

Antibiotics Used in Gastrointestinal Surgery Prophylaxis and Treatment of Postoperative Infection

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ABSTRACT

Aim of the work: surgical site infections are the second most common cause of hospital acquired infections and happens in 10%–30% of all patients undertaking gastrointestinal surgery. They are more likely to be admitted in critical care unit and have five times higher mortality than those patients without surgical site infections. Prophylactic use of antimicrobials and other preparations before surgery have shown significant reduction in infectious complication. After surgery the treatment of postoperative bacterial or fungal infections comprises cause control, antimicrobial cure, supportive and adjunctive approaches with the help of various types of antimicrobials. **Methodology:** we conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, from February 1986 to April 2017. The following search terms were used: perioperative surgical complications, post-operative infection after gastrointestinal surgery, antibiotics used in gastrointestinal surgery, MRSA in gastrointestinal surgery. This study aimed to explore the prevalence, prophylaxis and management of perioperative gastrointestinal infections and study about the types of antibiotics used for such management. **Conclusion:** better ways of post-operative management of infections must be studied such that the recommend use of antibiotics have full or specific coverage of pathogens and have minimal adverse effects

Keywords: perioperative gastrointestinal infection, management of surgical infection, surgical prophylaxis antibiotics, surgical antimicrobial.

INTRODUCTION

Surgical site infections are the second most common cause of hospital acquired infections and happens in 10%–30% of all patients undertaking gastrointestinal surgery. They are more likely to be admitted in critical care unit and have five times higher mortality than those patients without surgical site infections [1].

Prophylactic use of antimicrobials and other preparation before surgery have shown significant reduction in infectious complication. The essential spectrum for coverage in gastrointestinal surgery is decided by the flora found within the patient's large intestine. This is a mixture of both anaerobic and aerobic bacteria along with than introduction of bacteria from the patient's skin or the operating room, so antibiotic choices that protect against both anaerobic and aerobic bacteria showed the best results [2].

Common reasons of intra-abdominal infections after surgery in patients who stay in intensive care units are perforations of the upper gastrointestinal tract due to ulcer disease, or in case of the lower

gastrointestinal tract due to diverticular disease and cancer. Gut ischemia because of arterial embolism, thrombosis, or vascular disease lead to peritonitis, primarily in elderly patients. The treatment of postoperative bacterial or fungal infections comprises of cause control, antimicrobial cure, supportive and adjunctive approaches with the help of various types of antimicrobials. In this study, we explored the various prophylactic and post-operative antibiotics that can be used to reduce morbidity and mortality in gastrointestinal surgery [3].

METHODOLOGY

•Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE from February 1986 to April 2017. The following search terms were used:

•Data Extraction

Two reviewers have independently reviewed the studies, abstracted data and disagreements were

resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz University.

Surgical Site Infections

The Centers for Disease Control and Prevention (CDC) categorized postoperative infections as remote infection or surgical site infection (SSI). SSI was further classified into three types-- superficial, deep incisional and organ or space infection. SSI are the second most common cause of hospital acquired infections and happens in 10%–30% of all patients undertaking gastrointestinal surgery. The CDC estimated that around 500,000 SSIs happen yearly in the United States. 60% of the patients who experience SSIs get admitted in an intensive care unit. They are five times higher risk to be readmitted and unfortunately, have twice the mortality rate when compared to patients without an SSI. Therefore, health care costs are significantly increased in patients who are affected by SSIs ^[1].

Following a colorectal surgery, superficial infections are much more likely to occur than deep or organ SSIs. Deep organ infection represented surgical failure like anastomotic leak instead of a failure of prophylaxis. It is a primary care that the common type of infections was seen, with data recorded and a possibility of wrong care and healthcare costs, especially for use of antibiotics. Deep SSIs necessitate lengthy hospital stays, with the requirement of intensive care or additional surgical interventions and added treatments. All these complications and general survival were worsened following colorectal surgery, surgery for inflammatory bowel disease, lengthy operations, existence of a stoma and overweight or obesity ^[4]. Adherences with care along with surveillance programs for SSI incidence and prevention are not well-known in colorectal surgical practice and were unfortunately not supported by national institutions.

The significant clinical features of SSIs were erythema around site of incision, watery or purulent discharge and wound superficial dehiscence, which had additional systemic signs, all of which were nonspecific. The ASEPIS score system included:

- Additional treatment
- Serous discharge
- Erythema

- Purulent exudate
- Separation of deep tissue
- Isolation of bacteria, and
- Stay duration

This score offers interval data which can be useful in audit and research and permits an assessment of the severity of infection ^[5].

