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Abstract

Surgical site infections (SSIs) are a frequent cause of morbidity following surgical procedures. Gram-positive cocci, particularly staphylococci, cause many of these infections, although gram-negative organisms are also frequently involved. The risk of developing a SSI is associated with a number of factors, including aspects of the operative procedure itself, such as wound classification, and patient-related variables, such as preexisting medical conditions. Antimicrobial prophylaxis (AP) plays an important role in reducing SSIs, especially if patient-related risk factors for SSIs are present. The major components of antimicrobial prophylaxis are the timing, the selection of drugs and patients, the duration and the costs. Compliance with these generally accepted preventive principles may lead to overall decreases in the incidence of these infections. Ideally the administration of the prophylactic agent should start within 30 minutes from the surgical incision. The duration of the AP should not exceed 24 hours for the majority of surgical procedures. The shortest effective period of prophylactic antimicrobial administration is not known and studies have demonstrated that post-surgical antibiotic administration is unnecessary. Furthermore, there were no proven benefits in multiple dose regimens when compared to single-dose regimens. The choice of an appropriate prophylactic antimicrobial agent should be based primarily on efficacy and safety. Broad spectrum antibiotics should be avoided due to the risk of promoting bacterial resistance. Cephalosporins are the most commonly used antibiotics in surgical prophylaxis; specifically, cefazolin or cefuroxime are mainly used in the prophylaxis regimens for cardio-thoracic surgery, vascular surgery, hip or knee arthroplasty surgery, neurosurgical procedures and gynaecologic and obstetric procedures. A review of the prophylactic regimens regarding the main surgical procedures is presented.

Introduction

Surgical site infections (SSIs), defined by the Centers for Disease Control (CDC) as infections occurring after surgery in the part of the body where the surgery took place, still represent a major factor of patients' mortality and morbidity (1). Furthermore, health care costs are doubled by SSIs and the length of stay increased by an average of 7 days (1). For these reasons, the importance of perioperative antimicrobial prophylaxis has been well established (1; 2). Antimicrobial prophylaxis (AP) plays an important role in reducing SSIs, especially if patient-related risk factors such as comorbidities (i.e., poor nutritional status, diabetes, immunosuppreSSIon), coexistent remote body-site infections, length of preoperative hospitalization, and microbial colonization are present (1)(3).

The special population category represented by obese patients (BMI over 30 kg/m^2) has been under-represented in studies and has been shown to have a five-fold higher risk of SSIs compared to non-obese patients; therefore, the choice of an antimicrobial agent and the pharmacokinetic properties in these patients deserve special consideration (4).

AP is efficient in surgical procedures associated with a high rate of infection and in certain clean procedures where the onset of an infection could lead to severe consequences such as prosthetic implants or in cataract surgery (1; 2; 5).

Major components of antimicrobial prophylaxis are represented by the selection, the timing, and the duration of antimicrobials administration (1; 2). Both benefits and the risks should be considered while selecting a prophylactic regimen and the choice should be individualized. The ideal prophylactic antimicrobial agent should prevent SSI-related morbidity and mortality, reduce the duration of hospitalization, have few side effects, and avoid the selection of patients and hospital's resistances. Furthermore, it should be active against the most common pathogens expected to be found at the surgical site and administered at an adequate dosage for the shortest effective period to ensure an efficient serum and tissue concentrations and minimize the adverse effects (1; 2; 5)(3). The route of administration of the prophylactic antimicrobials varies with the type of surgical

procedure. While intravenous administration is overall the preferred route, in selected procedures topical administration (i.e., irrigation, pastes, and washes) was proved to be efficient (1; 2).

Here we reviewed the main notions regarding antimicrobial prophylaxis in surgery, including the pharmacological principles of routinely administered antibiotics (molecule choice, dosing, and timing) and the use of antimicrobial prophylaxis in certain settings (bone cement in orthopedic prosthetic surgery, antibiotic sponges in sternotomy, and antibiotic impregnated shunts in neurosurgery). A review of the studies used in international guidelines regarding the characteristics and recommended regimens of antimicrobial prophylaxis for some of the most discussed specific surgical settings (ocular, neurosurgical, vascular, breast surgery, cesarian section, cholecystectomy, hernias, and surgery of the lower gastrointestinal tract) is also included.

