REVIEWER #1

1. The susceptible microbial communities existing in various parts mentioned in the conclusion section should be introduced in the background of the manuscript.
Many thanks for the suggestion: We moved the susceptible microbial communities existing in various parts, mentioned in the conclusion section, in the Microbiology section of the manuscript (lines 318-332).
2. In the abstract section, the manuscript proposes "focusing on aetiology and treatment", but the content of the manuscript does not provide a detailed overview of the etiology mechanisms and treatment of postoperative abdominal infections.
We apologize for the lack of clarity. By aetiology, we mean the causative agents, that is, the pathogens that cause the infection and not the etiological mechanism by which the infection is established. We have replaced aetiology with the term "causative pathogens" (line 153)

3. The content emphasized in the manuscript is unclear, as it does not focus on the antimicrobial methods for infection after abdominal surgery, but rather emphasizes the methods for preventing infection after abdominal surgery.
To emphasize the antimicrobial therapeutic approach, we have inserted an additional figure (Figure 2)

4. The Classification section of the manuscript mentions that different types of surgeries have varying SSI rates. However, the subsequent text fails to provide a comprehensive description of the antibacterial treatment for each specific type of surgery.
We emphasized the antimicrobial methods for infection after abdominal surgery as suggested (lines 433-437).

5. The sources and timestamps of the incidence rate data mentioned concerning SSI are mostly concentrated before 2017, and the recent years' incidence rates should also be included.
We added references published after 2017 as requested (Table 2, references 19, 27, 30, 31, 32, 33, 42, 44, 46, 51, 54, 57, 58, 60, 78, 80)

6. In the section "Antimicrobial treatment" on page 8 of the manuscript, indications for antimicrobial therapy and the treatment of different bacterial infections should be described, rather than summarizing the conclusions of published articles directly.
We added an algorithm for the different bacterial infections and described it in the text (Figure 2, lines 434-436, 510-519)

7. The content of the "Future Perspectives" and "Conclusions" sections on page 10 of the manuscript is redundant and fails to clearly express the central theme of the document.
We moved the susceptible microbial communities mentioned in the conclusion section in the Microbiology section of the manuscript and rewritten the conclusion of the manuscript.

8. The conclusion of the manuscript should not cite literature.
As suggested, we rewrote the conclusion of the manuscript without citing literature.

9. The conclusion section of this article mentions that the concentration of bacteria in different parts of the gastrointestinal tract varies, and it vividly expresses this information through a graph. However, this part appears to be somewhat abrupt, as it has not been introduced in the preceding context.

As previously suggested, we moved the susceptible microbial communities existing in various parts of the gastrointestinal tract, mentioned in the conclusion section, in the Microbiology section of the manuscript and rewritten the conclusion of the manuscript.

REVIEWER #2

1.The most important thing of writing a review is organizing the manuscript focusing on the topic, in this review of which is the antibiotic "antimicrobial approach" in "post-abdominal surgical site infections". Therefore, the section "ANTIMICROBIAL MANAGEMENT" should be reviewed more detailedly, from the current antimicrobial strategies and their limitations, to resolutions and future research directions, but not just listed some results of trials.
Many thanks for the suggestion, we have synthesized the pieces of evidence reported in the paragraph in a pragmatic therapeutic algorithm for approaching the main empirical antimicrobial therapy for the management of SSI (Figure 2, lines 434-436, 510-519)

2.Future perspectives should focus on the perspectives of the authors, but not just list the ongoing clinical trials.
we have added the reasonable future perspectives in the management of abdominal post-surgical infections (lines 596-606)

3.Conclusions should focus on summarization of the content of the review and should reach an appropriate conclusion. The variations of bacterial species and gradient across anatomical locations can be moved to section "MICROBIOLOGY".
Thank you. We have moved the text of the section "CONCLUSIONS" in the section "MICROBIOLOGY" and in the section "ANTIMICROBIAL MANAGEMENT". We rewrote the "CONCLUSIONS" section again according to the suggestions of the reviewers

4.The keywords can be revised more precisely, such as: abdominal post-surgical infections; antimicrobial approach.
Thank you. We followed the suggestion and added more precise and fitting keywords to the topic according MESH terms.

5.The writing of the manuscript have been disordered, for example, "MDR Acinetobacter and MDR Pseudomonas are increasing and are related to higher rates of treatment failure camp", need to be revised.
We ordered the writing of the manuscript as suggested.

Name of Journal: *World Journal of Gastrointestinal Surgery*
Manuscript Type: REVIEW

Antimicrobial approach of abdominal post-surgical infections.

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Author contributions: This review was mainly written by Marco Fiore and Sebastiano Leone; Francesca Martora, Sveva Di Franco, Aniello Alfieri, and Antonio Corrente, collected the data; Claudio Mauriello and Maria Caterina Pace supervised the writing of the paper; Stephen Petrou revised and polished the language; All authors approved the final version to be published.

