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## Antimicrobial approach of abdominal post-surgical infections

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### Abstract

Abdominal surgical site infections (SSIs) are infections that occur after abdominal surgery. They can be superficial, involving the skin tissue only, or more profound, involving deeper skin tissues including organs and implanted materials. Currently, SSIs are large global health problem with an incidence that varies significantly depending on the United Nations' Human Development Index. The purpose of this review is to provide a practical update on the latest available literature on SSIs, focusing on causative pathogens and treatment with an overview of the ongoing studies of new therapeutic strategies.

**Key Words:** Surgical site infections; Multidrug resistance; Carbapenem-resistant Enterobacterales; Carbapenem-resistant Klebsiella; Abdominal post-operative complications; Post-surgical infections

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**Core Tip:** Abdominal surgical site infections (SSIs) are infections that occur after abdominal surgery. The knowledge of the site of infection and the probability of antibiotic resistance is fundamental to initiating appropriate empirical antibiotic treatment. The purpose of this review is to provide a practical update on the latest available literature on SSIs, focusing on causative pathogens and treatment with an overview of the ongoing studies of new therapeutic strategies.

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## INTRODUCTION

Abdominal surgical site infections (SSIs) are infections that occur after abdominal surgery. They can be superficial, involving the skin tissue only, or more profound, involving deeper skin tissues including organs and implanted materials. Currently, SSIs are a large global health problem with an incidence that varies significantly depending on the United Nations' Human Development Index (HDI). The incidence rates are observed at 9.4% in high HDI countries (HHDICs), 14.0% in middle HDI countries (MHDICs), and 23.2% in low HDI countries (LHDICs). Consensually, the antibiotic resistance incidence of the causative pathogen significantly varies in HHDICs (16.6%), MHDICs (19.8%), and LHDICs (35.9%). Intuitively, the highest incidence of abdominal SSIs is found in dirty surgery: HHDICs (17.8%), MHDICs (31.4%), and LHDICs (39.8%)[1]. Since approximately 234.2 [95% confidence interval (CI): 187.2-281.2] million major surgical procedures are carried out each year globally[2], with abdominal procedures (both major and minor surgery) the majority[3], abdominal SSIs are some of the largest concern worldwide. The United States Centers for Disease Control and Prevention (CDC) provide guidelines and resources to help end SSIs, along with assisting the public to understand and take measures to safeguard their health when possible[4]. Unfortunately, the CDC's latest document, published in 2017, focuses only on SSI prevention[5].

The purpose of this review is to provide a practical update on the latest available literature on SSIs antimicrobial treatments.

## CLASSIFICATION

In the 1960s, the National Academy of Sciences defined SSIs according to the type of surgery. Clean, clean-contaminated, contaminated, infected, or dirty surgery was the risk class. The SSI rate was 2.1%, 3.3%, 6.4%, and 7.1%, respectively[6]. However, a study by Neumayer *et al*[7] on general and vascular procedures reported that wound class was an independent predictor of SSI; odds ratios (ORs) were 1, 1.04, 1.7, and 1.5 for clean, clean-contaminated, contaminated, and infected, respectively. In the 2000s, the CDC and the National Healthcare Safety Network (NHSN) later classified SSIs according to the infection site, distinguishing superficial (infection of the skin and subcutaneous tissue), deep (fascia and muscle layers), or organ/space infections. Superficial SSIs occur within 30 d while deep SSIs occur within 30-90 d after the operative procedure, involving primary incision or secondary incision(s); their characteristics are reported in Table 1. An infection that involves both superficial and deep incision sites has to be classified as deep incisional SSI. Organ/space infections involve parts of the body being opened or manipulated during the operative procedure. If the organ/surface infection drains through the incision, it is classified as a deep SSI[8].

## EPIDEMIOLOGY

The incidence of SSIs worldwide is highly variable, depending on the country and the type of surgery, but is approximately between 0.5% and 3%[9]. Abdominal surgery has a much higher rate of SSIs than other types of surgery, with an incidence of 15%-25%[10]. The main factors that determine this variability are attributed to the geographical region, the type of hospital, the type of intervention, the presence of surveillance institutions and how data is collected. Another crucial factor in the determinism of SSIs is the duration of surgery as demonstrated by Gillespie *et al*[11]. In a study conducted by the GlobalSurg collaborative group on patients undergoing an emergency appendectomy, there was a variable incidence of HHDICs, MHDICs, and LHDICs of 4.4%, 12%, and 14.8%, respectively[12]. The very high incidence of SSIs in low- and middle-income countries and Southeast Asia compared to the United States, Europe, and Australia can be related to several factors such as lack of standardized procedures, lack of epidemiological surveillance, lack of data interpretation, epidemiological data collected but not validated, poor-quality data records, and inefficient microbiological tools/poor laboratory capacity. According to a recent meta-analysis using the World Health Organization's regions, Africa had the highest incidence, with Tanzania leading at 26%. The lowest incidence was found in the Western Pacific region within 0.6%[13]. There is significant variability in SSI surveillance practices resulting from differences in infection control resources among institutions, even in the United States[14]. Such hospitals using rigorous surveillance and broad

**Table 1 Definitions and clinical characteristics of surgical site infections according to Centers for Disease Control and Prevention and National Healthcare Safety Network criteria**

Distinction	Superficial incisional SSI	Deep incisional SSI	Organ/space infections
Localization	Subcutaneous tissue and/or skin	Fascial and muscle layers	Organ manipulated during surgery
Timing	Within 30 d post-surgery	Within 30 or 90 d post-surgery/1 yr (implant in place)	
Diagnosis at least one of the following			
Pain	Yes	Yes	Yes
Swelling	Yes	Inconstant	Inconstant
Erythema or heat	Yes	Inconstant	Inconstant
Purulent drainage	Yes (superficial)	Yes (from deep incision)	No
Wound dehiscence	Yes (superficial)	Yes	No
Culture	Yes	Recommended	Recommended
Abscess	No	Yes	Yes
Fever (temperature > 38 °C)	Inconstant	Yes	Yes

SSI: Surgical site infection.