General concepts

Antimicrobial Choice

Recent studies assessing the current practice of prophylaxis throughout the world have shown that over-consumption of antimicrobial drugs, inadequate use of antibiotics and inappropriate timing of administration still remain a remarkable issue in surgical prophylaxis, leading to an increasing risk of adverse effects, hospital costs and emerging resistant microorganisms with associated mortality (1; 6; 7). The selection of the most appropriate antimicrobial agent for prophylaxis in surgical procedures must consider the local resistance patterns along with the SSIs rates at a certain site. Gram-positive cocci, particularly staphylococci, cause many of these infections, although gram-negative organisms are also frequently involved (1) (Table 1). The choice of the antimicrobial should aim to provide: 1. Activity against the common bacteria that might contaminate the surgical site; 2. Adequate serum and tissue concentrations; 3. Safety; 4. Administration for the shortest effective time in order to reduce the side effects, the development of resistance, and the costs (1)(3).

Nevertheless, the choice of an appropriate prophylactic antimicrobial agent should be based primarily on efficacy and safety. Broad spectrum antibiotics should be avoided due to the risk of promoting bacterial resistance. Table 2 reports the recommended doses for different antibiotics used in prophylaxis. Cephalosporins are the most commonly used; specifically, cefazolin or cefuroxime are mainly used in cardio-thoracic surgery, vascular surgery, hip or knee arthroplasty, neurosurgery and gynaecologic procedures (Table 3). History of allergic reactions to beta-lactams should always been investigated in order to prefer alternative regimens in this settings (i.e., vancomycin or clindamycin). Prophylactic regimens in colorectal surgery must associate metronidazole with aminoglycosides or fluoroquinolones as alternatives to beta-lactams in allergic patients. Fluoroquinolones are not recommended as routine prophylactic agents because their extensive use in the past years generated an high rate of resistant strains among enterobacteriaceae (6; 8).

The role of vancomycin in the prophylaxis of surgical procedure is yet to be discussed. In 1995 the CDC developed recommendations for controlling the spread of vancomycin resistance due to the selection of vancomycin-resistant enterococci. Currently, the routine use of vancomycin prophylaxis is not recommended and should be considered only under specific situations (1; 9) (3) (10). Vancomycin prophylaxis is recommended in patients with known or who might be at high risk of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization (i.e., recent hospitalization, contacts with health-care facilities, nursing home residents, haemodialysis patients) undergoing major surgical procedures that involve prosthetic materials or device implantation (9). In patients with documented beta-lactam allergy, the use of prophylactic vancomycin is recommended for gram positive coverage on a case by case basis (1)(3). Due to its long half-life, a single dose of vancomycin administered before surgery is sufficient unless the procedure lasts more than 6 hours, in which case the dose should be repeated. Prophylaxis should be discontinued after a maximum of two doses (1; 2; 9). In a study encompassing 2048 patients undergoing coronary bypass graft or valve replacement surgery receiving vancomycin prophylaxis, the SSIs rate was lowest in the group with a 60 minutes infusion before incision (11; 12). In conclusion, vancomycin prophylaxis should be administered according to the general consideration of the

guidelines but taking in consideration both the resistance patterns of the surgical facility and the patient's characteristics (13).

Antimicrobial administration

Timing and dosing

Ideally, the administration of the prophylactic agent should start within 30 minutes from the surgical incision (2). An exception is represented by fluoroquinolones and vancomycin, that require an infusion starting around 120 minutes before incision due to their long half-lives and in order to prevent antibiotic associated reaction. Duration of the AP should not exceed 24 hours for the majority of surgical procedures (2).

Intraoperative redosing is recommended if the duration of the procedure is longer than two half-lives of the antibiotic agent and/or in case of major blood losses. Although the shortest effective period of AP administration is not known, and studies have demonstrated that post-surgical antibiotic administration is unnecessary. Furthermore, there were no proven benefits in multiple dose regimens when compared to single-dose regimens. Thus, prolonged duration of antimicrobial prophylaxis (up to 48 hours), is no longer recommended by the American Society of Health System Pharmacists (ASHP), even in case of cardiothoracic procedures (1; 6-8; 14).

Topical use of antibiotics in prophylaxis

Local administration of antibiotics is usually preferred to achieve high concentrations in infected tissues and to reduce side effects (15). Not all types of topic administration will be investigated in this paper, but we will focus on the specific use of bone cement in orthopedic prosthetic surgery, antibiotic soaked sponges in sternotomy, and antibiotic impregnated shunts**.**

