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Spinal Infections

Antibiotic use in spine surgery: A narrative review based in principles of antibiotic stewardship

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ABSTRACT

Background: A growing emphasis on antibiotic stewardship has led to extensive literature regarding antibiotic use in spine surgery for surgical prophylaxis and the treatment of spinal infections.
Purpose: This article aims to review principles of antibiotic stewardship, evidence-based guidelines for surgical prophylaxis and ways to optimize antibiotics use in the treatment of spinal infections.
Methods: A narrative review of several society guidelines and spine surgery literature was conducted.
Results: Antibiotic stewardship in spine surgery requires multidisciplinary investment and consistent evaluation of antibiotic use for drug selection, dose, duration, drug-route, and de-escalation. Developing effective surgical prophylaxis regimens is a key strategy in reducing the burden of antibiotic resistance. For treatment of primary spinal infection, the diagnostic work-up is vital in tailoring effective antibiotic therapy. The future of antibiotics in spine surgery will be highly influenced by improving surgical technique and evidence regarding the role of bacteria in the pathogenesis of degenerative spinal pathology.
Conclusions: Incorporating evidence-based guidelines into regular practice will serve to limit the development of resistance while preventing morbidity from spinal infection. Further research should be conducted to provide more evidence for surgical site infection prevention and treatment of spinal infections.

Introduction

Antibiotic resistance is a unique public health threat in that much of the problem originates within the healthcare system itself [1]. Antibiotic resistance results in over 2.8 million antibiotic-resistant infections and over almost 50,000 deaths per year, with associated costs grossing $20 billion per year [2,3]. With the rise in antibiotic resistance worldwide [1], it is incumbent upon all medical specialties to reevaluate the use of antibiotics within their practice, review the newest guidelines for use and practice antibiotic stewardship.

Antibiotic resistance must be addressed at many levels within healthcare [4]. Individual barriers to adhering to antibiotic use recommendations include lack of knowledge regarding guidelines, level of experience, lack of personal responsibility for antibiotic stewardship [4,5]. Organizational barriers include a lack of emphasis on antibiotic stewardship within institutional culture and poor communication regarding antibiotic use [5]. Enablers of adherence include multidisciplinary involvement in interventions, education regarding guidelines, use of clinical support tools, specific role delegation, regular audits, and reporting of outcomes [5]. Nationally and internationally, public healthcare organizations such as the CDC and WHO monitor antibiotic prescribing practices, efficacy of antibiotic stewardship programs, and threats of antibiotic-resistant pathogens [6].

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In spine surgery, the established indications for antibiotics are in the treatment of spinal infection and for surgical prophylaxis [7,8]. Both areas offer key opportunities for reducing unnecessary antibiotic use through evaluation of the 5 D's of antibiotic stewardship: drug, dose, drug-route, duration, and de-escalation [9]. The balance between coverage that is too broad or too narrow is delicate. While broad coverage may foster antibiotic resistance, undertreating spinal infections poses the additional risk of significant morbidity and mortality [9]. This review will focus on reviewing principles of antibiotic stewardship, evaluating the 5 D's for surgical prophylaxis, tailoring antibiotic therapy for primary spinal infection, and presenting considerations for future study.

Principles of antibiotic stewardship programs

A 2019 Statement from the CDC detailed an updated list of key components of antibiotic stewardship programs: "Hospital Leadership Commitment, Accountability, Pharmacy Expertise, Action, Tracking, Reporting, and Education." [10] Hospital leaders must influence the culture of an institution from a top-down approach, emphasizing their commitment to antibiotic stewardship through dedication of resources (Hospital Leadership Commitment) [10]. Specific providers from various disciplines, including pharmacists, should be appointed to take responsibility for antibiotic stewardship programs (Accountability; Pharmacy Expertise) [10]. Interventions must be designed to improve antibiotic stewardship (Action), and adherence to, and outcomes of such interventions must be recorded (Tracking) and reported for continual evaluation (Reporting) [10]. Finally, all healthcare team members and patients should be educated on the importance of antibiotic stewardship and consequences of antibiotic resistance (Education) [10]. Between 2013 and 2019, the CDC reported an 18% decrease in overall deaths and 28% decrease in deaths of in-hospital patients by antimicrobial resistance, demonstrating efficacy of antimicrobial stewardship and infection control protocols [10,11].

