Current challenges in the prevention, management and outcomes of surgical site infections in elective colorectal surgery

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CURRENT CHALLENGES IN THE PREVENTION, MANAGEMENT AND OUTCOMES OF SURGICAL SITE INFECTIONS IN ELECTIVE COLORECTAL SURGERY

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A la meva família i amics

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M; VINCat Colon Surgery Group. J Infect. 2017 Jun;74(6):555-563. doi: 10.1016/j.jinf.2017.03.002. Epub 2017 Mar 16. Impact Factor: 4.20 (1st Quartile)

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A) SLIDE SESSIONS:

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- **Epidemiology and outcome differences in surgical site infections associated to elective colon and rectal surgery. Are we talking about the same surgical procedure?** A. Gomila, J. Badia, V. Diaz-Brito, A. Cruz, D. Camprubi, R. Escofet, D. Fraccalvieri, E. Shaw, M. Piriz, E. Limón, F. Gudiol, M. Pujol. *26th European Congress of Clinical Microbiology and Infectious Diseases*. Amsterdam, Netherlands. April 2016. Abstr: O341.

B) POSTER SESSIONS:

- **Surgical site infections caused by *Pseudomonas aeruginosa* after elective colorectal surgery.** A. Gomila, D. Camprubi, J. Carratalà, E. Shaw, J. Badia, M. Piriz, V. Diaz -Brito Fernandez, E. Espejo, C. Nicolas, M. Brugués, F. Obradors, A. Lérida, R. Vázquez, A. Castro, D. Fraccalvieri, E. Limón, F. Gudiol, M. Pujol. *27th European Congress of Clinical Microbiology and Infectious Diseases*. Vienna, Austria. April 2017. P0646.

- **Impact of surgical site infection on in-hospital mortality in patients undergoing elective colorectal surgery: a multicentre prospective cohort.** E. Shaw, A. Gomila, M. Piriz, F. Obradors, R. Vázquez, J. Badia, L. Martin, D. Fraccalvieri, M. Brugués, C. Nicolas, E. Espejo, A. Castro, V. Diaz-Brito Fernandez, E. Limón, J. Carratalà, F. Gudiol, M. Pujol. *27th European Congress of Clinical Microbiology and Infectious Diseases*. Vienna, Austria. April 2017. P0642.

- **Are there differences in risk factors for organ-space surgical site infections in patients undergoing elective colon or rectal surgery?** A. Gomila, JM. Badia, E. Shaw, C. Nicolás, M. Piriz, M. Brugués, F. Obradors, E. Limón, F. Gudiol, M. Pujol on behalf of VINCat colon surgery group. *Federation of Infection Societies (FIS) Annual Conference and the 10th Healthcare Infection Society (HIS) International Conference 2016*. Edinburgh, United Kingdom. November 2016. Abstr: 4947.

- **Epidemiología y evolución de la infección de órgano-espacio en cirugía electiva colo-rectal.** A. Gomila, D. Camprubí, R. Escofet, E. Shaw, D. Fraccalvieri, JM. Badia, M. Piriz, E. Limón, F. Gudiol, M. Pujol. XX *Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)*. Barcelona, Spain. May 2016. Abstr: 751.

- **Cost of organ/space infection in elective colorectal surgery. Is it just a problem of rates?** E. Shaw, A. Gomila, M. Piriz, F. Obradors, R. Escofet, R. Vazquez, JM. Badia, L. Martin, D. Fraccalvieri, M. Brugués, C. Nicolás, E. Espejo, A. Castro, A. Cruz , E. Limón, F. Gudiol, M. Pujol. *4th International Consortium for Preventium and Infection Control Congress*. Geneva, Switzerland. June 2015. Abstr: ICPIC15-ABS-1449**.**

INDEX

6.1. Specific characteristics and surgical approach in colon and rectal surgery.

Risk factors and outcomes of organ-space surgical site infections after elective colon and rectal surgery. Gomila A, Carratalà J, Camprubí D, Shaw E, Badia JM, Cruz A, Aguilar F, Nicolás C, Marrón A, Mora L, Perez R, Martin L, Vázquez R, Lopez AF, Limón E, Gudiol F, Pujol M; VINCat colon surgery group. Antimicrob Resist Infect Control. 2017 Apr 21;6:40. doi: 10.1186/s13756-017-0198-8.

6.2. Timing of the development of surgical site infection in elective colorectal surgery

Predictive factors for early and late-onset surgical site infections in patients undergoing elective colorectal surgery. A multicentre, prospective, cohort study. Gomila A, Carratalà J, Biondo S, Badia JM, Fraccalvieri D, Shaw E, Diaz-Brito V, Pagespetit L, Freixas N, Brugués M, Mora L, Perez R, Sanz C, Arroyo N, Iftimie S, Limón E, Gudiol F, Pujol M; VINCat colon surgery group. J Hosp Infect. 2018 May;99(1):24-30. doi: 10.1016/j.jhin.2017.12.017.

6.3. Management and outcomes of surgical site infection after elective colorectal surgery

Current outcomes and predictors of treatment failure in patients with surgical site infection after elective colorectal surgery. A multicentre prospective cohort study. Gomila A, Badia JM, Carratalà J, Serra-Aracil X, Shaw E, Diaz-Brito V, Castro A, Espejo E, Nicolás C, Piriz M, Brugués M, Obradors J, Lérida A, Cuquet J, Limón E, Gudiol F, Pujol

M; VINCat Colon Surgery Group. J Infect. 2017 Jun;74(6):555-563. doi: 10.1016/j.jinf.2017.03.002.

6.4. Analysis of the health costs of organ-space surgical site infection in elective colorectal surgery

Multistate modeling to estimate excess length of stay and risk of death associated with organ/space infection after elective colorectal surgery

Shaw E, Gomila A, Piriz M, Perez R, Cuquet J, Vazquez A, Badia JM, Lérida A, Fraccalvieri D, Marron A, Freixas N, Castro A, Cruz A, Limón E, Gudiol F, Biondo S, Carratalà J and Pujol M, on behalf of VINCat colon surgery group. J Hosp Infect 2018 Dec;100(4):400-405. doi: 10.1016/j.jhin.2018.08.010. Epub 2018 Aug 17.

6.5. An organism of special interest in surgical site infections: *Pseudomonas aeruginosa*

Preoperative oral antibiotic prophylaxis reduces *Pseudomonas aeruginosa* surgical site infections after elective colorectal surgery: A multicenter prospective cohort study. Gomila A, Carratalà J, Badia JM, Camprubí D, Piriz M, Shaw E, Diaz-Brito V, Espejo E, Nicolás C, Brugués M, Perez R, Lérida A, Castro A, Biondo S, Fraccalvieri D, Limón E, Gudiol F, and Pujol M, on behalf of VINCat Colon Surgery Group. BMC Infect Dis. 2018 Oct 5;18(1):507. doi: 10.1186/s12879-018-3413-1.

1. INTRODUCTION

Surgical Site Infection: Burden of the disease

The introduction of antisepsis and the antibiotic revolution in the decade of the 1940s caused a fundamental change in modern surgery; it permitted the prevention and control of wound infection and sepsis, which had complicated almost all surgeries until that moment, and allowed a far more technical and invasive approach to surgery which achieved much better results. Despite these advances, however, the risk of wound infection was not completely eliminated, and surgical infections remain an important complication after surgery even today. Several studies have identified specific factors such as the timing of administration of the antibiotic prophylaxis, which have a great influence on the development of surgical infection (Mandell et al. 2014).

The term “Surgical Site Infection” (SSI) was introduced in 1992 to replace the previous nomenclature of “wound infection”, and refers to infections that occur within 30 days (or one year if an implant is left in place) after surgery (Owens et al. 2008). These infections may be superficial and deep incisional, or organ-space SSI (OS-SSI).

Currently, SSIs are the most frequent healthcare-associated infections (HAIs) in Europe and in the United States (US). The last point prevalence survey in European acute care hospitals performed in 2011-2012 showed that SSIs represented 19.6% of all HAIs (Zarb et al., 2012), being even more frequent than pneumonia and urinary tract infections. This percentage was even higher when analysing HAIs present at hospital admission, where SSIs accounted for 33% of the total. A previous multistate point-prevalence survey of HAI, conducted

by the Centers for Disease Control and Prevention (CDC's) in the US, estimated that 157,000 SSIs were associated with inpatient surgeries in 2011, as many as cases of healthcare-associated pneumonia (Magill et al., 2014). The development of SSIs has been associated with increases in hospitalization of 7 to 11 additional days, higher readmission rates and a two to 11-fold increase in the risk of death compared to postoperative patients who do not develop SSI (Kirkland et al. 1999) (Coello et al. 2005). It has been estimated that SSIs involve an annual extra cost of 3.5 to 10 billion dollars in healthcare expenditures in the US (Anderson et al. 2014). Despite these high rates, however, it seems that a considerable advance in the prevention of SSIs has been made; the last analysis conducted by the National Healthcare Safety Network (NHSN) showed a decrease of 17% in SSIs among 10 selected procedures between 2008 and 2014 (Centers for Disease Control and Prevention, 2016).

On the other hand, the incidence of colorectal cancer (CRC) has fallen by almost 45% in the last three decades and its related mortality by more than 50% due to screening programs. Nonetheless, CRC remains the third most common cancer in men and the second most common in women worldwide (Welch & Robertson, 2016) (Aran, Victorino, Thuler, & Ferreira, 2016) (Torre et al. 2015). In this scenario, colorectal surgery remains very common and has the highest SSI rates of all elective procedures, reaching 20% at some institutions (Kirby, Burnside, Bretsztajn, & Burke, 2015) (Limón et al. 2014) (Petrosillo et al. 2008). This high rate is due to the contamination inherent in the procedure since billions of bacteria are present in the intestinal bowel and can cause infection even when adequate preoperative

intravenous antibiotic prophylaxis is administered. Also, the increasing complexity of the procedures and the higher age of the patients involved contribute to maintaining the high rates of SSI. In contrast, multiple strategies have shown to be successful in preventing SSIs, such as laparoscopic surgery, the improvements in the preoperative antibiotic prophylaxis mentioned above and the implementation of bundles of preventive measures (Aimaq, Akopian, & Kaufman, 2011), (Morris, Graham, Chu, Cannon, & Hawn, 2015) (Allegranzi et al. 2016) (Zywot, Lau, Stephen Fletcher, & Paul, 2017).

