Important issues for perioperative systemic antimicrobial prophylaxis in surgery

Bhanu Sinha[a], *Sander van Assen*[b], *and Alexander W. Friedrich*[a]

Purpose of review
Prevention of surgical site infections is a key issue to patient safety and the success of surgical interventions. Systemic antimicrobial prophylaxis is one important component of a perioperative infection prevention bundle. This review focuses on selected recent developments and important concepts in the field.

Recent findings
Joint guidelines (American Society of Health-System Pharmacists, Infectious Diseases Society of America, Surgical Infection Society, Society for Healthcare Epidemiology of America) for antimicrobial prophylaxis in surgery have been recently revised and updated. Furthermore, European Centre for Disease Prevention and Control has issued a report identifying key factors for success. Important updated fields include the duration of prophylaxis; the selection and dosing of the antimicrobial drug; the precise timing of administration; and common and basic principles, including the implementation of local guidelines and attributing the responsibility of appropriate timing to anaesthesiologists. Additionally, the role of preoperative selective digestive decontamination (SDD) in gastrointestinal surgery receives increasing attention. A major concern of SDD, namely increasing microbial resistance, has not been demonstrated to date.

Summary
Most frequently, anaesthesiologists administer perioperative antimicrobial prophylaxis. Identification of core principles and harmonization of protocols should facilitate this task and thus help to improve patient safety and to monitor compliance. However, local and regional epidemiology have to be taken into account in order to establish local protocols.

Keywords
infection control, perioperative systemic antimicrobial prophylaxis, prevention of surgical site infections, selective digestive decontamination

INTRODUCTION

Postoperative surgical site infections (SSIs) are among the most frequent nosocomial infections in surgical patients. Thus, prevention of SSIs is a key issue to patient safety and maintained success of surgical interventions. Systemic antimicrobial prophylaxis is one important component of perioperative infection prevention bundles, which consist of several individual measures. Recently, a technical report by the European Centre for Disease Prevention and Control has been published [1▪], and the common guideline for antimicrobial prophylaxis in surgery by American Society of Health-System Pharmacists, Infectious Diseases Society of America, Surgical Infection Society, and Society for Healthcare Epidemiology of America has been revised and updated [2▪▪]. Most important fields of update include the duration of prophylaxis; the selection and dosing of the antimicrobial drug; the precise timing of administration; and an emphasis on common pertinent principles. These points turn out to have apparently the highest importance for the success of systemic antimicrobial prophylaxis, as they are discussed in several recent detailed sources

[a]Department of Medical Microbiology and Infection Prevention and [b]Department of Internal Medicine, Division of Infectious Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Correspondence to Bhanu Sinha, MD, PhD, Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen, HPC: EB80, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. Tel: +41 50 361 3480; fax: +41 50 361 9105; e-mail: b.sinha@umcg.nl

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KEY POINTS

- Effective systemic perioperative antimicrobial prophylaxis requires embedding it in an adequate bundle of measures, which involve the complete chain of care around an operative procedure.
- The prevalence of β-lactam allergy as a basis for a contraindication has been probably largely overestimated.
- The implementation of perioperative antimicrobial prophylaxis requires attention to a number of different factors, which are generally interdependent.
- Five special key issues have been identified: establishment of multidisciplinary antimicrobial management teams and choice of drugs (local protocols); defining responsibility for administration; appropriate timing; appropriate dosing and repeat dosing; and duration and termination.
- The responsibility of anaesthesiologists for appropriate timing of perioperative antimicrobial prophylaxis will increase. Identification of core principles and harmonization of protocols should facilitate this task and thus help improve patient safety.

[1▪,2▪▪,3▪,4▪]. An additional field of interest, the role of which still has to be determined, is the preoperative start of selective digestive decontamination (SDD) in gastrointestinal surgery [5▪].

GOALS, DEFINITIONS, PATHOGENESIS, RISK ASSESSMENT, AND INDICATION

SSIs are caused by facultative pathogenic microorganisms of the endogenous flora of the human body. This comprises mostly skin flora (e.g., staphylococci and streptococci), and additionally flora of the gastrointestinal (and urogenital) tract in procedures in which the integrity of internal mucosal surfaces is compromised (e.g. gram-negative rods and anaerobes). All measures to prevent SSIs are aiming at reducing the bacterial load to a level that is no longer sufficient to establish an infection at the site of the breached barrier in clean and clean-contaminated operations. The choice of the regimen is mainly directed by the expected microflora that will be encountered. Usually, the drug with the narrowest possible spectrum should be chosen [2▪▪]. This is mainly based on the consideration to produce as little collateral damage as possible to the endogenous microflora, which provides a natural colonization resistance, and to spare broader drugs for treatment of (severe) infections.