Surgical prophylaxis

According to the Centers for Disease Control (CDC), prevention of infection has proven to be one of the most important ways to reduce morbidity and mortality associated with antibiotic resistance [3]. Several opportunities exist to reduce the risk of antibiotic resistance within the realm of surgical prophylaxis [12]. The North American Spine Society (NASS), American Society of Health-System Pharmacists (ASHP), CDC, and the World Health Organization (WHO), among others, have established guidelines with empirically based recommendations that all spine surgeons should review and follow [8,13–15].

Prophylactic Antibiotic Selection

Several society guidelines recommend choosing a prophylactic agent based on the patient's history, comorbidities, length of procedure, and local patterns of antibiotic resistance procedure. [8,13] However, specific guidelines for patients with comorbidities are not established [8,13]. The 2013 ASHP guidelines noted that there has not been one superior antimicrobial agent established for spine surgery with and without instrumentation. However, first-generation cephalosporins, specifically cefazolin, are most commonly utilized and studied. [13] Cefazolin provides coverage of gram positive organisms such as *Staph aureus* as well as gram negative rods that make up skin flora and are common causative agents of surgical site infections (SSI). [13,16] The ASHP guidelines recommended against using agents with broader coverage such as second- or third-generation cephalosporins due to the risk of increased resistance. [13]

Specific patient factors should aid in preoperative antibiotic selection, such as diagnosed colonization with MRSA [17]. However, the most common MRSA screening tool, a singular intranasal swab, is not as sensitive as testing multiple sites or more costly methods such as Polymerase Chain Reaction (PCR) assays [17]. Numerous prior studies have found that many MRSA surgical site infections (SSIs) that develop despite prophylaxis are in patients who were MRSA negative by nasal swab [17]. The costs of more sensitive tests should be weighed with the risks of SSIs to determine guidelines for screening. Should more sensitive screening tests be adopted, antibiotic coverage may be more appropriately tailored to individual patients which may prove effective in decreasing SSIs. For patients colonized with MRSA, the AHSP guidelines suggest the addition of vancomycin to cefazolin for prophylaxis [13].

A history of allergies to antimicrobials will also guide prophylactic antibiotic choice [18]. However, the vast majority of patients who report a penicillin allergy do not have a true allergy and have been found to have a 50% increased odds of SSI due to the use of alternative surgical prophylaxis such as clindamycin or vancomycin. [18] These second-line antibiotics may facilitate the development of resistant pathogens such as MRSA and vancomycin-resistant enterococcus (VRE) and risk of *Clostridium difficile*. [18] Further, a 2022 review by Sarfani et al. [18] determined that there is a significantly lower rate of cross-reactivity between first-generation cephalosporins and penicillin than previously thought. Sarfani et al. [18] proposed a risk stratification tool for patients with reported penicillin allergy label. The authors suggested those with minor reported reactions or remote reactions receive cefazolin, those with severe reactions receive vancomycin or clindamycin, and patients with intermediate reactions be considered for allergy testing for elective procedures. [18] Prior research into preoperative allergy skin testing suggests that a majority of the time, patients are able to tolerate cefazolin, decreasing the risk of SSIs, and decreasing healthcare costs. [18]