data sources have reported higher SSIs rates compared with hospitals with lower surgical volumes that used fewer data to conduct surveillance and tend to have fewer SSIs rates. The accuracy of facility-reported SSIs rates is uncertain[15]. Data from the NHSN collected in the United States between 2006 and 2008 presented an overall SSIs rate of 1.9%[16]. Between 2008 and 2014, there was an overall 17% decrease in SSIs. A report from 2016 on the rates of hospital-acquired infections based on data from 2014 described an overall rate of 1.15%[17], with abdominal surgery-related SSIs as 50% of the overall SSIs. Furthermore, open surgery may significantly increase the incidence of SSIs if compared with laparoscopic surgery. A systematic review published in 2018 compared the incidence of SSIs in appendectomy performed worldwide. It reported that in HHDICs, the incidence rate of SSIs was 1.3%/3.8% for the open procedure and 0.8%/2.9% for the preventive laparoscopic technique. In LHDICs and MHDICs, the SSIs incidence rate was significantly higher with 17.9% reported for the open procedure and 8.8% for the laparoscopic approach[18]. A recent report from the European Centre for Disease Prevention and Control (ECDC) provided similar findings. The SSIs rates for open cholecystectomy *vs* laparoscopic and open *vs* laparoscopic colon surgery were 3.8% *vs* 1.5% and 9.5% *vs* 6.7%, respectively[19]. The overall surgery distribution of SSIs has changed both in high- and low-income countries over the past couple of decades, concerning antimicrobial prophylaxis[20]. The overall surgery distribution of pathogens associated with SSIs has varied over the years and the major organisms for abdominal surgery related to SSIs are *Escherichia coli*, *Enterococcus faecalis*, and *Staphylococcus aureus*[21]. By contrast, in developing countries, even in clean surgery, there is quite a high prevalence of Gram-negative bacilli such as *Klebsiella* species, *E. coli* and *Pseudomonas aeruginosa*[22]. The presence of Gram-negative bacilli is important because of high extended-spectrum beta-lactamase (ESBL) producer rates, and carbapenem-resistant *Enterobacteriaceae* (CRE) prevalence among these organisms that make antibiotic prophylaxis for clean or contaminated surgeries a challenge. The geographical distribution of the incidence of SSIs is depicted in Table 2. In Table 3, we synthesized data on the microbiology of SSIs subdivided for type of abdominal surgery, based on those reported by the ECDC annual epidemiological report for 2018–2020[19].

## MICROBIOLOGY

SSIs are one of the most common complications of abdominal surgery and are associated with increased morbidity, mortality, and costs[10]. SSIs can be defined as a wound infection with microorganisms within 30 d following a surgical procedure. They are caused by bacteria that enter the surgical site, originating from the patient's endogenous flora or by nosocomial pathogens. The source of infection can be from the patient's microbial flora, present on the skin and skin appendages, mucous membranes and the gastrointestinal tract, or insemination from a distant focus of infection. To prescribe antimicrobial therapy for an endogenous infection, knowledge of endogenous bacterial flora is crucial. The bacterial concentration increases along the gastrointestinal tract, with small numbers in the stomach and very high concentrations in the colon. This gradient is generated because the gastroduodenal tract is highly inhospitable for bacterial growth due to its pH, bile and pancreatic enzymes. Therefore, very few bacteria develop the ability to survive and multiply. The bacterial gradient is represented schematically in Figure 1. The stomach harbors only 10<sup>1</sup> bacteria per gram content. Increasing densities and bacterial diversities are found in the duodenum (10<sup>3</sup>/g), jejunum (10<sup>4</sup>/g), ileum (10<sup>7</sup>/g), and colon (10<sup>12</sup> bacteria/g)[86]. Besides a longitudinal gradient, there is also longitudinal diversity with *Streptococcus*, which is the most represented bacterium in the distal esophagus, duodenum, and jejunum. *Helicobacter* and *Streptococcus* are the dominant genera present in the stomach. The predominant phyla that inhabit the large intestine



Table 2 Geographical distribution of the surgical site infections' incidence

Continent	Country	Period	SSIs incidence	Ref.
Africa	Cameroon	2013-2014	Overall: 15.25%	[23]
	Egypt	2013-2017	CSEC: 5.34%	[24]
		2016-2018	Overall: 2.3%, CSEC: 2.8%	[25]
	Ethiopia	2015	Overall: 19.1%	[26]
		2019	Overall: 21.1%; ABDS: 49.06%	[27]
	Ghana	2017-2018	Overall: 10%; APPY: 13.4%; GAST: 12.7%; HER: 5.9%; ABDS: 13.7%	[28]
	Kenya	2015	CSEC: 4%	[29]
	Morocco	2018-2019	Overall: 6.3%	[30]
	Rwanda	2019-2020	CSEC: 5.7%	[31]
	Sierra Leone	2019-2020	CSEC: 10.3%; HER: 1.2%	[32]
		2021	Overall: 11.5%; ABDS: 79.5%	[33]
	South Africa	2017	APPY: 25%	[34]
	Tanzania	2009-2010	Overall: 26%; APPY: 15%; CHOL: 14.3%; XLAP: 27.9%	[35]
		2018-2020	CSEC: 14%	[36]
	Tunisia	2015-2016	CSEC: 5%	[37,38]
		2015	APPY: 9.8%; CHOL: 1.1%; BILI: 13.6%	
America	Brazil	2008-2011	Overall: 3.4%	[39]
		2008-2018	BAR open: 3%; BAR VLP: 0.5%	[40]
	Canada	2015-2016	CSEC: 5.9%	[41]
		2015-2019	COLO: 10.28%; BILI: 16.13%	[42]
	Colombia	2008-2010	APPY: 3.9%; HYST: 5.5%; SPLE: 4.5%; CHOL: 3%	[43]
		2022	HER: 7.9%; CHOL: 8.3%; CSEC: 22.2%	[44]
	Cuba	2017-2018	APPY: 13.8%; HER: 5.7%	[45]
	Ecuador	2018	CSEC: 1.35%	[46]
	Honduras	2017-2018	CSEC: 5.1%	[47]
	Mexico	2011-2012	Overall: 12.1%; COLO: 5.2%; APPY: 4.9%; CHOL: 0.8%; HER: 0.9%	[48]
		2013-2015	CHOL: 5.5%	[49]
	Peru	2005-2010	APPY: 2.9%; CHOL: 2.8%; CSEC: 2.2%	[50]
		2015-2018	CSEC: 2.4%	[51]
		2019-2020	CSEC: 0.88%; CHOL: 0.18%; HER: 0.38%	[52]
	Uruguay	2012-2013	APPY: 3.2%; CHOL: 6.2%; COLO: 15.4%	[53]
		2021	CSEC: 1.74%; CHOL open: 1.85%; CHOL VLP: 0.23%	[54]
	Venezuela	2019-2021	Overall: 9.7%; APPY: 10.42%; BILI 3.79%	[55]
	United States	2011-2014	Overall: 0.9%; COLO: 3.99%-9.47%; CHOLO: 0.23%-1.72%; HER: 0.74%-5.25%; REC: 3.47%-26.67%; SB: 3.44%-6.75%	[16,17,56]
		2015-2019	COLO: 6.82%; BILI: 12.72%	[42]
		2016-2017	CHOL: 0.96%	[57]
Asia	China	2020	ABDS: 2.9%; COLO 7.1%	[58,59]
		2018	GAST: 5.2%	[60]

