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Prevention of surgical site infections in orthopaedic surgery: a synthesis of current recommendations

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Abstract. – Despite adopted precautions, surgical site infection (SSI) rate in orthopaedic surgery and its consequences still remain a major problem. Worldwide, infection prevention and control in perioperative settings are considered of primary importance for every healthcare system. The management of perioperative infections carries a heavy psychological and financial burden, since patients who experience SSI have increased hospital length of stay, morbidity and mortality rates, and higher hospital costs. As the treatment of such infections is particularly difficult in the presence of an implanted biomaterial, the prevention of SSI in orthopaedic surgery represents a challenging key issue, requiring the integration of a range of measures before, during and after surgery. In fact, over the years several aspects of SSI prevention have been studied in order to identify the best SSI prevention strategies and set out appropriate clinical practices. This article will review and summarize the recent international guidelines released on this subject together with other published relevant evidence.

Key Words:
Surgical site infections, Orthopaedic surgery, Infection prevention.

Introduction

Surgical site infection (SSI) in orthopaedic surgery remains a challenging issue for surgeons and a potential disaster for patients. The current incidence of SSI in orthopaedic surgery makes it difficult to carry out studies with adequate sample size and it is, therefore, difficult to draw firm conclusions on all subjects related to the prevention of infection.

Even though over the years increasing evidence has been gathered on many crucial clinical questions, some important issues remain unsolved. Several guidelines (GL) have been produced by different international bodies; interestingly, in 2016 and 2017, three separate important documents were released or updated within few months by World Health Organization (WHO)[1], Centers for Disease Control and Prevention (CDC)[2], and National Institute for Health and Care Excellence (NICE)[3], respectively. This prompted us to analyze and compare them with other existing similar documents and papers, retrieved with a systematic search, producing the present synthesis. We will report the main conclusions following a sequential order (preoperative, perioperative and postoperative) in the interventions or clinical questions.

Risk Factors

The risk of developing a SSI in orthopaedic surgery is likely to be influenced by several factors such as patients' characteristics, surgical intervention, and perioperative care. Identifying these risk factors is crucial for two different reasons. First, a better knowledge of what predisposes to SSI in orthopaedic surgery can help controlling or eliminating it, when possible, to decrease SSI rates (modifiable risk factors). Secondly, understanding the importance towards SSI risk of individual patient status or comorbidities (even if non-modifiable) can help developing scores to to accurately identify individuals at high risk[4].

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Table I. Recent scientific literature on risk factors for SSI in orthopaedic surgery.

Authors	Year of publication	Journal	Study design	Patient number
Kerkhoffs et al[5]	2012	JBJS Am	Systematic review/Meta-analysis	15,276
Dale et al[6]	2012	Acta Orthopaedica	Prospective cohort study	432,168
Bozic et al[7]	2012	JBJS Am	Retrospective cohort study	40,919
Namba et al[8]	2012	JBJS Br	Prospective cohort study	30,491
Maoz et al[9]	2014	Clin Orthop Relat Res	Retrospective study	4,078
Zhu et al[10]	2015	J Hosp Infect	Systematic review/Meta-analysis	147,549
Kong et al[11]	2016	Int J Clin Exp Med	Systematic review/Meta-analysis	108,987
Kunutsor et al[12]	2016	PLoS One	Systematic review/Meta-analysis	512,508
Kim et al[13]	2017	J Arthroplasty	Meta-analysis	21,770

Risk prediction scores are useful for the surgeon not so much to implement targeted preventive strategies, since the standards for SSI prevention should be applied to any surgical interventions, but to get reliable information to share with the patient, thus supporting appropriate clinical choices and achieving the formulation of a more conscious informed consent. Over the years several studies explored the association between SSI and risk factors related to patient, surgical intervention and hospital setting. Many of them had limitations, such as poor sample size, short follow-up, inconsistent definitions of infection, that impaired the reliability of results. Following the publication of more recent studies, the possibility to conduct meta-analyses on a wider number of data generated more reliable information confirming the earlier results. The major studies conducted in the last five years, with relevant details, are listed in Table I. Among them, the metanalyses by Zhu et al[10] and Kunutsor et al[12] allowed to overcome the limitations of previous research. Table II shows the risk factors for SSI identified in orthopaedic surgery, specifying whether the association to SSI is confirmed by recent literature or not.

Screening and Treatment of Asymptomatic Bacteriuria in Patients Undergoing TJA: a Common Practice to be Critically Reconsidered

Asymptomatic bacteriuria (ASB) is quite common in the general population, with higher prevalence in females, elderly people and patients with diabetes or genitourinary abnormalities[14]. ASB incidence ranges from 5.1% to 35.7% in patients on waiting list for total joint arthroplasty (TJA)[15] and hits a 50% peak in the elderly living in a long-term care facility[14] or in non-institutional community settings[16]. To date, the benefit of ASB screening and treatment in patients undergoing major orthopaedic surgery has not been demonstrated, whilst this approach is useful in the preparation of urologic surgery, mainly transurethral resection surgery. Nevertheless, for several years some authors have been advising to adopt such practice also in patients undergoing orthopaedic surgery, mainly hip and knee arthroplasty procedures. This was probably due to a series of case reports published in the 1970s[17-20], that correlated urinary tract infections (UTI) with prosthetic joint infection, without providing any conclusive evidence of such relationship. These studies together with the fear of some UTI that are asymptomatic in elderly and immunocompromised patients led to the indiscriminate adoption of ASB screening and treatment. Several authors reported the

Table II. Risk factors for SSI in orthopaedic surgery and related association as confirmed by literature.