Aside from patient-specific factors, future recommendations for antibiotic selection may also be guided by the anatomic surgery location [17]. Long et al. [17] examined the pathogens responsible for cervical SSIs compared to lumbar SSIs, noting an anatomic gradient in causative pathogens. More gram-positives and skin flora caused cervical SSIs, and more gram-negative and enteric bacteria caused lumbar SSIs [17]. As traditional surgical prophylaxis typically covers for Gram-positive bacteria, current regimens may be better suited for preventing infections of the cervical spine. [17] The study authors suggested an alternative antibiotic regimen of cephazolin and gentamicin for lumbar spinal surgery to broaden coverage of gram-negative bacteria as well. [17] It has previously been demonstrated that mixed gram-positive and gram-negative SSIs require more debridements and longer durations of intravenous antibiotics [19]. If conventional surgical prophylaxis is not targeting the correct bacteria, then ultimately it may be contributing to the rise of antimicrobial resistance. However, more research must be conducted on the efficacy of alternative antibiotic regimens depending on the surgical site.

Dosing of Antibiotic Prophylaxis

The 2013 NASS guidelines suggest a single preoperative dose of antibiotic prophylaxis for uncomplicated spinal procedures [8]. Currently, there are no widely accepted differences in antibiotic prophylaxis regimens for instrumented versus non-instrumented procedures, primary versus revision, or single level versus multi-level procedures [8,13]. The 2013 AHSP guidelines suggest the following doses: 2g of cefazolin, or 3 g cefazolin in patients weighing over 120 kg; 15 mg/kg of vancomycin; 900 mg of clindamycin [13]. Karamian et al. [20] determined that inadequate dosing of cefazolin was a significant risk factor for SSI following spine surgery. They noted that patients receiving 2 g of cefazolin had lower infection risk compared to patients receiving 1g [20]. However, in patients with impaired renal function, renal dosing should be used [21].

Conventionally, antibiotic prophylaxis has been administered within sixty minutes of the first incision. [22] This convention is based on pharmacokinetics of commonly used prophylactic antibiotics. [22] The 2016 WHO SSI prevention guidelines recommended administration of antibiotic prophylaxis within 2 hours of incision, and within 1 hour for an-

tibiotics with shorter half-life including penicillins and cephalosporins often used for antibiotic prophylaxis for orthopedic procedures [13,14]. Specifically for spine surgery, one study reported that patients receiving antibiotic prophylaxis more than 60 minutes before incision had 11 times higher risk of developing SSI as compared to patients receiving antibiotics closer to skin incision [23]. However, in a large, randomized control trial of patients undergoing various surgeries including orthopedic procedures, Weber et al. [22] evaluated the importance of antibiotic prophylaxis timing. Patients either received prophylaxis with cefuroxime early (a median of 42 minutes before incision) or late (a median of 16 minutes before incision) and found that there was no significant difference in the incidence of SSIs. Though most international guidelines currently recommend administration within sixty minutes, there is insufficient evidence regarding the importance of further narrowing the window for administration [22]. Interestingly, Rosenberg et al. [24] developed an intervention in an effort to improve timing of antibiotic prophylaxis and found that verifying prophylactic antibiotic administration at the same time as wrong-site surgery time-out increased compliance significantly, helping to time antibiotics appropriately before orthopedic procedures including spine surgery.

The 2013 NASS guidelines recommend redosing intraoperatively as needed only [8]. However, the CDC itself determined there was insufficient evidence to recommend for or against intraoperative redosing but noted that other clinical practice guidelines based on expert opinion recommended intraoperative redosing in patients with blood loss greater than 1500 mL, surgery duration greater than 3 to 4 hours, or surgery duration exceeding the half-life of the antibiotic, with redosing performed at intervals of 1 to 2 times the half-life [15].

Drug-route

Several forms of antibiotic prophylaxis are currently used including preoperative parenteral antibiotics, intraoperative vancomycin powder, and antibiotic bone cement [8,25,26]. The addition of vancomycin powder, antibiotic-laced beads, and antibiotic bone cement may further limit the incidence of SSI, with varying risks of antibiotic resistance [25,26]. Intraoperative vancomycin powder does not increase the risk of MRSA and is associated with decreased deep SSIs [26]. Antibiotic bone cement has been previously demonstrated to be effective in the prevention of SSIs due to direct delivery of antibiotics to the target site [25]. One study related increased roughness of antibacterial bone cement to increased bacterial adhesion and antibiotic resistance [27], while another noted increased resistance related to bone cement with gentamicin [28]. Further research is necessary to characterize risk of resistance in various bone cements to inform future recommendations.