Europe	India	2017-2020	CSEC: 23.30%	[61]
		2011-2017	Appendix: 35.3%	[62]
		2016	CSEC: 10.3%	[63]
	Iran	2005-2011	XLAP: 6%; HER: 3.8%	[64]
		2018	Overall: 0.29%	[65]
		2021	Overall: 5.2% surveillance	[66]
	Japan	2008-2010	COLO: 15%; REC: 17.8%	[67,68]
		2009-2019	APPY: VLP 4.19%, OPEN 6.60%	[69]
			CHOL: VLP 1.91%, OPEN 7.42%	
			SB: VLP 8%, OPEN 15%	
			COLO: VLP 7.27%, OPEN 15.5%	
			REC: VLP 11.3%, OPEN 8.8%	
	Kuwait	2016	SB: 6.5%; GAST: 0.7%	[70]
	Nepal	2019	CSEC: 8.54%	[71]
	Pakistan	2014-2019	BILI: 40%	[72]
		2016-2017	APPY: 32.7%; CHOLO: 20.7%; HER: 37.6%	[73]
	Philippines	2018-2019	Overall: 9.7%	[74]
	Republic of Korea	2008-2012	GAST: 3.12%	[75]
	Saudi Arabia	2016	Overall: 16.3%; open surgery: 34.8%; VLP surgery: 3.5%	[76]
	Taiwan	2021	Overall: 4.0%; regional hospital: 4.7% medical center	[77]
	Thailand	2007-2016	Overall: 2.98%	[78]
	Turkey	2005-2011	CHOL: 1.3%; COLO: 11.4%; CSEC: 3%; GAST: 4.3%; HYST: 3.1%; SPLE: 5%; XLAP: 2.6%	[79]
	United Arab Emirates	2016-2017	CSEC: 1.4%	[80]
	Austria	2018-2020	CHOL: 0.4%; COLO: 3.6%; CSEC: 0.5%	[19]
	England	2017-2022	HYST: 1.7%; BILI: 15.4%; CHOL: 9.7%; GAST: 1.9%; COLO: 8.6%	[81]
	Estonia	2018-2020	CSEC: 2.0%	[19]
	France	2018-2020	CHOL: 0.7%; CSEC: 1.7%	[19]
	Germany	2018-2020	CHOL: 0.9%; COLO: 8.9%; CSEC: 0.6%	[19]
	Hungary	2018-2020	CHOL: 1.1%; COLO: 10.4%; CSEC: 1.3%	[19]
	Italy	2018-2020	CHOL: 0.7%; COLO: 5.9%; CSEC: 0.7%	[19]
	Lithuania	2018-2020	CHOL: 0.2%; COLO: 10.6%; CSEC: 0.6%	[19]
	Malta	2018-2020	COLO: 26.8%	[19]
	Netherlands	2018-2020	CHOL: 2.6%; COLO: 16.1%; CSEC: 1.5%	[19]
	Norway	2018-2020	CHOL: 2.8%; COLO: 11.7%; CSEC: 3.6%	[19]
	Portugal	2018-2020	CHOL: 2.3%; COLO: 14.5%; CSEC: 1.6%	[19]
	Slovakia	2018-2020	CHOL: 2.9%	[19]
	Spain	2016	COLO: 10.6%	[82]
		2013-2016	REC: 11.9%	[83]
		2009-2016	CHOL: 1.96%	[84]
	Switzerland	2017-2018	APPY: 3.1%; CHOL: 2.2%; HER: 0.9%; COLO: 13.5%; REC: 17.7%; GAST: 3.1%; CSEC: 1.8%	[85]
Oceania	Australia	2002-2013	Overall: 2.8%	[86]

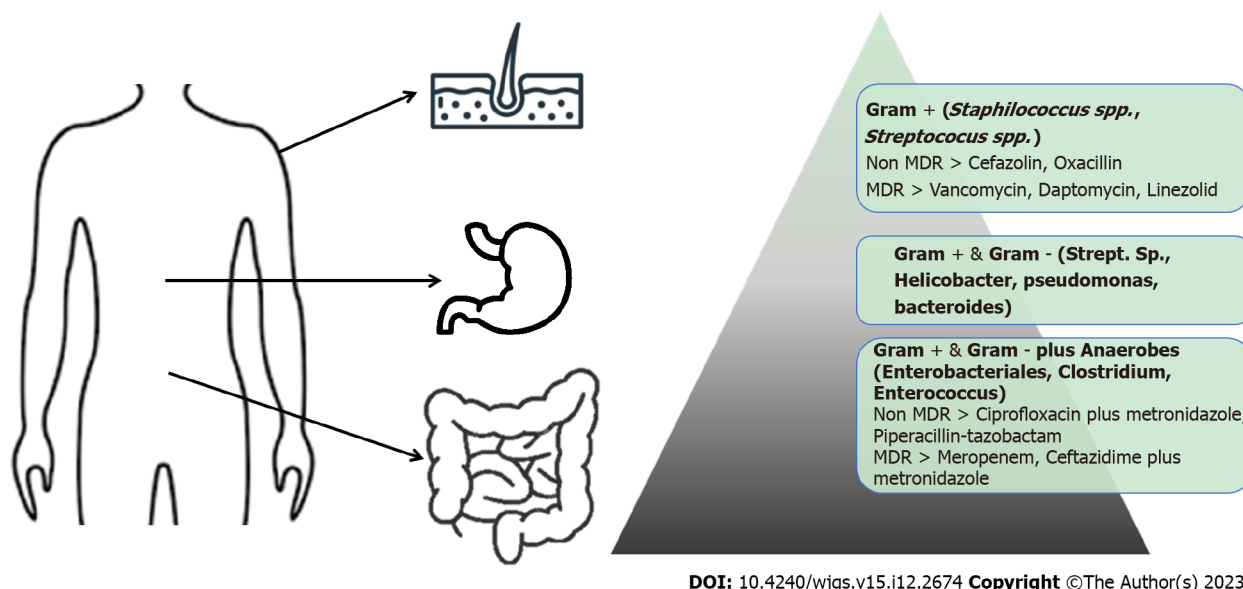
ABDS: Abdominal surgery (miscellany); APPY: Appendix surgery; BAR: Bariatric surgery; BILL: Bile duct, liver or pancreatic surgery; CHOL: Gallbladder surgery; COLO: Colon surgery; CSEC: Caesarean section; GAST: Gastric surgery; HER: Herniorrhaphy; HYST: Abdominal hysterectomy; REC: Rectal surgery; SB: Small bowel surgery; SPLE: Spleen surgery; SSI: Surgical site infection; XLAP: Exploratory laparotomy.

