

Antibiotic Prophylaxis in Colorectal Surgery: Evolving Trends

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Abstract

Introduction: Surgical antibiotic prophylaxis has become standard practice for patients undergoing colorectal surgery. This clinical practice has changed greatly over the last three decades, and it is currently accepted worldwide. It is phenomenal in minimizing postoperative wound infection in elective surgery. Clinical practice guidelines have been developed to herald this. However, the practice is yet to be established in some regions, particularly low-income countries. A review of the evolution of the practice is necessary.

Clinical Overview: Being a clean-contaminated procedure, colorectal surgery is a typical indication for antibiotic prophylaxis. The antibiotic for use is chosen on the basis of – its activity against endogenous flora likely to be encountered, its toxicity, and its cost, in that order. Controversy persists concerning the route of administration (oral, intravenous, or both), the number of administrations, and the duration of prophylaxis. Potent antibiotics used for serious infections are essentially not used for this purpose. A maximum dose is given preoperatively so that effective tissue concentration is present at and after the time of incision. In the absence of infection, the antibiotic is discontinued after the operative day.

Systematic improvements in the timing of initial administration, the appropriate choice of antibiotic agents, and shorter durations of administration have added value to the practice, with reductions in postoperative surgical infections, especially surgical site infections, for colorectal (clean-contaminated) procedures. The prevention of surgical site infections is an objective contained in the WHO Guidelines for Safe Surgery. They are a potentially morbid and costly complication following major colorectal surgery.

Conclusions: The practice of prophylaxis in surgery continues to improve. In recent years, growing attention is being placed on the accurate identification and monitoring of surgical complications and their costs. Advancements in antibiotic development and usage will translate into better prophylactic measures, which alongside other measures for control of surgical infections will give a better outcome for colorectal surgery.

Keywords: Antibiotics; β -lactamase; β -lactam Antibiotics; Colorectal Surgery; Drug Dosing and Re-dosing; Guidelines; Mechanical Bowel Preparation; Pathogens; Surgical Prophylaxis; Surgical Site Infections; Recommendations

Introduction

Prophylaxis loosely means the prevention of an infection and can be classified as primary prophylaxis, secondary prophylaxis, or eradication. Primary prophylaxis relates to the prevention of an initial infection. Secondary prophylaxis relates to the prevention of recurrence or re-activation of a pre-existing infection. Eradication refers to the elimination of a colonized organism to prevent the development of an infection. The theme of this review is chiefly primary prophylaxis.

Surgical antibiotic prophylaxis (SAP) is not a method of tissue sterilization, but a precisely timed measure to decrease the microbial load of intraoperative contamination to a level that does not overwhelm the host immune defence. It also does not refer to prevention of Surgical Site Infections (SSIs) following postoperative contamination. The scope of SAP is oriented around elective operations in which skin incisions are closed in the operation room [1]. In light of this, the indications are basically clean and clean-contaminated elective surgical procedures. Recommendations issued in clinical practice guidelines likewise, apply to elective surgery. The World Health Organization (WHO) Guidelines for Safe Surgery has one of its objectives as the prevention of SSIs, through the use of SAP and decontamination of the gastrointestinal tract [2].

SSIs are the most common complication following surgery. Patients undergoing clean-contaminated procedures have incidences of 11% for colonic resections [3], and 3-27% for rectal procedures [4]. Careful

follow up of patients in clinical trials reveals rates that are considerably higher [5]. Other septic complications, like enterocutaneous fistulae, complicated intra-abdominal infections, and septicemia, are serious but are much less common. Infectious complication rates range from 30% to 60% without SAP [6], and are <10% with it.

These infections cause delayed wound healing and treatment, time lost from work and, occasionally, death. For health-care institutions, they are a major contributor to increased costs owing to longer hospital stays, readmissions and additional use of antibiotics that can lead to bacterial antibiotic-resistance. They fit the description of being a major player in patient injury, mortality, and health care costs. Patients who experience SSIs are up to 60% more likely to spend time in the Intensive Care Unit (ICU), 5 times more likely to be readmitted to hospital and twice as likely to die compared with patients without a SSI [7].

Meta-analyses demonstrate that antibiotic prophylaxis is the most

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effective strategy for preventing SSIs following breast, appendix and colorectal surgery [8,9]. One meta-analysis of clinical trials of SAP in colon procedures demonstrated that antibiotic use significantly reduced mortality rates and SSI rates [10]. Despite evidence of effectiveness of antibiotics to prevent SSIs, previous studies have demonstrated inappropriate timing, selection, and excess duration of administration of SAP [11]. Guidelines for SSI prevention have been well developed in Europe, the United Kingdom, Australia, the United States and Canada [12]. To a less extent, some national and regional guidelines on SAP are established as well. Recommendations common to these protocols include: appropriate selection of antibiotics according to type of surgery; administration within 1 hour before surgical incision; discontinuation within 24 hours of surgery; hair removal only if necessary, by clipping; and maintenance of body temperature and serum glucose levels within the normal range (Table 1). Consensus on specific recommendations is yet to be reached. With this diversity in perspective, we undertook to conduct a review of SAP practice across the world to appreciate its clinical significance and the continuing pursuit for advances.

Methods

Relevant articles were identified by searching PubMed, Embase, Cochrane and Medline databases. A text word literature review was performed using the key words: 'surgical antibiotic prophylaxis', 'prophylactic antibiotics', 'surgical site infections', 'prophylaxis dosing and re-dosing', 'mechanical bowel preparation', 'prophylaxis guidelines', 'prophylaxis recommendations', 'colorectal surgery', 'pathogens and prophylaxis', 'prophylactic antimicrobials', and 'antimicrobial agents'. The reference lists of identified articles were used to perform searches for other relevant publications. Only articles with open access, or those with at least an appropriate abstract, constituted the material for review and discussion.

Principles of antibiotic prophylaxis

The practice of SAP is centered on fundamental principles. The antibiotic should be bactericidal in nature, with high tissue penetration ability and low toxicity (safe). It should cover relevant organisms likely to contaminate the surgical site. This agent is given in an appropriate dosage and at a time that ensures adequate serum and tissue concentrations during the period of potential contamination [1,6,13].

It is prudent that the specific agent should be decided upon in conjunction with microbiologists regarding contaminants and local resistance patterns. It is of paramount importance to ensure good surgical practice; a strict aseptic technique. SAP is not an alternative, and essentially comes in when the risk of infection is high (clean-contaminated operations), or when the results of infection, if it occurs,

are serious. The antibiotic is administered for the shortest effective period to minimize adverse effects, the development of resistance, and costs.