Deep wound infection following total joint replacement is not frequent but may represent a devastating complication. In addition to intravenous AP, antibiotic- impregnated bone cement (ABC) has been used replacing the hand-mixed antibiotic preparations. ABC are divided in low-dose ABC (<2.5% of total weight) and high-dose ABC (16). FDA approved ABCs only as a second line treatment for total joint revisions following the removal of the original prosthesis and elimination of active periprosthetic infection. The current guidelines recommendations are controversial; the Scottish Intercollegiate Guidelines Network (SIGN) recommends combined prophylaxis, based on different observational studies which showed a lowest risk of SSI and surgical revisions when AP included the use of ABC (17-19). The Italian National Guidelines System (SNLG) recommends intravenous prophylaxis and the UK National Institute for Health and Clinical Excellence (NICE) guidelines do not consider the issue. Finally, the American Society of Health-System Pharmacists (ASHP) does not recommend AP routinely because of the lack of a significant advantage. Nevertheless, the ASHP recommendation did not consider two studies and a meta-analysis displaying a significant reduction using ABC versus standard prophylaxis of deep SSIs (1.2 % versus 2.3%; OR=0.5; CI 95% 0.34-0.75) and surgical revision (3.1% versus 4%; OR=0.72; CI 95% 0.62-0.82) in high-risk patients (i.e., diabetics) (20-22). In conclusion, the effectiveness of ABC is not clearly demonstrated and it is not routinely recommended, although its use may be useful in revision surgery and in high risk patients (16).

Sternal wound infections and mediastinitis are uncommon but serious complications of thoracotomy; the incidence of mediastinitis ranges from 1% to 5% and the mortality rate can be as high as 30% (23-25). Use of local antibiotic, usually gentamicin, could reduce this infection. The SIGN guidelines considered a first study based on 542 patients showing a non-statistically significant reduction of SSIs and mediastinitis (26), while the second study reported a significant decrease of mediastinitis and SSIs in high risk patients (27). The SNLG guidelines did not consider this issue and the NICE guidelines cited two studies and a meta-analysis that showed a reduction of infection (OR=0.49, CI 95% 0.34-0.60). The effectiveness of antibiotic sponges as prophylaxis is uncertain and may be considered in high risk patients.

Antibiotic-impregnated shunts are used along with intravenous prophylaxis in neurosurgery to reduce infection of cerebrospinal fluid (CSF) in shunts or external ventricular drainage devices (28; 29). The SIGN guidelines are based on an experimental study and three trials, showing a reduction of bacterial colonization of catheters (from 37% to 18%) and positive CSF cultures (from 9% to 1%) (30-32); accordingly, AP is recommended where a high incidence of infection is documented. The SNLG and NICE guidelines did not give any recommendations on the issue while the ASHP guidelines highlighted that many neurosurgeons did not use antibiotic-impregnated shunts (33). To date, the effectiveness of antibiotic-impregnated shunts is uncertain and cannot yet be recommended.

Antimicrobial prophylaxis in different clinical settings

Ocular surgery

The antimicrobial prophylaxis in ophthalmological surgery is aimed mainly against a rare, yet severe postoperative complication: the acute infectious endophtalmitis. Most of the data published involved mainly cataract procedures. The reported incidence of this complication after cataract procedures is low, approximately 0.082%, but the severity of endophtalmitis justifies the need for prophylaxis (1; 34; 35). The microorganisms responsible originate from the normal bacterial flora of the patient's eyelid and conjunctiva and in 25% to 60 % of cases are represented by coagulase-negative *Staphylococcus* species and, less frequently, by Gram negative microorganisms as reported in Table 1 (1; 5; 34; 35). The risk factors for developing ophthalmic infections are diabetes, lacrimal drainage system infection and/or obstruction, and immunodeficiency (3) (34; 35). Due to the low rate of endophtalmitis, data regarding the efficacy of antibiotic prophylaxis is limited [16]. Ideally, the antimicrobial prophylactic agent should be effective against the common periocular flora, and safe intraocular administration. Site preparation and disinfection with antiseptic solution such as povidone-iodine 5% and 10% solution and clorhexidine solution are mandatory (5; 35-37). Prophylactic regimens include cephalosporins

(especially cefazolin, cefuroxime and ceftazidime), vancomycin, and aminoglycosides combined with antiseptic solutions (1; 37; 38). Fluoroquinolones have been proved to have significant efficacy against common ocular pathogens with improved intraocular penetration, particularly moxifloxacin (5; 34; 35; 39-41)(42). The most efficient route of administration is still debated due to the lack of well-controlled studies. To date, preoperative topical antimicrobial drops, antimicrobial irrigation solution, subconjunctival injection of antimicrobial, and postoperative topical irrigation are equally effective (1; 34-36). The duration and timing reported in the literature ranged from one to multiple droplets administered combined pre-, peri-, intra- and post-operatory, but the data provided is still insufficient.