**Table 3 Microorganisms distributions for different type of abdominal surgery**

Microorganism	Type of surgery				
	Laparoscopic CHOL	Open CHOL	Laparoscopic COLO	Open COLO	CSEC
Gram-positive cocci	52.9	39	34.8	70.4	78.8
<i>Staphylococcus aureus</i>	23.9	7.6	4.3	25	38.4
<i>Coagulase-negative staphylococci</i>	9.2	6.2	2.2	27	22.6
<i>Enterococcus species</i>	11.1	18.9	24.5	9.3	5.6
<i>Streptococcus species</i>	4.8	1.9	2.3	3.7	5.7
Other Gram-positive cocci	3.9	4.4	1.4	5.4	6.5
Gram-positive bacilli	1.5	0.8	0.1	2	2.7
Gram-negative bacilli Enterobacterales	27.5	44.4	48.7	18.3	10.6
<i>Escherichia coli</i>	13.2	21.7	30.4	6.2	3.5
<i>Citrobacter species</i>	0.5	2.4	1.1	0.7	0.4
<i>Enterobacter species</i>	2.3	5.6	5.5	3.3	2.8
<i>Klebsiella species</i>	5	9.8	6.2	2.1	1.4
<i>Proteus species</i>	3.5	2.1	2.1	3.8	1.3
<i>Serratia species</i>	1.1	0.3	0.9	1	0.8
Other Enterobacteriaceae	2.1	2.5	2.5	1.1	0.4
Gram-negative nonfermentative bacilli	4.2	2.1	6	3.8	3.3
<i>Acinetobacter species</i>	0.5	0.3	0.4	0.6	0.6
<i>Hemophilus species</i>	0.2	0.1	0	0	0.1
<i>Pseudomonas aeruginosa</i>	2.1	0.9	5.3	2.9	1.6
<i>Pseudomonadaceae</i> family, other	0.2	0	0	0.2	0.6
<i>Stenotrophomonas maltophilia</i>	0	0.3	0.1	0.1	0.3
Other Gram-negative nonfermentative bacilli	1.4	0.5	0.2	0.1	0
Anaerobes	12	8.7	6.3	4.8	3.8
<i>Bacteroides species</i>	1.8	1.2	4.4	0.2	0.1
Other anaerobes	10.2	7.5	2	4.6	3.7
Other bacteria	1.8	3.5	1	0.4	0.6
Fungi, parasites	0.2	1.5	3.2	0.3	0.1
<i>Candida species</i>	0.2	1.5	3.2	0.3	0.1
Other fungi or parasites	0	0	0	0	0

Data obtained from the ECDC's Annual Epidemiological Report for 2018-2020 on surgical site infections. CHOL: Cholecystectomy; COLO: Colon surgery; CSEC: Caesarean section.

include Firmicutes and Bacteroidetes; the latter, together with *Streptococcus*, *Enterobacteriaceae*, *Enterococcus*, *Clostridium*, and *Lactobacillus* could be identified in stool[87]. The exogenous causes of infection are surgical personnel (surgeons and their teams), dirty clothing, potential “breakages” in aseptic techniques, and inadequate hand hygiene. Regarding the operating room, the causes of infection can be traced to the physical environment and the ventilation system, instrumentation, equipment, or other materials brought to the operating table. To reduce the risk of bacterial contamination preventative measures emphasize the importance of good patient preparation, aseptic practice, and attention to surgical



**Figure 1** Bacterial gradient with predominant bacteria. MDR: Multidrug resistance.

technique. Antimicrobial prophylaxis is also indicated in specific circumstances. The most frequently isolated pathogens include Gram-positive cocci, such as *S. aureus*, enterococci and streptococci. Gram-negative bacilli, common pathogenic Enterobacteriaceae, including *E. coli*, *Enterobacter* species, *Klebsiella* species and *Serratia marcescens* are also found. *P. aeruginosa* and *Acinetobacter baumannii* are other common causes of Gram-negative infection[88]. Nosocomial pathogens, including Gram-negative and Gram-positive bacteria, are major causative microorganisms leading to epidemiological exposure[89]. The intensity and timing of the exposure, along with the virulence of the organism affect morbidity and mortality. Currently, novel threats are arising from multidrug-resistant (MDR) bacteria. An increasing number of SSIs result from MDR microorganisms. Among Gram-positive bacteria, we recognize methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant Enterococci[90]. Recently, a high rate of drug-resistant Gram-negative bacteria has become a major and global health concern[91,92]. The prevalence of *Acinetobacter*, *Pseudomonas*, and Gram-negative bacilli, which produce ESβL and carbapenemase, are increasing and related to higher rates of treatment failure[93,94]. Another key problem is the link between the SSIs and biofilm, where as many as 80% of these infections may involve a microbial biofilm. Recent studies suggest that biofilm-producing organisms play a significant role in persistent skin and soft tissue wound infections in the post-operative surgical patient population. SSIs associated with biomedical implants are notoriously difficult to eradicate using antibiotic regimens that would typically be effective against the same bacteria growing under planktonic conditions. This biofilm-mediated phenomenon is characterized as antimicrobial recalcitrance, which is associated with the survival of a subset of cells including “persister cells.” The ideal method to manage a biofilm-mediated surgical site wound infection is to prevent it from occurring in the first place through rational use of antibiotic prophylaxis, adequate skin anti-sepsis before surgery, and the use of innovative *in situ* irrigation procedures [95].