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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 UN's Human Development Index. The purpose of this review is to provide a practical update on the latest available literature on SSIs, focusing on ~~aetiology~~ causative pathogens and treatment with an overview of the ongoing studies of new therapeutic strategies.

Key Words: Surgical Site infections; Multi-drug resistan*ce*; Carbapenem-resistant Enterobacterales; Carbapenem-resistant Klebsiella; Abdominal postoperative complications; Postsurgical infections; Review

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) with an incidence of 9.4% of surgical procedures in high HDI (HHDIC), 14.0% in middle HDI (MHDIC), and 23.2% in low HDI (LHDIC) countries. Consensually the antibiotic resistance incidence of the causative pathogen significantly varies in high (16.6%), middle (19.8%), and low (35.9%) HDI countries. Intuitively the highest incidence of abdominal SSIs are found in dirty surgery; high (17.8%), middle (31.4%), and low (39.8%) HDI, respectively[1]. Since approximately 234.2 (95% 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) provides guidelines and resources to help end surgical site infections (SSIs), along with assist the public to understand and take measures to safeguard their health when possible e[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 SSI 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.* 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[7]. 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. ~~Both~~ Superficial SSIs occur within 30 days while deep SSIs occur within 30-90 days 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].

Table 1. Definitions and clinical characteristics of surgical site infections according to CDC and NHSN criteria

~~**Classification to be adopted for SSI and the characteristics of SSI following abdominal surgery used to diagnose them according to the CDC and NHSN.**~~

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 days post-surgery**	**within 30 or 90 days post-surgery / 1 year (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

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] ~~About half of SSIs result from abdominal surgery (Table 2).~~ The main factors that determine this variability are attributable 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 SSI is the duration of surgery as demonstrated by Gillespie and colleagues'study[11]. In a study conducted by the GlobalSurg collaborative group on patients undergoing gastrointestinal surgery, according to HDI, there was a variable incidence between high (HHDIC), middle (MHDIC), and low HDI countries (LHDIC) of 9.4%, 14%, and 23% respectively[12]. The very high incidence of SSI in low Middle-Income Countries (LMIC) and Southeast Asia (SEA) compared to the US, 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 US[14]. Such hospitals using rigorous surveillance and broad data sources have reported higher SSI rates when compared with hospitals with lower surgical volumes, who used fewer data to conduct surveillance and tend to have fewer SSI rates. The accuracy of facility-reported SSI rates[15]. Data from the NHSN collected in the U.S. between 2006 and 2008 presented an overall SSI rate of 1.9%[16]. Between 2008 and 2014 there was an overall 17% decrease in SSIs. A report from 2016on the rates of Hospital-Acquired Infections (HAIs) based on data from 2014 described an overall rate of 1.15%[17], with abdominal surgery-related SSIs as 50% of the overall SSI. Furthermore open surgery may significantly increase the incidence of SSI if compared with laparoscopic surgery. A systematic review published in 2018 compared the incidence of SSI in appendectomy performed worldwide. It reported that in HHDICs the incidence rate of SSI was 1.3/3.8% for the open procedure and 0.8/2.9% for laparoscopic technique. In LHDICs

and MHDICs, the SSI incidence rate was significantly higher with 17.9% reported for the open procedure and 8.8% for the laparoscopic approach[18]. In a recent ECDC's report, there were similar findings. The SSI 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 SSI has changed both in high- and low-income countries over the past couple of decades, concerning antimicrobial prophylaxis[20]~~. In Table 3 we have synthesized the data on microbiology of SSIs sorted in the US between 1990 and 2017.~~ The overall surgery distribution of pathogens associated with SSI has varied over the years and the major organisms for abdominal surgery related to SSIs are *Escherichia coli*, *Enterococcus faecalis* and *Staphylococcus aureus*[21]. In contrast, in developing countries, even in clean surgery, there is quite a high prevalence of Gram-negative bacilli such as *Klebsiella* species, *Escherichia coli* and *Pseudomonas aeruginosa*[22]. The presence of Gram-negative bacilli is important because of high extended-spectrum beta-lactamase (ESβL) 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 microbiology of SSIs subdivided for type of abdominal surgery, based on those reported by the ECDC annual epidemiological report for 2018-2020[19].