Interestingly, the administration of mechanical bowel preparation (MBP) before colorectal surgery was discontinued in recent decades in most Spanish hospitals due to its lack of effectiveness (Dahabreh, Steele, Shah, & Trikalinos 2015). MBP also caused significant unpleasant effects such as nausea and vomiting. At the same time, and for reasons that have not been well established, the administration of preoperative oral antibiotic prophylaxis (OAP) was also discontinued. Currently, only a few hospitals in Spain use OAP in the elective surgery of the colon and rectum; elsewhere in Europe and in the US, however, OAP is part of daily practice.

The emergence of multidrug resistance, especially extended-spectrum betalactamase (ESBL) and carbapenemase-producing Gram negative bacteria (GNB), has meant a challenge for the prevention and treatment of SSIs in colorectal surgery (Ho, Tambyah, & Paterson 2010) (Khan, Dancer, & Humphreys 2012). The increasing presence of infections due to multidrug-resistant microorganisms requires physicians to consider the risk factors for multidrug-resistance of each

individual patient and their clinical condition in order to offer the most adequate and effective antibiotic treatment.

Moreover, the adequacy of the antibiotic therapy is not the only important factor for achieving clinical cure in patients with SSIs after colorectal surgery. The control of the infectious focus is also necessary. It has been shown that in OS-SSIs –the deepest and most serious infections– interventions aiming to control and eliminate the focus of infection (usually an anastomotic leakage or an abscess) are even more important than the early initiation of correct antibiotherapy (Sawyer et al. 2015) (Sartelli et al. 2017). The different factors involved in the outcome of patients with SSIs after colorectal surgery highlight the complexity of the disease.

Finally, the prevention of SSI has become a priority for most hospitals since it is considered a measure of the quality of hospital care and is used as an indicator by pay-for-performance programs. The "SENIC" study (Study Efficacy Nosocomial Infection Control) published in 1985 (Haley et al. 1985) assessed the active epidemiological surveillance of relevant nosocomial infections in US hospitals and demonstrated its efficacy in reducing the number of these infections. Since then, surveillance programs centered on compliance with the basic standards of clinical and surgical assistance and antimicrobial prophylaxis have been implemented in many hospitals from many countries. The Surgical Care Improvement Project (SCIP) was created with this purpose in the US by the CDC in collaboration with the Centers for Medicare & Medicaid Services (Mandell et al. 2014) (Rosenberger, Politano, & Sawyer 2011), and the "Vigilància de les Infeccions Nosocomials a Catalunya" (VINCat) Program in Catalonia,

Spain.

The VINCat Program ("VINCat. Generalitat de Catalunya" n.d.) is a HAI surveillance program created in 2006 that is responsible for reporting and preventing HAIs in Catalonia. Measures intended to report and prevent SSIs are an important part of the program, and colorectal surgery surveillance is considered a priority due to its high rates of SSI and its consequences for patients and the healthcare system. For this reason, and partly in view of the results presented in this report, in 2016 the implementation of a bundle of preoperative preventive measures in colorectal surgery was proposed. These measures consist in the application of adequate intravenous antibiotic prophylaxis (adequate type and timing), administration of preoperative MBP combined with OAP, laparoscopic surgery, maintenance of normothermia and the use of a double-ring abdominal wall plastic protector, and have been shown to reduce SSI. Similar experiences with the implementation of bundles have demonstrated great efficacy in other scenarios of HAIs and also for SSI (Tanner et al. 2015) (Waits et al. 2014), (Pronovost 2008) (Resar et al. 2005). Initial assessment of the efficacy of this bundle by the VINCat Program has shown a significant reduction in SSI rates in colorectal surgery.

For all these reasons, a comprehensive approach to some of the scarcely explored aspects of SSIs in patients undergoing elective colorectal surgery may be useful in the daily practice of physicians. In the following sections, we outline the rationale for our hypotheses and place the findings of our research within the context of current medical knowledge.

2. SPECIFIC ISSUES IN THE ASSESSMENT OF RISK FACTORS, MANAGEMENT AND OUTCOMES OF SURGICAL SITE INFECTIONS AFTER ELECTIVE COLORECTAL SURGERY

GENERAL DESCRIPTION AND RATIONALE OF OBJECTIVES

2.1. Specific characteristics and surgical approach in colon and rectal surgery

It has been suggested that the rates and risk factors for developing an SSI after colon and rectal surgery may be different (Konishi, Watanabe, Kishimoto, & Nagawa 2006) (Morikane, Honda, Yamagishi, Suzuki, & Aminaka 2014) due to the differences found in the surgical approach and the degree of bacterial contamination between both surgeries. Nevertheless, most surveillance studies carried out to date have analysed colon and rectal surgery together (Blumetti et al. 2007) (Tang, Chen, Wang, Changchien, & Chen 2001). Separate assessments of risk factors and rates of SSIs in patients undergoing colon and rectal surgery are scarce (Konishi et al. 2006) (Serra-Aracil et al. 2011).

It has been proposed that incisional SSI and OS-SSI may have distinct pathogenesis and risk factors. Incisional SSI has been associated with increased body mass index or the presence of an ostomy (Blumetti et al. 2007) (Ho et al. 2011). On the other hand, OS-SSI has been more frequently related to blood transfusion, previous abdominal surgery or poor nutritional status (Blumetti et al. 2007) (Tang et al. 2001) (Frasson et al. 2016). Interestingly, the development of an OS-SSI has more severe consequences than the development of an inicisional SSI; in many cases OS-SSI requires reoperation and increases morbidity and length of stay (LOS) (de Lissovoy et al. 2009) (Eagye & Nicolau 2009). Moreover, while many of the most significant advances in colon and rectal surgery such as laparoscopy and other minimally invasive techniques have decreased incisional SSI rates, they have had a lesser impact on OS-SSI (Aimaq et al. 2011) (Kiran et al.

2010).

The aim of this study was to compare the incidence, risk factors and outcomes of OS-SSI in patients undergoing elective surgery of the colon or rectum in a large, representative cohort of Spanish hospitals.

2.2. Timing of the development of surgical site infection in elective colorectal surgery

The concept of early-onset (EO) and late-onset (LO) infection has been widely applied to different types of HAI. This distinction is based on the idea that infection risk factors, pathogenesis, microbiology and outcomes can differ depending on when they develop. Moreover, this classification has led to the adoption of specific prevention measures and different empirical treatments in each infection type (Giard et al. 2008) (Penel et al. 2007) (Khan et al. 2016) (Garnacho-Montero et al. 2008) (Chittick et al. 2013).

However, despite SSI currently being the leading cause of HAI, the risk factors for the developments of EO-SSI vs LO-SSI have not yet been elucidated. Studies focusing on this topic are scarce (Kok et al. 2016), and none of them address the large population undergoing colorectal surgery. In this setting, an EO-SSI may be associated with more severe sepsis, requiring expeditious source control and adequate antibiotic therapy (Guirao et al. 2013). Taking into account that colorectal surgery has the highest SSI rates among elective procedures (Petrosillo et al. 2008) (Kirby et al. 2015), the identification of specific risk factors of severe SSI is of paramount relevance to adopt targeted preventive strategies.

Therefore, the aim of this study was to identify the distinctive predictive factors for EO-SSI and LO-SSI in a large cohort of patients who underwent elective colorectal surgery.

2.3. Management and outcomes of organ-space SSI after elective colorectal surgery

Although risk factors for SSI in colorectal surgery have been well established (Baucom et al. 2015) (Bakker, Grossmann, Henneman, Havenga, & Wiggers 2014) (Biondo 2014), little is known about the frequency and predictors of treatment failure and poor outcomes in SSI. This is especially relevant in OS-SSI, which is the most serious and life-threatening type of surgical infection. Previous studies have found an association between postoperative adverse events, including SSI, and certain patient-related risk factors such as higher American Society of Anesthesiologists' (ASA) physical status classification, increased body mass index, or history of chronic obstructive pulmonary disease (Kohut, Liu, Stein, Sensenig, & Poggio 2015) (Francis et al. 2015). Preoperative chemoradiotherapy and poor compliance with an enhanced recovery program are also associated with higher readmission rates (Francis et al. 2015). Furthermore, the emergence of multidrug-resistance, particularly ESBL and carbapenemase production among GNB is a matter of particular concern (Ho, Tambyah, & Paterson 2010) (Khan, Dancer, & Humphreys 2012) and may negatively impact treatment response in SSI.

At present, data regarding predictors of treatment failure or mortality in patients with SSI after colorectal surgery remain limited.

Therefore, the aim of this large prospective multicentre cohort study of patients undergoing elective colorectal surgery was to assess the management and outcomes of patients with SSI, and to identify predictors of treatment failure in patients with an OS-SSI.

2.4. Analysis of the health cost of organ-space surgical site infection in elective colorectal surgery

Measuring the health cost of OS-SSI accurately can facilitate joint efforts by all stakeholders to implement targeted prevention strategies. Currently, from the hospital perspective, the cost of HAIs is mostly due to extending patient LOS, which determines missed new hospital admissions (Graves et al. 2007) (Graves et al. 2010). When estimating LOS due to HAIs, applying statistical models which consider the time-dependent nature of the infection has been recommended. This approach permits a better control of time-dependent bias and avoids overestimation of excess LOS (Barnett et al. 2011) (Stewardson et al. 2016).