Risk factor	Association
Male sex	Confirmed
Age	Confirmed
Obesity	Confirmed
Malnutrition and hypoalbuminemia	Confirmed
Smoking	Confirmed
Anaemia	Likely, still under evaluation
Coagulopathies	Likely, still under evaluation
Diabetes	Confirmed
Rheumatoid arthritis	Confirmed
Malignancies	Not confirmed
Steroid administration	Confirmed
ASA > 2-3	Confirmed
S. aureus colonization	Likely, still under evaluation
Intra-articular injections	Not confirmed
Previous septic arthritis	Likely, still under evaluation
Heritability	Not confirmed
Depression	Confirmed
Length of surgery	Confirmed
Length of hospitalization	Likely, still under evaluation
Transfusions	Confirmed

absence of postoperative hematogenous seeding to the prosthesis after the adoption of ASB treatment before TJA[21,22]. These *post hoc, ergo propter hoc* observations led to administering antibiotic therapy in case of positive urine culture results. The practice of routine preoperative screening for and treatment of ASB may, therefore, result in the administration of antibiotics to a large number of patients with the inherent risk of developing diarrhoea, allergies, *C. difficile* infections. Moreover, it may prolong preadmission length as well as hospitalization. In the current era of increasing antibiotic resistance resulting in enhanced focus on antibiotic stewardship programs, the ASB treatment is raising interest since such practice can actually promote antibiotic resistance. Therefore, this topic has been accurately reviewed within the recent international literature, in the attempt to draw reasoned conclusions. In the last years, a series of studies have evaluated ASB treatment in patients undergoing major orthopaedic surgery procedures[23-33]. The relevant conclusions are summarized in Table III. Overall, study results do not support the practice of ASB screening and treatment in patients undergoing TJA. In actual facts, the possible correlation between UTI and prosthetic joint infections is currently deemed a sign of susceptibility to infections rather than a direct cause-effect relationship, since the pathogens found in urine and joint infection are almost never the same. ASB would basically represent a surrogate marker of patients at higher risk of infection. However, the treatment of these patients with antibiotic therapy could expose them to an increased risk of being infected by resistant bacteria, instead of decreasing the risk of infection. With this in mind, NICE GL advises against antibiotic treatment of ASB patients (with the only exception of pregnant women), calculating a number needed to harm of only 3 patients (NNH = number of patients to be treated to have one adverse event)[34]. Similar conclusions were

Table III. ASB recent literature with relative conclusions.

Author	Year of publication	N patients	Study design	Journal	Summary
Ollivere[23]	2009	558 (THR/TKR)	Prospective	Int Orthop	Treat ASB
Uckay[24]	2009	6,101	Retrospective	J Infect	Do not treat ASB
Koulovaris[25]	2009	19,375 (THR/TKR)	Retrospective	Clin Orthop	No correlation UTI-infection
Martinez-Velez[26]	2010	200 (THR/TKR)	Prospective	JBJS Br	Treat ASB
Cordero-Ampuero[27]	2013	471 (THA/endoprosthesis)	Prospective	Clin Orthop	Do not screen
Drekonja[28]	2013	1,291 (orthopedic surgery)	Observational	JAMA Intern Med	Do not screen/Do not treat
Gou[29]	2014	771 (THR/TKR)	Retrospective	J Arthroplasty	Do not postpone surgery in case of leukocyturia
Bouvet[30]	2014	510 (THR/TKR)	Prospective	Bone Joint J	Do not screen
Sousa[31]	2014	2,497 (THR/TKR)	Prospective Multicentric	Clin Infect Dis	Do not postpone surgery/Do not treat/ ASB risk surrogate marker
Martinez-Velez[32]	2016	215 (TKR)	Prospective	Eur J Orthop Surg Traumatol	Do not screen/Do not treat
Honkanen[33]	2017	23,171 (THR/TKR)	Retrospective	Clin Microbiol Infect	ASB doesn't cause PJI/ Do not screen/Do not treat
Sendi[37]	2017	NA	Position paper	J Bone Jt Infect	Treatment of ASB does more harm than good/Do not postpone surgery
Koves[38]	2017	7,088 (various type of surgery)	Systematic review and Meta-analysis	European Urology	ASB should only be treated prior to transurethral resection surgery

THR = Total Hip Replacement; TKR = Total Knee Replacement; UTI = Urinary Tract Infection; ASB = asymptomatic bacteriuria; PJI = Prosthetic Joint Infection

drawn by the International Consensus Meeting (ICM)[35], that recommended not to perform preoperative urine screening in patients undergoing TJA, unless in case of symptomatic UTI. Other editorials and position papers[36,37] highlighted the lack of evidence supporting this practice, that can indeed increase antibiotic resistance. A recent systematic review[38] with meta-analysis conducted by the European Association of Urology recommended to treat ASB only prior to transurethral resection surgery, concluding that for most people treatment is not beneficial and may be harmful. In conclusion, in the last years, a trend inversion was observed, from ASB treatment to no treatment. Since there is a lack of evidence supporting ASB preoperative screening and treatment, in daily orthopaedic clinical practice this procedure is not recommended. Therefore, ASB screening is no longer necessary. When detected, in no way ASB should lead to postponing surgery or modifying perioperative antibiotic prophylaxis.