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72 **Table 2 Geographical distribution of the SSIs' incidence**

Continent	Country	Period	SSIs incidence	Ref
Africa	Cameroon	2013-2014	Overrall 15.25%	[23]
	Egypt	2013-2017 2016-2018	CSEC 5.34% Overall 2.3% CSEC 2.8	[24] [25]
	Ethiopia:	2015 2019	Overall 19.1% Overall 21.1% ABDS 49.06%	[26] [27]
	Ghana	2017-2018	Overall, 10% APPY 13.4% GAST 12.7% HER 5.9% Other Abdominal surgery 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 2021	CSEC 10.3% HER 1.2% Overall surgery 11.5% ABDS 79.5%	[32] [33]
	South Africa	2017	APPY 25%	[34]
	Tanzania	2009-2010 2018-2020	Overall 26% APPY 15% CHOL 14.3% XLAP 27.9% CSEC 14%	[35] [36]
	Tunisia	2015-2016 2015	CSEC 5% APPY 9.8% CHOL 1.1% BILI 13.6	[37] [38]
America	Brazil	2008-2011 2008-2018	Overall 3.4% BAR Open 3% BAR VLP 0.5%	[39] [40]
	Canada	2015-2016 2015-2019	CSEC 5.9% COLO 10.28% BILI 16.13%	[41] [42]
	Colombia	2008-2010 2022	APPY 3.9% HYST 5.5% SPLE 4.5% CHOL3% HER 7.9% CHOL 8.3% CSEC 22.2%	[42] [43]
	Cuba	2017-2018	APPY 13.8% HER 5.7%	[44]
	Ecuador	2018	CSEC 1.35%	[45]
	Honduras	2017-2018	CSEC 5.1%	[46]
	Mexico	2011-2012 2013-2015	Overall 12.1% COLO 5.2% APPY 4.9% CHOL 0.8% HER 0.9% CHOL 5.5%	[47] [48]

	Peru	2005-2010 2015-2018 2019-2020	APPY 2.9% CHOL 2.8% CSEC 2.2% CSEC 2.4% CSEC 0.88% CHOL 0.18% HER 0 .38	[49] [50] [51]
	Uruguay	2012-2013 2021	APPY 3.2% CHOL 6.2% COLO 15.4% CSEC 1.74% CHOL open 1.85% CHOL VLP 0.23	[52] [53]
	Venezuela	2019-2021	Overall 9.7% APPY 10.42% BILI 3.79	[54]
	USA	2011-14 2015-19 2016-17	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% COLO 6.82% BILI 12.72% CHOL 0.96%	[16, 17,55] [42] [56].
	China	2020 2018 2017-20	ABDS 2.9% COLO 7.1% GAST 5.2% CSEC 23.30%	[57, 58] [59] [60]
	India	2011-17 2016 2005-11	Appendix 35.3% CSEC 10.3% PMID 33610238 XLAP 6% HER 3.8%	[61] [62] [63]
	Iran	2018 2021	Overall 0.29% Overall 5.2% surveillance	[64] [65]
Asia	Japan	2008-2010	COLO 15% REC 17.8%	[66, 67]
		2009-19	APPY VLP 4.19% APPY OPEN 6.60% CHOL VLP 1.91% CHOL OPEN 7.42% SB VLP 8% SB OPEN 15% COLO VLP 7.27% COLO OPEN 15.5% REC VLP 11.3% REC OPEN 8.8 %	[68]
	Kuwait	2016	SB 6.5% GAST 0.7%	[69]
	Nepal	2019	CSEC 8.54%	[70]
	Pakistan	2014-2019 2016-2017	BILI 40% APPY 32.7% CHOLO 20.7% HER37.6%	[71] [72]
	Philippines	2018-2019	Overall 9.7%	[73]
	Republic of Korea	2008-2012	Gastrectomy 3.12	[74]
	Saudi Arabia	2016	Overall 16.3% Open surgery 34.8% VLP Surgery 3.5	[75]
	Taiwan	2021	Overall: 4.0% Regional Hospital 4.7% Medical Center	[76]
	Thailand	2007-2016	Overall 2.98%	[77]

	Turkey	2005-2011	CHOL 1.3% COLO 11.4% CSEC 3% GAST 4.3% HYST 3.1% SPLE 5% XLAP 2.6%	[78]
	United Arab Enirates	2016-17	CSEC 1.4%	[79]

73

	Austria	2018-2020	CHOL 0.4% COLO 3.6% CSEC 0.5%	[19]
	England	2017-22	HYST 1.7% BILI 15.4% CHOL 9.7% GAST 1.9% COLO 8.6%	[80]
	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]
Europa	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 2013-16 2009-16	COLO10.6% REC 11.9% CHOL 1.96%	[81] [82] [83]
	Switzerland	2017-2018	APPY 3.1% CHOL 2.2% HER 0.9% COLO 13.5% REC 17.7% GAST 3.1% CSEC 1.8%	[84]
Oceania	Australia	2002-2013	Overall 2.8%	[85]

ABDS: Abdominal surgery (miscellany); APPY; Appendix surgery; BAR: Bariatric surgery; BILI: 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; XLAP: Exploratory laparotomy.