Principles of Drug administration

Route: The preferred route of administration varies with the type of procedure, but for a majority of procedures Intravenous (IV) administration is ideal because it produces rapid, reliable, and predictable serum and tissue concentrations [1,6,11,13]. In addition, the oral route is important in colorectal surgery.

Timing of initial dose: Effective prophylaxis requires the delivery of the antimicrobial to the operative site before contamination occurs. This entails administration at such a time to provide serum and tissue concentrations exceeding the minimum inhibitory concentration (MIC) for the probable organisms associated with the procedure, at the time of incision, and for the duration of the procedure. Parenteral antibiotics, previously administered within 30 minutes of skin incision [14], are now administered within 1 hr of this [11]. This maintains an optimum concentration if intraoperative contamination occurs [15]. Administration of Vancomycin and fluoroquinolones should begin within 120 minutes before surgical incision because of the prolonged infusion times required for these drugs. Since these drugs have long half-lives, their early administration does not compromise serum levels of the drugs during most operations. For colonic procedures, oral antimicrobials should be administered starting 19 hours before the scheduled time of surgery [16].

Dosing: Specific pharmacokinetic and pharmacodynamic properties and patient factors must be considered when selecting a dose, to ensure the attainment of adequate serum and tissue concentrations of antibiotics. A maximum dose is used; lower doses being ineffective at reaching high drug concentrations at incision and operative sites. In general, prophylactic agents are administered in a manner that will ensure adequate levels of drug in serum and tissue for the interval during which the surgical site is open.

Weight-based dosing: The dosing of most antibiotics in pediatric patients is based on body weight, while the dosing of many agents in adults is not based on this, because it is safe, effective, and convenient to use standardized doses for most of the adult patient population. This tends to differ in obese patients (particularly the morbidly obese), whose serum and tissue concentrations of some drugs may differ from those in normal-weight patients. This is due to pharmacokinetic alterations that depend on the lipophilic properties of the drug, among other factors. Conclusive recommendations for weight-based dosing for SAP in obese

Recommendation; 2009[12]	Organisation									
	JCAHO	SCIP	CDC	ACS	IHI	NHS	SIGN	Europe	Australia	Canada
Appropriate antibiotic selection	√	√	√	√	√	√	√	√	√	√
Administration within 1 hr before surgical incision	√	√	—	—	√	√	√	√	√	√
Discontinuation within 24 h	√	√	—	—	√	√	√	√	√	√

JCAHO – Joint Commission on Accreditation for Healthcare Organizations
 SCIP – Surgical Care Improvement Project
 CDC – Centers for Disease Control and Prevention
 ACS – American College of Surgeons
 IHI – Institute for Healthcare Improvement
 NHS – National Health Service
 SIGN – Scottish Intercollegiate Guidelines Network
 Europe – several organizations
 Australia – Australian Council for Safety and Quality in Health Care
 Canada – Safer Healthcare Now! Campaign

Table 1: Summary of common (SAP-related) recommendations for SSI prevention, promoted by clinical practice guidelines or professional consensus.

patients are generally not made given that data demonstrating clinically significant decreases in SSI rates from the use of such dosing strategies are not readily available [11].

Re-dosing: Intraoperative re-dosing is needed to ensure adequate serum and tissue concentrations of the antibiotic if the duration of the procedure exceeds two half-lives of the drug, or if there is excessive blood loss (>1000 – 1500 mL). Many antibiotics for prophylaxis have a half-life of less than 2 hrs [17]. Because of this, dosing is usually repeated every 2 to 4 hrs intraoperatively. This re-dosing interval is measured from the time of administration of the preoperative dose. It is not justified in patients in whom the half-life of the antibiotic is prolonged (e.g., patients with renal insufficiency or renal failure).

Duration: Antibiotics administered postoperatively in the recovery room are not effective due to a combination of vasoconstriction, thrombosis, and the inflammatory response in tissues occurring at the wound, which leads to a form of wound isolation from the vascular system. This makes postoperative antibiotic administration unnecessary. Basically, SAP should last less than 24 hours for most procedures.

Preoperative screening and decolonization: Preoperative screening for *S. aureus* carriage and decolonization strategies have been explored as means to reduce the rate of SSIs. Anterior nasal swab cultures are most commonly used for preoperative surveillance. This practice is increasingly getting common in high-income countries. Intranasal mupirocin has been used in selected centres, to eradicate methicillin-resistant *S. aureus* (MRSA) nasal colonization in adult patients and health care workers. Many studies conclude that the use of preoperative intranasal mupirocin in colonized patients is safe and potentially beneficial as an adjuvant to IV SAP. However, the optimal timing and duration of administration are not standardized. This practice is uncommon in colorectal surgery.

Choice of antibiotics: Postoperative infections are caused by endogenous organisms at the operative site. The choice of antibiotic is based on knowledge of these organisms (Table 2). The aim of prophylaxis is to reduce the bacterial concentration in the tissues of the operative incision and site to below the threshold for infection. This is usually 10^5 – 10^6 organisms per gram of tissue. Additional antibiotics need not be added to a protocol proven to work through a RCT. Importantly; antibiotics used to treat serious infections should not be used in order to 'protect' them from emergence of resistance.

Objectives of prophylactic antibiotic usage

The principles highlighted go along with certain set objectives in surgical prophylaxis. SAP aims at preventing the development of SSI and/or ameliorating SSI-associated morbidity and mortality. It is meant to reduce the cost and duration of health care. The cost-effectiveness of SAP is eminent when the costs associated with the management of SSI are considered [18,19]. However, the practice ought not to produce any adverse effects, and should not alter the normal microbial flora of the patient or the health institution [20,21].

Overall, the final decision regarding the benefits and risks of prophylaxis may eventually come down to a case-by-case decision process. The use of SAP will then depend on: the patient's risk of SSI; the potential severity of the consequences of SSI; the effectiveness of prophylaxis in that operation; and the detrimental consequences of prophylaxis for that patient (eg. the development of colitis).

There are other important issues that are being increasingly considered in the practice of SAP. Treatment policies ought to be based on local epidemiological patterns of drug-resistant bacteria. In conjunction with this, there is a drive towards the reduction of inappropriate prolongation of SAP by use of special prescription forms. There is also special attention paid to penicillin/cephalosporin hypersensitivity, and avoidance of β -lactam antibiotics. Policies for SAP that recommend β -lactam antibiotics as first line agents ought to also recommend an alternative for patients with allergy to penicillins and cephalosporins.