MRSA

There is a current discussion regarding antibiotic prophylaxis; whether it should provide coverage to resistant bacterial strains, for example methicillin-resistant *Staphylococcus aureus* (MRSA) and if the patient was already colonized before the surgery. Most studies did not support the empirical use of perioperative prophylaxis against MRSA if the patient is occupied by resistant bacteria. Studies from hospitals with a high occurrence of MRSA proved contradictory results for a cohort of cardiac surgery and of neurosurgery patients ^[6].

The data in cardiac surgery patients did not display a difference in the frequency of surgical wound infections when comparing efficacy of vancomycin with cefazolin, while the same method considerably decreased shunt infections and death rate when neurosurgical patients were studied. Nevertheless, for patients at high threat of SSI, who needs identification in advance of surgery, the addition of antibiotic prophylaxis against MRSA and additional resistant bacterial strains can be considered.

In case of patients with known MRSA colonization, vancomycin must be considered as the suitable antimicrobial for prophylaxis. Some prefer to avoid vancomycin because it has a big molecular weight and fails to penetrate into the tissues. Clindamycin, rifampicin or fosfomycin can be used if the MRSA strain is sensitive to these agents. Linezolid and daptomycin can be considered as additional options ^[7].

Antibiotics used in GI Surgery Prophylaxis

Consensus panels usually recommend cefazolin and other cephalosporin since they meet the above-mentioned criteria. Broad-spectrum antibiotics for example, ertapenem must not be used for surgical prophylaxis. The surgical site will define if both Gram-negative and Gram-positive bacteria need to be covered.

The commonly used cephalosporin loses their Gram-positive strength from different generations, while their Gram-negative potency increases. However, this is not true for 5th generation cephalosporin e.g. ceftobiprole, which recover their efficiency against Gram-positive germs [8]. Cefazolin is appropriate if preventing infection of the skin and deeper soft tissue such as fascia and muscle layers is the foremost goal.

3rd generation cephalosporin are applicable for inhibiting infection of the abdominal cavity organs.

3rd generation ceftriaxon has a good permeability into tissues and a great plasma protein binding rate, which results in a long plasma half-life of up to eight hours. In contrast, 2nd generation cefotiam has a plasma half-life of thirty minutes and then is not sufficient as a single-dose perioperative prophylaxis if the time to wound closure will exceed 1 h. In cases where surgical intervention surpasses the plasma half-life of the selected antibiotic drug, a second dose after three hours may be given [2].

The essential spectrum for coverage in colorectal surgery is decided by the flora found inside the patient's large intestine. This is a mixture of both anaerobic and aerobic bacteria along with than introduction of bacteria from the patient's skin or the operating room, so antibiotic choices that protect against both anaerobic and aerobic bacteria showed the best results. Antimicrobial prophylaxis for colorectal surgeries can consist of an oral antimicrobial preparation and preoperative parenteral antibiotic, or a combination of both [9].

Suggested oral prophylaxis includes neomycin plus erythromycin, or neomycin with metronidazole, started between 18 to 24 hours before surgery alongside with a mechanical bowel preparation. Cefotetan and cefoxitin are advised for parenteral prophylaxis.

The combination of parenteral cefazolin and metronidazole is also suggested as an economic alternative. Although a new study proposed that the combination of oral prophylaxis with parenteral antimicrobial prophylaxis can result in lower SSI rates. A survey of colorectal surgeons established that combination oral and parenteral prophylaxis is usual practice in the United States [10].

Beta-lactam Allergy

Even though many patients have reported drug allergies, symptoms or circumstances of these are infrequently documented. A study had

established that the incidence of true drug allergy is lower than that documented in the medical records.

Since beta-lactam antimicrobial agents often signify agents of choice for prophylaxis, the medical history must be suitable to determine if the patient expected had a true allergy such as: urticaria, pruritus, angioedema, arrhythmia, bronchospasm, hypotension, or serious adverse drug reaction for example, drug-induced hypersensitivity syndrome, toxic epidermal necrolysis, or drug fever [11].

In operations for which cephalosporin signify appropriate prophylaxis, different antimicrobial agents must be given to those with a high probability of past serious adverse reaction or allergy established on patient history or diagnostic tests like skin testing. Though, the incidence of adverse reactions to cephalosporin is rare in patients with reported penicillin allergy and penicillin skin tests do not foresee the probability of allergic reactions to cephalosporin in patients complaining penicillin allergy [12].