## SOURCE CONTROL AND DRAINAGE

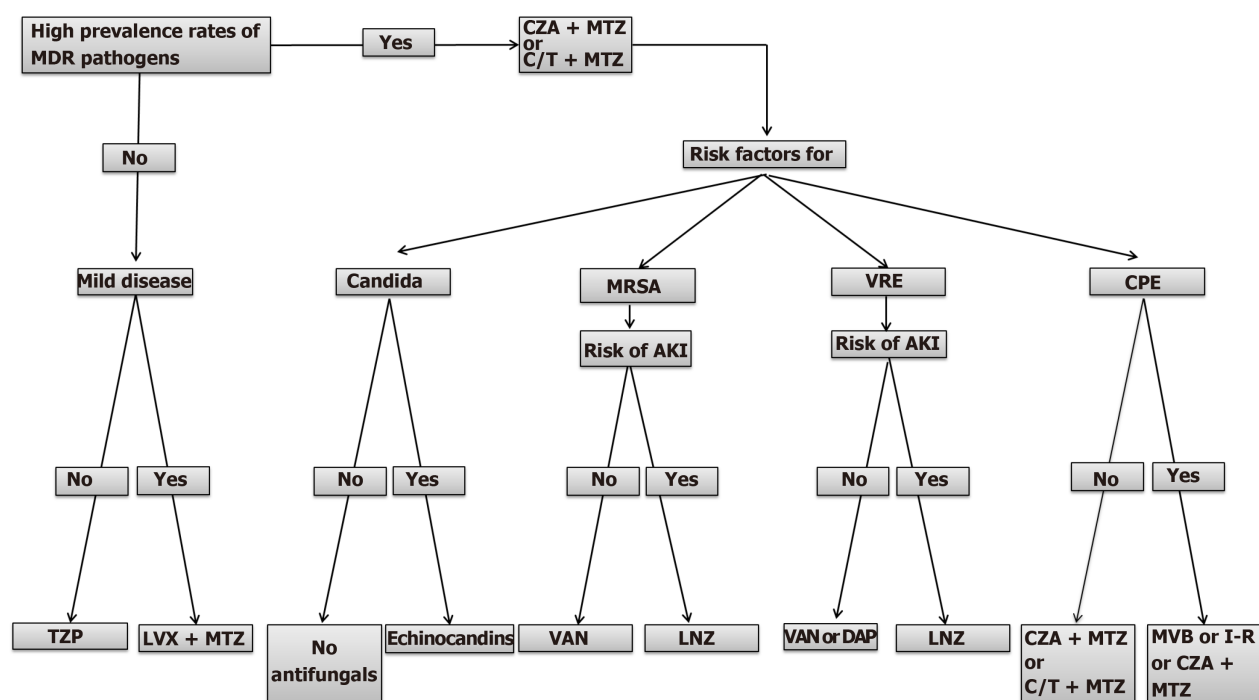
SSIs represent a serious problem for healthcare systems, especially in terms of length of hospital stay and cost. Over the years, many interventions have been proposed to reduce the SSIs rate. How an abdominal incision is closed has been largely investigated. A Cochrane meta-analysis reported there was no significant difference in terms of SSI rate and length of hospital stay when comparing continuous *vs* interrupted sutures for skin abdominal closure[96]. Moreover, the use of stitches with antimicrobial properties has been proven to reduce the SSIs rate in abdominal surgery. In particular, the use of triclosan-coated sutures is associated with a lower risk of SSIs[97]. Unfortunately, there is no evidence to prove the reduction of SSI with the use of intraoperative intraperitoneal irrigation and/or wound lavage with antibiotics. A topic that continues to be discussed and investigated in the literature[98,99]. Even wound irrigation before closure with saline or povidone solution has not proven to be valid in reducing SSIs[100]. Regarding mechanical devices, both single and dual-ring plastic wound protectors have proven to have a positive impact in preventing SSIs, with better results using the latter[101]. There is no concordance in the literature on the benefits related to the use of adhesive drapes (with or without antimicrobial properties) on a patient’s skin after surgical site cleaning. Also controversial is the role of subcutaneous drain placement before wound closure to reduce SSIs in high risk[102]. Regarding glove substitution during surgical procedures, changing gloves of all surgical teams at specific intervals especially in open surgery to avoid glove perforation or deterioration related to the duration of surgery appears to be beneficial[103]. Negative pressure wound therapy together with delayed abdominal closure (open abdomen technique) seems to be effective in preventing SSIs, especially in patients with a high risk of infection (highly contaminated peritoneum/wound)[104,105]. Nor-

moothermia, achieved with warming devices, is critical in reducing the rate of SSIs[106]. Perioperative oxygen supplementation is controversial and seems to be useless in reducing SSIs[107]. Understanding the time in which it can be useful to administer additional antibiotics intraoperatively is crucial to preventing SSIs, especially in patients undergoing urgent surgical procedures. Ultrasound-guided diagnostic and therapeutic drainage of fluid collections with the possibility of inserting a drain in a purulent cavity represents for surgeons a less-invasive bedside method to diagnose and solve a peritoneal pathological condition[108]. This useful tool represents an alternative to the classical surgical SSI source control gold standard consisting of debridement, removal of infected devices, drainage of collections, and decompression of the abdominal cavity. After an open abdomen technique, the timing to perform the gastrointestinal reconstruction and abdominal closure still widely debate in the literature. This suggests that further randomized clinical trials are needed to better define indications, timing, and techniques of the open abdomen technique in non-traumatic abdominal sepsis[109].

## ANTIMICROBIAL MANAGEMENT

Antimicrobial treatment is one of the pillars of adequate management of SSIs following abdominal surgery, mainly in organ/space infections[93]. As mentioned earlier in this paper, SSIs after abdominal surgery are often polymicrobial, including, above all, Gram-negative and anaerobic bacteria[94,110]. An adequate empirical antimicrobial therapy should be administered as soon as possible. It is mainly based on: (1) The site of infection; (2) Disease severity, with the use of wider spectrum antibiotics for moderate/severe infections; and (3) Local epidemiology of MDR pathogens, with the use of wider spectrum antibiotics in centers with MDR high prevalence. Inadequate initial empiric antimicrobial treatment is an independent risk factor that negatively impacts patients' outcomes. Several observations demonstrated that inadequate antimicrobial treatment is associated with an increased rate of morbidity and mortality. Moreover, an inadequate choice of initial treatments is associated with a longer hospital stay and higher costs of hospitalization compared with adequate antibiotic therapy[111,112]. The cornerstones of adequate antimicrobial therapy are proper etiological stratification, including local ecology and analysis of risk factors for MDR bacteria. This includes previous hospitalizations and antibiotic therapies (especially cephalosporins and quinolones) as well as stays in long-term care facilities and co-colonization with MDR bacteria. An evaluation of host characteristics, including hemodynamic status (presence or absence of signs of organ failure such as hypotension, oliguria, decreased mental alertness) and immunocompromised conditions (cancer or hematologic malignancy, human immunodeficiency virus, solid-organ transplant) that can influence the severity of abdominal SSIs is also relevant[100,113,114]. Every therapeutic choice must be framed within a broader antimicrobial stewardship strategy[115]. In non-critically ill patients without risk factors for MDR infections, a step-up approach can be reasonable. In these patients a single-agent therapy with broad-spectrum (*e.g.*, levofloxacin, piperacillin/tazobactam, tigecycline) or a combination of metronidazole with cephalosporins (ceftriaxone and cefotaxime) or quinolones (ciprofloxacin and levofloxacin) can be used[116]. In addition, clinicians should be informed about the increased risk of antibiotic resistance among Gram-negative bacteria, mainly *Enterobacteriaceae*-producing EsβLs, observed in the last years and the extended use of quinolones that may be associated with the emergence of MDR bacteria[100,117]. Among, the new β-lactam and β-lactamase inhibitor (βLβI) combinations, ceftolozane/tazobactam (C/T) and ceftazidime/avibactam (CZA) have activity against Gram-negative bacteria with various antimicrobial resistance phenotypes, including EsβL producing strains. In the ASPECT-cIAI phase 3 studies, C/T plus metronidazole combination was non-inferior to meropenem (MER) regarding clinical cure in the microbiologically intent-to-treat (83.0% *vs* 87.3%, respectively; difference: -4.2%; 95%CI: 8.91%-0.54%) and microbiologically evaluable (94.2% *vs* 94.7%, respectively; difference: -1.0%; 95%CI: -4.52% to 2.59%) populations. Among patients with infections due to EsβL producing strains, clinical cure rates were 95.8% and 88.5% in the C/T plus metronidazole and control groups, respectively[118]. Similarly, in the RECLAIM phase 3 studies, CZA plus metronidazole combination was non-inferior to MER regarding clinical cure in the microbiologically modified intention-to-treat (81.6% *vs* 85.1%, respectively; difference: -3.5%; 95%CI: -8.64% to 1.58%), in the modified intention-to-treat (82.5% *vs* 84.9%, respectively; difference: -2.4%; 95%CI: -6.90 to 2.10) and clinically evaluable (91.7% *vs* 92.5%, respectively; difference: -0.8%; 95%CI: -4.61 to 2.89) populations. A more aggressive approach should be considered in the clinical management of critically ill patients and those with risk factors for MDR bacteria. In these patients, carbapenems (MER and imipenem [IMI]/cilastatin [CIL]) or the above-mentioned βLβI combinations (plus metronidazole) represent the first line of treatment. However, the overuse of carbapenems has been associated with increased carbapenem resistance among Gram-negative bacteria, which has become a serious public health concern with worse clinical outcomes. Newly approved agents, MER/vaborbactam (MER/VAB) and IMI/CIL/relebactam (IMI/CIL/REL) are emerging options for the treatment of patients with abdominal SSIs, including those with infections due to MDR organisms (MDROs). MER/VAB is active against bacteria producing EsβL, KPC, and AmpC enzymes. In the TANGO-II phase 3 study, MER/VAB was associated with increased clinical cure and decreased mortality compared to the best available therapy (BAT) for the management of serious infections due to CRE. Overall, in the microbiologically modified intention-to-treat population, MER/VAB compared to BAT resulted in a higher rate of clinical cure at the end of therapy (65.6% *vs* 33.3%; *P* = 0.03) and the test-of-cure visit (59.4% *vs* 26.7%, respectively; *P* = 0.02). Furthermore, the 28-d all-cause mortality rate was 15.6% and 33.3% for MER/VAB *vs* BAT[119]. IMI/CIL/REL has a similar microbiological activity to MER/VAB. In the RESTORE-IMI-1 phase 3 study, IMI/CIL/REL was found to be an effective and well-tolerated treatment option for the management of serious infections due to CRE[120]. Another agent recently approved is eravacycline (EVC). It is a broad-spectrum antibiotic with activity against Gram-positive and Gram-negative MDROs, including CRE but not against *P. aeruginosa*. In IGNITE 1 and 4 phase 3 studies, EVC was compared to ertapenem and MER, respectively. Overall, EVC demonstrated non-inferiority to the comparators for the treatment of patients with complicated intra-abdominal infections[121,122]. In a *post hoc* analysis