MRSA Screening and Nasal Decolonization

Infections caused by *S. aureus* represents a high percentage of all SSI. Over the last years, the increase of methicillin-resistant *S. aureus* (MRSA) infections has been observed also in orthopaedic surgery. The adoption of strategies for screening and nasal decolonization of the carriers was recently proposed, based on the encouraging results observed in cardiac surgery. Several studies showed a higher risk of infection in patient with *S. aureus* carriage and a reduction of SSI rate following the adoption of screening and decolonization procedures, although statistical significance was not always found. In 2010 Bode et al[39] observed that the use of mupirocin/chlorhexidine (CHG) in nasal carriers of MRSA allows a reduction of MRSA SSI rates compared to placebo (3.4 treated *vs.* 7.7 placebo). Despite the increased number of studies on nasal decolonization performed in orthopaedic surgery, the scientific literature is still impaired by the methodological limitations of the earlier studies. The inconsistency of study designs (prospective *vs.* retrospective) and the heterogeneity of patient/surgery types (elective, trauma, arthroplasty) restrict the possibility to draw conclusions and justify the doubts expressed by some authors[40-42]. In fact, due to data inadequacy, it is often not possible to establish if the pathogen causing the MRSA infection and the one identified during the screening are the same. Most of the studies are underpowered to demonstrate a statistically significant reduction of SSI because of the low incidence of infection in prosthetic surgery[43]. However, the efficacy of decolonization procedure was recently demonstrated in elective TJA by a retrospective study with a large sample size, showing a decrease of SSI from 1.11% to 0.34% in decolonized patients[44]. Moreover, Stambough et al[45] reported that the implementation of a universal decolonization protocol in patients undergoing primary TJA could decrease global hospital costs. The contradictory recommendations expressed by the international GLs, as a reflection of this controversy, are shown in Table IV. Despite the described limitations, scientific literature shows a significant trend towards SSI reduction following MRSA screening and decolonization. However, so far no definitive evidence supports the implementation of this procedure, probably due to the difficulties in reaching adequate sample sizes. As a matter of fact, according to a recent Cochrane review[46] to date, there is only limited rigorous evidence on the clinical effectiveness of nasal decontamination in the prevention of SSI. The potential benefits that this strategy could have in the prevention of MRSA infections in TJA justify the implementation of properly designed trials to confirm cost-effectiveness and correct execution of the procedure.

Preoperative Bathing

Despite being an effective barrier against microbes, skin hosts many pathogens responsible for SSI. Actually, patient skin is considered the main source of microbial agents involved in orthopae-

Table IV. MRSA screening and decolonization: different recommendations from international bodies and consensus documents.

ICM[35]	WHO[1]	CDC[2]	SHEA*	NICE[3]
Against universal decolonization. Mupirocin agent of choice in known carriers	Mupirocin 2% agent of choice in known carriers	Not evaluated	Screening and decolonization before high- risk surgery	Against routine decolonization

*SHEA = Society for Heathcare Epidemiology of America

dic infections. Skin colonization provides a reservoir from which bacteria can be introduced when the skin barrier is breached. Pathogens can reach the surgical site directly, during the intervention, or through hematogenous dissemination later on. Accurate personal hygiene of the operative staff and the patient is standard practice before any type of intervention. A debated topic is the possible effect on SSI rates of patient skin preparation performed using a suitable antiseptic agent on the day of or before surgery. Preoperative whole-body showering or bathing have been long studied as a way to decrease patient skin microbial load. It is demonstrated that preoperative showers using some types of antiseptic agents can significantly decrease skin colony counts[47]. This effect does not appear associated to the type of wash agent used: different solutions based on CHG, triclocarban, and povidone-iodine (PI) have been evaluated[47,48]. In 2007, a Cochrane review[49] assessed seven trials involving more than 10,000 surgeries overall and concluded that there is no clear evidence that the use of CHG solution before surgery is better than other wash products or placebo at preventing SSI. However, this review was then criticized by some authors since based on rather old studies. Further studies[50] in orthopaedics reported results supporting the use of 2% CHG products the night before and the morning of surgery. Thereafter, Kamel et al[51] conducted a systematic review of twenty comparative studies including randomized and nonrandomized trials, on a total of 9,520 patients, to evaluate the effectiveness of three antiseptic agents (PI, alcohol, CHG) used for patient preoperative body washing and skin antisepsis and surgical hand preparation or the application of antiseptic-impregnated incise drapes in thoracic, cardiac, plastic, general and orthopaedic surgery. Given the heterogeneity across the studies, a formal meta-analysis was not conducted, but preoperative antiseptic bathing/showering resulted effective for reducing skin flora, whilst clinical evidence on the effectiveness for the reduction of SSI rates remained inconclusive. In 2015 the Cochrane review[52] on this subject was updated but no change to conclusions was made. In 2016 Kapadia et al[53] retrospectively compared preadmission skin preparation by mean of CHG-impregnated cloth (n=995) with perioperative standard disinfection (n=2,846). Despite study limitations, most notably the retrospective design, the authors concluded that the use of CHG-impregnated cloth on the night before and the morning of surgery is associated with reduced infection rates. Thereafter, a randomized comparative trial (RCT)[54] investigated the use of CHG-impregnated cloth *vs.* standard-of-care antiseptic bathing with soap. Despite the number of recruited patients was lower than planned sample size due to study early termination, a significant difference was observed at 1-year follow-up. So, ultimately, many of the published studies are flawed due to several methodological gaps, such as low sample size, inconsistencies in the formulation, strength and application of antiseptic agents, variable quality of randomization, clinical heterogeneity of the included surgical specialties (i.e., clean *vs.* clean-contaminated surgery) and the not demonstrated correlation between skin colony counts and SSI risk. Probably, this is the reason why even a recent systematic review failed to show a significant effect of preoperative bathing with 4% CHG on SSI rate[55]. In conclusion, there is no clear evidence of the benefit for preoperative antiseptic bathing in SSI prevention and further research studies with bigger sample size are needed. ICM[35], WHO[1], CDC[2], and NICE[3] recommend patient bathing or showering prior to surgery on the day or the night before it. The type of wash product and the use of antiseptic agents such as CHG or CHG-impregnated cloths is still debated. However, despite lack of evidence supporting the use of CHG for SSI prevention, CHG is widely used for skin and mucus membrane antisepsis, since it is active against a broad spectrum of pathogens including MRSA[56]. As a result of this controversy, WHO recommends skin wash with plain or antimicrobial soap[1], CDC advises, as an alternative to soap, the use of a non-specified antiseptic agent[2], whilst ICM specifically recommends the use of CHG or antiseptic soap, if CHG is not available[35].