Systemic antimicrobial prophylaxis aims at further reducing the number of viable microorganisms that have gained access to tissue during the operation. Procedures involving contaminated or dirty operations are not eligible for prophylaxis, as in this situation, (preemptive) antimicrobial therapy is indicated. To establish an infection, facultative pathogenic microorganisms need to gain access to deeper tissues. During operations, this happens because a major first line of defence, the integrity of skin/mucosa is compromised. This does not only apply to the mechanical barrier, but also to local antimicrobial defence mechanisms, for example, antimicrobial peptides and immune cells.

Appropriate risk-assessment involves the estimation of two factors, frequency and severity of complications. The combination of these two factors in a scoring system allows us to balance the benefits against risks of systemic antimicrobial prophylaxis. In this case, effects on the individual patient (reduced risk of infection vs. adverse effects, including superinfections and acquiring resistant microorganisms), effects on the population (i.e., driving selection of resistance), and cost-effectiveness have to be taken into account. As one critical parameter (i.e., the minimum infectious dose required to establish an infection) differs for different procedures and even according to comorbidities, this may also tip the balance. Patient-related risk factors include, but are not limited to, obesity, very young or very old age, smoking, diabetes mellitus, bad nutritional status, immunocompromised state (including use of corticosteroids and immunosuppressive medication, malnourishment, neutropenia), as well as a coexistent remote infection, a risk of exposure to resistant microorganisms (long hospitalization), and a recent operation [2▪▪,6].

ALLERGY

Presumed allergy to penicillins or cephalosporins is a frequent contraindication for a substantial proportion of the patients. Generally, the prevalence of penicillin allergy by history is overestimated. Often any negative reaction following use of antibiotics is termed 'allergy', which would lead to second-choice medication with a less favorable effectiveness and/or safety profile. A true anaphylactic reaction (type I allergy; immediate: urticaria, delayed: laryngeal edema, bronchospasm, or angioedema), and the type IV allergic manifestations (Steven-Johnson syndrome, toxic epidermal necrolysis), represent true contraindications [3▪,7]. Prevalence of type I allergy to penicillins is estimated to range from 5 to 10% of all allergic reactions, and 80–95% of patients with a reported penicillin allergy are found to be not (or no longer) allergic [8,9]. This would result in less than 0.5–1% in the total population [9]. Allergic

cross-reactivity between penicillins and cephalosporins is primarily determined by the (R1) side chains, not by the β-lactam ring. Currently, global cross-allergy for cephalosporins is estimated to be less than 1% and less than 2% in patients with a history of penicillin allergy and a positive penicillin skin test, respectively [7]. However, rates of cross-reactivity appear to be somewhat higher with similar (R1) side chains. Skin testing appears to have a good negative predictive value for significant clinical reactions, but sometimes a rather poor positive predictive value [7].

POSITION OF PRE-OPERATIVE ANTIBIOTIC PROPHYLAXIS WITHIN BUNDLES FOR PREVENTION OF INFECTIONS

Bundles for prevention of infections consist of several individual measures. These may comprise: correct basic and hand hygiene, aseptic procedures; good surgical technique (e.g., reasonably short duration of operation, gentle traction, removal of dead tissue, effective hemostasis, avoidance of dead space, irrigation of tissues with saline to reduce drying, careful use of closed suction drains, use of fine nonabsorbed monofilament suture material, and wound closure without tension); preoperative screening for *S. aureus* with subsequent decolonization and whole body washing; hair removal, immediately preoperatively (clipping/ointment, not shaving); blood glucose control below 200 mg/dl (preoperatively, until at least 48 h postoperatively); maintaining perioperative normothermia; and preoperative systemic antibiotics [1▪,2▪▪,6]. However, not all of these isolated measures or basic bundles are directly supported by nonconflicting evidence, and some (e.g., laminar airflow and supplemental oxygen) appear to have no demonstrable effect [6].

Five core measures ('modalities') for improving quality of perioperative antimicrobial prophylaxis have been identified in the recent European consensus article [1▪]: establishment of multidisciplinary antimicrobial management teams and choice of drugs (local protocols); defining responsibility for administration; appropriate timing; appropriate dosing and repeat dosing; duration and termination.

