ANTIBIOTIC PROPHYLAXIS AND THERAPY IN COLORECTAL SURGERY

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Abstract

Complications in colorectal surgery carry a high risk of morbidity and mortality, prolong hospitalization time and increase treatment costs, and the largest number of postoperative complications is related to surgical site infection (SSI). Antibiotic prophylaxis started in the fifties of the last century and changed with each new antibiotic. The following were used in order: aminoglycosides (1943), macrolides (1952), polymyxins (1958), and cephalosporins (1965). With the discovery of metronidazole in 1970, the prophylactic spectrum was extended to include anaerobic bacteria, which are an indispensable part of the flora in this anatomical region. Due to the nature of the gastrointestinal tract, it was believed that oral antibiotic prophylaxis and mechanical bowel preparation (MBP) could achieve intestinal sterilization and thus ensure a safe surgical intervention. However, studies have shown that MBP did not have an overall beneficial effect on postoperative complications and caused significant patient discomfort, so it was almost abandoned. Today, it is known that about 16% of surgical infections are caused by multiresistant bacteria, and only oral antibiotic prophylaxis is not sufficient to prevent these infections. Namely, in the race between bacterial resistance and the development of new antibiotics, antibiotics are increasingly lagging, and the treatment of complications remains a nightmare for surgeons. For this reason, the prevention of SSI in colorectal surgery is a challenge for 21st-century medicine. In modern surgery, both open and laparoscopic, the first and second generations of intravenous cephalosporins are most often used for prophylactic purposes, as antibiotics of a sufficiently broad spectrum, with favorable pharmacokinetics and rare side effects. New research indicates that in colorectal surgery, the combination of standard intravenous prophylaxis with the addition of an oral antimicrobial the day before surgery is superior when it comes to SSI prevention. However, there are still no clear recommendations on the regimen and type of antibiotics and they should be given in institutional guides and protocols, taking into account the bacterial spectrum in the local environment, as well as resistance, and the availability of appropriate drugs. Therapeutic use of antibiotics is reserved for acute conditions in colorectal surgery and its complications. For therapeutic purposes, more potent antibiotics are used against the expected pathogens, usually a combination of several antibiotics, such as third or fourth-generation cephalosporins, metronidazole, fluoroquinolones, or piperacillin/tazobactam and others. When it comes to the therapeutic use of antibiotics in colorectal surgery, research indicates that the most important thing is to recognize the infection in time and immediately start treatment, correct the therapy according to the causative agent, and also, stop the administration of antibiotics in time, to avoid unwanted complications and already advanced bacterial resistance.

Keywords: colorectal surgery, antibiotics, prophylaxis, therapy, bacterial resistance

Introduction

Surgical infections account for 1/3 of all intrahospital infections, with approximately 16% being caused by multi-drug-resistant bacterial strains. They can be categorized into different groups based on the time of occurrence, characteristics, and diagnostics. Numerous risk factors contribute to the development of infections, which can originate from the patient's characteristics, the surgical procedure itself, and all the materials used within it, as well as how it was carried out[1]. Risk factors for the occurrence of postoperative infections can be categorized as general and local. General factors include those related to the patient, such as the presence of

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comorbidities, particularly diabetes, obesity, advanced age, malnutrition, smoking, recent surgical procedures, massive transfusions, and the use of corticosteroids. Local factors related to surgical preparation and the surgical procedure itself include foreign bodies, inadequate sterilization of surgical instruments, electrocautery, as well as prior radiation of the surgical area[2]. They occur within 30 days after the surgery, or one year for foreign bodies and implants[3]. Among the most frequently isolated pathogens, *Staphylococcus aureus*, coagulase-negative *staphylococci*, *Enterococcus spp.* and *Escherichia coli* are mentioned. Surgical site infections (SSI) lead to increased mortality, prolonged hospital stays, and higher treatment costs. In most cases of SSI, the source of pathogens is the patient's endogenous flora from the skin, mucous membranes, or hollow organs. When a surgical incision is made, subcutaneous tissue is exposed to excessive endogenous flora. Typically, aerobic Gram-positive *cocci* like *staphylococci* serve as contaminants, while resistant pathogens like Methicillin-Resistant Staphylococcus Aureus (MRSA) have been increasingly involved in such infections in recent years. Entry into hollow internal organs exposes surrounding tissue to Gram-negative bacilli, such as *E. coli*, Gram-positive organisms like *enterococci*, and occasionally anaerobes like *Bacillus fragilis*[4].