Hair Removal

Removal of hair from the intended site of surgical incision has traditionally been part of the routine preoperative preparation of patients undergoing surgery with the aim to reduce SSI rates. Hair has been associated with a lack of cleanliness potentially causing SSI. Hair removal may actually facilitate adequate exposure and preoperative skin marking, as well as suturing and the application of adhesive dressings. However, so far there is no evidence that preoperative hair removal reduces SSI rates, as concluded by a Cochrane review published in 2011[57] and confirmed by subsequent studies[58,59]. Consistently with this evidence, ICM[35], WHO[1], CDC[2], NICE[3] and the Society for

Healthcare Epidemiology of America (SHEA)[60] in the respective GLs recommend not to routinely perform preoperative hair removal unless deemed necessary by the surgeon who believes that the presence of hair will interfere with the operative site. In this case, the use of electric clippers instead of razors is strongly recommended, since clipping rather than shaving appears to result in fewer SSI probably by preventing the microscopic trauma of the skin caused by the sharp blade of traditional razors[57]. Without conclusive evidence on the optimal timing, and the most appropriate setting for hair removal, most of the GLs recommend that, when necessary, hair removal should be limited to the surgical site, timed on the day of surgery[3] or as close as possible to the surgical procedure[35,1] and performed outside the operating room (OR)[35,60].

Glycaemic Control

Hyperglycaemia, even if not related to diabetes, is associated to an increased risk of SSI, as shown by observational studies conducted in several surgical specialties[61-63]. It is known that blood glucose levels rise during and after surgery due to surgical stress. Therefore, both diabetic and non-diabetic patients are at high risk for hyperglycaemia in the peri- and postoperative time period, hence exposed to an increased risk of SSI. Major health organizations, such as WHO and CDC, in the respective GLs, consistently recommend the implementation of intensive perioperative blood glucose control protocols in all patients in order to decrease the risk of SSI[1,2]. Conflicting results have been reported by studies conducted in different types of surgery regarding the optimal perioperative target levels of blood glucose, the ideal timing and treatment for glucose control and the relevant adverse effects. A systematic review[64] performed on behalf of WHO demonstrated that intensive protocols with stricter blood glucose target levels (≤ 150 mg/dL), compared to conventional protocol with higher target levels (≤ 220 mg/dL), are associated with a reduction in the number of SSI, with an inherent risk of hypoglycaemic events but without increased risk of stroke or death. Within intensive protocols, very strict target levels (≤ 110 mg/dL) and stricter target levels (≤ 150 mg/dL) showed similar effects. Moreover, with regard to timing of control, the effect was smaller in studies that used intensive blood glucose control during surgery only, compared with studies that used intensive blood glucose control after surgery or both during and after operation[64]. Based on these conclusions, WHO recommends the adoption of intensive control protocols in all patients without specifying an optimal blood glucose target level[1]. In contrast, based on two RCTs in cardiac surgery on mainly non-diabetic patients[65,66], CDC recommends fasting blood glucose levels <200 mg/dL in all surgical patients, without giving any indications of the optimal timing, duration, or delivery method of the control[2], whilst SHEA recommends to maintain postoperative blood glucose < 180 mg/dL and advice against levels ≤ 110 mg/dL due to the inherent risk of hypoglycaemic events[60]. Since there are no RCT evaluating the optimal glycosylated haemoglobin (HbA1c) target levels for the prevention of SSI in diabetic and non-diabetic patients, only ICM and SHEA recommend to reduce HbA1c levels to less than 7% before surgery in diabetic patients[35,60]. A HbA1c threshold value of 7.5% was also indicated by a recent study[67].

