found to be an independent risk factor for postoperative infection in this retrospective review despite the use of prophylactic antibiotics. This study offers Level IV

J Spinal Disord. 1998;11(2):124-128.			evidence that obesity is a risk factor for perioperative infection, but does not offer clear evidence for a specific adjustment of antibiotic prophylaxis in obese patients.

Antibiotic Prophylaxis
- Comorbidities -

Question 11:
For patients receiving antibiotic prophylaxis prior to spine surgery, do comorbidities such as diabetes, smoking, nutritional depletion and immunodeficiencies alter the recommendations for antibiotic prophylaxis?

-Evidentiary Table-

Article (Alpha by Author)	Level (I-V)	Description of study (Including analysis of methodological strengths/weaknesses)	Conclusion
Kanafani ZA, Dakdouki GK, El-Dbouni O, Bawwab T, Kanj SS. Surgical site infections following spinal surgery at a tertiary care center in Lebanon: incidence, microbiology, and risk factors. *Scand J Infect Dis.* 2006;38(8):589-592.	III	This study reported the incidence of postoperative infection after spinal surgeries at a single institution. They also compared infected cases with control samples from the same population in order to identify risk factors. The presence of diabetes, older age, and implants (spinal hardware) were the only three variables that were significantly higher in the infected group. Both cases and controls received preoperative antibiotic prophylaxis, but infected cases received a first generation cephalosporin more often. The authors documented infection rates for patients who received 1st generation cephalosporin, 2nd generation, 3rd generation cephalosporin, or a glycopeptide. The average duration of antibiotic administration was 2.2 days in infected cases and 1.5 hours in controls.	In critique of the current study, the efficacy of antibiotic prophylaxis could not be analyzed for instrumented versus noninstrumented cases. The study offers Level III evidence that DM, older age, and the use of instrumentation are risk factors for postoperative wound infection despite the use of perioperative antibiotic prophylaxis. This study does not offer any evidence suggesting alterations in antibiotic prophylaxis in the presence of specific co-morbidities.
Piotrowski WP, Krombholz MA, Muhl B. Spondylodisc	III	In this retrospective study of 5041 patients, the rate of postoperative discitis was evaluated during two time periods: one in which perioperative antibiotics were	In critique of this study, “lumbar disc surgery” was not defined as either instrumented or noninstrumented. It might be presumed that these simple

itis after lumbar disk surgery. *Neurosurg Rev.* 1994;17(3):189-193.		given, and one in which they were not. During the former, the rate of discitis was 0.6%; during the latter, it was 2.3%. This was statistically significant. There were no other reported differences during these two time periods.	discectomies. While it was stated that 1st or 2nd generation cephalosporins were given, the dosing protocol was not detailed. This study offers Level III evidence that perioperative antibiotics lower the infection rate after lumbar disc surgery. It does not offer any evidence regarding the influence of comorbidities on the efficacy of specific antibiotic prophylaxis regimen.

Appendix F:
Comparing the Prevalence of Rare Events

COMPARING THE PREVALENCE OF RARE EVENTS

Nikolai Bogduk, MD

When events, such as infections, are uncommon or rare, comparing their prevalence in two separate populations requires large sample sizes in order to achieve statistical significance.

If the prevalence in one sample is p_1, and the prevalence in a second sample is p_2, and the sample size is n, the two prevalences are significantly different statistically if the 95% confidence intervals of the two prevalences do not overlap. Algebraically, this condition is determined by the equation:

$$p_1 + 1.96\sqrt{\frac{p_1(1-p_1)}{n}} < p_2 - 1.96\sqrt{\frac{p_2(1-p_2)}{n}}$$

For this condition to apply, when p_1 and p_2 are small, as applies in the case of postoperative infection rates, n needs to be large.

For example, if:

p_1 = 2%
p_2 = 6%

n needs to be larger than 343, effectively 350 in round numbers.

$$0.02 + 1.96\sqrt{\frac{0.02(0.98)}{n}} = 0.06 - 1.96\sqrt{\frac{0.06(0.94)}{n}}$$

$$0.02 + 1.96\sqrt{\frac{0.0196}{n}} = 0.06 - 1.96\sqrt{\frac{0.0564}{n}}$$

$$1.96\sqrt{\frac{0.0196}{n}} + 1.96\sqrt{\frac{0.0564}{n}} = 0.06 - 0.02$$

$$\sqrt{\frac{0.0196}{n}} + \sqrt{\frac{0.0564}{n}} = 0.04/1.96$$

$$\sqrt{\frac{0.0196}{n}} + \sqrt{\frac{0.0564}{n}} = 0.0204$$

$$\sqrt{0.0196} + \sqrt{0.0564} = 0.0204\sqrt{n}$$

$$0.0196 + 0.0564 + 2\sqrt{(0.0196)(0.0564} = (0.0204)^2 n$$

$$0.0196 + 0.0564 + 0.0665 = 0.000416n$$

$$0.0196 + 0.0564 + 0.0665 = 0.000416n$$

$$0.1425 = 0.000416n$$

$$0.1425 / 0.000416 = n$$

n = 342.5

Such a number is prohibitively large for a study to undertake with the express purpose of showing a statistically significant difference in infection rates of this order of magnitude. It would require deliberately exposing 0.06 x 343 = 21 patients to infection and its risk of complications.

V. Antibiotic Prophylaxis in Spine Surgery References

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