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

Microorganisms	Type of surgery				
	Laparoscopic CHOL	Open CHOL	Laparoscopic COLO	Open COLO	CSEC
Gram-positive cocci	52.9	39	34.8	70.4	78.8
Staphylococcus aureus	23.9	7.6	4.3	25	38.4
Coagulase-negative staphylococci	9.2	6.2	2.2	27	22.6
Enterococcus species	11.1	18.9	24.5	9.3	5.6
Streptococcus species	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
Escherichia coli	13.2	21.7	30.4	6.2	3.5
Citrobacter species	0.5	2.4	1.1	0.7	0.4
Enterobacter species	2.3	5.6	5.5	3.3	2.8
Klebsiella species	5	9.8	6.2	2.1	1.4
Proteus species	3.5	2.1	2.1	3.8	1.3
Serratia species	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
Acinetobacter species	0.5	0.3	0.4	0.6	0.6
Haemophilus species	0.2	0.1	0	0	0.1
Pseudomonas aeruginosa	2.1	0.9	5.3	2.9	1.6
Pseudomonadaceae family, other	0.2	0	0	0.2	0.6
Stenotrophomonas maltophilia	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
Bacteroides species	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
Candida species	0.2	1.5	3.2	0.3	0.1
Other fungi or parasites	0	0	0	0	0

84

85 Data obtained from the ECDC's Annual Epidemiological Report for 2018-2020 on surgical site infections. CHOL:
86 cholecystectomy, COLO: colon surgery, CSEC: caesarean section

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MICROBIOLOGY

SSIs are one of the most common complications of abdominal surgery and are associated with increased morbidity, mortality and costs[86]. SSIs can be defined as a wound infection with microorganisms within 30 days 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. In order 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 harbours only 101 bacteria per gram content. Increasing densities and bacterial diversities are found in the duodenum (103/g), jejunum (104/g), ileum (107/g), and colon (1012 bacteria/g)[87]. Besides a longitudinal gradient, there is also longitudinal diversity with Streptococcus which is the most represented bacterium in the distal oesophagus, duodenum and jejunum, Helicobacter and Streptococcus are the dominant genera present in the stomach. The predominant phyla that inhabit the large intestine include Firmicutes and Bacteroidetes; the latter, together with Streptococcus, Enterobacteriaceae, Enterococcus, Clostridium and Lactobacillus could be identified in stool[88]. The exogenous causes of infection are surgical personnel (surgeons and their teams), dirty clothing, potential "breakages" in aseptic techniques, and inadequate hand hygiene. As for 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 the preventative measures emphasize the importance of good patient preparation, aseptic practice, and attention to surgical technique. Antimicrobial prophylaxis is also indicated in specific circumstances. The most frequently isolated pathogens include: gram-positive cocci, such as *Staphylococcus aureus*, enterococci and streptococci. Gram-negative bacilli, common pathogenic Enterobacteriaceae, including *Escherichia coli*, *Enterobacter* species, *Klebsiella*