To date, studies which report the effect of SSI on LOS in colorectal surgery have not considered time-dependent bias (Kirkland, Briggs, Trivette, Wilkinson, & Sexton 1999) (Eagye & Nicolau 2009) (Hennessey et al. 2016). The purpose of the present study is therefore to assess the health costs of OS-SSI measured in terms of excess LOS and risk of death during the hospital stay in a prospective cohort of patients undergoing elective colorectal surgery, taking into account timing of infection and competing events.

2.5. An organism of special interest in colorectal surgery: *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is an important cause of HAI worldwide. It has been estimated that it is the fourth microbiological cause of HAI (Zarb et al. 2012), related to patients with serious underlying conditions, entailing poor prognosis and high mortality.

Despite the outstanding position of SSI among HAI (Zarb et al. 2012), risk factors for *P. aeruginosa* in intraabdominal SSI have been scarcely studied. One previous study (Augustin et al. 2013) found that higher Acute Physiology And Chronic Health Evaluation (APACHE) II score and respiratory failure were associated with *P. aeruginosa* postoperative peritonitis after gastrointestinal surgery.

Given the significance of the organism and its potential serious outcome, it is of paramount relevance to establish predictive factors for developing SSI caused by *P. aeruginosa* after colorectal surgery. Therefore, the aim of this study involving a large, multicenter, prospective cohort of patients undergoing elective colorectal surgery was to identify specific predictive factors for the development of SSI caused by *P. aeruginosa*, to establish specific preventive measures and appropriate empirical antibiotic treatment.

3. HYPOTHESES

1. Risk factors and rates of OS-SSI in colon and in rectal surgery will differ due to their different characteristics and surgical approaches.

2. Surgical site infections developed early after elective colorectal surgery and late after surgery will have different predictive factors, characteristics and microbiology.

3. Management of OS-SSI represents a challenge for physicians due to the increase in multidrug-resistance among GNB and the need for source control in most cases.

4. Patients who developed an OS-SSI after elective colorectal surgery will present an increase of LOS and a higher risk of death compared to those with incisional SSI or without SSI.

5. Surgical site infections caused by *P. aeruginosa* after elective colorectal surgery will have specific characteristics and outcomes, and will be more difficult to treat than SSIs caused by other pathogens.

4. OBJECTIVES

4.1. Specific characteristics and surgical approach in colon and rectal surgery

- To evaluate the differences in terms of the prevalence of overall and OS-SSI between colon and rectal surgery.
- To determine the specific risk factors for developing OS-SSI after colon and rectal surgery.
- To investigate the outcomes of patients with OS-SSI in colon and rectal surgery in a large cohort of Spanish hospitals.

4.2. Timing of the development of surgical site infection in elective colorectal surgery

- To compare the specific risk factors for EO-SSI with those for LO-SSI after elective colorectal surgery.
- To determine the most frequent types of EO-SSI and of LO-SSI and their outcome.
- To investigate whether the causative organisms of SSI and their resistant patterns differ in infections developing early and in those developing late after colorectal surgery.

4.3. Management and outcomes of surgical site infection after elective colorectal surgery

- To determine the prevalence of overall, incisional and OS-SSI in a large cohort of patients undergoing elective colorectal surgery.

- To assess the surgical and antimicrobial management of patients with OS-SSI.
- To determine whether there are differences in the most frequent causative microorganisms of incisional and OS-SSI.
- To evaluate the outcome of patients with incisional and OS-SSI, and to determine the predictive factors of treatment failure in patients with OS-SSI.

4.4. Analysis of the health cost of organ-space surgical site infection in elective colorectal surgery

- To measure and compare patients' excess LOS as a result of developing OS-SSI with that of patients who develop incisional SSI or do not develop SSI, taking into account the time-dependent bias of the SSI variable.
- To assess and compare the effect on in-hospital mortality of developing OS-SSI compared with that of developing incisional SSI or not developing SSI.

4.5. An organism of special interest in colorectal surgery: *Pseudomonas aeruginosa*

- To determine predictive factors for the development of SSI caused by *P. aeruginosa* in a large cohort of patients undergoing elective colorectal surgery.
- To compare the specific characteristics and outcomes of patients

with SSI caused by *P. aeruginosa* and of those with SSI caused by other microorganisms.

5. SETTING AND METHODOLOGY

5.1 Setting and patients

This study was conducted in 10 Catalan hospitals of different characteristics, participating in the VINCat program ("VINCat. Generalitat de Catalunya" n.d.). Three of the hospitals were tertiary care university hospitals with more than 500 beds, five had between 200 to 500, and two had less than 200 beds.

The study included all consecutive adult patients (≥ 18 years old) hospitalized in any surgical department of the hospitals involved and who underwent elective colorectal surgery: in the case of studies 1, 2, 3 and 5 from 1st January 2011 to 31st December 2014 and in study 4 from 1st January 2012 to 31st December 2014.

These 10 hospitals were the following:

Hospitals with more than 500 beds:

- Hospital Universitari de Bellvitge
- Consorci Sanitari Parc Taulí
- Hospital Universitari Mútua de Terrassa

Hospitals with 500-200 beds:

- Hospital General de Granollers
- Hospital Universitari Sant Joan de Reus
- Consorci Sanitari de Terrassa
- Consorci Sanitari de l'Anoia
- Fundació Althaïa

Hospitals with fewer than 200 beds:

- Parc Sanitari Sant Joan de Déu
- Hospital de Viladecans

5.2. Surveillance program

In 1999 an infections surveillance program called **VINICS,** based on the NHSN model ("National Healthcare Safety Network | Centers for Disease Control and Prevention," n.d.), was launched at the hospitals of the Institut Català de la Salut (ICS). The program progressively implemented the concept of teamwork, promoted the incorporation of nurses with exclusive dedication to infection control and achieved significant reductions in certain indicators.

The design of the VINICS program was meant to facilitate coordinated teamwork by using the same protocols, definitions and data collection systems, but at the same time guaranteeing independence in the internal organization of each center. The enrollment at each center of at least one infection control nurse within the work team was considered essential.

In the VINICS model, the Infection Commission at each center is in charge of controlling infections in its hospital. The Commission functionally depends both on an Infection Control team, which must perform the agreed epidemiological surveillance tasks and apply the appropriate control measures, and an Antibiotics Committee, which is responsible for the preparation, implementation and monitoring of the center's antibiotic policy. In order to coordinate the hospital teams, analyse the data and inform the corporate centers a Representative Group of the Permanent Committees was set up.

Following on from the positive experience of the VINICS program, a similar program was introduced throughout the Catalan hospital network. In fact, the vast majority of the Xarxa d'Hospitals

d'Utilització Pública (XHUP) hospitals have both Infection Commissions and Nosocomial Infection Control programs, as recommended in the region's Health Plan. Although many of these hospitals do not belong to the ICS, in recent years they have incorporated the VINICS Program's objectives and the surveillance indicators. For this reason, the introduction of a common homogeneous program was considered a necessary step in the Catalan health system. This larger surveillance program, which included most Catalan hospitals, was called **VINCat,** and it was created in 2006.

In the **VINCat Program** trained infection control staff follow patients up to 30 days after surgery and prospectively collect data on preoperative demographics, comorbidities, surgical procedure and microbiology of all HAI surveyed (Pujol et al. 2012). Post-discharge surveillance of SSI is mandatory and consists of reviewing electronic clinical records in primary and secondary care, checking readmissions and emergency visits, and reviewing microbiological and radiological data (Limón et al. 2014). For the purposes of this project, treatment and 30-day postoperative outcomes for eligible surgical procedures were also recorded. Patients with an existing surgical site infection at the time of surgery were excluded.

The program provides regular feedback on results and benchmarking to hospitals, and promotes preventive actions and scientific research.

5.3. Design of the studies

All the studies included were **prospective observational cohort studies.** The analysis of each study is specified below:

5.3.1. Specific characteristics and approach in colon and rectal surgery

In this study, patients with OS-SSI in colon and rectal surgery were compared in a univariate analysis with those who did not develop OS-SSI. After that, two multivariate analyses with statistically significant variables from the univariate stage were performed to search for independent predictive factors for OS-SSI in each type of surgery (colon and rectum). Clinical and epidemiological data of patients in each type of surgery were also provided.

5.3.2. Timing of the development of surgical site infection in elective colorectal surgery

Patients in the cohort were classified into three groups depending on the development of an SSI: (i) patients with an EO-SSI; (ii) patients with a LO-SSI; (iii) patients who did not develop an SSI within 30 days after surgery (no-SSI). The cut-off point distinguishing EO-SSI and LO-SSI was 7 days after surgery, which was the median time for SSI development.

Afterwards, following the methodology described by *Harris* et al. (Harris et al. 2002), two separate analyses were performed in order to identify the distinctive predictive factors for: (1) EO-SSI in comparison with no-SSI occurrence, and (2) LO-SSI in comparison with no-SSI occurrence. Variables with statistical significance in the first analysis but not in the second were considered distinctive factors for EO-SSI; those with statistical significance in the second analysis but not in the first were considered distinctive predictors of LO-SSI. Significant

factors present in both analyses were considered common predictive factors of SSI.

5.3.3. Management and outcomes of surgical site infection after elective colorectal surgery

This study started with a comparison of the clinical, epidemiological and microbiological data of incisional SSI patients and OS-SSI patients. Secondly, only patients with OS-SSI were selected for a description of the antimicrobial and surgical management. Finally, a multivariate logistic regression model was performed to identify independent predictive factors for treatment failure in patients with OS-SSI.

5.3.4. Analysis of the health cost of organ-space surgical site infection in elective colorectal surgery

We analysed the adjusted excess LOS taking into account the time-dependent nature of the variable SSI. We compared this outcome in patients developing OS-SSI with that of patients developing incisional SSI or not developing SSI. A multivariate analysis of risk factors associated with the longest LOS in patients with OS-SSI was also performed. Finally, an analysis of the risk of in-hospital mortality was conducted, comparing patients with OS-SSI with patients with incisional SSI or with no SSI occurrence.

