

REVIEW

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Application of antimicrobial drugs in perioperative surgical incision

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Abstract

Infection in surgical incision often results in poor wound healing, and one of the main factors for wound infection is the use of antimicrobial agents. Rational use of antibiotics is one of the key factors to prevent incision infection in general surgery. The number of current clinical studies on antibiotic use before and during surgery is greater than that of systematic studies on antibiotic use after surgery. For the rational use of antibiotics and improvement of wound healing rate, researchers around the world have gradually focused on the use of antibiotics after surgery. Despite the familiarity on the concept of "rational use of antibiotics", few clear and systematic studies were conducted to elucidate the effect of different antibiotics on wound healing. Therefore, this review focuses on the use of different types of antimicrobial agents in surgical wounds.

Keywords: Surgical operation, Incision infection, Antibacterial drugs, Antibiotic

Background

Surgical operation is a medical procedure performed by surgeons or professionals that use instruments to repair damage, arrest disease, or place an implant in a living body [1].

Incision infection that results in poor wound healing is a potential risk for many postoperative patients [2]. Surgical site infection (SSI) is a postoperative complication and an important part of nosocomial infection [2]. Factors affecting postoperative wound infection include operating room, type and duration of surgery [3, 4], surgical personnel, physiological states of patient [4, 5], and antimicrobial drug use [6]. Given that antibiotics are the most widely used antimicrobial agents, the rational use of this medicine is the key to prevent incision infection in surgical operations [7, 8].

The rational use of antibiotics indicates that antibiotics cannot be misused. Misuse of antibiotics includes use of the wrong antibiotics, in the wrong dose, for the wrong duration, and not in accordance with associated guidelines and principles [9]. Clinical studies on the

preoperative and intraoperative use of antibiotics are more numerous than those about the postoperative use of antibiotics. Preoperative and intraoperative uses of antibiotics belong to prophylactic use, whereas postoperative use of antibiotic belongs to therapeutic use. In general surgery, the postoperative use of antibiotics is more ineffective than the prophylactic use of antibiotic [10, 11]. In fact, the prophylactic use of antibiotics cannot be conducted ideally, and the optimal time for prophylactic administration for clinical application is still controversial. Patients should use antibiotics rationally to restrict incision infection and increase wound healing rate. Many studies [6, 8, 9] involving clinical intervention and retrospective analysis highlighted the concept of rational use of antibiotics. However, no systematic report on the influence of different antibiotics on wound healing has been conducted.

This article focuses on various antimicrobials (especially on antibiotics) that are mainly used in surgical wounds to provide a reference for further understanding of the rational use and effect of antimicrobial treatment on surgical incision infection.

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Surgical operation

Surgery is an operation that destroys the integrity of the tissue or restores the integrity of damaged tissues. In early medicine, surgery was performed to cut, incise, and suture the body surface via simple manual methods. With the development of surgical technic and operating instruments (such as surgical knives, including electric, microwave, ultrasonic, and laser scalpel), operation can be performed at any site of the body. However, infection remains an issue for surgical operation. SSI is a main obstructive factor restraining the success of surgical treatment.

Surgical site infection

SSI is a postoperative complication and one of the most important healthcare-associated infections [12]. SSI includes infections in superficial incision, deep incision, and organ/tissue space (such as encephalopyosis, and peritonitis) [13]. Superficial incision includes incisions in the skin and subcutaneous tissue, deep incision refers to incisions in deep soft tissues (such as fascia and muscle layer), and organ/tissue space refers to any anatomical structure that has been opened or treated by surgery. The diagnostic criterion for SSI is that the infection occurs within 30 days after operation or within 1 year after implantation [13], that is, the presence of a purulent exudate within the said period can be identified as an SSI. The presence of fever, local tenderness or pain, incision swelling, and other symptoms should prompt diagnosis by clinician after microbial cultivation.