In the modern era, the incidence of postoperative surgical site infections in colorectal surgery remains high, given the presence of a large number of microorganisms in the gastrointestinal tract. These infections occur with an incidence of around 26%. Despite significant advances in surgical protocols aimed at reducing SSI incidence, surgical field infections continue to contribute significantly to morbidity and mortality in the surgical population and increase treatment costs[5, 6].

Basic principles of antibiotic prophylaxis in elective surgery

The prophylactic use of antibiotics involves the action of that antibiotic against the most common, but not necessarily all, pathogens and surgical site infections. An important factor in selecting the appropriate antibiotic is the anatomical area of the surgical procedure. Additionally, when choosing antibiotics for prophylaxis, it is essential to differentiate this choice from antibiotics used for curative purposes in order to prevent the development of resistance and ensure effective treatment in case an infection does occur. The optimal timing for administering antibiotics is 30 minutes before the incision[7]. The critical period for the onset of surgical site infections is the four hours after bacteria enter the wound. Perioperative antimicrobial prophylaxis aims to achieve the maximum drug concentration during the surgical procedure, and the effective tissue concentration should cover the duration of the surgery, including up to the closure of the skin. Therefore, a single dose of antibiotics is considered sufficient for the majority of surgical procedures. Administering an additional dose of antibiotics should be considered when the procedure lasts longer than double the elimination half-life (t½) of the antibiotic (e.g, if cefazolin is used in prolonged procedures, a second dose should be given after three hours, intraoperatively). Additionally, in colorectal surgery, prophylaxis can be extended up to 48 hours[8]. On the other hand, De Jonge and colleagues emphasize that postoperative antibiotic prophylaxis should not be administered. Through their meta-analysis, they have demonstrated that there is no additional benefit from the prophylactic use of antibiotics in the postoperative course[9]. Prophylactic doses of medications are often equivalent to standard therapeutic doses, with dosages calculated based on the patient's body weight or body mass index (BMI)[8].

History of Antibiotic Prophylaxis in Colorectal Surgery

The discovery of penicillin in 1928 marked the beginning of the antibiotic era, leading to significant research into new antibiotics. Among the first antibiotics used in colorectal surgery were aminoglycosides (1943), macrolides (1952), and polymyxins (1958). These antibiotics had poor enteral absorption. Lockwood and colleagues pointed out that the use of streptomycin led to the rapid development of resistant *E. coli* strains in patients who exhibited a favorable early response[10]. Afterward, Lockwood demonstrated that the role of streptomycin was in the treatment of tuberculosis rather than achieving bowel sterilization. When Waksman isolated another aminoglycoside, neomycin (1944), it became the first choice for bowel sterilization and for treating hepatic encephalopathy[11]. Colistin, the first polymyxin (1949), was a good choice due to its mechanism of action and its effective impact on luminal Gram-negative rods (bacilli) such as *E. coli*, *Klebsiella spp.* and *Pseudomonas spp*[12]. The discovery of erythromycin (by McGuire and colleagues) made this antibiotic attractive for colorectal surgery due to its poor absorption from the intestine. All three classes of antibiotics, due to their limited absorption from the gastrointestinal tract, provided an opportunity to reduce the number of bacteria in the colon, primarily because of their action in the intestinal lumen. These drugs were effective mainly against Gram-negative bacteria with limited anti-anaerobic activity[13]. Oral administration of antibiotics became popular as surgical prophylaxis for colorectal surgery in the 1970s[14]. It was believed that orally administered antibiotics would be self-effective when the colon was simultaneously cleansed of its contents. Therefore, mechanical bowel preparation was introduced, a technique involving the use of osmotic substances to induce bowel evacuation and combined with preoperative oral antibiotic administration[15, 16]. However, by the late 1970s, intravenous metronidazole and tetracyclines came into use for surgical infection prophylaxis. This combination became standard practice in colorectal surgery as well, especially after an increased incidence of pseudomembranous colitis was mistakenly attributed to "colon sterilization" with oral neomycin. The further development of