Historical aspects

The effectiveness of antibiotics administered moments prior incision of the skin, for prevention of SSIs, was first established in the 1960s. It has subsequently been repeatedly demonstrated since then [21-27]. Previously, there had been debate about the efficacy of these drugs in surgery following the publication of clinical trials during the 1950s. Errors in study design of these early studies included: non-randomization, lack of blinding, faulty timing of initial antibiotic administration, prolonged antibiotic use, incorrect choices of antimicrobial agents, and inappropriate choices of controls [28]. Experimental studies that followed in the 1960s helped in ironing out these discrepancies and yielded a more scientifically accurate approach to SAP.

However, in spite of evidence of this effectiveness and the publication of guidelines for SAP, its clinical application is often suboptimal [1,29-34]. Various studies have demonstrated inappropriate timing of drug administration, inappropriate selection of the agent, and prolonged duration of prophylaxis [35-40]. The clinical researcher, Burke, first demonstrated the important relationship between timing of antibiotic administration and its prophylactic effectiveness [22]. His study showed that to greatly reduce skin infection, the antibiotic had to be present in the skin just before or at the time of bacterial exposure. This important change in strategy helped correct the then common mistake of administering the first prophylactic antibiotic in the recovery room, after surgery.

In 1964, Bernard and Cole successfully used prophylactic antibiotics in a randomized, prospective, placebo-controlled clinical study of abdominal operations on the gastrointestinal tract [41]. Their success was likely due to their appropriate patient selection and wise choice of available agents, as well as the timing of administration. Further advances in the understanding of antibiotic prophylaxis in abdominal surgery occurred in the 1970s. During this period, the qualitative and quantitative nature of the endogenous gastrointestinal flora was appropriately described [42]. Many prospective, blinded clinical trials in the 1980s and 1990s gave rise to definitive recommendations concerning better approaches to SAP [43].

Colon and rectum: Gram negative bacilli <i>E. coli</i> , <i>Klebsiella sp.</i> , <i>Enterobacter</i> Gram positive cocci <i>Enterococci</i> Anaerobes <i>B. fragilis</i> , <i>Peptostreptococci</i> , <i>Clostridia</i>
Skin: Gram positive aerobes <i>S. aureus</i> , <i>S. epidermidis</i> , <i>Diphtheroids</i> Gram positive aero-tolerant anaerobes <i>Propionibacterium acne</i>

Table 2: Common endogenous pathogens encountered in colorectal surgery.

More recent studies have yielded a wealth of information. There is an estimation of 40% to 60% of SSIs being preventable with proper SAP [1]. It is then reiterated that therapeutic levels of antibiotics must be present at the time of the incision to achieve effective prophylaxis. Timing of drug administration is critical, with both early and late administration associated with increased SSI rates [27]. Consensus guidelines developed over time have stated that prophylactic antibiotics should be given within 60 minutes before incision to achieve therapeutic levels [1,44]. Globally, few regions and countries have developed standard guidelines on prophylaxis over the past 6 decades. Most work has been restricted to high income countries. It is worth noting the utilization of SAP in certain countries that have had the practice on going.

India has utilized the Scottish Intercollegiate Guideline Network (SIGN) and American Society of Health-system Pharmacists (ASHP) guidelines [45]. Individual institutions have endeavored to establish their own guidelines [46]. A relatively similar scenario is being practiced in parts of China, where institutions went by the “guiding principles for clinical application of antibiotics”, though they did not have an established standard set of guidelines [47]. Since 2007, The Ministry of Health in China issued a series of regulations. These include: the National Guidelines [48], the Guideline on Infection Control with Antibiotics in Surgeries [49], and the Notice of Further Strengthening the Regulation on Antibiotics Clinical Use [50]. However, putting them into practice has been difficult. In Jordan, the Middle East, practice guidelines are adopted from the American Society of Health-System Pharmacists (ASHP) guidelines, just as is the case in India [51]. In Japan, SAP use was not fully recognised before 2000 [52]. The first nationwide guidelines were published in 2001. Since then the use of SAP has improved steadily.

The picture in sub Saharan Africa is not far different. No institutional guidelines were published by 2009 [53]. Some institutions now have guidelines in place, and a number of countries are in the process of developing them. The WHO likewise, has previously not had international standard guidelines. There is an ongoing research project being conducted by Johns Hopkins’s University, The Armstrong Institute and the Patient Safety Division of the WHO, towards the development of an international set of guidelines. This institution (Department of Surgery, Makerere University College of Health Sciences) is one of the African sites involved in this study. Meanwhile, there is a basic set of guidelines contained in the WHO guidelines for safe surgery [2].

The high-income countries of North America, Western Europe, Japan and Australia, currently, have established practice guidelines. Most of this has been developed over the last 2 decades. These recommendations from conducted clinical studies, have led to the contemporary better understanding of the phenomenon of SAP.

Common surgical pathogens

For most SSIs, the source of pathogens is the endogenous flora of the patient’s skin, mucous membranes, or hollow gastrointestinal viscera [54]. These organisms are summarized in Table 2. Another source of SSI pathogens can be a distant focus. Exogenous sources include the operating room personnel and environment (including air), and all tools, instruments and materials brought to the surgical field. These bacteria are primarily aerobes (staphylococci and streptococci).

In colorectal procedures (clean-contaminated), the predominant organisms include gram-negative rods and enterococci in addition to skin flora. However, the causative pathogens associated with SSIs have changed over the past two decades. In the US, the percentage of

SSIs caused by gram-negative bacilli decreased from 56.5% in 1986 to 33.8% in 2003 [55]. *S. aureus* was the most common pathogen, causing 22.5% of SSIs during this time period. More recently, the proportion of SSIs caused by *S. aureus* increased to 30%, with MRSA comprising 49.2% of these isolates [56]. MRSA infections are associated with higher mortality rates, longer hospital stays, and higher hospital costs compared with other infections.

While ensuring effectiveness of SAP, it is vital that measures are taken to minimize the development of drug resistance. Antibiotics with the narrowest spectrum of activity required for efficacy in preventing infection are recommended in practice guidelines. Along with this, individual institutions ought to study local resistance patterns of organisms and overall SSI rates at their site when adopting recommendations.

This is against the background that SAP can alter individual and institutional bacterial flora, leading to changes in colonization rates and increased bacterial resistance [57,58]. It can also predispose patients to *Clostridium difficile* -associated colitis [59]. Risk factors for development of *C. difficile*-associated colitis are longer duration of prophylaxis or therapy, and use of multiple antimicrobial agents [60]. It is difficult to zero-down onto a suitable agent for SAP in the event of this. Patients need to be treated on a case-by-case basis.