For patients with established allergy or adverse reaction to beta-lactam agents, usage of one of the following routines is recommended: clindamycin combined with gentamicin, ciprofloxacin, or aztreonam or metronidazole joined with gentamicin or ciprofloxacin. Levofloxacin, can be replaced with ciprofloxacin.

The choice to use vancomycin or clindamycin must include examination of local antimicrobial resistance patterns as well as institutional incidence of infections initiated by organisms, for example *Clostridium difficile* and *Staphylococcus epidermis*. In terms of antimicrobial spectrum, vancomycin and clindamycin are suitable alternatives to beta-lactams, though few data are available in favor of the use of the above drugs for routine prophylaxis [11].

Other Methods of Reducing SSI in Gastrointestinal Surgery

Mechanical Bowel Preparation

Traditionally, the likelihood of having the high bacterial load amount of feces coming in contact with a recently made anastomosis led to the construction of a dysfunctional stoma when colon was not ready. Colorectal resections have a greater SSI rate compared to other elective abdominal procedures because of the high bacterial load existing within its lumen, expected to be 10¹² colony-forming units in every gram of stool. Washing the colon of gross fecal content is a logical

strategy to decrease microbial pollution at the surgical location and possibly reduce infections. Hypothetically, this would reduce the intraluminal pressure of firm, possibly impacted stool, and decrease ischemia at the newly made anastomosis. In laparoscopic surgery, a vacant colon might be easier to operate than a colon filled with stool. And undoubtedly, when the surgeon recognizes he or she wants to rely on palpation to find the lesion, having an empty colon is a benefit ^[13].

Mechanical bowel preparations are preparations that are done by mouth to attain clearance of the colonic substances. Even though enemas and diet constraints are also a manually driven method of lower intestinal cleansing, they are typically not classified as mechanical bowel preparation. There are 3 classes of cleansing approaches: osmotic agents, stimulant laxatives, and procedures that include a mixture of osmotic and laxatives. It is clear that mechanical bowel preparation alone does not decrease SSIs in the elective colon and rectal operation. Clinical evidence favors the use of mechanical bowel preparation as an addition to the usage of the oral antibiotic bowel preparation ^[14].

Surgical Hand Preparation

Surgical hand preparation is perhaps the most significant SSI prevention approach. Its significance is supported by professional opinion, experimental studies and previous successful stories of SSI reduction via simple hand hygiene promotion programs. Hand rubbing with alcohol-based preparation is considered as beneficial as scrubbing, for which the perfect duration remains unidentified, even though it is possible that the minimum time was 2-3 min for both methods ^[15]. Either alcohol hand rubs or water-based antiseptic scrubs can then be successively used among patients, provided hands were not noticeably soiled. Nevertheless, the quick antimicrobial action, broader spectrum of activity, minor side effects and the lack of the possibility of hand contamination by washing water in resource-poor areas will favor alcohol-based solutions. Brushes are not suggested for surgical preparation ^[16].

Antiseptics

The increase of the incidence of hospital acquired infections and antibiotic resistant organisms, has been responsible for the overuse of antibiotics. However, as per the newest report by the US Food and Drug Administration, almost 80% of all antibiotics that are used in the United States are fed

to farm animals. All of these antibiotics eventually end up in the atmosphere and food chain, leading to the accumulation of resistant organisms. Before antibiotics turned out to be widely accessible, there was prosperity of knowledge and use of topical antimicrobials called the antiseptics ^[17].

There are numerous antiseptics accessible and are used in surgical practice, such as povidone-iodine and chlorhexidine, for pre-operative cleaning, skin and hand preparation, and for open wound treatment. Triclosan is a phenolic antiseptic which is used effectively to impregnate or coat artificial absorbable sutures including polydioxanone, polyglactin and poliglecaprone. These antiseptics have been used for skin and dental care and many inappropriate other uses, with a broad coverage of antibacterial and antifungal features and a low toxicity ^[18].

The mechanism of action of triclosan antimicrobial activity is multifactorial and can be bacteriostatic or bactericidal based on concentration. Some doubts remain: whether it can attack resistant organisms, or if it can affect antibiotic resistance and its transmission, or if its overuse has ecological issues, and whether it can decrease SSIs when coated on sutures ^[17].