Neurosurgery

Nosocomial central nervous system (CNS) infections have low incidence rates but pose serious consequences. *Narotam et al*. claSSIfied the neurosurgical procedures in clean, clean with a foreign body, clean contaminated, contaminated, and dirty (43). Clean procedures in neurosurgery include elective craniotomy, spinal procedures, laminectomy; foreign body clean procedures include *in situ* devices (e.g. shunt, intracranial pressure monitors, clamps, external ventricular drains, acrylic cranioplasties and metal rods). Postoperative CNS infections include meningitis, ventriculitis, cerebrospinal fluid (CSF) infection, and less frequently, SSIs. Overall, the reported incidence of postoperative infections in clean procedures (primarily craniotomy) ranges from 0.15% to 6.1% with antimicrobial prophylaxis (44). Risk factors for postoperative neurosurgical infections are: American Society of Anaesthesiologists (ASA) claSSIfication > 2, postsurgical monitoring of intracranial pressure or ventricular drains implant for more than 5 days, cerebrospinal fluid (CSF) leakage, prolonged (> 2 hours) surgical procedure, reintervention, concurrent (remote, incision or shunt) infection, diabetes, and emergency procedures. The majority of neurosurgical site infections and other postoperative infections typically occur within two weeks to one month of the procedure (1; 33; 43-46). The organisms that are most frequently implicated are reported in Table 1. Gram negative bacteria are rarely implicated and, in this case, the infection is usually polymicrobial (1; 43; 44).

Antibiotic prophylaxis is recommended in clean procedures and antimicrobial agents usually used are represented by cephalosporins (table 3). Other antimicrobials such as clindamycin, vancomycin, cefotiam (currently not available in the United States), cloxacillin, oxacillin, cefuroxime, trimethoprim-sulfametoxazole, cefazolin, penicillin G, and amoxicillin-clavulanate proved to have similar efficacy in various studies (32; 46-49). The recommended timing of the prophylaxis administration is within 60 minutes before surgical incision and a single dose of antibiotic is generally efficient (1; 44)(3). Antibiotic prophylaxes for CSF-shunting procedures have proven beneficial in reducing the infection rates but the issue is still open for discussion. Routinely use of impregnated devices in neurosurgery is not recommended but may be considered under special circumstances, especially if the local CSF infection rates are high (1; 32; 44). Studies compared antimicrobial-impregnated shunts to standard non-microbial impregnated shunts in patients undergoing antibiotic prophylaxis before the procedure showing no significant decrease of infection rates between the two groups (48; 49). No significant reduction of the risk of infection was demonstrated with prolonged prophylaxis administration (33; 45).

Vascular surgery

SSI are a rather rare complication following vascular surgery but are associated to a high rate of morbidity and mortality. Antimicrobial prophylaxis is widely used and especially in procedures involving implantation of graft material and procedures at risk of developing infection, such as vein bypass and thrombendarectomy (1; 50; 51). Surgical procedures with no prosthetic material implantation, such as brachial artery repair or carotid endarterectomy do not appear to benefit from antimicrobial prophylaxis. Routine prophylaxis is recommended for: endograft placement, aortic and superficial femoral artery recanalization, dialysis accesses, embolization and chemoembolization angiography, angioplasty, thrombolysis, arterial closure device placement, and central venous access in immunocompromised patients. Furthermore, prophylaxis should be considered in patients with long surgical time (≥2 hours), reintervention on site within the first week, vascular stent implementation in the inguinal canal, immunosuppreSSIon, and history of prosthetic surgery (3)(1; 52). The bacterial flora implicated is mainly

represented by Gram positive as reported in Table 1 (53). MRSA colonization is an important, independent factor associated to higher risk of post-procedural complications (50; 51; 54). As reported in Table 4, cefazolin remains the antimicrobial agent recommended (55-58). Alternative recommended prophylactic agents in patients with beta-lactams allergies are clindamycin, vancomycin, fluoroquinolones or aztreonam (1; 50; 51). If gram negative bacteria are a concern, a single dose of aminoglycosides or fluoroquinolones should be used. Intranasal mupirocin should be considered for staphylococcal nasal decolonization. The timing of administration should be within one hour before skin incision, with a single dose and for a maximum of 24 hour postoperatively (50).

