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Review Article

An overview on prophylactic antibiotics in operative patients to combat post-surgical complications

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ABSTRACT

Antibiotics are the class of medications intended to treat and prevent bacterial infections by predominantly acting on bacteria by either making it difficult for the organism to grow and multiply or by killing them. They play a significant role in modern healthcare in improving patient health outcomes by reducing infective complications. In the emerging use of antibiotics, the pre and post-antibiotic regimen has a huge role in reducing the post-surgical complication which thereby increases the quality of life in surgical patients. Due to the irrational use of antibiotics, there is a rapid increase in the resistance to antimicrobial agents. Therefore, the rational operative antibiotic usage depends upon the factors like skin incision time; duration and frequency of administration; immunological status of the patient. Thus the importance of operative prophylaxis antibiotics has been discussed as a part of preventing surgical complications such as surgical site infections (SSI), antimicrobial resistance, septicaemia and adverse events during the patient's stay. This review is focused on the importance of prophylactic antibiotics, especially on major clean or clean-contaminated open surgeries which include cardiac surgery, gastro surgery and neurosurgery.

1. Introduction

Antibiotics are the class of medications intended to treat and prevent bacterial infections by predominantly acting on bacteria by either making it difficult for the organism to grow and multiply or by killing them.[1] They play a major role in the recent modern healthcare in improving the patient's health outcomes mainly in the areas of medicine or surgery, chronic conditions, Diabetes mellitus, end-stage renal disease, rheumatoid arthritis, organ transplants, or cardiac surgeries.[2] The antimicrobial agents are classed based on their pharmacology and in vitro effects into 2 major brackets: bactericidal and bacteriostatic. The bacteriostatic drugs "kill" the bacterial growth, has an MBC to MIC ratio of more than 4, and the bacteriostatic drugs that "retards the growth", have an MBC to MIC ratio less than or equal to 4. Further, to accurately group each category, criteria such as minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) must be clearly known. The minimum inhibitory concentration can be defined as the lowest concentration of an antimicrobial that shows a visible inhibition of bacterial growth within 24 hours. And, minimum bactericidal concentration is the concentration of the agent that causes a 1000-fold reduction of bacterial density within 24 hours.[3,4] In surgical procedures, a prophylactic antibiotic indicates an antimicrobial agent that is administered in patients who have no established infections, which is further beneficial in preventing surgical site infections and other infections.[5] Prophylactic antibiotics should be administered intravenously to patients undergoing surgery. But, the choice of antibiotic, dose, and frequency of the regimen need further clarity. An efficient regimen can be beneficial

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in improving the health status of the patient which further reduces the economic burden on the patient.[6,7]

The main aim of this literature review is to provide information on the importance of prophylaxis in different surgical departments, the timing of prophylaxis, incision time after administration, and the recent trends that are practised in surgery.

2. Appropriate Prophylactic Antibiotic Selection

The correct choice of the prophylactic agent is crucial in achieving the desired therapeutic outcome. In various animal studies and scientifically controlled clinical studies, the importance of prophylaxis against postoperative complications has been elucidated.[8] Certain standard measures have to be noted in selecting the right antibiotic therapy which include: The anatomic site of the surgery. The spectrum of activity of the antimicrobial; and the pharmacokinetic parameters. Some criteria have to be also taken into consideration with the above ones which include: resistance to the drug, possible interaction of the drug with other drugs, toxicity, and economic factors. Due to the irrational use of antibiotics, there is a rapid increase in the resistance to antimicrobial agents. In recent times, the use of broad-spectrum beta-lactam agents for surgical prophylaxis is not commended. The appropriate choice of Antibiotic prophylaxis is also dependent on multi-drug resistance, allergic reaction and the rate of infection. Clean contaminated surgical procedures and prosthesis insertion are the classic reasons for antibiotic prophylaxis. The NRC (National Research Council) has devised a 4-classification system which describes wounds. It is classified as clean, clean-contaminated, contaminated and dirty. For each of the above classes of the wound, the infection rates respectively are; <2%, 5-15%, and >30%.[9,10] The main basis of this classification was the density of bacteria in the wound. Certain other factors that could be associated with an increased degree of post-operative infection include; weight reduction, depletion of protein, physiological dysfunction of an organ system, and overall poor health of the subject.[11] The increased mortality in patients undergoing surgery is associated with inappropriate or delayed antibiotic treatment. Therefore, the intravenous antibiotic regimen should have a broad-spectrum activity that covers all the likely infectious pathogens.[12] Generally for serious infections and major surgeries, potent antibiotics are not preferred to be used. To achieve the effective and maximum level of the drug in the serum and tissues during and after the incision, the maximum concentration of the prophylactic antibiotic should be administered preoperatively.[13,14]