5.3.5. An organism of special interest in colorectal surgery: *Pseudomonas aeruginosa*

All patients in the cohort with SSI caused by *P. aeruginosa* were analysed and compared to patients with SSI caused by other etiologies. To identify independent predictive factors for *P. aeruginosa* SSI, a multivariate model was created based on the differences drawn from the analysis referred to above. Information on concomitant microbiology in both groups and on antimicrobial management of *P. aeruginosa* SSI was also provided.

5.4. Clinical data and definitions

Surgical site infections were classified according to the CDCs ("CDC Surgical Site Infection (SSI) Event Definition" n.d.) criteria as superficial incisional, deep incisional, or OS-SSI. Surgical procedure categories were stratified (from -1 to 3) depending on the risk of surgical infection as defined by the NHSN.

Standardized data collection included age, sex, ASA score, MBP, OAP, surgical risk index category according to the National Nosocomial Infections Surveillance (NNIS) system criteria (Horan, Emori, & Atlanta 1997), adequate intravenous antibiotic prophylaxis, date and duration of surgery, laparoscopic surgery, wound classification, date of SSI, site of infection (superficial, deep incisional, or organ-space) and microbiology. Age, ASA score, NNIS risk index and site of infection were dichotomized for the analysis.

Intravenous antibiotic prophylaxis was considered appropriate when all of the following conditions met: (i) the antibiotic was administered according to the local protocol at each of the hospitals; (ii) the infusion was completed within the previous 60 minutes prior to the surgical incision; and (iii) perioperative antibiotic was supplied again if indicated.

OAP was considered as the administration of oral antibiotics the day before surgery. Patients also received MBP and the intravenous antibiotic prophylaxis mentioned above. The use of OAP was not mandatory and was decided according to the local protocol at each hospital. The combination comprised an aminoglycoside (neomycin, gentamicin or kanamycin) with anaerobic coverage (metronidazole or erythromycin).

EO-SSI was defined as the SSI occurring within the first week after surgery, and **LO-SSI** as that occurring between the 8^{th} day and 30^{th} day after surgery.

The **initial antibiotic treatment** was classified as **empirical or targeted** depending on the availability of microbiological sensitivity tests. The type and duration of the antibiotic therapy was decided by the attending surgeon according to the local protocol.

Source control was defined as any procedure that removed the focus of infection or corrected anatomical derangements. It was classified as reoperation when a new surgical procedure was performed,

regardless of whether drainages were inserted or not, and as drainage when percutaneous or transrectal drainage was performed.

Treatment failure was defined as persistence of any sign or symptom of SSI (e.g.: wound inflammation, suppuration from wounds or drainage sites and/or fever) or all-cause death, both assessed within 30 days of the initial surgery.

P. aeruginosa **SSI** was considered to be present when this microorganism was isolated from surgical samples or in blood cultures with no other source of infection.

The **NNIS modified risk** index predicts the risk of SSI in colorectal surgery, ranging from -1 to 2 depending on the presence of one or more of the following factors: ASA score III-V (1 point), contaminated or dirty-infected surgery (1 point), length of surgery ≥ 75^{th} percentile of the procedure (1 point) and laparoscopic surgery (-1 point) (Gaynes et al. 2001). It was calculated for all the patients in our cohort.

Readmission for any cause within 30 days of initial surgery was documented.

LOS included readmission if appropriate.

Overall mortality was defined as death due to any cause occurring within 30 days of initial surgery. **Mortality attributable to SSI** was

defined as death directly related to SSI occurring within 30 days of initial surgery.

5.5. Microbiological studies

Microbiological samples from wounds and/or peritoneal fluid or abscesses of most patients with suspected SSI were taken for culture. Blood cultures were also taken when indicated by the attending physician.

Polymicrobial infection was defined as isolation of ≥ 2 microorganisms in the samples. If there were ≥ 3 microorganisms, the laboratory reported the sample as polymicrobial without identifying the species of microorganisms isolated.

Antibiotic susceptibility was tested using the microdilution method following Clinical Laboratory Standard Institute (CLSI) guidelines.

The antimicrobial susceptibility of isolates was interpreted according to current CLSI criteria ("M100-S25 Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. Clinical and Laboratory Standards Institute consensus process," 2015).

Screening of multidrug-resistant phenotypes including ESBL and carbapenemase production was conducted according to CLSI recommendations ("M07-A10 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Tenth Edition. Clinical and Laboratory Standards Institute consensus process" 2015). *Enterobacteriaceae* were identified using standard microbiological techniques at each participating center. ESBL

production was screened in all isolates with diminished susceptibility to cephalosporins and confirmed according to standard procedures. CLSI recommendations were used for susceptibility interpretation. Selected isolates from each center were characterized by PCR and DNA sequencing using established methods.

The following GNB were considered to be multidrug-resistant: (i) ESBL-producing *Enterobacteriaceae*, (ii) carbapenemase-producing *Enterobacteriaceae*, and (iii) multidrug-resistant strains of *Pseudomonas aeruginosa*. Multidrug-resistant GNBs were defined as those resistant to at least three of the following classes of antibiotics: carbapenems, ureidopenicillins, cephalosporins (ceftazidime and cefepime), monobactams, aminoglycosides and fluoroquinolones.

5.6. Statistical analysis

Categorical variables were described as totals and frequencies; continuous variables were described as medians and interquartile ranges (IQR) or as means and standard deviation (SD). To detect significant differences between groups, we used the Chi-square test or Fisher's exact test for categorical variables, and the Student t-test or Mann-Whitney test for continuous variables, as appropriate. Statistical significance was established at α=0.05. All reported p-values are two-tailed. Data were analysed using IBM SPSS 20.0 (Chicago, Ill.) for studies 1, 2, 3 and 5 and SAS v9.4, SAS Institute Inc. (Cary, NC, USA) and R v3.4.4 (etm package) for study 4.

5.6.1. Specific characteristics and surgical approach in colon and rectal surgery

Two binary logistic regression analyses of factors potentially associated with OS-SSI in colon and rectal surgery were performed including all variables that were significant in the univariate analysis. Results of multivariate analysis were given as Odds Ratios (OR) and 95% confidence intervals (95%CI). The final model's goodness-of-fit was assessed by the Hosmer-Lemeshow test.

5.6.2. Timing of development of surgical site infection in elective colorectal surgery

After creating subgroups in the cohort as described by *Harris* et al. (Harris et al., 2002), two binary logistic regression multivariate analyses with statistically significant variables of univariate analyses were performed to seek for independent predictive factors for EO-SSI and LO-SSI.

5.6.3. Management and outcomes of surgical site infection after elective colorectal surgery

Potential predictors of treatment failure in the subgroup of patients who developed OS-SSI were identified by binary logistic regression analysis. The statistically significant variables in the univariate analysis were entered into a multivariate logistic regression model. Also, an extra variable which referred to the initial antibiotic treatment was

introduced since it was considered clinically relevant. For this purpose, the variable was transformed into the binary factor "Combined antibiotic treatment: Yes/Not" and introduced in the multivariate analysis. Calibration of the model was assessed by the Hosmer–Lemeshow test.

5.6.4. Analysis of the health cost of organ-space surgical site infection in elective colorectal surgery.

Incidence densities in the cohort were calculated by dividing the number of events by the number of patient-days at risk per 1000. To estimate excess LOS, Beyersmann et al.'s multistate model (Beyersmann, Wolkewitz, Allignol, Grambauer, & Schumacher 2011) was used. Patients entered the initial state after the elective colorectal surgery and exited by entering one of the two competing states: death or discharge alive, with or without acquiring a SSI, which was the time-dependent exposure of interest. This approach allowed us to estimate the mean excess LOS of patients with SSI (either OS-SSI or incisional-SSI) with respect to uninfected patients. The multistate model established provided a weighted average of the LOS based on the patients' course. Patients who were still in hospital 30 days after surgery were artificially right-censored to avoid the influence of outliers on LOS.

Proportional hazards models were established for the time to mortality during admission and the time to discharge alive, with a set of risk factors including the SSI indicators. The results are shown as Hazard Ratio (HR) and the corresponding confidence intervals for the

univariate and multivariate models. HRs were obtained from the cause-specific hazard models for mortality or for discharge alive. In each model, "hospital" was introduced as strata variable to take into account potential differences in death or discharge alive between hospitals.

To characterize patients with the longest excess LOS, a binary indicator of excess LOS > percentile 75^{th} (p75th) was computed. Thus, Y=1 was assigned for values with the highest excess LOS (> p75th), and Y=0 was assigned otherwise. We established a generalized linear model for the response variable Y with demographic and clinical characteristics as covariates. The sample size used for this model was 2629, since patients with incisional SSI were excluded. The results are shown as OR and the corresponding confidence intervals for the univariate and multivariate models.

5.6.5. An organism of special interest in surgical site infections: *Pseudomonas aeruginosa*

Factors associated with *P. aeruginosa* SSI were evaluated by univariate and binary logistic regression multivariate analysis. The multivariate analysis included all significant variables (p value <0.05) in the univariate analysis except for the ASA score and the laparoscopic surgery, which were not included as they are part of the NNIS modified risk index and therefore had collinearity with the NNIS itself.

5.7. Ethical considerations

This study was approved by the Ethics Committee at the Hospital Universitari de Bellvitge (reference: PR305/15).

All the data were treated confidentially and anonymously. The ethical principles for medical research that were defined in the Helsinki Declaration of 1964, reviewed and updated by the World Medical Association (Fortaleza, Brazil, 2013), were followed at all times in human beings. Moreover, all data were processed in compliance with the Spanish Data Protection Act of 1999.

6. RESULTS

6.1. Specific characteristics and surgical approach in colon and rectal surgery

- Clinical and epidemiological characteristics of patients undergoing colon and rectal surgery
- Differences in rates of SSI between colon and rectal surgery
- Predictive factors for developing OS-SSI after colon and rectal surgery
- Outcome of patients who develop OS-SSI in colon and rectal surgery

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Risk factors and outcomes of organ-space surgical site infections after elective colon and rectal surgery

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Abstract

Background: Organ-space surgical site infections (SSI) are the most serious and costly infections after colorectal surgery. Most previous studies of risk factors for SSI have analysed colon and rectal procedures together. The aim of the study was to determine whether colon and rectal procedures have different risk factors and outcomes for organ-space SSI.