SSI related deaths account for more than one-third of postoperative mortalities worldwide [14]. The incidences of SSI in developed countries as USA (1.9%) [12], France (1.0%) [15] and Italy (2.6%) [16], are lower than those in developing nations including Turkey (4.1%) [17], China (4.5%) [18] and India (5.0%) [19]. The risk factors for SSI identified include the length of preoperative hospital stay, wound class and duration of surgery, which influence the breeding and proliferation of pathogens [20]. Among the pathogens that cause SSI, 48% of which are Gram-negative, 40.8% are Gram-positive, and 11.2% are fungi [21]. In China, *Escherichia coli* (25.9%), *Staphylococcus aureus* (14.3%), and *Pseudomonas aeruginosa* (11.9%) are the three dominate pathogens [22]. In the surgical incisions or wounds, the proliferation of pathogens usually results in postoperative infection. The rational use of antimicrobial agents can effectively reduce the occurrence of SSI [23].

Surgical incision

The occurrence of SSI is related to the contamination of trauma during the operation. Surgical incisions were previously divided into the following three categories [24]:

type I, clean incision; type II, possible contamination incision; and type III, contamination incision. According to healing and infection, an incision was classified into grades A, B, or C. However, this classification method is not perfect in practice. Incision cases are generally divided into four groups (Table 1) [25] to better assess the incision contamination. An in-depth understanding of the standard classification of surgical incisions is beneficial for the monitoring and prevention of SSI and provides a strong theoretical basis for the application of antimicrobial agents.

Antimicrobial agents

Antimicrobial agents, including various antibiotics and synthetic antibiotics that have bactericidal or bacteriostatic effects, are drugs that kill or inhibit the effects of bacteria [26]. In 1999, four classification methods were applied based on chemical structure, action mode, antimicrobial spectrum, and action mechanism of antimicrobial agents [27]. In 2004, Zhao [28] established a new interpretation for the classification of antimicrobial

Table 1 Incision classification

Classification	Definition
Class I Clean incisions	An uninfected surgical incision in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered. Surgical wound incisions that are made after nonpenetrating trauma should be included in this category if they meet the criteria
Class II Clean-contaminated incisions	A surgical incision in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, surgical procedures involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection is encountered
Class III Contaminated incisions	Open, fresh, accidental incisions. In addition, surgical procedures in which a major break in sterile technique occurs (e.g., open cardiac massage) or there is gross spillage from the gastrointestinal tract and incisions in which acute, non-purulent inflammation is encountered are included in this category
Class IV Dirty/infected incisions	Old traumatic incisions with retained or devitalized tissue and those that involve existing clinical infection or perforated viscera

agents in the book *Manual of Modern Pharmic Terms*. Based on their biological activity, antibacterial drugs were divided into anti-Gram-positive bacteria, anti-Gram-negative bacteria, broad-spectrum antibiotics, anti-anaerobias drugs, anti-*Mycobacterium tuberculosis*, and beta-lactamase inhibitors. Based on their action mechanisms, antibacterial drugs include those interfering with cell wall synthesis, inhibiting protein synthesis, interfering with nucleic acid synthesis, inhibiting metabolic pathways, and those disrupting bacterial membrane structures [29]. Based on their chemical structure, antibacterial drugs are classified as beta-lactams (e.g., penicillin), aminoglycosides (e.g., streptomycin), tetracycline (e.g., tetracycline), macrolides (e.g., erythromycin), sulfonamides (e.g., sulfadiazine), quinolones (e.g., norfloxacin), anti-mycobacterium tuberculosis (e.g., isoniazid), and other antibacterial drugs (such as clindamycin, vancomycin, fosfomycin, and bacitracin). In 2014, Zhuo and Zhong [30] classified the main antimicrobial agents as beta-lactams, macrolides, aminoglycosides, and quinolones.

Antimicrobial agents for external use

Some common antibacterial agents for external use are listed in Table 2 [31]. Application of these agents in open surgical incision or trauma treatment results in quick-acting and broad-spectrum antibacterial activity. Considering that these antibacterial agents cannot easily reach the site of infection through oral administration or intravenous injection, their external use is optimal. In addition, different antimicrobial agents have different antibacterial mechanisms and effectiveness on the same pathogen. An antibacterial agent has different antibacterial mechanisms and inhibition ranges for different pathogens to impede the development of drug-resistant strains.