3. Timing and Duration of Prophylactic Antibiotic

The timing of the antibiotic for surgical patients plays a major role in better treatment outcomes. The timing of antibiotic administration was classified into four categories[15] and is depicted (Table 1). In the studies performed it was found that there was a considerable reduction in the incidences of surgical site infections when the prophylaxis was administered within 2 hours before surgery[16] whereas to avoid the chances of intra-operative contamination, it was found that an effective tissue concentration should be maintained which is achieved by administering the prophylactic antibiotics 30 mins prior the skin incision.[17] It should be noted that when the antibiotic is administered postoperatively in the recovery room, it might not show to be effective due to a combination of factors that prevent antibiotic delivery. These factors include vasoconstriction, thrombosis, and separation of wounds from the vascular systems which causes an inflammatory response. Effective serum tissue levels will not be achieved at lower levels. The majority of antibiotics administered as prophylaxis have a half-life of fewer than 2 hours, continuing the antibiotic regimen beyond the day of operation is neither beneficial nor reduces the risk of developing postoperative infections.[18,19] In some cases the frequency of dosing is 2-4 hours intraoperatively even when the blood loss exceeds 1000ml.[18] Various studies have assessed the optimal duration of antibiotic prophylaxis peri operatively and suggested short term perioperative antibiotic regimen is as effective as long-term in the prevention of postoperative complications.[20] However long-term prophylaxis in certain cases can induce bacterial resistance that could vary from an individual patient and affect the clinical outcome.[21]

Table 1: Administration time of antibiotics'[15]

Administration time	Category
2 - 4 hours before skin incision	Early prophylaxis
2 hours before skin incision	preoperative prophylaxis
3 hours after skin incision	peri-operative prophylaxis
3 - < 24 hours after skin incision	post operative prophylaxis

4. Areas of Concern

4.1. Surgical site infection

Surgical site infections are the infections that develop and persist within 30 days of a surgical procedure in cases where there is no placement of an implant and within one year in cases of insertion of an implant.[22] They are the most frequently seen major serious post-operative complication seen in surgical patients. In a survey performed by TG Emori et al, according to the National Nosocomial Infections Surveillance (NNIS) system, it was reported that SSIs account for 12-16% of the major nosocomial infections among hospitalized patients.[23] SSI can have further effects

on the patient and healthcare like increased antibiotic prescribing rate, and economic burden on the patients like laboratory costs. The patients who were found to have an infection rate of 60% were more likely to be admitted to the ICU, 5% more likely to be readmitted, they had a 2% higher mortality rate as compared to the non-infected people. Another interesting fact is that 40-60% of these infections are well preventable.[24] In a study performed by HH Stone et al; on antibiotic prophylaxis, it was concluded that the administration of antibiotics within 2 hours of any surgery had the lowest occurrence of surgical wound infection which was further supported by the logistic regression analysis. SSI can be considered as the index of the health care system in any hospital. It can be concluded that the time of antibiotic administration is inversely proportional to the incidences of wound infection.[25] The major organisms causing these include gram-positive cocci predominantly staphylococci, even though gram-negative bacteria are also involved. Therefore, when compliance with the antibiotic policies is followed, an overall improvement in the rate of patient wound infection can be seen.[26]

5. Adverse Drug Reaction

Whenever an exogenous product is administered into the body, it has a potential for developing an adverse reaction and antibiotics also have a similar property.[27] Every 5 patients in a hospital who are on antibiotics have been shown to develop such reactions. A survey on adverse events from the National Electronic Injury Surveillance System concluded that a major population of emergency department visits were due to an adverse reaction due to an antibiotic.[28] An adverse event should be clear foreseen when initiating any therapy, especially antibiotic therapy. The most susceptible population include paediatrics, geriatrics, immunocompromised patients, patients with other co-morbidities and hospitalized patients.[29]Therefore, it is very crucial to monitor if the patient uses higher class antibiotics and check the compliance with the standard policies of patients on antibiotic regimen especially on the prophylactic and empirical antibiotics in surgical patients for better therapeutic outcomes.[30]