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**Figure 2 Empirical antimicrobial approach of abdominal post-surgical infections.** CPE: Carbapenem-resistant Enterobacterales; C/T: Ceftolozane/tazobactam; CZA: Ceftazidime/avibactam; DAP: Daptomycin; I-R: Imipenem-relebactam; LVX: Levofloxacin; LNZ: Linezolid; MDR: Multidrug-resistance; MRSA: Methicillin-resistant *Staphylococcus aureus*; MTZ: Metronidazole; MVB: Meropenem-vaborbactam; TZP: Piperacillin-tazobactam; VAN: Vancomycin; VRE: Vancomycin-resistant Enterococci.

of IGNITE 1 and 4 studies, EVC showed a similar clinical outcome and microbiologic eradication rate compared to the MDR controls in bacteremic patients with primary complicated intra-abdominal infections[123]. Among new agents recently approved for the treatment of MDR Gram-negative cefiderocol (CFD) and plazomicin (PLZ) should be mentioned. CFD is a siderophore cephalosporin antibiotic with a broad spectrum of activity against Gram-negative bacteria, including MDROs such as CRE and carbapenem-resistant *P. aeruginosa*, and *Acinetobacter baumannii*[110,111]. In the CREDIBLE-CR phase 3 study, CFD has similar clinical and microbiological efficacy compared to BAT in the management of carbapenem-resistant Gram-negative infections[124]. PLZ, a new aminoglycoside, has broad-spectrum activity for Gram-positive and Gram-negative MDROs, including CRE[110,111]. In the CARE phase 3 study, the PLZ-based regimen was clinically and microbiologically effective in patients with serious infections due to CREs[125]. Antifungal agents should not be given empirically. In a randomized, double-blind, placebo-controlled trial assessing empirical antifungal treatment with micafungin (100 mg/d) in intensive care unit patients requiring surgery for intra-abdominal infection the incidence of invasive Candidiasis was 8.9% for placebo and 11.1% for micafungin group, with no difference in median time to invasive Candidiasis. Patients with a positive (1,3)- $\beta$ -d-glucan ( $\beta$ DG) were 3.66 (95%CI: 1.01-13.29) times more likely to have invasive Candidiasis[126]. In cases of acute necrotizing pancreatitis, the use of antifungal agents seems to prevent fungal infection[127]. We have synthesized evidence in a pragmatic therapeutic algorithm for approaching the main empirical antimicrobial therapy for the management of SSIs (Figure 2).

## FUTURE PERSPECTIVES

On September 30, 2023, clinicaltrials.gov recorded 34 clinical studies in the field of pharmacological and physical strategies for the prevention of SSIs in abdominal surgery; 10 are in the recruiting phase. Two phase III, prospective, multinational, multicenter, randomized, controlled, two-arm, double-blind studies (NCT04411199 and NCT04233424) compared the use of a new formulation of extended-release of doxycycline (D-PLEX). D-PLEX is supplied as a sterile powder to be reconstituted to paste in the operating room and is intended for single administration. The non-active components of the extended-release antibiotic formulation are  $\beta$  tri-calcium polymer and a lipid matrix. It must be applied during the surgery at the final stage of incision closure. Falcon trial (NCT03700749) is a double-blind 2x2 factorial, stratified, multicenter randomized controlled trial where recruited participants will be randomly assigned to four arms receiving different combinations of skin preparation and sutures for wound closure: 2% alcoholic chlorhexidine for skin cleansing and non-coated suture (arm A); 2% alcoholic chlorhexidine for skin cleansing and triclosan coated suture (arm B); 10% aqueous povidone-iodine for skin cleansing and non-coated suture (arm C); and 10% aqueous povidone-iodine for skin cleansing and triclosan-coated suture (arm D). Preoperative antiseptic chlorhexidine-based alcohol has been established as the gold standard of care for clean contaminated wounds. Topical prophylaxis of the surgical wound with antibiotics is