Duration/de-escalation of antibiotic prophylaxis

The WHO guidelines on antibiotic prophylaxis do not recommend postoperative antibiotics for orthopedic procedures [14]. Abola et al. [29] analyzed propensity-matched cohorts undergoing spine surgery for patients who received 24 hours of postoperative antibiotics versus those who did not. The authors reported no significant difference in infection risk, rate of drug resistant infections, or *Clostridium difficile* infections between groups [29]. Further, 2 systematic reviews determined that there was no significant decrease in occurrence of SSIs when administering antibiotic prophylaxis postoperatively, specifically in trauma patients, instrumented and noninstrumented lumbar spine surgery, and in patients with drain placement with insufficient evidence regarding other types of spine surgeries [30,31]. The NASS guidelines reported insufficient evidence regarding discontinuation of antibiotics after 24 hours in patients with drain placement [8]. Pivazyan et al. [32] conducted a systematic review and meta-analysis, comparing different durations of postoperative antibiotics in patients with drain placement following posterior spine surgery. The authors noted no significant reduction in deep, superficial, or overall SSIs in prolonged postoperative antibiotics group after posterior surgery with surgical drain placement [32]. Going even further, the WHO guidelines recommend against continuing antibiotics while a wound drain is present [14].

Primary spinal infections

In contrast to the guideline-driven nature of antibiotic administration for surgical prophylaxis, management of primary spinal infections is highly dependent on the clinical presentation and diagnostic work-up to improve antibiotic stewardship [33]. The diagnosis and treatment of spinal infection remains challenging despite decades of research. The indolent nature of many spinal infections leads to delayed presentation, diagnosis and work-up [34]. As more common species associated with spinal infections, such as methicillin-resistant *S. aureus* (MRSA), or *Mycobacterium tuberculosis* in endemic regions have increased in prevalence in recent years, it is paramount to identify the specific organism involved to target proper treatment [3,35]. Limitations in identification include the nuances of culture collection. Prior literature suggests that the longer it takes for cultures to be drawn, the less likely they are to be positive [36]. In order to tailor antibiotic therapy, blood cultures should be drawn prior to initiating empiric antibiotic therapy in s patients, but negative cultures present a challenge when deciding on management [34,37]. CT-guided biopsy is the next best option for obtaining cultures before starting antibiotics [34,38]. Pathologic specimens should always be obtained and can be particularly helpful for diagnosis when cultures are negative [34,38]. For example, granulomatous pathology can suggest tuberculosis or brucellosis [33]. Open biopsy remains an option if other attempts have been unsuccessful [34,38]. If additional history or geography raises the risk of alternative pathogens, additional specific testing is warranted [34,38].

Empiric antibiotic therapy should be guided by patient history and clinical presentation [39]. Spinal infections are more likely in immunocompromised or immunosuppressed patients as well as patients with relevant exposure history such as intravenous drug use [33,37]. The most common causes of spinal infections include gram positives such as *S. aureus*, coagulase-negative staphylococcus, enterococci, streptococci, and gram negatives such as *E. coli and Pseudomonas* that have been demonstrating increasing resistance [34,40]. In developing countries, brucella and tuberculosis are also prevalent [33]. Empiric antibiotics should cover gram-negative organisms as well as MRSA and can include clindamycin/vancomycin/flucloxacillin and cefepime/ciprofloxacin/ceftriaxone for broad coverage [33,39]. For patients with negative cultures or biopsies, third-generation cephalosporins, or fluoroquinolones with clindamycin or vancomycin can be utilized. As the diagnostic work-up is completed, antibiotic coverage should be narrowed [33]. For methicillin-sensitive *S. aureus*, a penicillin with Staph coverage, or a first-generation cephalosporin is recommended [33]. For MRSA, vancomycin can be utilized. Streptococcus is covered by penicillin G [33]. Gram-negatives can be covered by second or third generation cephalosporins or quinolones [33]. Anaerobic coverage is provided by metronidazole or clindamycin [33]. Tuberculosis is managed with a 4-drug regimen consisting of rifampicin, ethambutol, pyrazinamide, and isoniazid [33]. Brucella can be treated with a combination of doxycycline and streptomycin/gentamicin [33,39].