Breast surgery

Breast surgery is heterogeneous because of type of treatment (needle biopsy, lumpectomy, and mastectomy), cause of surgery (tumour or plastic procedure) and presence of prosthesis. The incidence of SSIs ranges from 1% to 30% with a prevalence of gram negative bacteria (40-50%) (59; 60). A higher incidence is reported in mastectomies (61-63), in early reconstruction after mastectomy, chemotherapy, and / or local radiotherapy, in presence of implants, expanders or drainage and in reoperations (64-69). A lower incidence is reported in needle biopsies (70). The most recent American report of NHSN showed SSI rates ranging from 0.9% to 6.4% (71); European reports showed rates from 0.5-% and 4% (165-167). In 2007, AP was reported from European studies in 60-80% of mammoplasties and in 30% of mastectomies (70) and more frequently in reports from the US especially in presence of prosthesis and drainage (90%) (72). Recommendations regarding antimicrobial prophylaxis in breast surgery are controversial. SIGN guidelines do not suggest AP (73; 74), but a meta-analysis of Cochrane showed SSI reduction in oncological surgery (66). SNLG recommend AP in oncological surgery and reductive mammoplasty. NICE guidelines recommend AP in oncological surgery but not in reconstructive surgery (with or without prosthesis) (75)[139]. ASHP guidelines recommended AP in oncological surgery based on a metanalysis and retrospective studies (76-80). All these guidelines did not consider two recent metaanalysis that confirmed a reduction of SSI in patients undergoing AP (6.5% versus 9.3%, respectively) (81; 82). The type of

antimicrobial suggested is reported in table 4. Regarding the timing of prophylaxis administration, a retrospective study regarding reduction mammoplasty reported that the incidence of SSIs had increased when AP was administrated for only 24 h but other three retrospective studies had different results (83-85). Finally, a review demonstrated that the extension of AP did not change incidence of SSIs (86). Similar results were showed in oncologic surgery (87). Despite these conclusions, American surgeons tend to extend the duration of AP (72). So far, according to available data, the evidence is still unclear. However, considering the reliability of meta-analysis we suggest the use of AP in all breast surgery, with the exception of needle biopsy.

Cholecystectomy

Open cholecystectomy is classified as a clean/contaminated procedure involving the gastrointestinal tract without major contamination or inflammation (CDC Surgical Wound Classification, class II) (88). Laparoscopic cholecystectomy has become the gold standard treatment for symptomatic cholelithiasis over open cholecystectomy (89; 90). AP has been always recommended by the available guidelines in open cholecystectomy, whilst in laparoscopic cholecystectomy is still controversial because of the lower incidence of SSI (91-93). Before the introduction of AP the incidence of SSI was 10-20% (94). Data from recent US and European studies reported rates ranging from 0.2% to 1.7% and 0.4% to 6.8%, respectively (71)(165,166). Risk factors associated with an increased incidence of SSI (> 25%) in laparoscopic cholecystectomy include: emergency surgery, age >70, ASA ≥3, biliary colic in the last 30 days, jaundice, pregnancy, immunosuppreSSIon, diabetes, endoscopic or percutaneous drainage, acute cholecystitis, gallbladder exclusion, lithiasis, pancreatitis, intraoperative cholangiography, duration of surgery >2 hours, and intraoperative complications (1)(3)(89; 95). A review of available guidelines showed that SIGN guidelines, based on a meta-analysis published in 2004, did not suggest AP in laparoscopic cholecystectomy along with the NICE and SNLG guidelines which were based on the same meta-analysis and two additional reviews (96-98). The ASHP guidelines also included an observational study, which showed a lower incidence of SSI with AP (both in open cholecystectomy than in laparoscopic

cholecystectomy) (99) and two meta-analysis that did not confirm the efficacy of AP in low-risk patients (100; 101). A study where antibiotics were given after accidental perforation of the gallbladder during laparoscopic cholecystectomy did not change the incidence of SSI (2.5% versus 3.4%) (102). However, UK surveillance studies reported that 80% of patients undergoing laparoscopic cholecystectomy (103) received AP and a recent European study highlighted that 70% of hospital guidelines recommended AP only in high risk patients and 10% of guidelines recommended in all cases of laparoscopic cholecystectomy (104). The heterogeneity in recommendations may be based on the frequent exclusion of high risk patients from trials and limited number of patients enrolled. Given the low incidence of SSIs, a significant result would require randomized controlled trials with at least 1000 patients (94; 105). Furthermore, all trials are not based on the "intention-to-treat" method and results are calculated only with low risk patients. In conclusion, AP is mandatory in open cholecystectomy, while in laparoscopic cholecystectomy is recommended only in selected patients but there are no indications on low risk patients with complications during surgery. Preferred antimicrobial regimen is indicated in table 4.