Important pharmacological aspects

Most SAP for colorectal surgery involves a cephalosporin, a β -lactam drug. Other relevant drugs are summarized in Table 3. It is important to stick to the principles of administration and choice of antibiotic. Ideal agents are bactericidal, have high tissue penetration ability, low toxicity and a high safety profile. Development of resistance to antibiotics have meant that there has to be a ‘continuous’ change in the agent used. To minimize the development of this resistance, prophylactic antibiotics are not the new, highly effective drugs used for treating severe and life-threatening conditions. Instead, SAP utilizes high doses (provided the agent is safe) which effect high bactericidal tissue drug levels, administered as a single dose, or at most, not exceeding 24 hrs of the procedure. These conditions make development of drug resistance minimal. Furthermore, the more potent ‘drugs’ are spared from irrational use.

Challenging scenarios in SAP are: i) the presence of gram-negative bacilli that produce extended-spectrum β -lactamases, ii) Penicillin-resistant pneumococci, and iii) Vancomycin-resistant enterococci. The development of some resistance is almost certainly an inevitable consequence of the clinical use of antimicrobial drugs. There are a variety of mechanisms by which bacteria acquire resistance to antimicrobial drugs. The emergence of extended-spectrum β -lactamases in gram-negative bacilli is the mechanism of greatest significance when considering colorectal procedures.

Although there are a variety of mechanisms of bacterial resistance to β -lactam antibiotics, the most important are the β -lactamases, which are enzymes capable of hydrolyzing the β -lactam ring of Penicillins, Cephalosporins, and related antimicrobial drugs, rendering them inactive. There are dozens of β -lactamases, which vary in substrate specificity and host range [61,62]. Much of the drive to develop new β -lactam antibiotics has been the emergence of bacteria that produce β -lactamases capable of destroying existing antibiotics. The earliest cephalosporins (eg. Cephalothin) are susceptible to cleavage by a variety of β -lactamases commonly found in gram-negative bacilli, including the chromosomal cephalosporinases of pseudomonas, enterobacter,

Drug	Specific characteristic of prophylactic advantage
Parenteral	
Ampicillin-Sulbactam	Extended antibacterial activity to include β -lactamase-producing strains, including <i>Bacteroides fragilis</i> ; Sulbactam high tissue concentrations – greater stability and less induction of chromosomal β -lactamases than clavulanic acid
Aztreonam	Resistant to many plasmid-mediated β -lactamases; a monobactam – better stability against many β -lactamases
Cefazolin	Very effective in clinical trials.
Cefoxitin	A cephamycin; resistant to many plasmid-mediated β -lactamases
Cefotetan	A cephamycin; resistant to many plasmid-mediated β -lactamases
Ceftriaxone	Extended-spectrum cephalosporins; effective against most enteric gram-negative bacilli
Ciprofloxacin	More potent against gram-negative organisms than other fluoroquinolones; most active quinolone against <i>Pseudomonas aeruginosa</i>
Clindamycin	Useful against some MRSA infections; anti-anaerobic
Ertapenem	A carbapenem; activity retained against most strains with extended-spectrum β -lactamases
Gentamicin	Bactericidal; wide-spectrum of use especially against gram negatives
Metronidazole	Excellent anti-anaerobic activity; adjunct to other drugs
Oral	
Erythromycin base	In combination with neomycin, it is comparably effective, in clinical trials, as IV ceftriaxone-metronidazole preparation in colorectal surgery
Metronidazole	Reduces anaerobic bacteria load
Neomycin sulphate	Adjunct to erythromycin

Table 3: Antibiotics used in colorectal surgery prophylaxis, and their unique characteristics.

and other genera, as well as the common plasmid-borne enzymes of enterobacteriaceae. The latter group of enzymes also hydrolyses a variety of penicillins and, unlike the chromosomal cephalosporinases, is usually inactivated by β -lactamase inhibitors such as clavulanic acid [61].

Modifications of the structure of cephalosporins resulted in the cephamycins, including cefotetan and cefoxitin, which are resistant to many plasmid-mediated β -lactamases [63]. Further development resulted in the extended-spectrum cephalosporins – ceftazidime, cefotaxime, and ceftriaxone, as well as aztreonam (a monobactam), which have better stability against many β -lactamases. Because of their safety, efficacy, and favorable pharmacokinetics, the extended-spectrum cephalosporins have been used extensively.

About 3 decades ago, resistance to these drugs appeared in gram-negative bacilli with chromosomally encoded β -lactamases, most often as the result of mutations that led to the constitutive production of these normally inducible enzymes [64]. Around the same period enteric gram-negative bacilli with transferable resistance to extended-spectrum cephalosporins were described [65]. The majority of these strains, predominantly *Klebsiella* species and *Escherichia coli*, were resistant to all β -lactam antibiotics except cephamycins and carbapenems [66]. Genes encoding these extended-spectrum β -lactamases are typically carried on self-transferable plasmids that often carry other determinants of antibiotic resistance [67]. Because these genes may be located on transposable elements, they may move into various plasmids, permitting the dissemination of extended-spectrum β -lactamases among gram-negative bacilli [67]. Enterobacteriaceae strains that produce extended-spectrum β -lactamases likely arose in response to the selective pressure created by the use of extended-spectrum cephalosporins [68-70]. The prevalence of extended-spectrum β -lactamase production among gram-negative bacilli varies from country to country and among institutions within a country, partly because of patterns of antibiotic use.

Genes encoding extended-spectrum β -lactamases differ from those encoding common plasmid-borne enzymes, with more limited activity by substitutions of only a few nucleotides [71]. Extended-spectrum β -lactamases are the result of simple point mutations that alter amino acids near the active site of the enzyme, possibly facilitating the hydrolysis of extended-spectrum β -lactam antibiotics.

Clavulanic acid, sulbactam, and tazobactam are β -lactamase inhibitors that are currently available in combination with β -lactam

antibiotics. In general, clavulanic acid and tazobactam have better inhibitory activity than sulbactam against extended-spectrum β -lactamases and the enzymes from which they evolved [72]. Clinical studies describe Enterobacteriaceae resistant to combinations of β -lactams with β -lactamase inhibitors as a result of overproduction or mutation of β -lactamases. Bacteria producing extended-spectrum β -lactamases possibly also acquire these properties [73,74].

Vancomycin is now included in the regimen of choice when a cluster of MRSA cases have been detected at an institution. Vancomycin prophylaxis should be considered for patients with known MRSA colonization or at high risk for MRSA colonization in the absence of surveillance data, e.g. patients with recent long hospitalization [75,76]. The development of guidelines for its proper use remains the responsibility of individual institutions. All this notwithstanding, vancomycin has been observed to be less effective than cefazolin for preventing SSIs caused by methicillin-susceptible *S. aureus* (MSSA) [77,78]. For this reason, vancomycin is used in combination with cefazolin at some institutions with both MSSA and MRSA SSIs.