6. Antimicrobial Resistance

A major area that requires attention due to the misuse and overuse of antibiotics when not under physicians' vigilance is antibiotic resistance. Due to the emergence and dissemination of resistance by bacterial pathogens, the efficacy of antibiotics has been altered. Certain pathogens such as Staphylococcus Aureus, Enterococcus spp., Pseudomonas aeruginosa along with some gram-negative become to all available antibiotics therapy. This leads to totally drug-resistant phenotypes causing an "antibiotic resistance crisis".[31] Bacteria have a short growth cycle and evolve very rapidly in the environment, which enables them to live through harsh and unfavourable conditions.[32] For many decades Methicillin-resistant S. aureus (MRSA), has been a major pathogen causing an antibiotic crisis which has a major effect on the clinical outcomes versus the methicillin-susceptible S. aureus.[32–34] MRSA has the highest prevalence in Asia among all the other continents.[35,36] Generally, a higher MIC value above the susceptibility threshold can be concluded as antibiotic resistance. The resistance that occurs can have either intrinsic or acquired properties. All the available antibiotic classes of medications cannot act on all the various bacterial pathogens. Intrinsic resistance is termed when the bacteria do not have the target regions for antibiotic activity.[37] In cases where the pathogen acquires resistance from the genes of other bacteria or due to gene mutation, it leads to reduced antibiotic efficacy, which can be termed acquired resistance.[37] Vancomycin, a glycopeptide antibiotic which is often a drug of choice in treating the infections associated with MRSA for the last 7 years, shows that there is an increase in the incidence of vancomycin-intermediate S. aureus (VISA) and Vancomycin-resistant S. aureus (VRSA).[38] The inappropriate antibiotic prescribing pattern is a major contributing factor in the emergence of resistance.[10] Studies have also shown that in 30% and 50% of the cases, there is an inappropriate choice of an antibiotic, or false treatment indication.[39] The misuse and overuse of antibiotics lead to the development of resistance to all the antibiotic treatment modalities that cause the development of multi-drug resistant strains called "super-bugs".[40] These above factors influence the emergence of antimicrobial resistance which is a growing public health issue and requires appropriate awareness to promote the rational use of antibiotics.

7. Septicemia

Sepsis is one of the most dangerous post-operative complications observed. When an adequate antimicrobial prophylaxis has been administered, there is a lower rate of mortality among patients with gram-negative bacteraemia and other rate of infections.[41–43] Sepsis is defined as, the aggravated, inappropriate immune systemic immune response to the infection which is associated with organ dysfunction, hypoperfusion or hypotension.[44] This further creates a drastic burden on the healthcare system and economic burden. In a survey performed by Martin et al it was found that the number of sepsis related cases are increasing.[45] As per reports, this post operative infection still remains the leading cause of death in the U.S and one in three persons with sepsis are due to Surgical procedures.[46] The occurrence of sepsis is dependent on many factors which includes race, age, size of the hospital and the economic status of the patient. Furthermore, the evaluation

of the surgical procedure, the patient population may help the associated complication.[47] The biochemical studies and genetic markers help in better diagnosis which may further prevent chances of mortality.[48] An appropriate antibiotic prophylaxis treatment is an important determinant of survival. Thus, an inappropriate antibiotic treatment was associated with increased mortality where, the efficiency of the therapy is independent of the rate of survival in comparison with immunomodulatory properties.[40]