Methods: A multicentre observational prospective cohort study of adults undergoing elective colon and rectal procedures at 10 Spanish hospitals from 2011 to 2014. Patients were followed up until 30 days post-surgery. Surgical site infection was defined according to the Centers for Disease Control and Prevention criteria. Oral antibiotic prophylaxis (OAP) was considered as the administration of oral antibiotics the day before surgery combined with systemic intravenous antibiotic prophylaxis.

Results: Of 3,701 patients, 2,518 (68%) underwent colon surgery and 1,183 (32%) rectal surgery. In colon surgery, the overall SSI rate was 16.4% and the organ-space SSI rate was 7.9%, while in rectal surgery the rates were 21.6% and 11.5% respectively ($p < 0.001$). Independent risk factors for organ-space SSI in colon surgery were male sex (Odds ratio -OR-: 1.57, 95% CI: 1.14–2.15) and ostomy creation (OR: 2.65, 95% CI: 1.8–3.92) while laparoscopy (OR: 0.5, 95% CI: 0.38–0.69) and OAP combined with intravenous antibiotic prophylaxis (OR: 0.7, 95% CI: 0.51–0.97) were protective factors. In rectal surgery, independent risk factors for organ-space SSI were male sex (OR: 2.11, 95% CI: 1.34–3.31) and longer surgery (OR: 1.49, 95% CI: 1.03–2.15), whereas OAP with intravenous antibiotic prophylaxis (OR: 0.49, 95% CI: 0.32–0.73) was a protective factor. Among patients with organ-space SSI, we found a significant difference in the overall 30-day mortality, being higher in colon surgery than in rectal surgery (11.5% *vs* 5.1%, $p = 0.04$).

Conclusions: Organ-space SSI in colon and rectal surgery has some differences in terms of incidence, risk factors and outcomes. These differences could be considered for surveillance purposes and for the implementation of preventive strategies. Administration of OAP would be an important measure to reduce the OS-SSI rate in both colon and rectal surgeries.

Keywords: Surgical site infections, Organ-space surgical site infections, Colorectal surgery, Surveillance

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Background

Due to the clean-contaminated nature of the wound, rates of surgical site infections (SSI) after colorectal surgery are the highest among elective procedures, exceeding 20% in some institutions [1–3]. It has been suggested that the rates and risk factors for developing an SSI after colon and rectal surgery may be different [4, 5], due to the differences found in the surgical approach and the degree of bacterial contamination between both surgeries. Nevertheless, most studies carried out to date have analysed colon and rectal surgeries together [6, 7]. Separate assessments of patients undergoing colon and rectal surgery are scarce [4, 8].

It has been proposed that incisional SSI (I-SSI) and organ-space SSI (OS-SSI) may have distinct pathogenesis and risk factors. Incisional SSI has been associated with increased body mass index or the presence of an ostomy [6, 9]. On the other hand, OS-SSI has been more frequently related to blood transfusion, previous abdominal surgery or poor nutritional status [6, 7, 10]. Interestingly, the development of an OS-SSI has more severe consequences than the development of an I-SSI; in many cases OS-SSI requires reoperation and increases morbidity and length of stay (LOS) [11, 12]. Moreover, while many of the most significant advances in colon and rectal surgery such as laparoscopy and other minimally invasive techniques have decreased I-SSI rates, they have had a lesser impact on OS-SSI [13, 14].

Remarkably, the administration of mechanical bowel preparation (MBP) was discontinued in the last decades in most Spanish hospitals due to the lack of effectiveness [15]. In this scenario, and for reasons not well established, the administration of oral antibiotic prophylaxis (OAP) was discontinued too. Currently, only some hospitals use it in the elective surgery of the colon and rectum in Spain. This situation contrasts with that of other European and American countries, where the OAP is part of the daily practice.

The aim of this study was to compare the incidence, risk factors and outcomes of OS-SSI in patients undergoing elective surgery of the colon or rectum in a large, representative cohort of Spanish hospitals.

Methods

Patients, design and setting

We performed a multicentre observational study of a prospective cohort of adult patients (≥18 years old) undergoing elective colon and rectal surgery from January 2011 to December 2014 at 10 hospitals participating in the VINCat program. All consecutive patients hospitalized in any surgical department at the different hospitals were included and followed up until 30 days after surgery. Patients with a pre-existing SSI at the time of surgery were excluded. Post-discharge surveillance of SSI was mandatory and consisted of a review of electronic clinical records (primary and secondary care), checking readmissions and emergency visits, and reviewing microbiological and radiological data. For the purposes of the present study, patients were differentiated according to whether colon or rectal surgery was performed.

VINCat surveillance program

The VINCat program [16] is a healthcare-associated infection surveillance program in Spain, based on the National Healthcare Safety Network (NHSN) model [17]. It recruits hospitals on a voluntary basis and currently receives surveillance data from trained infection control staff at 66 hospitals, who submit information on preoperative demographics, comorbidities, operative characteristics, microbiology and treatment data, and 30-day postoperative outcomes for eligible surgical procedures [18].

Definitions

SSIs were defined according to the Centers for Disease Control and Prevention (CDC) criteria [19] and divided into superficial incisional, deep incisional and OS. Surgical procedure categories were stratified according to the risk of surgical infection (–1 to 3) as defined by the NHSN.

Independent variables

Predictor variables considered for the development of an OS-SSI were: age, sex, American Society of Anesthesiologists (ASA) physical status classification, MBP, OAP, adequacy of intravenous antibiotic prophylaxis, surgical risk index category according to the National Nosocomial Infections Surveillance (NNIS) modified system criteria [20], date and prolonged operation time (≥75th percentile of the procedure), laparoscopy, wound classification, date of SSI, site of SSI (I-SSI or OS-SSI), microbiology and underlying disease (neoplasia, inflammatory bowel disease –IBD- or others). Age (<65 and ≥ 65 years), ASA (I-II and III-IV) score and NNIS modified risk index (–1-0 and 1–2) were dichotomized for the analysis.

Adequacy of intravenous antibiotic prophylaxis was established when all the following three factors were met: antibiotics administered according to local protocol at each hospital, completion of the infusion within 60 min before the surgical incision, and perioperative antibiotic redosing if indicated.

The OAP was always considered as the administration of oral antibiotic prophylaxis the day before surgery in combination with systemic intravenous antibiotic prophylaxis perioperatively. The administration was not mandatory and was done according to local protocols at each hospital. It was applied in 4 of the 10 participating hospitals.

Dependent variables

The development of overall SSI and OS-SSI in both colon and rectal populations, readmission, LOS and mortality within 30 days of initial surgery were recorded. Readmission for any cause within 30 days of initial surgery was documented. LOS included readmission if there was. Overall mortality was defined as death due to any cause within 30 days of initial surgery.

Statistical analysis

Categorical variables were described as totals and frequencies; continuous variables were described as medians and interquartile ranges (IQR) and mean and standard deviation (SD) in some cases. Univariate analysis comparing the two populations was carried out using the chi-square test or Fisher exact test for categorical variables and the *t*-test or Mann-Whitney test for continuous variables. Comparisons between patients who developed an OS-SSI and those who did not (no OS-SSI) were performed separately for colon and rectal populations. Finally, multivariate analysis with all statistically significant variables ($p \leq 0.05$) associated with OS-SSI in colon and rectal populations were performed separately to determine independent predictive factors for the development of OS-SSI. In these cases, results were given as odds ratios (OR) and 95% confidence intervals (95% CI). The final model's goodness-of-fit was assessed by the Hosmer-Lemeshow test. Data were analysed with IBM SPSS 20.0 (Chicago, Ill.).

Results

Characteristics of patients and incidence of SSI in colon and rectal surgery

During the study period, a total of 3,701 patients undergoing elective colorectal surgery were prospectively followed-up, 68% after colon surgery and 32% after rectal surgery.

Characteristics of patients undergoing colon or rectal surgery are shown in Table 1. Patients who underwent colon surgery were older (median age 70.6 years, interquartile range [IQR] 62–79 *vs* 68 years [IQR 60–76], $p < 0.001$) and had higher proportions of ASA score III-IV (42.2% *vs* 36.7%, $p = 0.002$) than patients undergoing rectal surgery. In contrast, patients undergoing rectal procedures were more likely to be male (67.2% *vs* 59.3%, $p = 0.001$), to have neoplasia (97% *vs* 93.5%, $p < 0.001$), to have a longer duration of surgery (42.7% *vs* 37.6%, $p = 0.003$), and to have an ostomy (64% *vs* 8.3%, $p < 0.001$). The administration of correct intravenous antibiotic prophylaxis was 84% in colon surgery and 81.6% in rectal surgery, $p = 0.4$. In colon surgery, the overall SSI rate was 16.4% and the OS-SSI rate 7.9%, while in rectal surgery, the overall SSI was 21.6% and the OS-SSI 11.5% ($p < 0.001$), as shown in Fig. 1. When patients who received OAP combined with correct intravenous antibiotic prophylaxis ($n = 1.345$) were analysed, significant differences in