Cesarean section

The efficacy of AP during cesarean section is well known (1; 41)(106); a recent Cochrane metanalysis, based on 86 studies with 13,000 patients showed a reduction of endometritis (OR 0.38; CI 95% 0.34-0.48) as well as SSI (OR 0.39; CI 95% 0.32-0.48)] with AP. A Cochrane review reported an incidence of 10% for wound infection and of 17% for EN in absence of AP (165). The most recent American report of NHSN showed values from 1.5% (RI=0) to 3.8% (RI=2-3) (71); European reports showed rates from 0.7-2.7% (RI=0) to 0.7- 4.5% (RI=3) (165-167). Timing of AP administration is still controversial. Since 2000, AP was recommended after clamping the cordon (107; 108)(109)(110) to prevent that antibiotic could reach the newborn causing an increased risk of flora alteration, selection of resistant bacteria, neonatal sepsis and increased susceptibility to asthma (111). In the last decade several studies showed a higher efficacy of AP during cesarean section if compared to AP after cord clamping and no data confirmed the above mentioned side effects in neonates. Thus, currently AP after

cord clamping administration is not recommended. SIGN guidelines and NICE guidelines agreed on antibiotic administration before or after cordon clamp (112). ASHP guidelines strongly suggested preoperatory AP (113). A meta-analysis on three trials with 749 patients described a significantly reduction of endometritis (OR 0.47; CI 95% 0.26-0.85) and wound infections from 5.4 to 3.1% (OR 0.60 – CI 95% 0.30-1.21) (114). Data from recent literature agreed on efficacy of preoperatory AP to reduce endometritis (OR between 0.48 and 0.59), whilst data are controversial about wound infections reduction: three metanalysis confirmed a decrease of wound infections, while one described a slight insignificant increase of infections (113; 115-126)(127). One retrospective study, based on 4229 patients in US, reported a lower incidence of both EN and wound infections (2.2% vs. 3.9% and 2.5 % vs. 3.6%, respectively) (118). In conclusion, in the last decade data showed that preoperative AP administration is more effective than AP after cord clamping to reduce EN and even if with less efficacy, to reduce wound infections; moreover it does not cause side effects on newborns and it is therefore recommended. Table 4 reports evidence for recommended regimens.

Urological surgery

The purpose of antimicrobial prophylaxis in urological surgery procedures is to prevent bacteriemia, post-operative bacteriuria, SSI and nosocomial urinary tract infections (UTI), which are a common cause of patients' mortality and morbidity and increase the costs of hospitalization (8). Although the efficacy of antimicrobial prophylaxis in preventing post-operative complications has been established, surveys have shown that inadequate selection of agents, improper timing and/or duration of prophylaxis may interfere with the benefits (1; 128; 129). In addition to the general risk factors of the patient there are specific urologic risk factors that need to be considered: indwelling catheter, previous urogenital infection and long preoperative hospitalization (128; 130). The most common organisms isolated postoperative are reported in Table 1. Biofilm-forming bacteria are also of concern, therefore the antibiotics selected for prophylaxis must cover the expected microorganisms and should take into account the local resistance patterns (1; 8; 128)(3). The duration of antimicrobial prophylaxis therapy should be single dose or less than 24 hours (1; 129; 130)(3). No antimicrobial agent has proven to be

superior for urologic procedures and various regimens have been evaluated including cephalosporins, fluoroquinolones, aminoglycosides, nitrofurantoin and trimethoprim-sulfamethaxozole (131-133). The efficacy of fluoroquinolones has been well established, but the recent high fluoroquinolones bacterial resistance should be taken into consideration. Broad spectrum antibiotics such as third generation cephalosporins, carbapenems or glycopeptides are not recommended and due to their high costs, similar efficacy and the potential to promote resistance should be reserved for patients with active infections (134-137). Patients with preoperative bacteriuria or UTI should be treated before the procedure. For patients undergoing clean urologic procedures cefazolin is recommended with the alternative of fluoroquinolone or a combination of an aminoglycoside plus metronidazole (138). In patients with penicillin allergy, vancomycine or clindamycin are recommended (1; 129; 130)(3). For clean-contaminated procedures the antibiotic regimen should include a combination of cefazolin with or without metronidazole, cefoxitin, fluoroquinolone, trimethoprim-sulfamethoxazole or aminoglycoside combined with metronidazole or clindamycin (1; 8; 129; 138; 139). Surgical antimicrobial prophylaxis is recommended only if the potential benefits exceed the risks and anticipated costs.