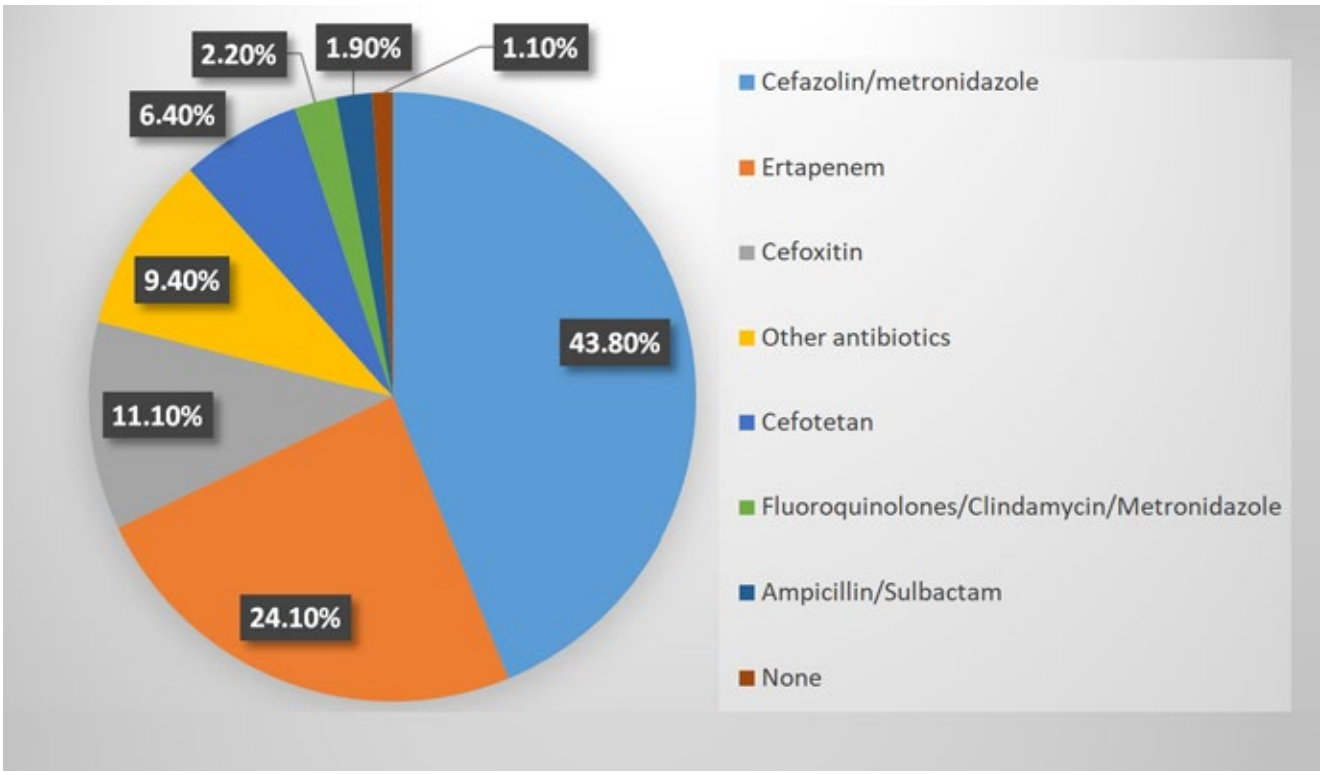
prophylactic antibiotic use relied more on the rational use of existing antibiotics due to the growing and globally threatening bacterial resistance, rather than the introduction of new antimicrobial agents. First-generation cephalosporins, discovered as far back as 1964, remain the gold standard in surgical prophylaxis due to favorable pharmacokinetics, cost-effectiveness, and low rates of allergic reactions[17]. The role of mechanical bowel preparation has been questioned by several major studies, as MBP alone did not show an overall favorable effect on postoperative complications and caused significant discomfort for patients. MBP was associated with an increase in inflammatory processes or leakage of liquid bowel contents when the preparation was inadequate, leading to higher rates of postoperative infections[18, 19].

New guidelines for antibiotic prophylaxis in colorectal surgery

Despite evidence-based recommendations for prophylaxis[20-22], there still exist broad variations in clinical practice for preventing surgical site infections following elective colorectal surgery. Beta-lactam antibiotics (aminopenicillins and cephalosporins) are more attractive than oral antibiotics due to their strong action against both Gram-positive and Gram-negative bacteria, favorable pharmacokinetics, and better bioavailability. According to the American guidelines (Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery) issued in 2013 and revised in 2018, preoperative intravenous antimicrobial prophylaxis with both anaerobic and aerobic coverage is recommended for colorectal surgery patients. Preference is given to the first-generation cephalosporin cefazolin due to its favorable pharmacokinetic profile and better activity against *staphylococci* compared to the previously used cefuroxime. In the United States, over 43% of patients undergoing colorectal surgery receive an intravenous combination of cefazolin and metronidazole, 21.4% receive ertapenem, and 11.1% receive cefoxitin[23, 24] (Image 1).