Triclosan stops bacterial fatty acid synthesis, building and reproduction of cell membranes by obstructing enoylacyl carrier protein reductase. However, there is innate resistance and high tolerability to triclosan among some bacterial strains due to bacterial efflux pumps, but these have minor clinical relevance, particularly in regard to SSI. This hypothetical danger of resistance has been exaggerated, as have other health possibilities relating to possibly harmful side products of degradation in the atmosphere. Likewise, there are no stated carcinogenic, mutagenic or teratogenic properties. The relatively very small quantities of triclosan are used to saturate or cover absorbable polymer sutures give no risk to humans or the ecosystem ^[18].

Antimicrobial Sutures

All surgical wounds are polluted by the phase of closure and related to numerous risk factors. All sutures both absorbable or non-absorbable, or synthetic or natural, symbolize a prosthetic implant since a 90 cm length of polyglactin covers a total surface area of 130 cm. The existence of a suture upsurges the incidence of a SSI and logarithmically decreases the number of organisms needed to create

a postoperative SSI from 10^6 to 10^2 colony forming units^[19].

The significance of the part of biofilms has also been recognized. Once a biofilm covers the surface of a suture, its existent organisms becomes refractory to traditional antimicrobials. Having a wide spectrum biocide such as antiseptic triclosan coated or saturated in a suture can deliver high confined antimicrobial concentrations nearby the suture, stopping it from turning to a nidus for biofilm and infection. The benefit of using an antiseptic instead of an antibiotic for this reason is that triclosan has the appreciated benefits suggested to earlier^[18].

Postoperative Infections

Surgical patients typically display a postoperative acute-phase response usually lasting from 48 up to 96 hours subsequent to the surgical procedure. If the acute-phase response continues for longer than 96 hours, or a secondary incidence of symptoms following the primary resolution happens, an infection is a possible reason. Systemic inflammatory response syndrome (SIRS) triggered by infection is considered as sepsis. Among all septic patients 21.4% are surgical. In a sepsis study the intra-abdominal infections seemed to be the cause of sepsis in around 20–38%. If only surgical patients were measured, the amount of the abdomen as the focus of sepsis would be significantly higher. Intra-abdominal infections are the cause of sepsis in septic patients following a general surgery in 85% of the cases^[20].

Common reasons of intra-abdominal infections in patients who stay in intensive care units are perforations of the upper gastrointestinal tract due to ulcer disease, or in case of the lower gastrointestinal tract due to diverticular disease, and cancer. Gut ischemia because of arterial embolism, thrombosis, or vascular disease lead to peritonitis, primarily in elderly patients. Super-imposed infection of the abdominal cavity usually complicates the progression of severe necrotizing pancreatitis or chronic liver failure. Previous abdominal surgery, anastomotic leakage, intra-abdominal abscess, or unintentional and undetected injury of the gastrointestinal tract could be the cause of additional abdominal sepsis. Long-term quality of life in survivors is relatively decent; therefore, all efforts are acceptable for treatment of postoperative bacterial or fungal infections^[21].

Martin *et al.*^[22] mentioned that till 1987, gram-negative bacteria were the major pathogens initiating sepsis. In the subsequent years gram-positive organisms have developed as the foremost pathogens. Drug-resistant pathogens are particularly widespread in ICUs with thorough antibiotic usage. MRSA, vancomycin-resistant Enterococci, multi-drug resistance in *Mycobacterium tuberculosis* strains, extended spectrum β -lactamase-producing bacteria, as well as multi-drug resistant Gram-negative bacteria are noted in postoperative surgical patients. Moreover, in the past twenty years fungal infections have become progressively ostensible in critically ill patients. The majority of fungal nosocomial pathogens in non-neutropenic surgical patients are *Candida* spp. The presently increasing amount of patients under systemic steroid treatment for other diseases, or those under immunosuppression after transplantation surfaces the way for a major increase of these fungal infections in surgical ICUs. However, also patients lacking drugs for immunosuppression can obtain aspergillus infections, particularly subsequent to severe peritonitis^[3].

Diagnosis of Postoperative Infection

The diagnosis of postoperative infections is challenging since clinical signs such as pain, changes in level of consciousness, and laboratory results such as elevated acute-phase reactants or fevers are unclear and may perhaps be centered only on the prolonged surgical procedure. Also organ dysfunctions are labeled related to postoperative SIRS without established infection. Nevertheless, persisting signs of over 72 hour after surgical procedure and elevated response parameters or their secondary increase specify postoperative sepsis^[23].