Hernia

Inguinal hernia is a very common problem and surgical repair is the current approach. Inguinal hernia repair is classified as clean surgery and AP is not recommended since SSI following hernia repair are usually superficial and they successfully treated with drainage. Since the 90s, with the introduction of prosthetic materials, some authors supported AP and experimental studies prophylaxis showed a reduction of infection after placement of propylene mesh (140-142). So far, there is no data showing an higher incidence of SSIs in hernioplasty (EP) compared to herniorrhaphy (repair without prosthetic material) (143). The incidence of SSI in this procedure is < 2% (73; 144; 145), but several studies reported an average incidence ranging from 4% to 10% (146)(147; 148). The most recent US and European studies showed incidence between 0.7% to 5.2% and from 0.3 % to 5.3%, respectively (165-167). A lower incidence of SSIs is described for laparoscopic hernia repair (149-151). However, recent studies confirmed a protective effect of AP in preventing SSI: a surveillance study conducted in

Italy and Spain showed that 50% of surgeons used AP in hernia repair (52; 152) while in the UK AP was used by 90% of surgeons (153). Recommended regimens are displayed in table 4. It should be stated that all these studies included a low number of patients, differences in dosages, time of infusion and way of antibiotics administration, without data about patients' risk factors, useful to identify patients in which AP should be effective. In conclusion, according to recent meta-analyses, AP in EP is recommended while in ER it should be considered, especially in hospitals with high incidence of SSIs. In some groups of patients, with low risk of SSIs, AP can be omitted, but the definitions of these patients remain unclear. For laparoscopic surgery and incisional hernia there are no studies available: some experts suggest to use AP according to same principles as in traditional technique.

Colorectal surgery

The effectiveness of AP is well documented in literature as it decreases the incidence of SSI from 30-60% (154; 155) to 5-15% (156) and mortality from 10% to 2-4% (157). There is a higher rate of SSIs in rectal resection compared to colic resection (158-160). Laparoscopic surgery seems to be associated with a lower incidence of SSI (161-163), especially for SSIs of incisional site (164). The most recent US study of NHSN describes an incidence of SSIs for colic resection ranging from 4% to 9% and for rectal resection from 3.5% to 26% (71) while, according to European reports, the incidence is between 3.9 - 6.6% and 11.5 - 16.8% (165)(166)(167). There are differences between US and European studies. In the US, oral AP was usually preferred (168; 169) with an association of aminoglycoside (neomycin or kanamycin) and an effective antibiotic against aerobic microorganisms (170-174). Combination of neomycin and erythromycin seems to be most effective compared to metronidazole monotherapy (175). There is no data of effectiveness of oral AP in colon surgery without mechanical bowel preparation (MBP) since, according to experimental models, MBP alone does not change intraluminal bacterial contamination (176) while MBP associated with oral AP reduce bacterial counts by a factor of 10^5 (177). Moreover, a recent retrospective study showed that oral AP is effective irrespectively of MBP

(178), but the question is still debated (179)(180)(181-190). Oral AP has been associated with an increased incidence of postoperative diarrhoea or *Clostridium difficile* infection (191), but this effect was not confirmed by others (192). Conversely, in Europe intravenous AP is usually preferred; its effectiveness was demonstrated in 1960 (193) with several studies with antibiotics effective on both aerobic and anaerobic bacteria (194; 195). The comparison between oral and intravenous AP is difficult (196; 197), also considering the recommendations of the existing guidelines. According to SIGN, SNLG and NICE guidelines, only intravenous administration was included while ASHP guidelines considered extensively oral AP, evaluating a combined administration (oral plus intravenous) versus systemic antibiotics alone (198; 199), as well as combined AP versus oral administration alone. In most cases, ASHP guidelines recommended combined prophylaxis. However, it should be specified that data from literature are highly heterogeneous because of the use of oral or intravenous AP, choice of the molecules, timing and length of administration. For example, not all studies considered as standard oral prophylaxis the administration of neomycin 1 gr plus erythromycin 1gr three times a day (169; 200-202). Nowadays, comorbidities, type of surgical procedure, surgical demolition and bacterial contamination are variables that should be considered (203). In conclusion, effectiveness of AP in colorectal surgery is certainly demonstrated. As reported in table 4, the ASHP guidelines support the use of oral plus intravenous AP while the utility of MBP is unclear.

Key messages

- Antimicrobial prophylaxis (AP) plays an important role in reducing SSIs, especially if patient-related risk factors for SSIs are present
- The administration of the prophylactic agent should start within 30 minutes from the surgical incision.
- The choice of the antimicrobial should aim to provide: 1. Activity against the common bacteria that contaminate the surgical site; 2. Adequate serum and tissue concentrations; 3. Safety; 4. Administration for the shortest effective time in order to reduce the side effects, the development of resistance, and the costs

- Cefazolin remains the antimicrobial agent recommended for the majority of surgical procedures. Alternative recommended prophylactic agents in patients with beta-lactams allergies are clindamycin, vancomycin, fluoroquinolones or aztreonam

- Duration of antimicrobial prophylaxis should not exceed 24 hours for the majority of surgical procedures

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Table 1. Pathogens commonly associated with different surgical procedures.