Table 4 Ongoing trials

Study name	ClinicalTrial.gov identifier	Design	Status	Type of surgery	Intervention(s)	Country
Iodine-Povidone Alcohol Compared to Chlorhexidine Alcohol as Preoperative Antiseptics in Major Abdominal Elective Clean Contaminated Surgery	NCT03859908	Single blind RCT	Terminated	Elective surgery categorized as clean contaminated surgery	Drug: Iodine povacrylex/isopropyl alcohol  Drug: Chlorhexidine gluconate/isopropyl alcohol	El Salvador
Examination of the Effect of Skin Antisepsis with Pre-heated Povidone Iodine on Surgical Site Infections: A Quasi-Experimental Study	NCT04969302	Single blind RCT	Completed	NS	Experimental: Povidone-iodine will heat to 37 °C using a gel warmer  Control: Povidone-iodine will heat to 20 °C using a gel warmer	Greece
Study to Assess the Safety & Efficacy of Oral Ciprodiazole Versus Currently Used Ciprofloxacin & Metronidazole (CIPRO-001)	NCT05863832	Open label RCT	Recruiting	Pelvi-abdominal surgery	Experimental  Ciprofloxacin  Active comparator: Ciprofloxacin 500 mg	Egypt
PVP Iodine vs Chlorhexidine in Alcohol for Disinfection of the Surgical Site (PICASSO)	NCT03685604	Single blind RCT	Completed	Colorectal surgery, cholecystectomy, herniotomy, appendectomy and bariatric surgery	Active comparator: Braunoderm®  Comparator  Softasept®	Switzerland
Delafloxacin IV and OS Administration Compared to Best Available Therapy in Patients with Surgical Site Infections (DRESS)	NCT04042077	Single blind RCT	Terminated	Abdominal surgery	Drug: Delafloxacin  Drug: Vancomycin  Drug: Linezolid  Drug: Piperacillin/tazobactam  Drug: Tigecycline	Rome
A Randomized, Blinded, Placebo and Standard of Care Controlled Efficacy, Safety, and Tolerability Study of up to 20 mL of DFA-02 in Patients Undergoing Abdominal Surgery	NCT01888367	Triple blind RCT	Completed	Abdominal surgery	Drug: DFA-02 Antibiotic Gel  Drug: DFA-02 Placebo Gel	United States
Reduction of Postoperative Wound Infections by Antiseptics? (RECIPE)	NCT04055233	Double blind RCT	Completed	Laparotomy for visceral surgery	Drug: Polihexanide; Serasept  Drug: NaCl; saline	Germany
Study of Chlorhexidine Gluconate as a Preoperative Antisepsis (CHG)	NCT01495117	Quadruple blind RCT	Completed	Resection surgery (clean-contaminated open surgery)	Drug: Povidone-Iodine  Drug: Chlorhexidine gluconate	Republic of Korea
A Randomized Controlled Trial of 2% Chlorhexidine Gluconate Skin Preparation Cloths for the Prevention of Post-Operative Surgical Site Infections in Colorectal Patients	NCT02385708	Open label RCT	Completed	Colorectal surgery	Drug: 2% chlorhexidine gluconate standard of care  Drug: 2% chlorhexidine gluconate chin to	United States

					toe	
Effect of Peritoneal Lavage with Clindamycin-gentamicin Solution on Postoperative Colorectal Cancer Infection in Elective Surgery	NCT01378832	Open label RCT	Completed	Colorectal surgery	Procedure: Intra-peritoneal antibiotic lavage	No location data
Collagen-Gentamicin Implant in the Treatment of Contaminated Surgical Abdominal Wounds - A Randomized Controlled Trial	NCT00977405	Double blind RCT	Terminated	Abdominal surgery	Device: Collatamp gentamicin implant	Singapore
CLinical Evaluation of Adults UNdergoing Elective Surgery Utilizing Intraoperative Incisional Wound Irrigation: A Randomized Controlled Trial (CLEAN Wound)	NCT04548661	Double blind RCT	Not yet recruiting	Laparotomy (clean-contaminated or contaminated incision). Laparoscopy (clean-contaminated or contaminated incision)	Procedure: Intraoperative incisional wound irrigation with povidone-iodine solution Procedure: Intraoperative incisional wound irrigation with saline	Canada
Randomized Controlled Trial to Evaluate the Optimal Timing of Surgical Antimicrobial Prophylaxis	NCT01790529	Quadruple blind RCT	Completed	Colorectal surgery	Procedure: Cefuroxime + metronidazole 75 to 30 min prior to skin incision Procedure: Cefuroxime + metronidazole within 30 min prior to skin incision)	Switzerland
A Pilot Clinical Evaluation of the Antimicrobial Effectiveness of Topically Applied ZuraPrep™	NCT02221232	Open label pilot study	Terminated	NS	Drug: Chloraprep Drug: ZuraPrep Drug: ZuraPrep Vehicle	United States
ROSSINI 2 - Reduction of Surgical Site Infection Using Several Novel Interventions (ROSSINI 2)	NCT03838575	Double blind RCT	Recruiting	Colorectal, hepatobiliary, upper GI, urological, vascular, or gynecological	Drug: 2% alcoholic chlorhexidine skin prep (SKIN PREP) Device: Iodophor Antimicrobial Incise Drapes (DRAPE) Device: Gentamicin-impregnated implants/sponges (SPONGE) Other: None (control)	United Kingdom
D-PLEX 311: Safety and Efficacy of D-PLEX in the Prevention of Post Abdominal Surgery Incisional Infection (SHIELD I)	NCT04233424	Triple blind RCT	Completed	Elective colorectal surgery	Drug: D-PLEX (new formulation of extended release of doxycycline) Other: SoC	United States
D-PLEX 312 - Safety and Efficacy of D-PLEX in the Prevention of Post Abdominal Surgery Incisional Infection (SHIELD II)	NCT04411199	Triple blind RCT	Recruiting	Elective colorectal surgery	Drug: D-PLEX + SoC Other: SoC	United States, Hungary, Serbia, Poland, Israel
Abdomen Closure Using Triclosan Coated Absorbable Suture <i>vs</i> Uncoated Sutures of the Same Base Material	NCT01620294	Double blind RCT	Completed	Elective colorectal surgery	Procedure: Abdominal wall closure Procedure: Surgical site infection	Hungary
Prophylaxis of Surgical Wound Infection with Topical Antibiotics	NCT04476212	Triple blind RCT	Recruiting	Elective abdominal wall surgery	Drug: Amoxicillin-clavulanate for topical prophylaxis	Spain