However, the side effects of antimicrobial agents limit their application in acute surgical incision treatment. Many antimicrobial agents have concentration-dependent tissue toxicity, and some of their components enhance local toxicity [32, 33]. Moreover, antimicrobial agents may also interfere with wound healing [34–36].

Antibiotics

Antibiotics are secondary metabolites and derivatives with physiological activity produced by microorganisms, including secondary metabolites produced by bacteria, molds, and other microorganisms, as well as synthetic analogues [37]. Antibiotics at low concentrations could selectively inhibit or interfere with normal life activities of other microbes. Antibiotics should be utilized rationally because the abuse of antibiotics causes serious consequences. In 2002, Zhang [38] introduced the rational use

Table 2 Antiseptic agents applied to open surgical incisions and used to prevent or manage post-operative surgical site infection

Antiseptic choice	Comments
Acetic acid solution	Diluted solution (0.25%) has been used in incisions with no evidence to support use. Higher concentrations may cause tissue injury. The solution has been used for otitis external management and bladder irrigation
Alcohols	Isopropyl alcohol with rapid bactericidal efficacy is most commonly used for topical skin application. Not recommended for application in open incisions, because it desiccates open incisions and is tissue toxic
Boric acid	It is used as eye irrigation, and not recommended for application in open incisions
Chlorhexidine	It is the most common antiseptic in skin preparation, and generally not recommended in open incisions at the conventional concentration (2–4%)
Chlorine compounds	Buffered sodium hypochlorite solution at a concentration of 0.25–0.5%, leading to oxidative injury of bacterial membranes and enzymes
Hydrogen peroxide	It is a common household remedy for cuts and bruises, and is generally tissue-toxic for use in open incisions
Iodine compounds	Tincture of iodine has almost disappeared for any application in operations. Iodophors, which are less toxic, have been used clinically for topical application in open incisions but have not been subject to evaluation for efficacy
Silver compounds	Silver nitrate and silver sulfadiazine have been widely used in burns and selectively in open infected incisions of soft tissue. Various sustained-release topical preparations are available but are not used commonly for prevention in open incisions
Triclocarban	A common antiseptic in commercial soaps; there is no data to evaluate its use in open incisions
Triclosan	Common antiseptic in cosmetics; used in the coating for selected surgical sutures. No data on use for open incisions

of antibiotics. In the *Journal of Modern Laboratory Medicine* issued in 2007, several scholars mentioned bacterial resistance and the necessity of rational use of antibiotics [39]. The overuse of antibiotics can lead to superbugs—a progressively escalating challenge [40, 41]. In 2010, Kumarasamy et al. [42] firstly reported the presence of NDM-1 superbugs, a drug resistant bacterium with a high replication capacity and high speed of transmission. The abusive use of antibiotics may lead to the development of superbugs, and bacteria can develop acquired resistance to antibiotics that they have encountered [43, 44]. Many powerful superbugs develop with the continual abuse of powerful new antibiotics [45]. With the current research on clinical intervention and retrospective analysis, the

rational use of antibiotics has received increasing attention. World Health Organization (WHO) has highlighted the importance of rational use of antibiotics and warned that drug-resistance caused by irrational use of antibiotics will result in frequent infections and even a small injury may result in death [46]. The rational use of antibiotics implies no overtime, no excessive use, symptomatic use, and the use of antibiotics in strict accordance with the standards. The rationality of the use of antibiotics is affected by various factors, including the type of surgical incision, the type of antibiotics and antibiotic combinations, and the time of administration. According to the time of administration, antibiotics can be classified into preventive medicine and therapeutic medicine.