Perioperative Antibiotic Prophylaxis

Antibiotic prophylaxis is crucial in the prevention of SSI. However, its value depends on proper administration, choice of the antibiotic and respective pharmacokinetics. As a matter of fact, inappropriate administration of antibiotics can not only be useless in terms of protection from SSI, but also results in unfavourable effects, such as systemic toxicity, increase of antibiotic resistance and raise of costs, as demonstrated by the escalation of *C. difficile* infections. Since more than 20 years, several attempts have been done to consolidate the wide literature on this topic, in order to generate recommendations useful in clinical practice. The research questions to be addressed, in order to properly implement perioperative antibiotic prophylaxis, are:

- which antibiotic should be administered,
- what is the optimal timing for the first administration respect to surgical incision and when redosing is necessary,
- how long should the antibiotic be administered with regard to the end of surgery.

Antibiotic Selection

Due to the low incidence of infections, comparative studies aimed at assessing the efficacy of different drugs are very seldom adequately sized to demonstrate the superiority of a specific antibiotic over another one. Therefore, the antibiotic is chosen based on patient supposed colonization and the type of pathogens commonly diffused in each surgical specialty. First- and second-generation cephalosporins are wide spectrum antibiotics acting mainly against aerobic gram-positive and

gram-negative bacteria, with excellent bactericidal activity, good distribution in bony, synovial and muscle tissues, very low systemic toxicity and reasonable cost. Identifying the target pathogen to be prevented is crucial for the choice of the right antibiotic. The vast majority of orthopaedic SSIs are due to coagulase-negative staphylococci, mainly *S. epidermidis*, and *S. aureus*, which are isolated in most cases. The half-life of the antimicrobial agent to be selected should cover the time interval that is crucial for SSI (two hours after incision or contamination). First- and second-generation cephalosporins have many of these features and cephazolin, the most tested in clinical studies[68,69], is recommended by all major GLs. Since more than 20 years a gradual increase of staphylococci resistance to beta-lactams (defined methicillin-resistance) has been observed in samples isolated from intraoperative contamination or infected prostheses. Several studies highlighted the raise of these pathogens, above all MRSA, in communities of individuals who had repeated contacts with nosocomial facilities. Although available evidence does not allow to establish whether there is a threshold of MRSA prevalence above which glycopeptide prophylaxis would be effective, the switch from cephalosporin to glycopeptide for all patients, mainly in orthopaedic prosthetic surgery, is currently debated. Some studies examined routine prophylaxis with glycopeptide alone or together with other antibiotics. In a large Australian database, with 18,342 hip and knee TJA patients, prophylaxis with vancomycin alone was found to be associated with an increased risk of SSI due to methicillin-sensitive *S. aureus* (MSSA) when compared with prophylaxis with a beta-lactam antibiotic[70]. Nevertheless, a study on a vancomycin-cephalosporin dual regimen showed an increased risk of developing acute kidney injury (AKI)[71]. A wide multicenter cohort study recently explored risks and benefits of an antibiotic prophylaxis with vancomycin plus a beta-lactam *vs.* either single agent alone (vancomycin or beta-lactam) in terms of SSI rate, development of AKI and colitis due to *C. difficile*. Among cardiac surgery patients, combined prophylaxis was associated with a lower incidence of SSI. Such association was not found for the other types of evaluated surgeries, including orthopaedic TJA procedures. In contrast, the risk of AKI increased in the combined prophylaxis group across all types of procedures, whilst no effect on *C. difficile* infections was observed[72]. Similarly, a study on 78,000 knee prostheses from the Swedish Registry showed a higher risk of infection when clindamycin was used in prophylaxis as an alternative to cloxacillin, as recommended in Sweden in case of allergy to beta-lactams[73]. Therefore, this controversial issue is still unresolved, since it is not yet clear whether switching to systematic prophylaxis with glycopeptides is justified to reduce the incidence of resistant staphylococcal SSI, considering the lower efficacy of glycopeptides on MSSA and their inefficacy on gram-negative bacteria. The conclusions of a recent meta-analysis advise against this change[74]. In fact, the potential benefits of a glycopeptides/cephazolin-combined prophylaxis must be pondered over, in a wider context, in terms of potential increase of renal adverse events and pharmacological resistance[75-77]. Moreover, the double prophylaxis would imply a higher organizational complexity and, probably, an increased risk of mistakes in the timing of administration. Therefore, for the time being and until more trials are designed and conducted on purpose, systematic reviews and GLs recommend to perform routine prophylaxis with first- and second-generation cephalosporins, using glycopeptides (vancomycin/teicoplanin) in patients with a history of MRSA colonization/infection or coming from environments with frequent MRSA infections (Table V). Glycopeptides or clindamycin are also the drug of choice for patients with allergy to beta-lactams. In 2016, after isolation of gram-negative bacteria from a high percentage of SSI following hip procedures

Table V. MRSA colonization risk factors.

Recent MRSA colonization/infection
Recent stay in rehabilitation or long term care facility
Hospital stay in previous 6-12 months
Presence in ICU or burn unit
Preceding antimicrobial therapy
Recent administration of fluoroquinolones/third generation cephalosporins
Diabetic patients
Patient on dialysis (or other frequent hospital admissions, chronic ulcers wound care, surgical procedures, etc.)

at their institution, some authors modified their standard protocol based on cephazolin, by adding gentamicin or aztreonam only for hip arthroplasty patients. This "expanded" prophylaxis resulted effective in decreasing SSI rate at local level[78]. In contrast, a large cohort study performed at Geneva University on orthopaedic procedures over an 11-year time period (2004-2014) did not find a rate of gram-negative infections adequate to justify any changes of their standard prophylaxis protocol[79]. In conclusion, modification of standard prophylaxis can be considered locally, when the local surveillance programs show a high incidence of microbial agents resistant to the protocols in use. Finally, whichever antibiotic is administered in prophylaxis, the dose must be adjusted on the basis of patient weight to decrease the risk of SSI.