8. Prophylaxis in Cardiac Surgery

As a routine practice, prophylactic antibiotics are generally administered to patients undergoing any type of cardiac surgical procedure.[48] But, the preferred choice of drug, dosage and frequency of the operative regimen is still under discussion. There is much evident morbidity, mortality and economic burden on the patient when nosocomial infections persist after surgery.[49] Hence, there are standard clinical practice guidelines that have been created that give the data on the choice of drug, duration, dose, frequency and therapy in case of predicted sepsis. The majority of the studies have shown that after the wound closure, the surgical prophylaxis is not needed and when single-dose studies were compared with double-dose antibiotic regimens, they did not show any further efficiency.[50] However, in recent times the guidelines have shown the importance of an elaborated prophylactic regimen in case of cardiac surgery like cardiopulmonary bypass, invasive devices after surgery, bleeding requiring blood transfusion and delayed extubation after a procedure. There are no sufficient data available on the pharmacokinetic parameters of antibiotics in cardiopulmonary bypass hence it is generally administered based on experience and historical practice.[51] Cardiac surgery has an increased chance of showing a high rate of systemic inflammatory response. The degree of this inflammatory response in an individual patient, and sometimes can be very harmful to the patient[52] In cardiothoracic surgery, it is recommended that all patients should be given prophylaxis and the antibiotics class of choice is first-or second-generation cephalosporin (cefazolin or cefuroxime)[53] Macrolides such as Clindamycin is used in cases of allergy to beta-lactams and vancomycin is used in cases of infection with methicillin-resistant staphylococcus aureus. The duration of the prophylaxis given should not be more than 48 hours; the skin incision should be done within 0.5 to 2 hours of the procedure. However, this timing can vary with the standard policies of other countries.[54] With regards to the choice of the antimicrobial agent, second-generation cephalosporins are more preferred compared to the other class of antibiotics, because they exhibit broad-spectrum activity and act on both the gram-negative and gram-positive pathogens. Further, they have a good safety with comparatively lesser side effects and can also be given to patients with penicillin allergies. But, the use of cephalosporins with Clostridium difficile infection is not well pronounced.[55] Recent studies have shown that there is an increasing trend in prescribing second-generation cephalosporins in cardiac surgeries due to their safety and efficacy profile.[56,57]

9. Prophylaxis In Gastroenterology Surgery

The prophylactic antibiotics in the case of gastroenterology are based on criteria such as the type of gastrointestinal infection, the non-classic gastrointestinal disease that does not involve an infectious agent, and prophylaxis for gastrointestinal procedures. There are variety of classes of antibiotics, hence the appropriate selection of the antibiotics is focused on here.[58] In the case of Bacterial Diarrhoea, the main focus of treatment is rehydration and other non-pharmacological management. Antibiotic treatment is recommended in case of shigellosis, cholera, and Clostridium difficile diarrhoea. Among the newer generation of antibiotics, fluoroquinolones have a broader spectrum of activity except Clostridium difficile.[59] with the increase in the incidence of antibiotic resistance to drugs such as ampicillin and trimethoprim-sulfamethoxazole, quinolones have become the most preferred class of antibiotic in the management of diarrhoea. This is also associated with the management of Salmonella typhi infections.[60,61] In case of relapsing Clostridium difficile infections, vancomycin in combination with rifampin is recommended.[62] There is not much-documented data on the infections due to endoscopy. But fatal infections have been reported after surgical procedures[63] While administering the antibiotics, certain criteria such as the nature of the organism, and the efficacy of the antibiotic administered should be taken into consideration. Other host factors that could also possibly increase the chance of infection include any cardio-vascular abnormalities, presence of prosthetic devices and immunocompromised state.[64,65] The recent practices for the prophylaxis are based on extrapolations from various data on the risk of bacteraemia[66] The major indications for antibiotic prophylaxis, include bacterial endocarditis, cholangitis or sepsis due to (ERCP) Endoscopic retrograde cholangiopancreatography and wound infections with PEG. The administration of prophylaxis is also recommended in procedures involving immunocompromised patients undergoing bone marrow transplantation and patients with the presence of neutropenia.[67,68]

10. Prophylaxis In Neurosurgery

The administration of a prophylactic antibiotic is the standard clinical practice before any neurosurgery. As per clinical studies, important criteria that should be taken into consideration include, the patient's immune system, the nature of the pathological organisms and the nature of surgery. Intravenous first and second generation of cephalosporins are most commonly used and in case of allergy, vancomycin is recommended.[69] In a survey performed by Mazda KT *et al.* on the prophylactic use of antibiotics in neurosurgery, it was found that a single dose of antibiotic was used for about 85% of the cranial surgeries. It was also found that, cephalosporins (alone or in combination) from different generations was about 89.8%, 97% in cranial surgeries.[70] When many parameters like cost of the therapy, economic status of the patient, drug toxicological parameters, and the duration of the antibiotic therapy cefazolin is generally recommended in case of clean neurological surgery.[71]