Therefore for colorectal procedures, where pathogens other than staphylococci and streptococci are likely, an additional agent with activity against these pathogens is considered. This may take the form of combining vancomycin with another agent (cefazolin), if the patient does not have a β -lactam allergy. If the patient has beta-lactam allergy, an aminoglycoside (gentamicin), aztreonam, or a fluoroquinolone, may be used. Vancomycin can almost always be used as a single dose due to its long half-life.

This information background gives us a peek preview of the current situation. Though antibiotic use entails dealing with various levels of resistance, it is important to stick to the principle of avoidance of the most potent drugs when administering SAP. The practice still stands – the use of an agent that has shown efficacy for SAP, not necessarily infection treatment, and has ‘passed’ the RCT test.

Current trends in SAP and infection prevention

The basis for SAP stems from the fact that surgical operations carry a risk of infection. The type and duration of the procedure affects this risk. Rectal surgery is associated with a higher risk of infection than that of intraperitoneal colon procedures [79-81]. Other risk factors include: extended procedure duration (>3.5 hours) [5,81,82], impaired patient

immunity, age of >60 years, hypoalbuminemia [82,83], bacterial or fecal contamination of the surgical site, inadvertent perforation or spillage during surgery, corticosteroid use, perioperative blood transfusion [81,84], hypothermia [85], hyperglycemia [86,87], and obesity.

The colon contains a huge reservoir of facultative and anaerobic bacteria. It is kept separate from the body tissues by an intact mucous membrane. An aim of surgeons throughout the last century has been realization of an effective method of 'sterilizing' the colon [88]. In the past 3 decades, clinical trials have demonstrated that to substantially reduce septic complications after elective colon surgery, antibiotics must have activity against both colonic aerobes and anaerobes [89]. Contemporary methods of mechanical bowel preparation (MBP) differ widely [90]. These include standard outpatient mechanical cleansing with dietary restriction, laxatives, and enemas (for varied periods of time), or whole-gut lavage with an electrolyte solution of 10% mannitol, Fleet's phospho-soda, or polyethylene glycol, usually done the day before the operation. Institutions have variance in their recommendations for MBP. Many surgeons use both antibiotics and MBP for preoperative preparation before elective colon resection [90]. This preparation often starts in the outpatient setting. This means that patient selection and education is critical, to ensure compliance and prevent complications.

Choice of antibiotic: These should have activity against the anaerobic and aerobic flora of the colon. The most appropriate regimen for SAP for colorectal procedures (oral only, IV only, or oral-IV combination), and the optimal choice of antibiotic have not been fully resolved. The efficacy of oral prophylactic antibiotics has been established in studies only when used with mechanical bowel preparation (MBP). A variety of oral agents administered after MBP have been evaluated (Table 4). The most common combinations include an aminoglycoside (neomycin and, less often, kanamycin) plus a medication with activity against anaerobes, usually erythromycin [16,91] or metronidazole [92-94].

IV regimens: Cephalosporins are the most commonly used antibiotics, usually administered as single agents (Table 4). Many previous studies found that single-agent first-generation cephalosporins

(cefazolin and cephalothin) [95,96] were ineffective, with postoperative SSI rates ranging from 12% to 39%. This low efficacy is ostensibly due to their lack of *B. fragilis* activity. A combination of a second or third-generation cephalosporin plus metronidazole was no more effective than the cephalosporin alone. The use of third- or fourth generation cephalosporins for routine SAP is not recommended as this may lead to development of resistant organisms. Other IV drugs that have been studied, both singularly and in combination, include: aminoglycosides, clindamycin, ampicillin, penicillins plus β -lactamase inhibitors, doxycycline, piperacillin, imipenem, and ciprofloxacin. Ertapenem, a broad-spectrum carbapenem, is also approved for SAP of SSIs after elective colorectal procedures [97]. It is an acceptable alternative to cefotetan and ceftioxin. Alternative drugs for patients with a high likelihood of adverse effects or allergy to β -lactams include: i) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and ii) metronidazole plus an aminoglycoside or a fluoroquinolone [44]. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.

Combination oral and IV regimens: The infection rate is significantly lower with the oral/IV combination in comparison with either IV or oral SAP alone [98]. In a wider perspective still, the combination of oral antibiotics with MBP, added to IV antibiotics reduces the rate of SSIs compared with IV antibiotics alone without MBP. However, oral antibiotic use is associated with an increase in gastrointestinal symptoms, and may not be well tolerated by patients.

Duration of SAP: IV antibiotics should be administered about 1 hr prior to making the skin incision for the operative procedure. Generally, SAP should not be continued for more than 24 hours, being typically stopped when the procedure is completed and the surgical site closed [99-101].

Redosing: An additional dose of the IV antibiotic is administered if it has a half-life shorter than the duration of the procedure (from the time of initiation of the preoperative dose), and if there is significant intraoperative blood loss [100,101]. Using an agent with a longer half-life can eliminate the need to re-dose during long procedures.

Antibiotic	Recommended dose		Half-life(hr)	Redosing interval(hr)
	Adult	Paediatric		
Parenteral				
Ampicillin-sulbactam ^a	3 g	5 mg/Kg	0.8-1.3	2
Aztreonam	2 g	30 mg/Kg	1.3-2.4	4
Cefazolin	2 g	30 mg/Kg	1.2-2.2	4
Cefoxitin	2 g	40 mg/Kg	0.7-1.1	2
Cefotetan	2 g	40 mg/Kg	2.8-4.6	6
Ceftriaxone	2 g	50-75 mg/Kg	5.4-10.9	NA
Ciprofloxacin ^b	400 mg	10 mg/Kg	3.0-7.0	NA
Clindamycin	900 mg	10 mg/Kg	2.0-4.0	6
Ertapenem	1 g	15 mg/Kg	3.0-5.0	NA
Gentamicin ^c	5 mg/Kg	2.5 mg /Kg	2.0-3.0	NA
Metronidazole	500 mg	15 mg/Kg ^d	6.0-8.0	NA
Oral				
Erythromycin base	1 g	20 mg/kg	0.8-3	NA
Metronidazole	1 g	15 mg/kg	6-10	NA
Neomycin	1 g	15 mg/kg	2-3 ^e	NA

^aAmpicillin component: Adults – 2 g; Children – 5 mg/Kg

^bFluoroquinolones have been associated with a tendinitis/tendon rupture; use of the drug for single-dose prophylaxis is generally safe.

^cGentamicin for surgical antibiotic prophylaxis should be limited to a single dose given preoperatively. Dosing is based on the patient's actual body weight.

^dNeonates weighing <1200 g should receive a single 7.5-mg/kg dose

^e3% of Neomycin dose is absorbed under normal gastrointestinal conditions

Table 4: Currently recommended Doses and Re-dosing intervals for commonly used antibiotics in colorectal surgical prophylaxis [11].