Other combinations used in less than 10% of cases include: fluoroquinolone + metronidazole, fluoroquinolone + clindamycin, and ampicillin/sulbactam. Alternatively, clindamycin + aminoglycoside, metronidazole + aminoglycoside, or fluoroquinolones alone could be considered. More recently, there has been renewed interest in the impact of oral antibiotics in colorectal surgery preparation, without mechanical bowel preparation. The large ORALEV study conducted in Spain, involving five clinics and 582 patients, demonstrated that prophylactic oral antibiotic use one day before colorectal surgery significantly reduces the incidence of surgical site infections (SSI) compared to patients receiving only IV prophylaxis. In this study, one day before the surgical procedure, oral therapy with 750 mg of ciprofloxacin at 12:00 and 00:00, along with 250 mg of metronidazole at the same times (12:00, 18:00, and 00:00), was prescribed. Additionally, all patients received intravenous cefuroxime at a dose of 1.5 g and metronidazole at a dose of 1 g at the induction of anesthesia[25]. The ongoing large COMBINE study is investigating whether adding a single dose of 1 g oral ornidazole to the standard IV antibiotic prophylaxis reduces the incidence of surgical site infections[26]. The initial results published in November 2022 support this hypothesis[27]. The

Image 1. Prophylactic Use of Intravenous Antibiotics in Colorectal Surgery[24]



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meta-analysis by Sangiorgia and colleagues also indicates the superiority of combined oral and intravenous antibiotic prophylaxis compared to IV prophylaxis alone in laparoscopic colorectal surgery, with a statistically significant lower incidence of anastomotic leakage and SSI[28].

Therapeutic use of antibiotics in colorectal surgery

The therapeutic use of antibiotics is reserved for infections of the colon, with diverticulitis being the most common indication. Other indications include colonic perforations caused by infection, inflammatory, malignant diseases, or trauma, as well as infectious complications following colorectal surgery, with the most common being surgical site infections (SSI). In the context of colorectal surgery, SSI encompasses wound infection, pelvic or intra-abdominal abscesses, with or without anastomotic leakage, as well as peritonitis that can potentially lead to sepsis[29]. Abscesses up to 3 cm in size without anastomotic leakage, as well as controlled enterocutaneous fistulas, can be treated solely with antibiotic therapy. However, a significant "leak" with large abscesses or stercoral peritonitis is managed surgically with adjuvant antibiotic therapy[30]. As the most common cause and a significant risk factor for the development of postoperative sepsis, anastomotic leakage is highlighted. Therefore, considerable importance is placed on early detection of colorectal anastomotic dehiscence. Specifically, a C-reactive protein value measured on the fourth postoperative day greater than 130 mg/L indicates anastomotic dehiscence with a diagnostic accuracy of 94%[31]. In these patients, early antibiotic therapy with appropriate antibiotics is imperative. Unlike prophylaxis, curative antibiotic therapy involves the use of newer and more potent broad-spectrum antibiotics, as well as adjusting the treatment based on wound culture results (abscess cavities, peritoneal cavity) and antibiotic susceptibility testing. The initial therapeutic regimen for intra-abdominal infections typically includes a beta-lactam antibiotic/beta-lactamase inhibitor (such as piperacillin/tazobactam), as well as a combination of third or fourth-generation cephalosporins with metronidazole, with the possible addition of a fluoroquinolone[32]. Other studies favor the initial use of carbapenems, which demonstrate a better survival rate in patients with intra-abdominal infection and accompanying sepsis compared to piperacillin/tazobactam[33]. Finally, newer carbapenems like ertapenem, as well as colistin, are usually administered based on antibiotic susceptibility results or if the initial therapy does not result in improvement of clinical and laboratory parameters within 48 hours of initiation. In the conclusion of the extensive STOP-IT study, which included 518 patients with complicated intra-abdominal infections, it is stated that four days of antibiotic therapy are sufficient if surgical control of the infection source has been established. Prolonging antibiotic therapy up to eight days does not lead to a higher survival rate or reduced hospitalization time; instead, it increases bacterial resistance and brings other complications for the patient[34].

Conclusion

While there are no universal guidelines for the application of antibiotic prophylaxis in colorectal surgery, clear principles are necessary to reduce the incidence of infectious postoperative complications. In the era of bacterial resistance and limited progress in developing new antibiotics, adequate prophylaxis in colorectal surgery to prevent the development of SSI and the prolonged use of antibiotics are of great significance to medicine. The use of well-known antibiotics effective against Gram-positive, Gram-negative bacteria, and anaerobes, along with the addition of an oral antimicrobial agent administered one day before the surgical procedure appears to be the method of choice in antibiotic prophylaxis for colorectal surgery. The exact regimen and types of antibiotics should be determined by institutional guidelines and protocols, taking into account the bacterial spectrum in the local environment, as well as resistance, availability of appropriate drugs, and further research should be directed toward these considerations.

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