Better compliance with at least two of three investigated core measures (i.e., appropriate timing and choice of antibiotic) has been shown to significantly reduce SSIs [10]. In this study, an increase of 10% in compliance led to a 5.3% decrease in SSI rates, whereas the third core measure (i.e., timely stop) not surprisingly had no demonstrable effect on SSI rates since it is important for other endpoints.

Individual measures and modalities will be discussed subsequently. It is important to note the development of SSIs is a complex and multifactorial process. This implies that systemic antimicrobial prophylaxis cannot compensate for neglecting other crucial measures of infection prevention bundles and vice versa; the positive effect of optimal antimicrobial prophylaxis can be annihilated by errors at other components within the chain of care.

KEY FACTORS 1 AND 2: CHOICE OF DRUGS, ROLE OF LOCAL PROTOCOLS, AND RESPONSIBILITY FOR APPROPRIATE ADMINISTRATION

There are recent guidelines and reviews available giving detailed advice on the choice of drugs, specified according to the type of surgery [2▪▪,3▪,4▪]. The most frequently used regimens for most situations include first-generation (best studied is cefazolin) or second-generation cephalosporins (e.g., cefuroxime). In the case of β-lactam allergy representing a true contraindication, clindamycin and vancomycin can be used, in procedures with a substantial risk for gram-negative bacilli, in a combination with a fluoroquinolone (frequently ciprofloxacin). In procedures in which a high concentration of anaerobes is encountered, usually the regimen contains also metronidazole. Only under exceptional circumstances, there is an indication for broad-spectrum substances for an individual patient [2▪▪].

Most importantly, the local/regional epidemiology and even hospital-specific factors need to be taken into account, as well as potentially relevant resistant organisms [e.g., methicillin-resistant *Staphylococcus aureus* (MRSA) rates]. This set of information should be incorporated in locally implemented and regularly updated guidelines. This has been identified recently as one of the five most important modalities [1▪]. The multidisciplinary guideline team should also monitor compliance with these guidelines. A major component of this modality is the clear assignment of responsibility for appropriate timing of perioperative antimicrobial prophylaxis to a dedicated member in the chain of care, ideally, the anaesthesiologist [1▪].

KEY FACTOR 3: IMPORTANCE OF CORRECT TIMING

The probably most important single modality for the effect of systemic antimicrobial prophylaxis is correct timing [1▪,2▪▪,3▪,4▪]. The initially identified interval (i.e., within 2 h preincision [11]) has been

narrowed down further. Later (i.e., postincision) or earlier than 2 h, preincision has a substantially weaker effect. Currently, the optimal window is considered to be within 1 h before, but not immediately prior to incision. Exceptions to this rule are vancomycin and fluoroquinolones, wherein the window between 2 h and 1 h before incision is considered optimal [1▪,2▪▪,3▪,4▪,12]. The latter is due to the fact that slower infusions are required, and that vancomycin slowly reaches adequate tissue levels because of its large size. Usually, timing the infusion in the window to start from 60 min and to stop before 30 min prior to incision will achieve optimal effects and should be relatively easy to implement in routine care.

KEY FACTOR 4: DOSING AND REPEAT DOSING

In the past years, weight-based dosing rather than one-size-fits-all has received more attention. Most specific recent changes in recommendations relate to cefazolin, which should be dosed accordingly (1 g <80 kg, 2 g >80 kg, and 3 g >120 kg), and vancomycin to achieve appropriate tissue levels [3▪,4▪]. Alternatively, a standard dose of 2 g cefazolin is recommended up to 120 kg, and 3 g cefazolin for patients with a higher weight [2▪▪]. This approach is considered both well tolerated and less error prone, thus more feasible. Generally, single-shot prophylaxis is recommended. Usually, in this situation, no adaptation for patients with impaired renal function is required.

Repeated intraoperative dosing is recommended in certain situations [1▪,2▪▪,3▪,4▪]: for drugs with a relatively short half life if the procedure takes longer than two half-lives of the substance used; and generally, also major blood loss (with various definitions in the range of 1–2 l) is considered an indication for repeat dosing. Timing of repeat dosing should be calculated from the first (preoperative) dose rather than from the time of incision. Prophylaxis should continue only for the duration of the procedure, and usually not continue after wound closure [1▪,2▪▪,3▪,4▪].