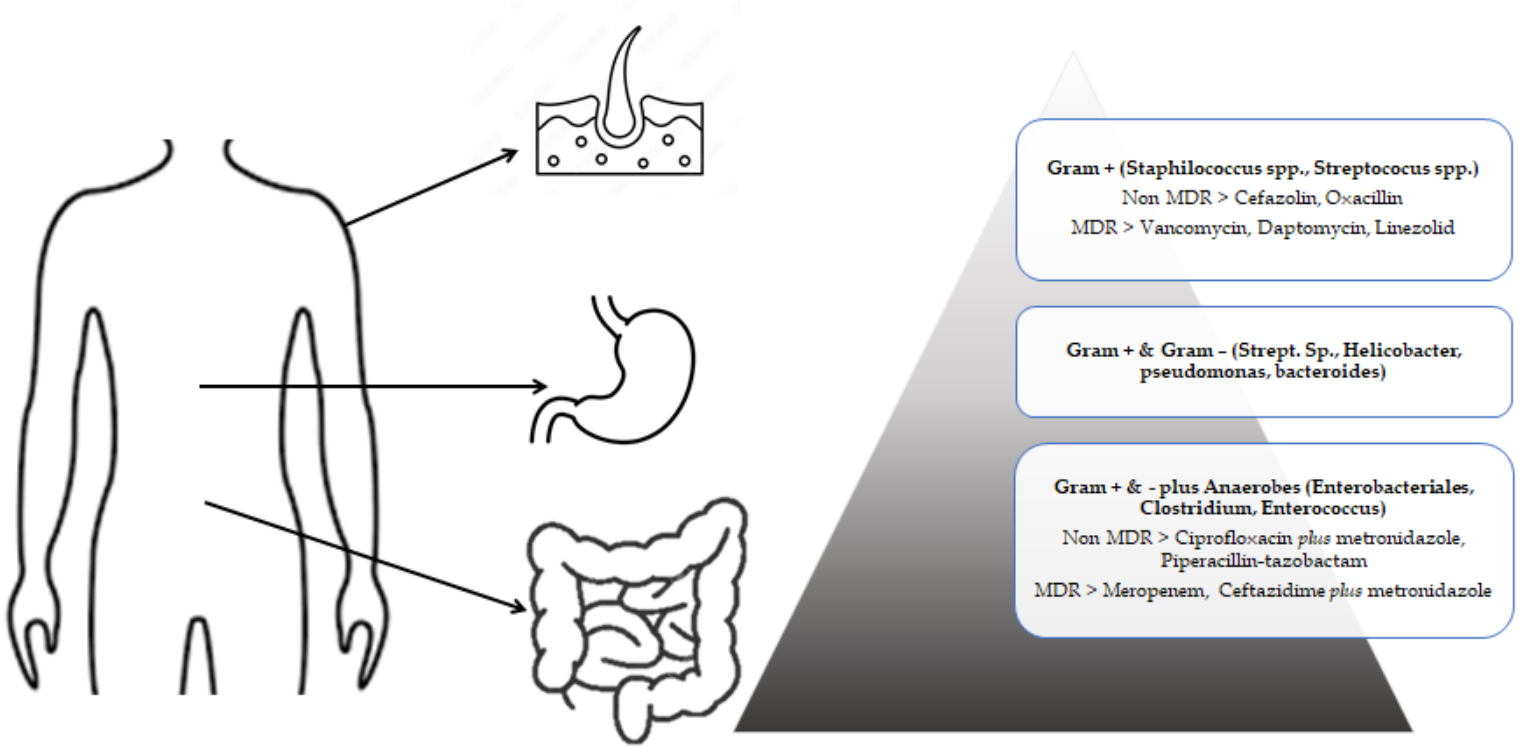
species and *Serratia marcescens* are also found. *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are other common causes of Gram-negative infection[89]. Nosocomial pathogens, including Gram-negative and Gram-positive bacteria, are major causative microorganisms leading epidemiological exposure[90]. The intensity and timing of the exposure, along with virulence of the organism affect morbidity and mortality. Currently, novel threats are arising from multi-drug resistant (MDR) bacteria. An increasing number of SSIs result from multidrug-resistant microorganisms. Among gram-positive bacteria, we recognize methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE)[91]. Recently, a high rate of drug-resistant Gram-negative bacteria has become a major and global health concern[92, 93]. The prevalence of *Acinetobacter*, *Pseudomonas* and Gram-negative bacilli, that produce ESβL and carbapenemase, are increasing and related to higher rates of treatment failure[94,95]. 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 postoperative 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[96].

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 SSI 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 versus interrupted sutures for skin abdominal closure[97]. Moreover, the use of stitches with antimicrobial properties has been proven to reduce the SSI rate in abdominal surgery. In particular, the use of triclosan-coated sutures

is associated with a lower risk of SSI[98]. 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[99, 100]. Even wound irrigation before closure with saline or povidone solution has not proven to be valid in reducing SSI[101]. Regarding mechanical devices both single and dual-ring plastic wound protectors have proven to have a positive impact in preventing SSI, with better results using the latter[102]. 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 SSI in high-risk[103]. 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 [104]. Negative pressure wound therapy together with delayed abdominal closure (open abdomen technique) seems to be effective in preventing SSI, especially in patients with a high risk of infection (highly contaminated peritoneum/wound)[105,106]. Normothermia, achieved with warming devices, is critical in reducing the rate of SSI[107]. Perioperative oxygen supplementation is controversial and seems to be useless in reducing SSIs[108]. 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[109]. 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 are still widely debated in the literature. This suggests that further randomized clinical trials are needed to better define indications, timing, and techniques of open-abdomen technique in non-traumatic abdominal sepsis[110].