Table 1 Characteristics of patients in colon and rectal surgery

Variable	Colon ($n = 2518$)	Rectum ($n = 1183$)	*p*-value
Age, median (IQR) years	70.6 (62–79)	68 (60–76)	<0.001
Age ≥65, *n* (%)	1711 (67.95%)	724 (61.20%)	0.001
Males, *n* (%)	1494 (59.33%)	795 (67.20%)	0.001
ASA III-IV, *n* (%)	1062 (42.18%)	434 (36.69%)	0.002
Neoplasia, *n* (%)	2355 (93.5%)	1147 (97%)	<0.001
Inflammatory bowel disease, *n* (%)	75 (3%)	16 (1.4%)	0.003
Other, *n* (%)	86 (3.4%)	17 (1.4%)	0.001
Duration of surgery ≥75th-percentile[a], *n* (%)	947 (37.61%)	505 (42.69%)	0.003
NNIS Risk index 1–2, *n* (%)	909 (36.10%)	398 (33.64%)	0.15
Laparoscopy, *n* (%)	1515 (60.17%)	782 (66.10%)	0.001
Correct IV antibiotic prophylaxis, *n* (%)	2117 (84.07%)	966 (81.66%)	0.41
Previous radiotherapy, *n* (%)	33 (1.31%)	545 (46.07%)	<0.001
Previous chemotherapy, *n* (%)	78 (3.10%)	533 (45.05%)	<0.001
Oral antibiotic prophylaxis, *n* (%)	1078 (42.81%)	489 (41.34%)	0.41
Mechanical bowel preparation, *n* (%)	1749 (69.46%)	1038 (87.74%)	<0.001
- Missing	58 (2.30%)	20 (1.69%)	
Ostomy, *n* (%)	208 (8.26%)	754 (63.74%)	<0.001

IQR interquartile range, *ASA* American Society of Anesthesiologists physical status classification, *NNIS* National Nosocomial Infections Surveillance, *IV* intravenous
[a]Greater than 75th percentile for the duration of surgery (180 min, 3 h)

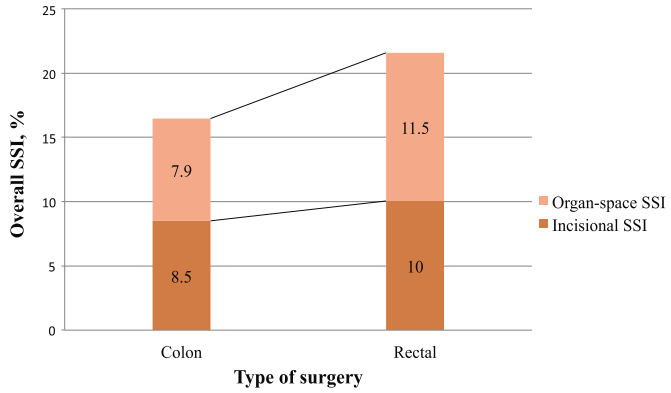

Fig. 1 Incidence of surgical site infection in colon and rectal surgery. Shows the incidence of overall surgical site infection, incisional surgical site infection and organ-space surgical site infection in colon and rectal surgery separately. SSI: surgical site infection

overall SSI rate between colon and rectal surgery (12.3% *vs* 19.9%, $p < 0.001$) were found, while there were no differences in the OS-SSI rate (6.2% vs 8.4%, $p = 0.1$).

Risk factors for OS-SSI in colon and rectal surgery

Univariate analyses of risk factors for OS-SSI in colon and rectal surgery are shown separately in Table 2. In colon surgery, male sex, NNIS ≥1 and ostomy creation were significantly associated with OS-SSI, while laparoscopic surgery and OAP had lower associations with OS-SSI. In rectal surgery, male sex, longer duration of surgery and NNIS ≥1 were associated with OS-SSI, whereas OAP had a lower association with OS-SSI.

A logistic regression multivariate analysis using significant predictive factors found in the univariate analysis is shown in Table 3. Independent risk factors for OS-SSI after colon surgery were male sex (OR 1.57, 95% CI 1.14–2.15) and ostomy creation (OR 2.65, 95% CI 1.8–3.9), while laparoscopy (OR 0.5, 95% CI 0.38–0.69) and the administration of OAP (OR 0.7, 95% CI 0.51–0.97) were independent protective factors. Independent risk factors for OS-SSI in rectal surgery were male sex (OR 2.11, 95% CI 1.34–3.31) and longer duration of surgery

Table 2 Univariate analysis of risk factors for organ-space surgical site infection in colon and rectal surgery

	Colon			Rectum		
Risk factor	No OS-SSI ($n = 2318$)	OS-SSI ($n = 200$)	*p*- value	No OS-SSI ($n = 1043$)	OS-SSI ($n = 136$)	*p*- value
Age, median (IQR) years	70 (61–79)	73 (63–79)	0.3	68 (60–76)	66.5 (58–74)	0.07
Age ≥ 65 years, (%)	67.6	72	0.2	61.5	58.8	0.5
Male sex, (%)	58.4	70	0.001	65.4	80.9	<0.001
ASA ≥ III, (%)	41.9	45.5	0.3	36.1	41.2	0.25
Correct IV antibiotic prophylaxis, (%)	84.3	81.5	0.3	81.4	83.8	0.5
Duration of operation ≥ p75th[a], (%)	37.5	39	0.7	41.2	54.4	0.003
Laparoscopy, (%)	61.6	44	<0.001	66.3	64.7	0.7
NNIS ≥ 1, (%)	35.5	43	0.03	32.7	41.2	0.05
Neoplasia, (%)	93.6	93	0.7	97.2	94.9	0.13
Inflammatory bowel disease, (%)	2.9	4	0.38	1.1	2.9	0.1
Chemotherapy, (%)	3.1	3.5	0.7	45.1	45.2	1
Radiotherapy, (%)	1.2	2.5	0.18	46	47.4	0.7
Oral antibiotic prophylaxis, (%)	43.7	33	0.004	43.3	26.5	<0.001
Mechanical bowel preparation, (%)	71.4	67.2	0.2	89.1	90.4	0.6
Ostomy, (%)	7.3	20	<0.001	63.8	65.2	0.7

No OS-SSI no organ-space surgical site infections (include patients with incisional SSI and patients without SSI), *OS-SSI* organ-space SSI, *IQR* interquartile range, *ASA* American Society of Anesthesiologists physical status classification, *IV* intravenous, *NNIS* National Nosocomial Infections Surveillance Risk Index.
[a]Greater than 75th percentile for the duration of surgery (180 min, 3 h)

Table 3 Multivariate analysis of risk factors for organ-space surgical site infection in colon and rectal surgery

	Colon				Rectum		
Risk factor	OR	95% CI	*p*-value	Risk factor	OR	95% CI	*p*-value
Male sex	**1.57**	**1.14–2.15**	**0.004**	Male sex	**2.11**	**1.34–3.31**	**0.001**
Laparoscopy	**0.5**	**0.38–0.69**	**<0.001**	Duration of operation ≥ p75th[a]	**1.49**	**1.03–2.15**	**0.07**
NNIS ≥ 1	1.17	0.83–1.64	0.36	NNIS ≥ 1	1.1	0.74–1.66	0.6
Oral antibiotic prophylaxis	**0.7**	**0.51–0.97**	**0.03**	Oral antibiotic prophylaxis	**0.49**	**0.32–0.73**	**0.001**
Ostomy	**2.65**	**1.8–3.92**	**<0.001**				

Signifficant OR and 95% CI appear in bold text
OR Odds ratio, *95%CI* 95% confidence interval, *NNIS* National Nosocomial Infections Surveillance Risk Index.
[a]Greater than 75th percentile for the duration of surgery (180 min, 3 h)

(OR 1.49, 95% CI 1–2.15), whereas the administration of OAP (OR 0.49, 95% CI 0.32–0.73) was the only independent protective factor.

Outcomes of patients with OS-SSI in colon and rectal surgery

Table 4 shows the outcomes of patients who developed an OS-SSI in colon and rectal surgery. There were no significant differences between colon and rectal procedures regarding median LOS (25 days [IQR 18–31] *vs* 23 days [IQR 16–33], $p = 0.1$), mean LOS (30.2 days ± SD 25 *vs* 32 days ± SD 28, $p = 0.19$) and readmission rate (19.5% *vs* 24.3%, $p = 0.3$). Overall 30-day mortality was significantly higher after colon surgery than after rectal surgery (11.5% [23/200] *vs* 5.1% [7/136], $p = 0.04$).

Discussion

This large multicentre cohort study found significant differences in the incidence, predictive factors and outcomes of OS-SSI after elective colon and rectal surgery. This suggests that the two procedures should be considered as different surgical interventions.

The separation of procedures according to patients' characteristics may allow more accurate assessment of their specific risk factors. Comparing colon and rectal populations, we found that they had different characteristics in terms of risk factors for SSI. Patients undergoing colon surgery were older, had more IBD and less laparoscopy, factors related to SSI. On the other hand, patients undergoing rectal surgery were younger but had more rate of malignancy; more frequently received chemoradiotherapy and had longer surgery duration. The surgical techniques were also different, something inherent to the anatomical location of the disease, in special with more ostomies performed in rectal resections. These factors, associated with the fact that the rectum has higher bacterial contamination load, conferred it greater risk of SSI. Accordingly, overall SSI and OS-SSI rates were higher in rectal surgery than in colon surgery. Although these rates were high, they were similar to these reported in previous studies [8, 21]. Data from surveillance systems in Europe an US vary widely [22, 23], being in most cases lower than ours, though post-discharge surveillance is not always performed.

We found significant differences in the predictive factors for developing an OS-SSI in colon and rectal surgeries. In colon surgery, independent risk factors predisposing to OS-SSI were male sex and ostomy creation, while laparoscopic surgery and OAP were protective factors. In rectal surgery, independent risk factors for OS-SSI were male sex and longer duration of surgery, whereas OAP was the only protective factor. Male sex was a common risk factor for developing OS-SSI in both colon and rectal surgeries; this association is well established [5, 7, 24], although the reasons are not known.