Timing of Prophylaxis Administration

Adequate tissue concentrations of the antibiotic should be present at the time of incision and throughout the procedure until wound closure for prophylaxis to be effective. Therefore, the optimal timing to administer an antibiotic for prophylactic purpose is prior to incision. It is well demonstrated that the first dose of first- or second-generation cephalosporins should be administered intravenously within 30-60 minutes before surgical incision (at least 5-10 minutes before tourniquet application, when used). It is also demonstrated that inadequate timing of administration increases the risk of SSI[80-82]. Timing depends on the specific antibiotic and its half-life; administration of vancomycin should begin within 120 minutes before incision because of the prolonged infusion times required for this molecule. The importance of the exact timing of prophylaxis administration justifies its inclusion in the intra-operative checklist. In case of a prolonged surgical procedure, a second dose should be administered. The standard time for redosing is assumed to be the double of antibiotic half-life. Therefore, if cephazolin is used, redosing is indicated in case surgical procedure lasts more than 4 hours.

Duration of Prophylaxis

In orthopaedic surgery, the effectiveness of short-term peri-operative antibiotic prophylaxis has been demonstrated since long time, and it is also well known that intra-operative redosing should be administered when necessary. Prolonging the antibiotic prophylaxis beyond 24 hours is useless in terms of SSI rate reduction, increases hospital costs, places patients at risk of systemic toxicity and colitis by *C. difficile* and negatively affects individual and community microflora facilitating the rise of pharmacological resistance. The use of a single-dose prophylaxis is still debated, and research on this topic is ongoing, as reflected by recommendations of major GLs (Table VI). Key issues of antibiotic prophylaxis are summarized in Box 1.

Surgical Site Skin Preparation

Surgical site skin preparation is usually performed on patient intact skin within the OR and includes not only the immediate site of the intended incision, but also a broader area of patient skin. This procedure is aimed at reducing the microbial load before incision of the skin barrier. The most frequently used antiseptic agents are CHG and PI in alcohol-based solutions, which have a wide spectrum of antimicrobial activity[56,83]. However, aqueous solutions, mainly containing iodophors, are also used. A systematic review[1] was con-

Box 1. Key issues of perioperative antibiotic prophylaxis.

Antibiotic prophylaxis is recommended in orthopaedic and trauma surgery requiring device implantation through open surgery (joint replacement, osteosynthesis) whilst in the other surgical procedures should be considered time to time, based on intervention invasiveness and patients' individual characteristics.

Choice of the antibiotic:
- First-/second-generation cephalosporins, in alternative glycopeptides or clindamycin in case of allergy or high incidence/risk of MRSA infection;
- Consider combination with antibiotics active on gram-negative in specific environments/local situations.

First dose: within 30-60 minutes prior incision for first-/second-generation cephalosporins, 2 hours for vancomycin.

Timing: maintain adequate serum and tissue levels for the whole length of procedure (redosing if beyond 2 half-lives of the selected antibiotic)

Duration: single or short term (24 h) administration.

Table VI. GL suggested perioperative antibiotic prophylaxis.

	ICM[35]	WHO[1]	CDC[2]	SHEA[60]	NICE[3]
First dose	Within 1 hour (2 hours for Vancomycin/ Clindamycin)	Within 2 hours (consider half-life)	Consider pharmacokinetics Obtain bactericidal activity at incision.	Within 1 hour (2 hours for Vancomycin)	At induction of anaesthesia Consider pharmacokinetics
Weight/Dose adjustment	Yes	Not evaluated	No recommendation	Yes	Not evaluated
Redosing	Procedure exceeding 2 times antibiotic half-life/considerable blood loss (> 2l)	Not evaluated	No recommendation	Procedure exceeding 2 times antibiotic half-life/considerable blood loss	Procedure exceeding 2 times antibiotic half-life
Postoperative Timing	No more than 24 hours	No postoperative doses	No postoperative doses	No more than 24 hours	Not evaluated

ducted by the WHO GL development group to assess the efficacy of different antiseptic agents and solutions in reducing the SSI rate. The review included 17 RCTs comparing different antiseptic agents (CHG or PI) in aqueous or alcohol-based solutions. The meta-analysis of 12 of these studies demonstrated that alcohol-based antiseptic solutions are more effective compared to aqueous solutions in reducing the risk of SSI. Moreover, the metanalysis of 6 RCTs comparing CHG with PI in alcohol-based solutions showed a significant reduction of SSI risk with the use of CHG compared to PI. However, most studies reported the number of colony-forming units as the primary outcome and not SSI rate. Anyway, based on this evidence, WHO issued a strong recommendation to use CHG alcohol-based antiseptic solutions for surgical site skin preparation. In contrast, other international GLs[2,3,35] consistently recommend to prepare surgical site skin using alcohol-based solutions but did not specify any specific antiseptic agent. Since the most effective application technique and the optimal number of applications are still debated questions, none of the mentioned GLs covers these aspects. Nevertheless, based on a RCT recently conducted in TJA[84], Parvizi et al[85] advise to consider dual-preparation of the skin, before and after surgical draping, as contamination could occur during such procedure.