Figure 1. The bacterial gradient with predominant bacteria



ANTIMICROBIAL MANAGEMENT

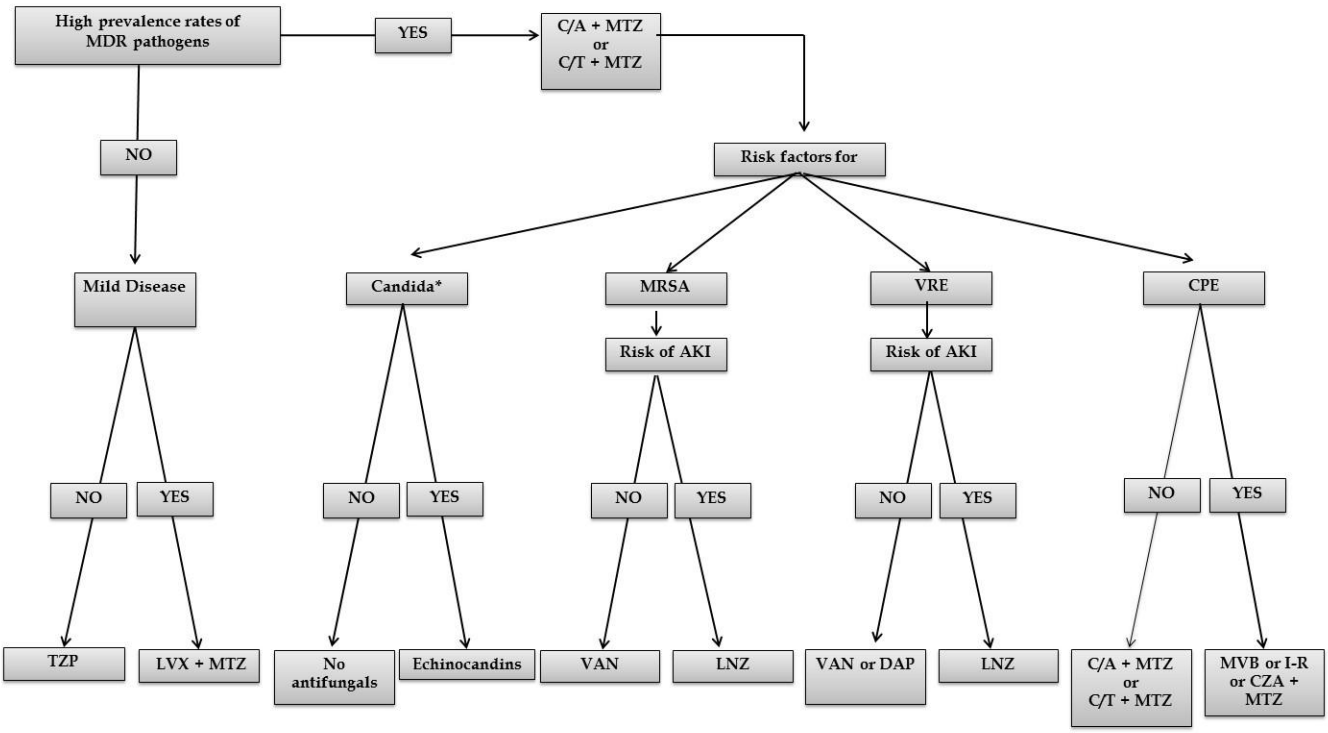
Antimicrobial treatment is one of the pillars for adequate management of SSIs following abdominal surgery, mainly in organ/space infections[94]. As mentioned earlier in this paper, SSIs after abdominal surgery are often polymicrobial, including, above all, Gram-negative and anaerobic bacteria[95,111]. An adequate empirical antimicrobial therapy should be administered as soon as possible. It is mainly based on i) the site of infection ii) disease severity, with the use of wider spectrum antibiotics for moderate/severe infections and iii) local epidemiology of MDR pathogens, with the use of wider spectrum antibiotics in centres 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[112,113]. The cornerstones for 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 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, HIV, solid-organ transplant) that can influence the severity of abdominal SSIs is also relevant[101,114,115]. Every therapeutic choice must be framed within a broader antimicrobial stewardship strategy[116]. 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[117]. 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[101, 118]. Among, the new β-lactam and β-lactamase inhibitor (βLβI) combinations, ceftolozane/tazobactam (CFT/TAZ) and ceftazidime/avibactam (CAZ/AVI) have activity against Gram-negative