Prophylactic medication

Prophylactic administration of antibiotics refers to the administration of antibiotics prior to the occurrence of contamination and the release of antibiotics to the site of surgery to ensure sufficient concentration of antibiotics in target tissues [47, 48]. Antibiotics are usually given before and during surgery. In 2000, Xi showed that prophylactic antibiotics should reach the tissues before bacterial contamination occurs; when the tissue contamination exceeds 4 h, the antibiotics lose their preventive effect [49]. In 2007, a prospective study of incisional infection showed that prophylactic medication administered at 0.5–1 h before surgery leads to a lower rate of incision infection than those administered 2 h preoperative [50]. Reasonable prophylactic use of antibiotics before surgery can effectively reduce the rate of postoperative infection [51]. Reasonable time of prophylactic administration greatly reduces postoperative infections. However, the prophylactic application of antibiotics is still far from perfect in general surgery [52, 53]. Strengthening the management and rational use of antibiotics is an urgent goal. In 2013, a guideline was issued for antimicrobial prophylaxis in surgery, which aims to contribute to the reasonable use of antibiotics [54]. In 2016, the WHO launched the first global guideline on the use of antibiotic prophylaxis to prevent SSI [55]. The guideline will have applicability in all countries and be especially welcomed in developing countries [56, 57]. The selection and application of prophylactic antibiotics should be conducted according to medical characteristics including the type of surgical incision, the possibility of infection, the type of potential pathogens and the prophylactic effect of antibiotics [58]. The best timing for the surgical antibiotics administration depends on the pharmacokinetics of each antibiotic. Guidelines provide divergent duration comprised from 30 to 60 min before incision [59, 60]; while exceptions including fluoroquinolones and vancomycin are recommended to be administered within 120 min

[55, 59]. A single administration is recommended in most cases and the favorite route of administration is intravenous [58], except for specific procedures as prostate surgery [61]. Prophylactic antibiotics are generally not recommended in type I incisions, except occasions below: (1) operation which last long and involve more tissues, leading to high risk of infection; (2) operation which involve the vital organs including heart, lung and brain; (3) operation which involve foreign body implantation; (4) patients with high risk factors of infection, such as malnutrition, immune dysfunction and diabetes [62]. Any drug used for type IV incisions doesn't belong to prophylactic medicine, because the infections occur before surgery. Therefore, prophylactic antibiotics are normally used for type II and III incisions. The choices of prophylactic antibiotics for perioperative surgical incisions (type II and III) are listed in Table 3. Patients with prophylactic antibiotic use had lower rates of postoperative infection [63].

Therapeutic medication

Therapeutic use of antibiotics indicates that antibiotics are used and released to the surgical site after contamination to exert their antibacterial effect. The prophylactic application of antibiotics leads to a reduced risk of postoperative infection. However, preventive administration can only reduce and not completely eradicate the possibility of postoperative infection [64–66]. Therefore, therapeutic drugs are still necessary sometimes. Also, therapeutic drugs are required for cases with preoperative infection, such as type IV incisions. For surgical infection, the proper selection of antibiotics and effective treatment of are based on the correct diagnosis, the location of the infection, the patient's condition, the pharmacokinetics and pharmacodynamics of antimicrobials, and so on [8]. When antibiotics are selected to treat surgical infection, pathogens should be identified first. Normally, pathogens can be identified by culturing infected tissues, secretions, or blood samples. Prior to the test results, an infection with a definite diagnosis may be treated according to clinical experience. For example, *Pseudomonas aeruginosa* produces blue-green secretions and can be treated with gentamicin or polymyxin [67]. After pathogens are identified, clinicians should choose antibiotics according to their properties including spectrum, pharmacokinetics, pharmacodynamics and clinical efficacy. For instance, urinary tract infection can be treated with aminoglycosides which are mainly excreted through the kidneys. However, aminoglycosides aren't the best choice because of their high toxicity [68, 69]. We can choose less toxic drugs, such as sulfonamides, furans and fluoroquinolones, which can also keep effective concentrations in the urethra. The patient's condition is also an important

Table 3 The choices of prophylactic antibiotics for perioperative surgical incision