Recommendations: Properly prepared clinical studies have led to the standardization of the choice of parenteral prophylactic antibiotic drugs, and the timing and route of administration [100]. A single dose of a second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan), or cefazolin plus metronidazole is recommended for colon procedures. In institutions where there is increasing resistance to first- and second-generation cephalosporins, it is recommended that a single dose of ceftriaxone plus metronidazole is used [11]. An alternative regimen is ampicillin-sulbactam.

Essentially, regimens ought to have MBP alongside administration of a combination of oral neomycin sulphate plus oral erythromycin base or oral neomycin sulphate plus oral metronidazole. This is in addition to IV prophylaxis. The oral antibiotics should be given as three doses, over approximately 10 hours, the day before the operation, and after MBP.

There are patients who may be receiving therapeutic antibiotics for a distant and unrelated infection before surgery. These ought to be given SAP to ensure adequate serum and tissue levels of an antibiotic with activity against likely bacteria for the duration of the operation. If the agents used therapeutically are appropriate for surgical prophylaxis, administering an extra dose within 60 minutes before surgical incision is sufficient. Otherwise, the SAP recommended for the planned procedure should be used.

Patients with allergy to β -lactam antibiotics: This is an important consideration in the selection of antibiotics. The β -lactam antibiotics, including cephalosporins, are the mainstay of SAP and are also the most commonly implicated drugs when allergic reactions occur. Cephalosporins and carbapenems can safely be used in patients with an allergic reaction to penicillins that is not an IgE-mediated reaction (involving anaphylaxis, urticaria, or bronchospasm) or exfoliative dermatitis (Stevens-Johnson syndrome, toxic epidermal necrolysis). This adverse effect is a life-threatening hypersensitivity reaction that can be caused by β -lactam antibiotics and other medications [102,103]. A careful history of antibiotic allergies should be sought for to determine whether a true allergy exists before selection of drugs for prophylaxis. Alternatives to β -lactam antibiotics are based mainly on the available evidence data on antibiotic activity profiles against predominant procedure-specific organisms.

Current SAP Clinical Practice Guidelines

Several guidelines for SAP have been published [29,30]. Although there is considerable agreement in recommendations for antimicrobial selection and timing (Table 1), inconsistencies exist, and several important issues are not addressed. Guidelines have been formulated in the context of SSI prevention and SAP per se. It is important to give a brief description about the practice in countries (largely high-income) which have had these guidelines in place for a number of years. These have in turn been developed by professional bodies and organisations. Notable among these guidelines are the following: The Sanford Guide to Antimicrobial therapy; Johns Hopkins Antibiotic Guidelines; and American Society of Health-System Pharmacists Report: Clinical practice guidelines for Antimicrobial prophylaxis in Surgery. The latter is adapted by other guidelines, namely: The Centers for Disease Control (CDC); Infectious Diseases Society of America (IDSA); Surgical Infection Society (SIS); and Society for Healthcare Epidemiology of America (SHEA). Other key guidelines developed are: The Scotland Antimicrobial Therapy Guidelines; Western Cape Antimicrobial Guidelines; The Scottish Intercollegiate Guidelines Network (SIGN); and National Institute for Health and Clinical Excellence (NICE) - NHS (UK). Consideration is now turned to the guidelines in countries which have developed national standards.

Japan: The drive towards standardization of SAP practice guidelines started with a multi-centre study conducted between 2004 and 2005. It was pursued against the background that there were no national standard guidelines, yet many studies [1,99] had shown that prophylactic antibiotics are essential for patients undergoing elective colorectal surgery [1,99,104,105]. On top of this, single-dose cephalosporin use, without metronidazole, had not been proved to be an ideal prophylactic for patients undergoing colorectal surgery. Many centres had been unofficially practicing the administration of single-dose cephalosporin and metronidazole, or just single dose cephalosporin. These centres generally followed the US-oriented 1999 Hospital Infection Control Practices Advisory Committee guidelines for prevention of surgical site infection (SSI) [1]. The study leading to these recommendations demonstrated that 3-dose administration of the second-generation cephalosporin, cefmetazole, was significantly more effective for SSI prevention than single-dose administration. Thus, the practice was recommended.

Compounded on the absence of national guide lines, Japan also had a problem with over use of antibiotics. It had the highest incidence of MRSA worldwide [106]. Several studies have shown the overuse and/or misuse of perioperative antibiotics in Japan [107]. Concern about this overuse has led to the development of multiple practice guidelines [108,109], and an increasing emphasis on evidence-based medicine. Yet while Japanese guidelines advise against the prolonged use of antibiotics, they do not set a definite standard for the duration of prophylaxis. The common practice of anti-microbial prophylaxis in Japan was remarkably different from the practice recommended by various guidelines in North America, and from those reported by other developed countries [107]. There is no definite recommendation concerning the duration of prophylaxis, and the antibiotic agent used. Adherence to institutional guidelines is sub-optimal.

Scotland: The Scottish Intercollegiate Guidelines Network in 2008 established national practice guidelines for their National Health Services. The first Scottish Intercollegiate Guidelines Network (SIGN) guideline on antibiotic prophylaxis in surgery was published in July 2000 to provide evidence-based recommendations to reduce inappropriate prophylactic antibiotic prescribing. The Scottish Surveillance of Healthcare Associated Infection Programme (SSHAIP) on SSI describes a high compliance with the guideline's recommendations. The original guidelines addressed risk factors for SSIs, benefits and risks of antibiotic prophylaxis, indications for SAP, as well as recommendations on administration of intravenous prophylactic antibiotics.

More recently, a review [110] was considered timely, in light of the ever increasing need to use antibiotics wisely, complicated by the increasing prevalence of more resistant organisms such as MRSA. Key recommendations contained in the guidelines relate to the benefits and risks of antibiotic prophylaxis. Patients with a history of anaphylaxis occurring immediately after a penicillin therapy are described as being potentially at an increased risk of immediate hypersensitivity, and should not receive prophylaxis with a β -lactam antibiotic. The duration of prophylactic antibiotic therapy should be limited to a single dose, except in the special circumstances of prolonged surgery and major blood loss. This antibiotic must cover the expected pathogens for that operative site. Regarding implementation of the guideline, also recommended is recording antibiotic prophylaxis as a legal requirement. However, this is not always done. By having it as an acceptable requirement, it constitutes a routine part of local audit and risk management.