Ostomy creation was a strong risk factor for the development of OS-SSI in colon surgery but not in rectal surgery, as previously reported elsewhere [8]. Ostomies are normally used to divert the faecal stream from a newly created immature anastomosis, or to definitively disconnect the gastrointestinal tract in some extensive colorectal

Table 4 Outcomes of patients with organ-space surgical site infection in colon and rectal surgery

Variable	Colon ($n = 200$)	Rectum ($n = 136$)	Overall ($n = 336$)	*p*-value
Readmission, *n* (%)	39 (19.5)	33 (24.3)	72 (21.4)	0.3
Readmission due to SSI, *n* (%)	34 (17)	30 (22.1)	64 (19)	0.2
Length of stay, median (IQR) days	25 (18–31)	23 (16–33)	24 (17–36)	0.1
Length of stay, mean (SD) days	30.2 (25)	32 (28)	27.6 (19.7)	0.1
Mortality, *n* (%)	23 (11.5)	7 (5.1)	30 (8.9)	0.04
Mortality attributed to SSI, *n* (%)	21 (10.5)	6 (4.4)	27 (8)	0.04

SSI surgical site infection, *IQR* interquartile range, *SD* standard deviation

surgeries. Nevertheless, ostomies have been associated with increased rates of SSI in previous studies [4–6, 9] because they allow organisms from the air, contaminated hands, or skin flora to reach the subcutaneous fat and the wound, and eventually the intraabdominal cavity [25]. In our study, patients with colon surgery who received an ostomy more frequently underwent laparotomy due to complex pathology like IBD or diverticulitis. These diseases have been associated with OS-SSI [26], and ostomy creation may act, in part, as a marker of this complex pathology.

The laparoscopic approach significantly reduced SSI rates in several large-database studies and also offered other benefits such as faster recovery of pulmonary function, less pain and shorter postoperative stay [13, 14]. In our study it served as an independent protective factor for the development of OS-SSI in colon surgery, but not in rectal surgery. Probably, the beneficial effect of laparoscopy was exceeded by the higher frequency of risk factors for SSI inherent in rectal surgery.

Importantly, we found that OAP was a protective factor for the development of OS-SSI in both colon and rectal surgeries, although the impact was higher in rectal surgery, probably because the rectum has a higher level of bacterial contamination. During the study period there was not a national or regional recommendation for the application of OAP, and for this reason the use of the measure was decided by each participating hospital (it was only applied in 4 of the 10 hospitals). The findings of the present study lead to a change in the clinical practice of hospitals participating in the VINCat program and in 2016 the use of OAP was institutionally recommended. The OAP combined with intravenous prophylaxis and MBP significantly reduces SSI rates after colon and rectal surgery by decreasing the intraluminal bacterial load [27–30]; in a previous meta-analysis of randomized controlled trials comparing the effectiveness of OAP plus intravenous antibiotic prophylaxis *vs* intravenous antibiotic prophylaxis alone, the association of OAP was estimated to reduce the incidence of SSI by 43% [31]. Nevertheless, the use of MBP has been widely questioned, due to its unpleasant gastrointestinal effects, and in many studies it has failed to reduce SSI rates [15]. Currently, since almost all studies that demonstrate the effectiveness of OAP have been performed in combination with MBP, the use of MBP will have to be raised again. Last World Health Organization (WHO) recommendations on preoperative measures for surgical site infection prevention suggest using OAP with MBP in all adults undergoing elective colorectal surgery [32, 33].

Longer duration of surgery was an independent risk factor for the development of an OS-SSI in rectal surgery. This association has often been described in the colorectal surgery population [21, 34, 35], and it also favours other risk factors for SSI like the hyperglycaemia or hypothermia [33]. Given the capacity of this parameter to predict SSI, it was included as one of the components of the NNIS risk index. Rectal tumours close to the anal verge usually require extensive surgery with additional organ resection, requiring longer operative time and causing greater bleeding, factors that have been associated with an increased risk of SSI [24, 36]. Moreover, in these prolonged surgeries, antibiotic redosing is not always administered correctly.

Significantly, mortality of patients with OS-SSI after colon surgery was higher than after rectal surgery. The fact that patients in the colon group were older and more frequently had complicated diseases other than neoplasia could explain this result.

Among the strengths of the study is its multicentre nature, the large number of patients included and the fact that all data were collected by trained infection control staff. However, the study has a number of limitations that should be acknowledged. Firstly, the retrospective analysis of prospectively collected data may lead to bias and is unable to control for confounding factors. Secondly, certain risk factors that have been linked to SSI such as perioperative hyperglycaemia, hypothermia and blood transfusion were not recorded here.

Conclusions

We found differences in the incidence, risk factors and outcomes of overall SSI and OS-SSI between colon and rectal surgery, suggesting that they could be considered as different surgical procedures. These differences should be borne in mind for the purpose of surveillance and for the implementation of preventive strategies. Administration of OAP would be an important measure to reduce the OS-SSI rate in both colon and rectal surgeries.

Abbreviations

95% CI: 95% confidence interval; ASA: American Society of Anesthesiologists; CDC: Centers for disease control and prevention; IBD: Inflammatory bowel disease; IBM SPSS: International business machines Corp. Statistical package for the social sciences; IQR: Interquartile range; I-SSI: Incisional SSI; LOS: Length of stay; MBP: Mechanical bowel preparation; NHSN: National Healthcare Safety Network; NNIS: National Nosocomial Infection Surveillance; OAP: Oral antibiotic prophylaxis; OR: Odds ratio; OS-SSI: Organ-space surgical site infection; SD: Standard deviation; SSI: Surgical site infection; WHO: World Health Organization

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions
AG and MP conceived and designed the study, AG analyzed and interpreted the patient data regarding surgical site infections after colon and rectal surgery. AG, JC and MP were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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The authors declare that they have no competing interests.

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Not applicable.

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This study was approved by the Ethics Committee at Hospital Universitari de Bellvitge (reference: PR305/15).

Publisher's Note

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References

1. Kirby A, Burnside G, Bretsztajn L, Burke D. Postoperative infections following colorectal surgery in an english teaching hospital. Infect Dis (Lond). 2015;47:825–9.
2. Limón E, Shaw E, Badia JM, Piriz M, Escofet R, Gudiol F, et al. Post-discharge surgical site infections after uncomplicated elective colorectal surgery: impact and risk factors. The experience of the VINCat Program. J Hosp Infect. 2014;86:127–32.
3. Petrosillo N, Drapeau CMJ, Nicastri E, Martini L, Ippolito G, Moro ML, et al. Surgical site infections in Italian Hospitals: a prospective multicenter study. BMC Infect Dis. 2008;8:34.
4. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Elective colon and rectal surgery differ in risk factors for wound infection: results of prospective surveillance. Ann Surg. 2006;244:758–63.
5. Morikane K, Honda H, Yamagishi T, Suzuki S, Aminaka M. Factors associated with surgical site infection in colorectal surgery: the Japan nosocomial infections surveillance. Infect Control Hosp Epidemiol. 2014;35:660–6.
6. Blumetti J, Luu M, Sarosi G, Hartless K, Mcfarlin J, Parker B, et al. Surgical site infections after colorectal surgery: do risk factors vary depending on the type of infection considered? Surgery. 2007;142:704–11.
7. Tang R, Chen HH, Wang YL, Changchien CR, Chen J-S. Risk factors for surgical site infection after elective resection of the colon and rectum : a single-center prospective study of 2, 809 consecutive patients. Ann Surg. 2001;234:181–9.
8. Serra-Aracil X, Espin-Basany E, Biondo S, Guirao X, Orrego C, Sitges-Serra A, et al. Surgical site infection in elective operations for colorectal cancer after the application of preventive measures. Arch Surg. 2011;146:606.
9. Ho VP, Stein SL, Trencheva K, Barie PS, Milsom JW, Lee SW, et al. Differing risk factors for incisional and organ/space surgical site infections following abdominal colorectal surgery. Dis Colon Rectum. 2011;54:818–25.
10. Frasson M, Granero-Castro P, Ramos Rodriguez JL, Flor-Lorente B, Braithwaite M, Martí Martínez E, et al. Risk factors for anastomotic leak and postoperative morbidity and mortality after elective right colectomy for cancer: results from a prospective, multicentric study of 1102 patients. Int J Colorectal Dis. 2016;31:105–14.
11. de Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence and impact on hospital utilization and treatment costs. Am J Infect Control. 2009;37:387–97.
12. Eagye KJ, Nicolau DP. Deep and organ/space infections in patients undergoing elective colorectal surgery: incidence and impact on hospital length of stay and costs. Am J Surg. 2009;198:359–67.
13. Aimaq R, Akopian G, Kaufman HS. Surgical site infection rates in laparoscopic versus open colorectal surgery. Am Surg. 2011;77:1290–4.
14. Kiran RP, El-Gazzaz H, Vogel JD, Remzi FH. Laparoscopic approach significantly reduces surgical site infections after colorectal surgery: data from national surgical quality improvement program. J Am Coll Surg. 2010;211:232–8.
15. Dahabreh IJ, Steele DW, Shah N, Trikalinos TA. Oral mechanical bowel preparation for colorectal surgery: systematic review and meta-analysis. Dis Colon Rectum. 2015;58:698–707.
16. VINCat Program. Generalitat de Catalunya. http://vincat.gencat.cat/ca/. Accessed 8 May 2016.
17. National Healthcare Safety Network | Centers for Disease Control and Prevention. http://www.cdc.gov/nhsn/. Accessed 8 May 2016.
18. Pujol M, Limón E, López-Contreras J, Sallés M, Bella F, Gudiol F. Surveillance of surgical site infections in elective colorectal surgery. Results of the VINCat program (2007–2010). Enferm Infecc Microbiol Clin. 2012;30 Suppl 3:20–5.
19. CDC Surgical Site Infection (SSI) Event definition. http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf. Accessed 8 May 2016.
20. Horan TC, Emori G, Atlanta M. Definitions of key terms used in the NNIS system. Am J Infect Control. 1997;25:112–6.
21. Hennessey DB, Burke JP, Ni-Dhonochu T, Shields C, Winter DC, Mealy K. Risk factors for surgical site infection following colorectal resection: a multi-institutional study. Int J Colorectal Dis. 2016;31:267–71.
22. Surveillance of surgical site infections in NHS hospitals in England 2015/16. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/577418/Surgical_site_infections_NHS_hospitals_2015_to_2016.pdf.. Accessed Mar 2017.
23. Young H, Knepper B, Moore EE, Johnson JL, Mehler P, Price CS. Surgical site infection after colon surgery: national healthcare safety network risk factors and modeled rates compared with published risk factors and rates. J Am Coll Surg. 2012;214:852–9.
24. Bakker IS, Grossmann I, Henneman D, Havenga K, Wiggers T. Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. Br J Surg. 2014;101:424–32. discussion 432.
25. Fraccalvieri D, Biondo S, Saez J, Millan M, Kreisler E, Golda T, et al. Management of colorectal anastomotic leakage: differences between salvage and anastomotic takedown. Am J Surg. 2012;204:671–6.
26. Eskicioglu C, Nelson J, Roberts PL, Marcello PW, Read TE, Hall JF, et al. Is patient diagnosis a risk factor for organ space infection after colorectal resections? Dis Colon Rectum. 2014;57:733–9.
27. Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. Oral antibiotic bowel preparation significantly reduces surgical site infection rates and readmission rates in elective colorectal surgery. Ann Surg. 2015;261:1034–40.
28. Englesbe MJ, Brooks L, Kubus J, Luchtefeld M, Lynch J, Senagore A, et al. A statewide assessment of surgical site infection following colectomy: the role of oral antibiotics. Ann Surg. 2010;252(3):514–9. discussion 519–20.
29. Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined mechanical and oral antibiotic bowel preparation reduces incisional surgical site infection and anastomotic leak rates after elective colorectal resection: an analysis of colectomy-targeted ACS NSQIP. Ann Surg. 2015;262:331–7.
30. Machuca I, Gutiérrez-Gutiérrez B, Pérez Cortés S, Gracia-Ahufinger I, Serrano J, Madrigal MD, et al. Oral decontamination with aminoglycosides is associated with lower risk of mortality and infections in high-risk patients colonized with colistin-resistant, KPC-producing Klebsiella pneumoniae. J Antimicrob Chemother. 2016;71:3242–9.
31. Bellows CF, Mills KT, Kelly TN, Gagliardi G. Combination of oral non-absorbable and intravenous antibiotics versus intravenous antibiotics alone