The duration of treatment highlights yet another opportunity for managing antibiotic stewardship. Six weeks of antimicrobial therapy is typically recommended for treatment, though duration can range anywhere from 4 to 12 weeks depending on the severity of infection and causative pathogen [40]. A longer duration of treatment is recommended for undrained spinal abscesses and instrumented spine infection [33]. Specifically for Brucella, a duration of 3 to 6 months is recommended, while mycobacterium tuberculosis is treated with the 4- agent regimen for 2 months, and rifampicin and isoniazid for the remainder of the treatment course for a total of 9 to 12 months for eradication [33]. Clinical improvement and serial inflammatory marker monitoring throughout the treatment course may assist in informing physicians

with regard to antibiotic efficacy and necessary duration [34]. CRP levels may be more informative than ESR, given CRP normalizes faster and may be more sensitive to treatment of infection [40]. A 50% weekly decrease in CRP levels indicates response to treatment [33]. It is a fine balance to determine the course of antibiotic therapy, as it has been previously demonstrated that insufficient antibiotic duration for less than eight weeks portends a significantly higher risk of recurrent discitis while prolonged duration may contribute to antibiotic resistance [40].

Regarding de-escalation of antibiotic therapy, the evidence is mixed, and depends highly on the infection, and clinical response to treatment [33]. In choosing whether to switch to oral antibiotic therapy, bioavailability and adequate coverage of the causative agent should be considered [33]. Agents with good oral bioavailability include fluoroquinolones relative to beta-lactam antibiotics [33].

Future considerations

Additionally, continued evolution of surgical techniques and forms of antibiotic delivery may help to decrease the risk of SSIs and reduce the need for antibiotics. A large body of literature has demonstrated that minimally invasive techniques reduce the incidence of SSIs [41–45]. As minimally invasive approaches grow more popular, prophylactic antibiotic regimens should be reevaluated to determine if decreased duration or dosing remains effective in comparison to traditional care.

Apart from treatment of spinal infection and prevention of SSI, there is a potential new indication for antibiotics in spine surgery [46]. Emerging evidence suggesting a contribution of common low-virulent flora such as *Cutibacterium acnes* in the pathogenesis of degenerative disc disease has controversial implications for the possible role of antibiotics in treatment [46]. Two prior randomized, double-blind placebo-controlled trials have demonstrated efficacy of a 100-day course of antibiotics for the treatment of chronic low back pain with significant improvements in disability, and back pain at 1 year following treatment [46]. Future research should evaluate patient selection guidelines for such therapy, determine the minimum effective duration, evaluate the risk of antibiotic resistance, and calculate the risks and benefits of antibiotic therapy.

Conclusion

Antibiotic stewardship in spine surgery requires multidisciplinary investment and consistent evaluation of antibiotic use for drug selection, dose, duration, drug-route, and de-escalation. Developing effective surgical prophylaxis regimens is a key strategy in reducing the burden of antibiotic resistance. For treatment of primary spinal infection, the diagnostic work-up is vital in tailoring effective antibiotic therapy. The future of antibiotics in spine surgery will be highly influenced by improving surgical technique and evidence regarding the role of bacteria in the pathogenesis of degenerative spinal pathology. Incorporating evidence-based guidelines into regular practice will serve to limit the development of resistance while preventing morbidity from spinal infection.

Declarations of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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