Laminar Flow Ventilation Systems

Ventilation system within the OR is an extrinsic factor that can affect the SSI rate. Intraoperative wound contamination can happen directly, e.g., by contact with non-sterile devices, or indirectly by airborne microbial agents. While conventional ventilation systems pass air with a mixed or turbulent flow into the OR generating an irregular movement of aerosols and particles within the room, the goal of systems with laminar flow (LF) is to pass air unidirectionally to drive air, aerosols, and particles out of the room, thus potentially reducing SSI risk. Although the initial evidence generated in the 1970s and 1980s was supporting LF implementation in TJA[86,87], more recent studies failed to demonstrate a benefit in terms of SSI decrease. A review[88] of the New Zealand Joint Registry at ten years showed that the rate of revision for early deep infection had not been reduced by LF. Moreover, a systematic review[89] published in 2012 on the influence of LF on prosthetic joint infections found significantly higher SSI rates after knee and hip TJA in the presence of LF. This issue has been addressed in various ways by different institutions: SHEA refers to the American Institute of Architects' recommendations for proper air handling in the OR[60], the question is unresolved for CDC[90] whilst ICM believes, with a 85% consensus, that TJA may be performed in ORs without LF[35]. A systematic review was conducted in 2017 on behalf of WHO to evaluate whether LF is more effective in reducing SSI risk than conventional ventilation systems. Most data were obtained from national registries, and although these sources had a large sample size, the databases were not specifically designed for this comparison that may be therefore affected by several confounding factors. The review of 12 large-sized observational studies[91], including more than 160,000 hip and knee TJA overall, showed no benefit for LF compared with conventional ventilation in reducing the risk of SSI and confirmed that LF equipment should not be in-

stalled in new ORs. Based on these conclusions, WHO suggests that LF should not be used to reduce the risk of SSI for patients undergoing TJA[1].

Adhesive Incise Drapes

Among all available sterile surgical drapes, the adhesive incise ones, either plain or impregnated with an antimicrobial agent (mostly an iodophor), are applied on patient's skin after completion of the surgical site preparation. Since the film adheres to the skin, the surgeon cuts through the skin and the drape itself. Such drapes are believed to prevent wound contamination by microorganisms colonizing the skin around the operative site, thus reducing the risk of SSI. Actually, in 2007 a Cochrane review[92] found that there was no evidence that plastic adhesive drapes reduce SSI rates. In contrast, there was some evidence that they may increase infection rates. The following Cochrane updates confirmed such conclusions[93,94]. Based on this evidence SHEA and NICE advise against the routine use of adhesive incise drapes[60,3], and NICE recommends to use iodophor-impregnated drapes in case adhesive incise draping is required[3]. In contrast, no recommendation on this topic came up from ICM[35]. More recently, the meta-analyses conducted by WHO and CDC confirmed that the use of plastic adhesive drapes with or without antimicrobial properties is not necessary for the prevention of SSI[1,2]. However, in major orthopaedic surgery, particularly in joint replacement, the use of adhesive incise drapes may facilitate the preparation of the operating field and help to isolate surgical site from possible contamination. In such an application, drapes full adhesion should be checked throughout the surgery.

Traffic in OR

Traffic in the OR, measured by number of people in the OR and number of door openings during surgery, is another extrinsic factor that may lead to an increased rate of SSI. In fact, people are the major source of environmental contamination in the OR[95]. The rationale behind limiting personnel and movement in the operating theatre is to reduce the shedding of pathogens from the skin of personnel and contamination of the air as a result of air entering from outside[85]. An observational study[96] investigated the air quality during 30 orthopaedic trauma procedures and showed a positive correlation between microbial airborne and the number of people present in the OR. Traffic in the OR is extremely high during TJA procedures and even higher in revision cases, as demonstrated by another observational study[97] aimed at defining the incidence of door opening during primary and revision TJA. The authors postulated that the difference observed between primary and revision TJA was due to the complexity of revision procedures and the necessity of additional supplies and equipment. A systematic review[98] performed in 2015 on 14 studies to assess the impact of surgical-staff behaviours on the risk of SSI identified a correlation between the number of people in the OR and SSI rate or airborne contaminants and a correlation between the number of door openings and airborne bacteria counts. In line with this evidence, NICE recommends to the staff wearing non-sterile theatre wear to keep their movements in and out of the OR to a minimum[3], SHEA advises to implement policies to reduce unnecessary traffic in OR[60] and ICM recommends (with a 100% consensus) that OR traffic is kept to a minimum[35].