The diagnosis of peritonitis after surgery is mostly difficult. It is largely based on clinical signs. In case of abnormal clinical indicators in the postoperative period an intra-abdominal infection must be ruled out. Radiographic imaging, particularly computer tomography and ultrasonography, allow the assessment of intra-abdominal septic foci and establish the gold-standard for diagnosis of intra-abdominal infections after surgery^[24].

If in patients with a septic syndrome, who show no response to a broad-spectrum antibiotic treatment, a disseminated fungal infection must be considered. Positive blood cultures approve the diagnosis of a fungal sepsis. Nevertheless, their sensitivity is only

about 70%. Intra-operative samples, drainage fluids and urine cultures, percutaneous punctures can lead to the diagnosis of fungal infection, but do not demonstrate the infection. Only histological investigations confirmed invasive fungal growth in a biopsy settles the diagnosis [25].

Treatment of Postoperative Infections

Treatment of postoperative bacterial or fungal infections comprises of cause control, antimicrobial cure, supportive and adjunctive approaches. Verdant *et al.* [26] lists the three cardinal values of cause control:

- (1) Drainage of infected discharge collections;
- (2) Debridement of infected tissue and elimination of devices or foreign bodies, and
- (3) Absolute actions to correct anatomic derangements resultant from ongoing microbial contamination and to reestablish optimal function.

Kumar *et al.* [27] emphasized that time from the start of infection to giving of antibiotics is a serious factor to decrease mortality in sepsis management and they showed that existence of septic shock was reduced by 5–10% for each extra hour of delay in antibiotic management. Best outcomes were gained when adequate antibiotics were set within the first half hour after the incidence of hypotension. A satisfactory antimicrobial routine is the main prerequisite in sepsis treatment and leads to decreased lethality. A perfect antimicrobial agent for sepsis treatment must cover the sepsis-inducing pathogens, diminished growth of resistant bacterial or fungal strains and it was obtainable at reasonable prices. For nosocomial infections, counting intra-abdominal infections, the usage of antimicrobial treatments with extended spectra may be necessary [28].

Suggested treatments for therapy of nosocomial sepsis without information of the presumable pathogen are carbapenems (including imipenem/cilastatin or meropenem) and piperacillin with tazobactam. Besides, established replacements are the 3rd and 4th generation cephalosporins (e.g. ceftazidime or cefepime), fluorochinolones (including ciprofloxacin or levofloxacin) and aztreonam, which have to be pooled with metronidazole to act against anaerobic bacteria as well. Though, resistance rate of *Escherichia coli* to chinolones was increased up to more than 30% universal preventing its use in empirical therapy [29]. Whether the grouping of carbapenems or

piperacillin/tazobactam in addition to a chinolone or an aminoglycoside may be promising in high-risk ICU patients, for example after extended surgery or in patients who are on mechanical ventilation, has yet to be confirmed in randomized trials. In hospitals with great MRSA amounts and after positive culture labs, a combined treatment with linezolid or with a glycopeptide like vancomycin, or with tigecycline is suggested. For patients with extensive intra-abdominal infections without fatal sepsis, cefotaxim and ceftriaxone joint with metronidazole or moxifloxacin, ertapenem can be used as mono-therapeutics [27].

New beneficial options like triazole derivatives like voriconazole and the echinocandin agents like caspofungin or lipid preparations of amphotericin B disclose new likelihoods in the antifungal management of surgical ICU patients. Presently, it is uncertain whether prophylactic antifungal management has helpful effects when usually used in surgical ICUs. For ICU patients *Candida* peritonitis may grow in link with repeated gastrointestinal perforations or anastomotic leakage after surgical interference. *Candida* species are found in 20% of all patients with peritonitis. If these patients are getting better under antibiotics, there is no necessity for antifungal management. Nevertheless, patients who got chemotherapy for neoplasm or immunosuppressive treatment for transplant or other inflammatory illnesses are at great risk and have to be managed. Amphotericin B is the standard treatment for invasive aspergillosis, even though the cure rate of less than 40% [30].

CONCLUSION

We have seen in this review that infections are one of the most feared complications after a gastrointestinal surgery. It could be cause of prolonged hospital stay, critical care admission, readmission, and mortality. Newer methods of prophylaxis and prevention were ever-emerging and better ways of post-operative management of infections must be studied such that recommend use of antibiotics that have full or specific coverage of pathogens and have minimal adverse effects.

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