Operation name	Incision type	Potential pathogens	Antimicrobial agents
Ophthalmic surgery	I, II	<i>Staphylococcus aureus</i> (<i>S. aureus</i>), coagulase negative Staphylococci (CNS)	Tobramycin or levofloxacin in topical application
Amputation	I, II	<i>S. aureus</i> , CNS, Streptococcus (Strep), Gram-negative bacilli (GNB), Anaerobic bacteria (AB)	(First or second generation) cephalosporin (Cepha) ± metronidazole (MNZ)
Cerebral surgery (through the nasal sinuses, nasal cavities and oropharynx)	II	<i>S. aureus</i> , Strep, oropharyngeal AB (e.g., Peptostreptococcus)	Cepha ± MNZ, or clindamycin + gentamicin (C + G)
Head and neck surgery (through the oropharynx mucosa)	II	<i>S. aureus</i> , Strep, oropharyngeal AB (e.g., peptostreptococcus)	Cepha ± MNZ, or C + G
Otorhinolaryngologic surgery	II	<i>S. aureus</i> , CNS	Cepha ± MNZ
Thoracic surgery	II	<i>S. aureus</i> , CNS, Strep pneumoniae, GNB	Cepha ± MNZ
Urology surgery (entering the urinary tract vaginal)	II	GNB	Cepha or fluoroquinolones
Urology surgery (involving intestinal tract)	II	GNB, AB	Cepha or aminoglycosides (AG) + MNZ
Urology surgery (with prosthesis implantation)	II	Staphylococcus, GNB	Cepha + AG, or vancomycin
Hysterectomy	II	GNB, Enterococcus, Group B Streptococci (GBS), AB	Cepha (plus MNZ in vaginal surgery), or cephamycin
Laparoscopic myomectomy (using uterine manipulator)	II	GNB, Enterococcus, GBS, AB	Cepha ± MNZ, or cephamycin
Premature rupture of amniotic membrane or cesarean section	II	GNB, <i>Enterococcus</i> spp., GBS, AB	Cepha ± MNZ
Artificial abortion—curettage odinopoeia	II	GNB, <i>Enterococcus</i> spp., GBS, AB	Cepha ± MNZ, or doxycycline
Flap transfer or skin grafting	II	<i>S. aureus</i> , CNS, Strep, GNB	Cepha
Implantation of external fixator	II	<i>Staphylococcus aureus</i> , CNS, Strep	Cepha
Open fracture internal fixation	II	<i>Staphylococcus aureus</i> , CNS, Strep, GNB, anaerobic bacteria	Cepha ± MNZ
Hepatic, biliary, and pancreatic surgery	II, III	CNS, AB	Cepha or ceftriaxone ± MNZ, or cephamycin
Stomach, duodenum, small intestine surgery	II, III	CNS, Strep, oropharyngeal AB	Cepha or cephamycin
Colon, rectum, appendectomy	II, III	CNS, AB	Cepha or ceftriaxone ± MNZ, or cephamycin
Repair of perineal laceration	II, III	GNB, Enterococcus, GBS, AB	Cepha or ceftriaxone ± MNZ

± That two or more drugs can used in combination or not in combination

consideration in the choice of antibiotics. For children, the dosage of antibiotics should be reduced appropriately; and for older people, who metabolize and excrete antibiotics at a slower pace, there should be longer intervals between the doses of antibiotics [70]. In a word, the rational use of drugs is the key to the prevention and treatment of surgical infection.

Summary

Incisions are mostly performed in surgical operations, and surgical incision infections can cause poor surgical wound healing. Postoperative incision infection is often called surgical site infection, one of the complications after the operation and an important part of hospital infection. Antimicrobial agents are a factor affecting the prevention and treatment of postoperative infections.

Therefore, studies on the range of application, incompatibility, method of administration, treatment time, adverse reactions, and other related characteristics of various antibiotics have been initiated. As a common antibacterial drug, antibiotics have been widely used by medical personnel. However, during the use of antibiotics, some adverse effects have emerged because of antibiotics abuse. In addition, the characteristics of certain antibiotics have not been clearly defined. Postoperative antibiotics used in clinics have gradually become the research focus worldwide to achieve the rational use of antibiotics and improve the wound healing rate. Exploring the types of antibiotics used in clinical practice will help medical staff to prevent and treat surgical infection, thereby indicating its far-reaching scientific and clinical significance.

Abbreviation

SSI: surgical site infection.

Authors' contributions

XY and XX draft the manuscript and participated in its design. LW, YA and YS participated in the literature search and helped to draft the manuscript. HbW and HnW conceived of the study and design it. XY and HnW edited the final version. All authors read and approved the final manuscript.

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