KEY FACTOR 5: DURATION (AND STOP) OF PROPHYLAXIS

Many centers have chosen to apply antimicrobials for prolonged periods after surgery, because, for example, drains are still present. This policy is lacking supporting evidence. In exceptional situations, in which consequences of infections would be deleterious (e.g., sternotomy, major implants bone/joints) administration up to 24 h is accepted, albeit not supported by nonconflicting evidence. A duration for more than 24 h is not supported by evidence [1▪,2▪▪,3▪,4▪]. For procedures in which prolonged prophylaxis is currently accepted, also repeat dosing is recommended (cf. above), and might even be more important. Unnecessary continuation of prophylaxis can be considered both a risk for the patient (toxicity, superinfection, acquiring resistant microorganisms) and the society (driving microbial resistance, cost).

PREOPERATIVE START OF SELECTIVE DIGESTIVE DECONTAMINATION IN GASTROINTESTINAL SURGERY

In several countries, SDD for patients with anticipation of a longer stay on intensive care has been implemented. More recently, several investigators have examined the role of a preoperative start of SDD in patients with elective gastrointestinal surgery. A recent systematic review and meta-analysis has evaluated the data of eight randomized controlled trials published between 1988 and 2011, including a total of 1668 patients [5▪]. It shows a significantly reduced infection rate in the SDD group [19.2 vs. 28.2% in the control group; odds ratio [OR]: 0.58, 95% confidence interval (CI) 0.42–0.82, $P = 0.002$]. This was paralleled by a significantly lower incidence of anastomotic leakage in the SDD group (3.3 vs. 7.4% in the control group; OR: 0.42, 95% CI 0.24–0.73, $P = 0.002$). This effect holds true for both upper and lower gastrointestinal tract procedures.

A major concern of SDD has been an inevitable higher selective pressure, which should drive resistance rates. This in turn would render these efforts ultimately ineffective. General implementation of SDD would further hasten this process. A recent systematic review and meta-analysis re-evaluated data from 35 studies published between 1987 and 2012 [13▪]. Overall, neither an increase in gram-positive (MRSA, vancomycin-resistant enterococci) colonization or infection could be identified, nor an increase in resistance rates in gram-negative bacilli to aminoglycosides, polymyxins/colistin, fluoroquinolones, and third-generation cephalosporins. Surprisingly, resistance rates in gram-negative bacilli to polymyxins/colistin and third-generation cephalosporins dropped significantly in the SDD group.

As a note of caution, preoperative start of SDD for all patients with elective gastrointestinal surgery might still represent a different scenario. However, this measure appears to have the potential for a substantial benefit for a large group of surgical patients.

CONCLUSION

The field of perioperative antimicrobial prophylaxis is currently undergoing harmonization and some dear concepts appear not to withstand evidence-based scrutiny. Identification of important core principles and harmonization of protocols should facilitate administration and thus help improve patient safety. These important issues comprise, for example, the precise timing and duration of prophylaxis, as well as common principles.

Some more recent developments, such as the role of preoperative SDD in gastrointestinal surgery, receive increasing attention. The role of anaesthesiologists has become even more important, being considered now responsible for appropriate timing. Consequently, they will be also part of the multidisciplinary management teams for the development and implementation of local guidelines, which should take into account local and regional epidemiology.

On the contrary, there are still major areas of uncertainty, which require more in-depth research in order to base more recommendations on solid evidence in the future.

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Conflicts of interest

S.vA. has no conflicts of interest to declare; A.F. has no conflicts of interest to declare; he receives funding from European Union (IVa III-1-01=073).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. ■ European Centre for Disease Prevention and Control (ECDC). Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis. Stockholm: ECDC; 2013–; doi 10.2900/85936 http://www.ecdc.europa.eu/en/publications/Publications/Perioperative%20antibiotic%20prophylaxis%20-%20June%202013.pdf.

This report reviews in-depth and detailed the current literature to central questions related to systemic antimicrobial prophylaxis in surgery.

2. ■■ Bratzler DW, Dellinger P, Olsen KM, *et al.* Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013; 70:195–283.

This recent and most comprehensive guideline and review provides both general and detailed information on specific fields, covering virtually all surgical specialties.

3. ■ Hansen E, Belden K, Silibovsky R, *et al.* Perioperative antibiotics. J Orthop Res 2014; 32 (Suppl 1):S31–59.

This consensus statement review discusses several key questions point-per-point (with a focus on orthopedic surgery).

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