England and Wales: NICE clinical guidelines are recommendations

about the treatment and care of people with specific diseases and conditions in the National Health Services (NHS) in England and Wales [111]. These constitute the national clinical practice guidelines for SSI prevention and treatment. Key recommendations included in this document pertaining to SAP are: use of the local antibiotic formulary based on prevalent pathogens; consideration of potential adverse effects when choosing specific antibiotics for prophylaxis; and the use of a single dose of antibiotic prophylaxis intravenously on starting anaesthesia. Antibiotic prophylaxis administration at induction of anaesthesia was due for revision. Other constituents of the guidelines are: consideration of the timing and pharmacokinetics of the drug (the serum half-life), and necessary infusion time of the antibiotic, prior to its administration; administration of a repeat dose of antibiotic prophylaxis when the operation is longer than the half-life of the antibiotic given; and provision of information to patients before the operation about the need for antibiotic prophylaxis.

Australia: SAP practice in this setting is based on local institutional protocols. In addition, many institutions follow the guidelines laid out by the AHSP and CDC, among others. Widely accepted indications for antibiotic prophylaxis are contaminated and clean-contaminated surgery [112]. A review featuring multiple hospitals and health focused institutions in 2005 made certain observations about the status of prophylaxis practice there. The guiding principles common to most centres are: the decision on whether prophylaxis is appropriate; determination of the bacterial flora most likely to cause postoperative infection; and the choice of antibiotic based on antibacterial spectrum required.

Other cardinal principles include the choice of the less expensive drug if two drugs are otherwise of equal antibacterial spectrum, efficacy, toxicity, and ease of administration. The antibiotic administration should cover a short period. This is viewed as one dose if surgery is of four hours duration or less. It is considered prudent to avoid antibiotics likely to be of use in the treatment of serious sepsis. Emphasis is given to good surgical technique; antibiotic prophylaxis should not replace this. A continuous review of antibiotic prophylaxis protocols is encouraged regularly. Both the drug costs and hospital antibiotic resistance patterns may change.

Putting into consideration the above discussion, it is deduced that the use of 'third generation' cephalosporins, such as ceftriaxone and cefotaxime, should be avoided in SAP. Commonly used surgical prophylactic antibiotics recommended include: 'first generation' cephalosporins (IV) – cephazolin or cephalothin; gentamicin (IV); and metronidazole (IV or rectal) and tinidazole (oral) for anaerobic infections. Flucloxacillin (IV) is indicated when methicillin-susceptible staphylococcal infection is likely, while vancomycin (IV) is used if MRSA infection is likely.

It is advocated that β -lactam allergy must be sought for prior to anaesthesia to minimise the risk of anaphylaxis under anaesthesia. Oral or rectal antibiotics need to be given earlier to ensure adequate tissue concentrations during surgery. Metronidazole suppositories are commonly used in bowel surgery and must be given 2–4 hours before it begins. In prolonged surgery of greater than four hours, further antibiotic doses may be required to maintain a minimum inhibitory concentration (MIC).

A set of guidelines recently introduced are the Surgical Antibiotic Prophylaxis Guidelines for Gastrointestinal Surgery, by the South Australian expert Advisory Group on Antibiotic Resistance (SAAGAR), February, 2013 [113]. Important recommendations involving colon

surgery are: administration of metronidazole 500mg IV (child <12 years: 12.5 mg/kg up to 500 mg) plus either cephazolin 1g IV (2 g for patients \geq 80 kg) (child <12 years: 25 mg/kg up to 1g) or gentamicin 2 mg/kg IV; and post-operative antibiotics are not indicated unless infection is confirmed or suspected, regardless of the presence of surgical drains. Also, certain vital parameters concerning the method of administration are considered. For IV bolus administration, this should be timed to within 60 minutes before skin incision. An optimum period of 30 minutes is described as more easily applicable. Drug administration after skin incision or >60 minutes before incision is noted for being less effective. IV infusion is described similarly. Specifically, antibiotic infusions should be timed to end \leq 30 minutes before skin incision (e.g. metronidazole, vancomycin).

Particular attention is given to penicillin/ β -lactam allergy. It is recommended that penicillin or cephazolin is replaced with vancomycin, in cases involving severe type 1 penicillin or cephalosporin allergy. An addition of gentamicin IV 2 mg/kg is administered when gram negative cover is required. For patients with MRSA risk (history of MRSA colonisation or infection), it is recommended that vancomycin replaces penicillin or cephazolin. Vancomycin is administered as 1 g (1.5 g for patients > 80kg) (child <12 years: 30 mg/kg up to 1.5 g) by IV infusion over one hour. A single pre-operative dose is sufficient for most procedures.

Canada: Despite the availability of practice guidelines, there is considerable evidence that antibiotics are used excessively and inappropriately for the prevention of SSIs [12]. A study showed that only 5% of colorectal surgery patients receive appropriate preoperative antibiotic administration [114]. Considering the huge burden of disease represented by SSIs and the widespread lack of adherence to guidelines for antibiotic prophylaxis, quality-improvement efforts are necessary.

Practice guidelines are otherwise related to the AHSP and SIGN guidelines. Also in use are those guidelines prepared by the professional corporations (CMQ, OPQ), the federations (FMOQ, FMSQ) and Québec associations of Pharmacists and Physicians. Important components contained therein are: timing of preoperative antibiotic administration at induction of anaesthesia; and a single dose of antibiotic prophylaxis being sufficient except in situations where antibiotic therapy must be continued (e.g. perforated gut). Cefoxitin and cefazolin are the standard agents used. A single 2 g IV dose at induction may be used in patients >80 kg. Importantly, we note that the practice was administration at induction of anaesthesia. This was later to change. Cefoxitin was described as being of greater benefit, when compared with cefazolin.

The Ontario Antimicrobial Stewardship Project Evidence-Based Summary for Appropriate Duration of Antimicrobial Therapy proposed other guidelines in 2010 [115]. These are now the preferred practice. Significant inclusions to SAP are noted here. A single dose of antibiotic prophylaxis should be delivered intravenously 15–60 minutes before surgery. For prolonged procedures, >3 hours or 2 half-lives of the administered antibiotic, re-dosing may be needed to maintain adequate concentrations in the tissues. Postoperative administration of antimicrobial prophylaxis is not beneficial and is not recommended for most types of surgery. Furthermore, the selection of antibiotics for surgical prophylaxis should target the most likely offending organisms and should be appropriate for the particular surgical procedure. Current recommendations in the literature and issues related to resistance and allergies ought to be taken into consideration.

USA: The USA, with a wealth of experience, has been at the

frontline of research, development and implementation of SAP guidelines. A standard package is contained in the Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery of the AHSP [11]. The guidelines were developed jointly by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA). It represents an update to the previously published ASHP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery [31], together with guidelines from IDSA and SIS [29,30]. There are important recommendations that provide, arguably, the most comprehensive developments in SAP worldwide.