11. Prophylaxis In Obstetrics and Gynaecology

SSIs are one of the most common complications associated with patients undergoing surgery. In gynaecological surgical patients it has a prevalence of 8-10% and the rate of infection varies from every individual patient depending on condition of the patient as well as surgical factors[72,73] Generally in case of obstetric or gynaecological surgeries, multiple doses of the antibiotic is not recommended apart from the initial dose of the drug which includes the anaesthetic regimen. Further, studies performed on multiple doses of the antibiotic show no differences compared to the single dose of the drug.[74,75] Preferably, the prophylactic antibiotic administered should be narrow spectrum in order to avoid chances of resistance.[76] Before every surgical procedure, it is very important to consider the source of pathogens. For majority of the obstetrics or gynaecological procedures, the source of pathogens is endogenous in nature present in the vagina or skin. The flora of the genital tract in women is polymicrobial, presence of anaerobes, gram-negative aerobes and gram-positive cocci. Further, in comparison with laparoscopic procedures where there is no mucosal surface and more chances of skin contamination only. While administering the antibiotic, the drug administered need not cover all the nature of the pathogens. Narrow spectrum cephalosporins are used more often in contrast to the second and third generation antibiotics because they have shown more incidences of antibiotic resistance and have less activity against Staphylococci.[77] The women undergoing C-section surgeries have more risk of developing infection compared to the women delivering vaginally.[78] Recent studies have shown that women undergoing C-Section surgery should be adequately administered with a surgical prophylaxis. A single dose of the antibiotic is generally administered within 30 minutes before the surgery.[79] The prevalence of infection in the first trimester of pregnancy is from 0.01 to 2.44% and there is a similar rate of prevalence in the second trimester also,[80,81] Both oral doxycycline and metronidazole is beneficial in reducing the risk of post-abortal infection,[82]In procedures such as hysterectomy, it has been well established that for both vaginal and abdominal hysterectomy, the antibiotic prophylaxis benefits reduce post-operative infection.[83,84] When a randomised non-blinded controlled trial was performed on women with bacterial vaginosis, it was seen that there was a significant reduction in the rate of vaginal cuff infection in post-hysterectomy patient on treatment with rectal metronidazole.[85] But, for certain low risk obstetrics and gynaecological procedures, such as laparoscopy, IUD or medical termination of pregnancy (MTP) does not require the administration of antibiotics.

12. Conclusion

In conclusion, it was found that surgical prophylaxis administered prior to surgery improves the treatment outcomes which is beneficial in the prevention of post-surgical complications. Further, the selection of the appropriate antibiotic is based on the cost, and the pharmacokinetic parameters including half-life, toxicity parameters, antimicrobial resistance, effectiveness and safety profile. In the case of major surgeries like cardiac surgery, gastric surgery, vascular surgery, obstetrics and gynaecological surgeries, the prophylaxis should be given 30-60 minutes before the incision time. However, the prophylactic antibiotic should be given 2 hours prior in case of neurosurgery and the antibiotic chosen should have a longer half-life in order to maintain the tissue levels during the entire procedure. Cephalosporins which are a broad-spectrum class of antibiotics are the most preferred class of drugs in major surgeries due to their bioavailability, half-life and safety parameters. Moreover, resistance to antimicrobials because of irrational use of antibiotics is an area of concern in recent times and adequate measures should be taken to reduce the unnecessary overuse and limit the spread of resistance. From this review, it was found that when suitable prophylaxis was administered there is a significant reduction in the rate of surgical site infections as well as other post-surgical complications. Thus, the prophylactic antibiotic administration long with appropriate post-operative care has proved a potent role in uneventful surgeries.

13. Abbreviations

SSI – Surgical Site Infection; MBC - Minimum Bactericidal Concentration; MIC – Minimum Inhibitory Concentration; NRC – National Research Council; NNIS – National nosocomial Infections Surveillance; ICU – Intensive Care Unit; MRSA – Methicillin Resistant Staphylococcus aureus; VISA – Vancomycin Intermediate Staphylococcus aureus; VRSA – Vancomycin Resistant Staphylococcus aureus; ERCP – Endoscopic Retrograde Cholangiopancreatography; PEG – Percutaneous Endoscopic Gastrostomy; IUD – Intrauterine Device; MTP – Medical Termination Of Pregnancy.

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None.

15. Conflict of Interest

None.

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