Incisional Wound Irrigation

Intraoperative wound irrigation is widely practiced at the end of surgery just before wound closure, to help reducing SSI risk. In addition to acting as a physical cleaner by removing debris, body fluids, and possible contamination, irrigation solution is believed to function as a local antibacterial agent when an antiseptic or antibiotic agent is added. Mixed recommendations have been issued on this topic by major institutions: whilst SHEA recommends performing antiseptic wound lavage[60], ICM recognizes the mechanical advantage of irrigation but makes no recommendation regarding the type of solution[35]. In contrast, NICE advises against the use of wound irrigation to reduce the risk of SSI[3]. The available evidence on this topic was assessed by WHO through a systematic review with meta-analysis, demonstrating no significant difference between wound irrigation with saline solution *vs.* no irrigation on the incidence of SSI, while irrigation with an aqueous PI solution of clean and clean-contaminated wounds appeared associated to a decrease of SSI risk compared to saline solution[1,99]. Moreover, when diluted PI still shows bactericidal activity without the cytotoxic effects associated to other antiseptics[100]. The benefit of irrigation with an aqueous PI solution in SSI prevention, with no increased risk of product-related adverse events or iodine toxicity, were also confirmed by the meta-analyses conducted by CDC[2]. In contrast, wound irrigation with an antibiotic solution does not appear to be beneficial compared to saline solution or no irrigation[1,99]; therefore, it is not recommended by all major institutions, not only because not

supported by evidence but, above all, in light of the risk to increase antibiotic resistance with such a practice[1-3].

Perioperative Oxygenation

The effect of perioperative oxygenation on the risk of SSI is well documented in the literature. This practice consists in providing patients with 80% fraction of inspired oxygen (FiO_2) compared to the usual administration of 30% FiO_2. Several trials have assessed the use of high FiO_2 concentrations during the perioperative period and the potential association with lower rates of SSI. In fact, a high FiO_2 would increase oxygen tension in blood, thus compensating a potentially not adequate perfusion of the surgical site. Moreover, a higher oxygen tension is known to improve the host defence systems, particularly by enhancing neutrophil oxidative killing[101]. Several organizations, including SHEA and NICE, have highlighted the importance to optimize perioperative tissue oxygenation to reduce the risk of SSI[60,3]. However, in 2015 a Cochrane review[102] concluded that evidence is insufficient to support the routine use of a high FiO_2 during surgery to reduce the risk of SSI. To shed light on this controversial issue, WHO conducted a systematic review of the same 15 RCTs included in Cochrane review, but studies were sub-grouped according to type of anaesthesia and respiratory control (general anaesthesia with endotracheal intubation and mechanical ventilation or neuraxial anaesthesia with nasal cannula or a facemask) and according to the type of surgery (colorectal surgery or mixed surgical procedures). This approach allowed to demonstrate that increased perioperative FiO_2 compared to standard perioperative FiO_2 is associated to a reduction of SSI in surgical patients undergoing general anaesthesia with endotracheal intubation, whilst no association was observed for surgical patients under neuraxial anaesthesia. Within the group of patients under general anaesthesia, no association was found between the effect of hyperoxygenation and the type of surgery[1]. A further meta-analysis performed by CDC suggested a benefit of supplemental 80% FiO_2 administered via endotracheal intubation intraoperatively and non-rebreathing mask for 2-6 hours postoperatively in patients with normal pulmonary function under general anaesthesia, whilst hyperoxygenation administered via endotracheal intubation during the intraoperative period only appeared to have no benefit for the prevention of SSI[2]. Therefore, to reduce the risk of SSI both WHO and CDC strongly recommend to administer 80% FiO_2 intraoperatively and in the immediate postoperative period for 2-6 hours to adult patients undergoing surgery under general anaesthesia with endotracheal intubation[1,2].

Maintaining Normal Body Temperature (Normothermia)

Hypothermia is defined as a core temperature <36°C and is common during and after major surgical procedures lasting more than two hours. Anaesthetic-induced impairment of thermoregulatory control, more than the exposure to a cold OR environment, is the main event leading to hypothermia. Furthermore, cool intravenous and irrigation fluids directly cool patients. In fact, inadvertent hypothermia is considered to be an adverse effect of anaesthesia and is associated with adverse cardiac events[103,104]. In contrast, it appears that this increased risk can be reversed by the maintenance of normothermia[105]. Moreover, hypothermia may increase blood loss and transfusion requirement[106], lengthen hospitalization[107], and predispose patients to the risk of SSI[107,108]. Several strategies are used to maintain normothermia in patients undergoing surgery, such as the use of pre- and intraoperative warming devices and the administration of pre-warmed intravenous fluids. A meta-analysis conducted by WHO on 2 RCT evaluating systemic body warming to achieve normothermia *vs.* no warming for the prevention of SSI confirmed that maintaining normothermia through pre- and intraoperative body warming can reduce the incidence of SSI[1]. Based on the conclusions of another RCT aimed at comparing the effect of additional perioperative systemic warming on postoperative morbidity[109], CDC highlighted the importance of perioperative warming *vs.* intraoperative only warming, thus recommending to maintain perioperative normothermia to reduce the incidence of SSI[2]. Recognising the significance of patient normothermia, ICM[35], and SHEA[60] issued similar recommendations and NICE developed a dedicated GL[110]. None of the above GLs recommends an optimal device for warming the patient, but concerns regarding the use of air warming and the potential for contamination have been raised by some authors advising to use air-free warming over forced-air warming[111]. With regard to the target temperature to be reached and maintained and the optimal pre- and postoperative time for warming, WHO[1], and NICE[110] suggest to consider the generally accepted target of >36°C, and

NICE recommends to start active warming at least 30 minutes before induction of anaesthesia and maintain active warming throughout the intraoperative phase[110].

Conflict of Interest

The Authors declare that they have no conflict of interest.

Disclosure

This literature search served as a basis for the development of SIOT guidelines on the topic, GIOT 2018; 44: 6-29.

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