Concerning preoperative-dose timing, an optimal time for administration of antibiotics is within 60 minutes before the surgical incision. This recommendation is more specific, and puts to rest the previous ideology of “at induction of anesthesia”. Fluoroquinolones and Vancomycin, require administration over one to two hours. The administration of these agents should begin within 120 minutes before the surgical incision.

Parameters for selection are contained in Table 5 and in the section of ‘current trends in SAP’, above. It is advocated that doses should be weight-based in obese patients [116-118]. The pharmacokinetics of drugs may be altered in obese patients, so dosage adjustments based on body weight may be warranted in these patients. Intraoperative re-

Year	Practice recommendations	Landmark developments
1984 ^a	<ul style="list-style-type: none"> No popular standard guidelines in place Oral antibiotics for use alongside mechanical bowel preparation – Neomycin plus erythromycin base IV drugs – cefoxitin, clindamycin, gentamicin or tobramycin Optional – metronidazole 	<ul style="list-style-type: none"> Role of metronidazole recognized, though controversial Choice of usable drugs dependent on site of the operation and the most probable contaminants encountered. Possible adverse reactions: <ul style="list-style-type: none"> suppression of the normal microbial flora superinfection by drug-resistant microorganisms continued infection with the initial pathogen through the emergence of drug-resistant mutants.
1993 [11]	<ul style="list-style-type: none"> Drugs for administration: <ul style="list-style-type: none"> Neomycin and Erythromycin (oral), or Gentamicin (1.5 mg/kg) plus metronidazole (500mg), or Clindamycin (300 mg), or Cefixitin (2 g IV), or Cefotetan (2 g IV) Timing – parenteral initial dose immediately before the operation. Second dose short half-life drugs Route – IV is optimal for adequate tissue levels; oral drugs are an alternative Duration – single dose sufficient Choice – effective against pathogens most frequently responsible for SSIs Side effects – Rare; main ones are allergic reactions and antibiotic-associated colitis. 	<ul style="list-style-type: none"> Specific recommendations made; initiation of formal practice guidelines The significance of preoperative initial dosing was recognised; the hallmark of prophylaxis Oral drugs described as alternatives to the Ideal IV route of administration Multiple dosing not essential; a single dose is adequate
1999 [31]	<ul style="list-style-type: none"> Drugs for administration: <ul style="list-style-type: none"> Neomycin sulphate 1 g plus erythromycin base 1 g p.o. (after MBP is completed) at 19, 18, and 9 hr before surgery if oral route is contraindicated, cefoxitin, cefotetan, or cefmetazole 2 g IV, at induction of anesthesia for patients undergoing colorectal resection oral neomycin and erythromycin plus an IV cephalosporin Timing – before the initial incision; within 30 minutes to one hour before the incision <ul style="list-style-type: none"> oral drugs should be administered starting 19 hours before the scheduled time of surgery, then at 18 and 9 hrs Duration – 24 hours or less; if a short-acting agent is used, it should be re-administered if the operation extends beyond three hours in duration, or in case of prolonged or excessive bleeding Route – oral and IV Patients undergoing colorectal surgery should receive MBP 	<ul style="list-style-type: none"> IV and oral combination is recommended as a preserve of colorectal (high-risk) surgery Preoperative oral drugs are given way ahead of the time of surgery A maximum duration of prophylaxis of 24 hours identified The role of MBP in colorectal surgery made clear Role of re-dosing described
2013 [11]	<ul style="list-style-type: none"> Drugs for administration: <ul style="list-style-type: none"> First line – any of the following (single or combinations): Cefazolin plus metronidazole, cefoxitin, cefotetan, ampicillin–sulbactam, ceftriaxone plus metronidazole, ertapenem Second line: any of the following: Clindamycin plus an aminoglycoside, Aztreonam, a fluoroquinolone, metronidazole plus an aminoglycoside, a fluoroquinolone If β-lactam allergy is present, any of the following: <ul style="list-style-type: none"> clindamycin plus gentamicin or a fluoroquinolone or aztreonam metronidazole plus gentamicin or a fluoroquinolone vancomycin to replace cephalosporins above Timing – within 60 minutes before surgical incision Dosing – intraoperative re-dosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the drug or there is excessive blood loss during the procedure Duration – single dose or continuation for less than 24 hours Weight-based dosing – For obese patient and paediatric patients > 40 kg; to be considered Colonization – consider Intranasalmupirocin to eradicate MRSA nasal colonization in adult patients and health care workers. MBP and oral antibiotics have role as previously described 	<ul style="list-style-type: none"> First line and second line alternatives identified Broader range of drugs identified The significance of body weight introduced – weight-based dosing More alternatives available in case of β-lactam allergy Remedies for MRSA colonisation introduced

^aPositano RG, Shafer N, Lupo PJ (1984) Antimicrobial Prophylaxis. Journal of the National Medical Association, 76(7): 729-736 [11], [14] and [31] – Main references' section

Table 5: Evolving trends in SAP over the last 3 decades.

dosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the drug or there is excessive blood loss during the procedure. All these measures are taken to ensure good blood and tissue drug concentrations at the time of contamination during surgery.

On the duration of prophylaxis, a shortened post-operative course of antibiotics is encouraged, involving a single dose. If there is continuation, it should be for less than 24 hours, even in the presence of indwelling drains and intravascular catheters.

Future outlook

The clinical practice of SAP is ever evolving. Additional research is needed in several areas. The risks and benefits of continuing antimicrobial prophylaxis after the conclusion of the operative procedure, including dosing and duration, need to be further evaluated. In addition, there is more need for clarity on specific recommendations for intraoperative repeat dosing, weight-based dosing in obese patients, and timing of pre-surgical antimicrobials that must be administered over a prolonged period (e.g., vancomycin, fluoroquinolones). Along with this, more information is sought regarding targeted antimicrobial concentrations and intraoperative monitoring of antimicrobial serum and tissue concentrations to optimize efficacy.

The role of topical administration of antibiotics as a substitute for, or an adjunct to IV SAP needs to be further evaluated. Additional studies are needed to guide the selection of antibiotics for prophylaxis, particularly combination regimens, for patients with allergies to β -lactam antibiotics. There is need to develop strategies to optimise prophylaxis in patients and facilities with a high risk or high prevalence of resistant organisms implicated in SSIs. Practicable methods for screening for *S. aureus* and decolonization for certain procedures need to be sought.

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Authors' contributions

PAO conceptualised the theme, gathered the data, designed and wrote the manuscript. SCK scientifically edited, and made essential modifications to the manuscript. Both authors read and approved the final manuscript.

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