bacteria with various antimicrobial resistance phenotypes, including ESβL producing strains. In the ASPECT-cIAI Phase 3 studies, CFT/TAZ plus metronidazole combination was non-inferior to meropenem regarding clinical cure in the microbiological intent-to-treat (83.0% *vs* 87.3%, respectively; [difference - 4.2%; 95%CI: 8.91% to 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 CFT/TAZ plus metronidazole and control groups, respectively[119]. Similarly, in the RECLAIM Phase 3 studies, CAZ/AVI plus metronidazole combination was non-inferior to meropenem 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% [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 (meropenem and imipenem/cilastatin) 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, meropenem/vaborbactam (MER/VAB) and imipenem/cilastatin/relebactam (IMI/CIL/REL) are emerging options for the treatment of patients with abdominal SSIs, including those with infections due to 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 carbapenem-resistant *Enterobacteriaceae* (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-day all-cause mortality rate was 15.6% and 33.3% for MER/VAB *vs* BAT[120]. 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[121]. Another agent recently approved is eravacycline (EVC). It is a broad-spectrum antibiotic with activity against Gram-positive and Gram-negative MDR bacteria, including CRE but not against *Pseudomonas. aeruginosa*. In IGNITE 1 and 4 Phase 3 studies, EVC was compared to ertapenem and meropenem, res. Overall, EVC demonstrated non-inferiority to the comparators for the treatment of patients with complicated intra-abdominal infections[122, 123]. In a posthoc analysis of IGNITE 1 and 4 studies, EVC showed a similar clinical outcome and microbiologic eradication rate compared to the controls in bacteremic patients with primary complicated intra-abdominal infections[124]. Among new agents recently approved for the treatment of MDR Gram-negative cefiderocol and plazomicin should be mentioned. Cefiderocol (CFD) is a siderophore cephalosporin antibiotic with a broad spectrum of activity against Gram-negative bacteria, including MDROs such as CRE and carbapenem-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*[111, 112]. 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[125]. Plazomicin (PLZ), a new aminoglycoside, has broad spectrum activity for MDR Gram-positive and Gram-negative bacteria, including CRE[111, 112]. In the CARE Phase 3 study, the PLZ-based regimen was clinically and microbiologically effective in patients with serious infections due to CREs[126]. Antifungal agents should not 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)-β-d-glucan (ßDG) were 3.66 (95% CI, OR 1.01-13.29) times more likely to have Invasive Candidiasis[127]. In cases of acute necrotizing pancreatitis, the use of antifungal agents seems to prevent fungal infection[128]. We have synthesized evidence in a pragmatic therapeutic algorithm for approaching the main empirical antimicrobial therapy for the management of SSI (Figure 2).

Figure 2. The 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-resist; MRSA: Methicillin-resistant S. aureus; MTZ: metronidazole; MVB: meropenem-vaborbactam TZP: piperacillin-tazobactam; VAN: Vancomycin; VRE: Vancomycin-resistant enterococci.

FUTURE PERSPECTIVES

On September 30th 2023, clinicaltrial.gov had recorded thirty-four clinical studies in the field of pharmacological and physics strategies for the prevention of surgical site infections in abdominal surgery. Ten are in the recruiting phase. Two phase III, prospective, multinational, multicenter, randomized, controlled, two-arm, double-blind studies (NCT04411199 and NCT04233424) compare 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 β 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, multi-centre RCT 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. ~~if It was compared to Iodine solutions non-alcohol based; alcohol-based solution could, however, be a confounder in the comparison. On this basis, an RCT (NCT03859908) conducted by the University of El Salvador compare the efficacy of both solutions alcohol-based, 0.7% iodine povacrylex plus 74% alcohol, against gluconate chlorhexidine 2% plus 70% alcohol, in clean-contaminated wounds, in major abdominal elective surgeries. ROSSINI 2 trial (NCT03838575) evaluate the use of three in-theatre interventions to reduce SSI rates in patients undergoing surgery with an abdominal incision: use of 2% alcoholic chlorhexidine skin prep (SKIN PREP), Iodophor Antimicrobial Incise Drapes (DRAPE) and Gentamicin impregnated implants/ sponges (SPONGE). It is a non-factorial superiority design with the allocation of various combinations of the three interventions to be used during the same operation, via seven possible treatment arms plus one control arm initially.~~

Topical prophylaxis of the surgical wound with antibiotics is one of the most controversial measures proposed for SSI 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) versus saline irrigation. Closed incision negative pressure therapy (CINVt) is a new potential treatment strategy to reduce Surgical Site Infections. This technique is based on the application of local negative pressure to the wound surface. ~~In the case of open abdomens, the procedure is performed by applying a sterile abdominal dressing, which consists of a fenestrated soft plastic non-adherent layer with enclosed central foam, which is placed on the surface of the viscera. Then, two layers of porous sponge dressings are applied over the plastic layer. Finally, a transparent adhesive is placed over the foam and the wound to seal the abdominal cavity. The entire system is then connected, by suction tubes, to a device that ubiquitously applies negative pressure (cyclically or continuously) on the surface. The fluid from the wound is collected into a container.~~ Literature on its effectiveness is unclear. Two ongoing trials NCT04496180 and NCT04110353 compare the effectiveness of CINVt in reducing the incidence of SSI versus simple standard dressing. Table 4 summarizes the ongoing trials on pharmacological and physics strategies to prevent and reduce SSI, registered clinicaltrials.gov up until July 2023. 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[129]. Li et al. 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 postoperative infections in the elderly. The deep learning model predicted postoperative 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)[130]. In view of 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.