Type of surgery	Common pathogens
Placement of graft, prosthesis or implant	*Staphylococcus aureus*; CoNS
Cardiac	*S. aureus*; CoNS
Neurosurgery	*S. aureus*; CoNS
Breast	*S. aureus*; CoNS
Ophthalmic	*S. aureus*; CoNS; streptococci; Gram-negative bacilli
Orthopaedic	*S. aureus*; CoNS; Gram-negative bacilli
Vascular	*S. aureus*; CoNS
Appendectomy	Gram-negative bacilli; anaerobes
Biliary tract	Gram-negative bacilli; anaerobes
Colorectal	Gram-negative bacilli; Enterococcus spp.; anaerobes
Gastroduodenal	Gram-negative bacilli; streptococci; oropharyngeal anaerobes (e.g. peptostreptococci)
Obstetric and gynaecological	Gram-negative bacilli; enterococci; Group B streptococci; anaerobes

CoNS: coagulase-negative staphylococci

Table 2. Recommended dosage for commonly used antibiotics in surgical prophylaxis

Antimicrobials	Recommended Dose for Adults
Ampicillin-sulbactam	3 g
Ampicillin	2 g
Aztreonam	2 g
Cefazolin	2g; 3 g for patients with body weight > 120 kg
Cefuroxime	1, 5 g
Cefotaxime	1 g
Cefoxitin	2 g
Cefotetan	2 g
Ceftriaxone	2 g
Ciprofloxacin	400 mg
Clindamycin	900 mg
Ertapenem	1 gr
Gentamicin	5 mg/ Kg (single dose given preoperatively)
Levofloxacin	500 mg
Metronidazole	500 mg
Moxifloxacin	400 mg
Piperacillin-tazobactam	3,375 g (4,5 g in Italy)
Vancomycin	15 mg/kg

Table 3. Recommended agents for different types of surgical procedure

Type of procedure	Recommended agents	Alternative agents in patients with B-lactams allergy
Cardiac -Coronary artery by-pass -Cardiac device insertion procedures -Ventricular assist device	Cefazolin; Cefuroxime	Clindamycin; Vancomycin
Thoracic -non cardiac procedures - video-assisted thoracoscopic surgery	Cefazolin; Ampicillin-sulbactam	Clindamycin; Vancomycin
Gastrointestinal -involving entry in the lumen -without entry in the lumen	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Biliary tract -	Cefazolin; cefotetan; cefoxitin; ceftriaxone; amp/sulbactam	Clindamycin+ aminoglycoside or aztreonam or fluoroquinolone; metronidazole+ aminoglycoside or fluoroquinolones
Appendectomy	Cefoxitin; cefotetan; cefazolin+metronidazole	Clindamycin+ aminoglycoside or aztreonam or fluoroquinolone; metronidazole+ aminoglycoside or fluoroquinolones
Hernia repair (hernioplasty and herniorrhaphy)	Cefazolin	Clindamycin Vancomycin
Colorectal	Cefazolin/ceftriaxone + metronidazole; cefotetan; amp/sulbact; cefoxitin	Clindamycin+ aminoglycoside or aztreonam or fluoroquinolone; metronidazole+ aminoglycoside or

		fluoroquinolones
Neurosurgery	Cefazolin	Clindamycin vancomycin
Cesarian	cefazolin	Clindamycin+ aminoglycoside
Orthopedic Spinal procedures with or without instrumentation	cefazolin	Clindamycin Vancomycin

Table 4. Evidence for antimicrobial recommended regimens in the surgical procedures described

Type of procedure	Recommended agents	Reference
Ocular surgery	cephalosporins, vancomycin, aminoglycosides, quinolones	[35-42]
Neurosurgery	cephalosporins	[46-49]
Vascular surgery	cefazolin	[54-57]
Breast Surgery	cefalosporins	[76-82]
Cesarian section	Cefazolin (± metronidazole)	[165-167]
Urological surgery	cephalosporins, fluoroquinolones, aminoglycosides, nitrofurantoin and trimethoprim-sulfamethaxozole	[131-133]
Hernia repair	cefazolin	[108]
Colorectal surgery	Cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin–sulbactam, ceftriaxone + metronidazole, ertapenem (± oral antibiotics)	[108]