				Elective and emergency colorectal surgery	No intervention: Control	
D-PLEX 310: Safety and Efficacy of D-PLEX in the Prevention of Post Abdominal Surgery Incisional Infection	NCT03633123	Single blind RCT	Completed	Elective colorectal surgery	Drug: D_PLEX	Israel
					Other: SoC	
Antibiotic Prophylaxis in the Prevention of Surgical Site Infections After Selected Urgent Abdominal Surgical Procedures	NCT01524081	Double blind RCT	Completed	Emergent surgery for: Acute appendicitis/perforated gastric or duodenal ulcer/small bowel obstruction	Drug: Metronidazole, cefuroxime	Czech Republic
					Drug: Amoxicillin (+ clavulanic acid) and fluconazole	
					Drug: Placebo	
					Drug: Placebo	
Study the Efficacy of Topical Antibiotherapy in the Prophylaxis of Incisional Surgical Infection in Colorectal Surgery (PROTOP)	NCT03574090	Triple blind RCT	Completed	Colorectal surgery	Drug: Amoxicillin clavulanate	Spain
					Drug: Physiological saline	
Parenteral Antibiotics Compared to Combination of Oral and Parenteral Antibiotics in Colorectal Surgery Prophylaxis (ORALEV)	NCT02505581	Quadruple blind RCT	Completed	Colorectal surgery	Drug: Extra dosage - cefuroxime (750 mg) intravenous	Spain
					Drug: Ciprofloxacin 750 mg oral	
					Drug: Metronidazole 250 mg oral	
					Drug: Cefuroxime 1.5 g intravenous	
					Drug: Metronidazole 1 g intravenous	
Impact of Triclosan-coated Suture on Surgical Site Infection After Colorectal Surgery	NCT01869257	Single blind RCT	Completed	Colorectal surgery	Device: Triclosan coated suture	Italy
					Device: Regular suture	
Intravenous <i>Versus</i> Combined Oral and Intravenous Antimicrobial Prophylaxis for the Prevention of Surgical Site Infection in Elective Colorectal Surgery (COMBINE)	NCT02618720	Double blind RCT	Completed	Elective colorectal surgery	Drug: Ornidazole	France
					Drug: Placebo	
Prophylactic Effect Preoperative Antibiotics with Mechanical Bowel Preparation in SSIs	NCT03856671	Open label RCT	Completed	Laparoscopic colorectal surgery	Drug: Neomycin, metronidazole	China
Frequency of Surgical Site Infection in Abdominal Hernia with Gentamycin Spray on Mesh <i>Versus</i> no Spray	NCT04164524	Case-Control trial	Completed	Elective surgery; Para umbilical hernia, umbilical and epigastric hernia,	Drug: Gentamycin 160 mg spray applied over the mesh	Pakistan
Antibiotic Instillation in Acute Complex Appendicitis for Prevention of Deep Space Surgical Site Infections	NCT05470517	Single blind RCT	Recruiting	Appendectomy	Drug: Ceftriaxone	United States
					Procedure: Intra-peritoneal fluid aspiration	
Prophylaxis of Surgical Wound Infection in Incisional Hernia Repair With Topical Antibiotics (PROTOP-PAR)	NCT05508152	Triple blind RCT	Recruiting	Elective surgical procedure due to an abdominal wall incisional hernia	Drug: Wound irrigation with amoxicillin-clavulanate in saline solution	Spain
					Drug: Wound irrigation with a saline solution	
Orally Administered Trimethoprim-sulfamethoxazole and	NCT00613769	Triple blind	Completed	Colorectal surgery	Drug: Trimethoprim-sulfamethoxazole +	Sweden

Metronidazole as Prophylaxis of Infection Following Elective Colorectal Surgery		RCT			metronidazole	
					Drug: Cefuroxime and metronidazole	
The Effect of Intraoperative Peritoneal Lavage With Super-Oxidized Solution on Surgical Site Infections and Mortality in Patients With Secondary Peritonitis: A Randomized Controlled Trial	NCT05050253	Open label RCT	Recruiting	Emergency abdominal surgery by laparotomy	Device: Super-oxidized solution	Switzerland
					Device: Ringer's solution	
Reducing Infection at the Surgical Site With Antibiotic Irrigation During Ventral Hernia Repair (RINSE Trial)	NCT03945357	Open label RCT	Completed	Elective, open ventral hernia repair	Drug: Gemcitabine/clindamycin	United States
					Drug: Normal saline	
Preoperative Oral Antibiotics With <i>vs</i> Without Mechanical Bowel Preparation to Reduce Surgical Site Infections Following Colonic Resection: an International Randomized Controlled Trial. (ORALEV2)	NCT04161599	Single blind RCT	Recruiting	Colectomy	Drug: Cefuroxime (750 mg) intravenous	China
					Drug: Cefuroxime 750 mg oral	Italy
					Drug: Metronidazole 250 mg oral tablet	Spain
					Drug: Metronidazole 1 g intravenous	Russia
					Drug: Cefuroxime 1.5 g intravenous	Greece
					Drug: Sodium picosulfate, light magnesium oxide, anhydrous citric acid 10 mg/3.5 g/10.97 g oral	United Kingdom
Standard <i>Versus</i> Pre-emptive Antibiotic Treatment to Reduce the Rate of Infectious Outcomes After Whipple's Procedure (SPARROW): a Multicenter, Randomized Controlled Trial	NCT05784311	Open label RCT	No yet recruiting	Elective pancreatoduodenectomy	Drug: Cefuroxime	Netherlands
					Drug: Metronidazole	

NS: Not specified; RCT: Randomized controlled trial; SoC: Standard of care.

one of the most controversial measures proposed for SSIs prevention and the World Health Organization considers irrigation with antibiotics an unresolved issue. Some ongoing trials compare the use of topical antibiotics or their irrigation such as gemcitabine/clindamycin in the RINSE trial (NCT03945357) or amoxicillin-clavulanate (NCT04476212) *vs* saline irrigation. Closed incision negative pressure therapy (CINvt) is a new potential treatment strategy to reduce SSIs. This technique is based on the application of local negative pressure to the wound surface. The literature on its effectiveness is unclear. Two ongoing trials NCT04496180 and NCT04110353 compare the effectiveness of CINvt in reducing the incidence of SSIs *vs* simple standard dressing. The overview of ongoing trials shows that there is currently no introduction of new effective molecules in the treatment of abdominal post-surgical infections (Table 4). In fact, despite increased antibiotic resistance, pharmaceutical companies are hesitant to develop new antibiotics due to scientific, regulatory, and financial obstacles[128]. Li *et al*[129] in an observational cohort study, enrolling 2014 elderly patients who had elective surgery from 28 hospitals in China, developed and validated deep learning-based predictive models for post-operative infections in the elderly. The deep learning model predicted post-operative infections with an OR of 0.763 (95%CI: 0.681-0.844) with a sensitivity of 63.2% (95%CI: 46-78.2) and a specificity of 80.5% (95%CI: 76.6-84). Given the lack of new antibiotics deep learning models that incorporate risk factors for the prediction of abdominal post-surgical infections should be explored in future studies.



## CONCLUSION

Abdominal infections are some of the most common healthcare-associated problems, occurring 15%-25% after surgical procedures. Rapid clinical diagnosis and empirical antimicrobial therapy are essential. According to the CDC and NHSN; after a clinical diagnosis of SSI is made, adequate empirical antimicrobial therapy should be administered as soon as possible. The choice of antimicrobial therapy is based on three pillars: The site of infection, the disease severity, and the local epidemiology of MDROs. Few antibiotics are now available to treat such infections, and thus should not be used for mild infections in centers where the incidence of MDROs is low. This strategy is essential to prevent bacterial resistance. This review was written to provide a practical update on the latest available literature on SSIs and antimicrobial treatments. Due to the decreasing of number of new antibiotics development and improvement artificial intelligence should be explored for the prediction of abdominal post-surgical infections in future studies.

## FOOTNOTES

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