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390 **Table 4. Ongoing trials**

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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: - Ciprodiazole - 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

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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	USA
Reduction of Postoperative Wound Infections by Antiseptica? (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

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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% Chlorohexidine Gluconate Standard of Care - Drug: 2% Chlorohexidine Gluconate Chin to Toe	USA
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 minutes prior to skin incision - Procedure: Cefuroxime + metronidazole within 30 minutes 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	USA

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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 gynaecological	- Drug: 2% alcoholic chlorhexidine skin prep (SKIN PREP) - Device: Iodophor Antimicrobial Incise Drapes (DRAPE) - Device: Gentamicin-impregnated implants/ sponges (SPONGE) - Other: NONE (Control)	UK
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: Standard of Care (SoC)	USA
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: Standard of Care (SoC)	USA Hungary Serbia Poland Israel

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Abdomen Closure Using Triclosan Coated Absorbable Suture vs 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 elective and emergency colorectal surgery	- Drug: amoxicillin-clavulanate for topical prophylaxis - No Intervention: Control	Spain
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 - Other: Standard of Care (SoC)	Israel
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 - Drug: Amoxicillin (+ clavulanic acid) and Fluconazole - Drug: Placebo - Drug: Placebo	Czech Republic
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 - Drug: Physiological Saline	Spain

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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 (750mg) I.V - Drug: Ciprofloxacin 750 mg oral - Drug: Metronidazole 250 mg oral - Drug: Drug: Cefuroxime 1.5 g Intravenous - Drug: Metronidazole 1 g Intravenous	Spain
Impact of Triclosan-coated Suture on Surgical Site Infection After Colorectal Surgery	NCT01869257	Single blind RCT	Completed	Colorectal Surgery	- Device: Triclosan coated suture - Device: regular suture	Italy
Intravenous Versus 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 - Drug: Placebo	France
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 Versus 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 - Procedure: Intra-peritoneal Fluid Aspiration	USA
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 - Drug: Wound irrigation with a saline solution	Spain
Orally Administered Trimethoprim-sulfamethoxazole and Metronidazole as Prophylaxis of Infection Following Elective Colorectal Surgery	NCT00613769	Triple blind RCT	Completed	Colorectal surgery	- Drug: trimethoprim-sulfamethoxazole + metronidazole - Drug: cefuroxime and metronidazole	Sweden

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 (SOS) - Device: Ringer's solution	Switzerland
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 - Drug: Normal saline	USA
Preoperative Oral Antibiotics With vs 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 (750mg) I.V - Drug: Cefuroxime 750mg oral - Drug: Metronidazole 250 MG Oral Tablet - Drug: Metronidazole 1 g I.V - Drug: Cefuroxime 1,5 g I.V - Drug: Sodium picosulfate, light magnesium oxide, anhydrous citric acid 10 mg/3.5 g/10.97 g Oral	China Italy Spain Russia Greece UK
Standard Versus 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 - Drug: Metronidazole	Netherlands

CONCLUSIONS

~~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 stomach is highly inhospitable for bacterial growth, and very few bacteria are resistant to this acidic condition, to bile or pancreatic enzymes, and they can survive or multiply. The bacterial gradient is represented schematically in Figure 1. The stomach harbours only 10^1 bacteria per gram content, and increasing densities and bacterial diversities are found in the duodenum (10^3/g), jejunum (10^4/g), ileum (10^7/g), and colon (10^{12} bacteria/g)[57]. Besides a longitudinal gradient, there is also a longitudinal diversity with *Streptococcus* which is the most represented bacterium in the distal oesophagus, duodenum and jejunum, *Helicobacter* and *Streptococcus* are the dominant genera present in the stomach. The predominant phyla that inhabit the large intestine include *Firmicutes* and *Bacteroidetes;* the latter, together with *Streptococcus*, *Enterobacteriaceae*, *Enterococcus*, *Clostridium* and *Lactobacillus* could be identified in stool[58]. The knowledge of the site of infection and the probability of MDR is fundamental to initiate an empirical antibiotic treatment with the use of an antibiotic active against Gram-positive bacteria for the infection involving the skin and soft tissue infections and antibiotics for anaerobic germs if the site of infection involves large intestine.~~

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. Choice of antimicrobial therapy is based on three pillars: the site of infection, the disease severity and the local epidemiology of MDR pathogens. Few antibiotics are now available to treat such infections, and thus should not be used for mild infections in centres where incidence of MDR is low. This strategy is essential to prevent bacterial resistance. ~~We focused this review on a practical cut to avoid slowing the start of adequate antibiotic therapy. We have also focused on ongoing trials on the treatment of post-abdominal SSI, of these none seems to promise an imminent introduction of effective antibiotics.~~ This review was written to provide a practical update on the latest available literature on SSIs and antimicrobial treatments. Due to the decreasing of the number of new

antibiotics development and approvement Artificial Intelligence should be explored for the prediction of abdominal post-surgical infections in future studies.

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Footnotes

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