in the prevention of surgical site infections after colorectal surgery: a meta-analysis of randomized controlled trials. Tech Coloproctol. 2011;15:385–95.
32. De Jonge S, Atema JJ, Gans S, Boermeester MA, Gomes SM, Solomkin JS, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16: e276–87.
33. Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16:e288–303.
34. Gervaz P, Bandiera-Clerc C, Buchs NC, Eisenring M-C, Troillet N, Perneger T, et al. Scoring system to predict the risk of surgical-site infection after colorectal resection. Br J Surg. 2012;99:589–95.
35. Watanabe M, Suzuki H, Nomura S, Hanawa H, Chihara N, Mizutani S, et al. Performance assessment of the risk index category for surgical site infection after colorectal surgery. Surg Infect (Larchmt). 2015;16:84–9.
36. Kwaan MR, Melton GB, Madoff RD, Chipman JG. Abdominoperineal resection, pelvic exenteration, and additional organ resection increase the risk of surgical site infection after elective colorectal surgery: An American College of Surgeons National Surgical Quality Improvement Program Analysis. Surg Infect (Larchmt). 2015;16:675–83.

6.2. Timing of the development of surgical site infection in elective colorectal surgery

- Comparison of clinical and epidemiological characteristics in EO-SSI and LO-SSI patients
- Microbiology and resistance patterns of EO-SSI and LO-SSI
- Independent predictive factors for EO-SSI and LO-SSI
- Differences in outcomes between EO-SSI and LO-SSI

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Predictive factors for early- and late-onset surgical site infections in patients undergoing elective colorectal surgery. A multicentre, prospective, cohort study

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SUMMARY

Background: Surgical site infections (SSIs) are the leading cause of healthcare-associated infections in acute care hospitals in Europe. However, the risk factors for the development of early-onset (EO) and late-onset (LO) SSI have not been elucidated.

Aim: This study investigated the predictive factors for EO-SSI and LO-SSI in a large cohort of patients undergoing colorectal surgery.

Methods: We prospectively followed-up adult patients undergoing elective colorectal surgery in 10 hospitals (2011–2014). Patients were divided into three groups: EO-SSI, LO-SSI, or no infection (no-SSI). The cut-off defining EO-SSI and LO-SSI was seven days (median time to SSI development). Different predictive factors for EO-SSI and LO-SSI were analysed, comparing each group with the no-SSI patients.

Findings: Of 3701 patients, 320 (8.6%) and 349 (9.4%) developed EO-SSI and LO-SSI, respectively. The rest had no-SSI. Patients with EO-SSI were mostly males, had colon

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surgery and developed organ-space SSI whereas LO-SSI patients frequently received chemotherapy or radiotherapy and had incisional SSI. Male sex (odds ratio (OR): 1.92; $P < 0.001$), American Society of Anesthesiologists' physical status >2 (OR: 1.51; $P = 0.01$), administration of mechanical bowel preparation (OR: 0.7; $P = 0.03$) and stoma creation (OR: 1.95; $P < 0.001$) predicted EO-SSI whereas rectal surgery (OR: 1.43; $P = 0.03$), prolonged surgery (OR: 1.4; $P = 0.03$) and previous chemotherapy (OR: 1.8; $P = 0.03$) predicted LO-SSI.

Conclusion: We found distinctive predictive factors for the development of SSI before and after seven days following elective colorectal surgery. These factors could help establish specific preventive measures in each group.

Introduction

Surgical site infections (SSIs) are the most frequent healthcare-associated infections (HCAIs) in acute care hospitals in Europe [1,2]. The development of an SSI significantly increases length of stay (LOS), readmissions, and hospital costs worldwide [3].

The concept of early-onset (EO) and late-onset (LO) infections has been widely applied to different types of HCAIs. This distinction is based on differing infection risk factors, pathogenesis, microbiology, and outcomes depending on when they develop. Moreover, this classification has led to the adoption of specific prevention measures and different empirical treatments in each infection type [4–7].

However, despite SSI currently being the leading cause of HCAIs, the risk factors for EO-SSI versus LO-SSI development have not yet been elucidated. Studies focusing on this topic are scarce, and none of them addresses the large population undergoing colorectal surgery [8]. In this setting, an EO-SSI may be associated with more severe sepsis, requiring expeditious source control and adequate antibiotic therapy [9]. Taking into account that colorectal surgery has the highest SSI rates among elective procedures, the identification of specific risk factors for severe SSI is of paramount importance for the adoption of targeted preventive strategies [10,11]. Therefore, the aim of this study was to identify the distinctive predictive factors for EO-SSI and LO-SSI in a large cohort of patients who underwent elective colorectal surgery.

Methods

Study location and patients

We performed a multicentre, prospective, cohort study from January 2011 to December 2014 in 10 Spanish hospitals. Three of the hospitals were tertiary care university hospitals with >500 beds, five had 200–500 beds, and two had <200 beds. All of them participated in the VINCat programme [12]. All consecutive patients hospitalized for elective colorectal surgery with bowel resection were enrolled and followed up by trained infection control staff members until 30 days after surgery. Active post-discharge surveillance was mandatory and consisted of electronic clinical records review in primary and secondary care, checking readmissions and emergency visits, and reviewing microbiological and radiological data [13]. Patients with a pre-existing infection at the surgical site at the time of surgery were excluded.

Surveillance programme

The VINCat programme [12] is a nosocomial infection surveillance programme in Catalonia, Spain, based on the National Healthcare Safety Network (NHSN) model [14]. It prospectively collects preoperative demographics, comorbidities, operative characteristics, microbiological and treatment data, and 30-day postoperative outcomes for eligible cases [15].

Study design

All the patients in the cohort were classified into three groups according to SSI development: (i) EO-SSI patients; (ii) LO-SSI patients; (iii) patients with no SSI within 30 days after surgery (no-SSI). The cut-off distinguishing EO-SSI and LO-SSI was seven days (the median time for SSI development) after surgery.

First, univariate analysis comparing clinical, epidemiological and microbiological characteristics of EO-SSI and LO-SSI was performed. Second, following the methodology described by Harris *et al.*, two separate analyses were performed to establish the distinctive predictive factors for: (i) EO-SSI, and (ii) LO-SSI, each in comparison with no-SSI occurrence [16]. Variables with statistical significance in the first analysis but not in the second, and those significant in the second analysis but not in the first, were considered distinctive factors for EO-SSI and LO-SSI, respectively. Significant factors present in both analyses were considered common predictive factors for SSI. This analysis would avoid the bias of considering these common predictive factors for SSI as specific for a determined time-point (EO-SSI or LO-SSI).

Definitions

Surgical site infection was defined according to the Centers for Disease Control and Prevention (CDC) [17] as superficial incisional, deep incisional or organ-space (OS), and was stratified into categories according to surgical infection risk as defined by the NHSN [14]. EO-SSI was defined as occurrence within the first week after surgery, and LO-SSI as occurrence between the 8th and 30th days after surgery.

Standardized data collection included age, sex, American Society of Anesthesiologists' (ASA) physical status,

administration of mechanical bowel preparation (MBP) and oral antibiotic prophylaxis (OAP) in combination with adequate intravenous antibiotic prophylaxis (IAP), surgical risk index category according to the National Nosocomial Infections Surveillance (NNIS) system criteria, operation date, prolonged operation time ($\geq 75^{th}$ percentile for the procedure), laparoscopic surgery, wound classification, date of SSI, infection site (superficial incisional, deep incisional or OS), microbiology and underlying disease (neoplasia, inflammatory bowel disease (IBD) or others) [18].

Adequate IAP occurred when the following three conditions were met: antibiotics administered according to the evidence-based local protocol at each hospital, completion of the infusion within 60 min before the surgical incision, and perioperative antibiotic redosing if indicated.

The use of OAP the day before surgery was not mandatory but based on the local protocol at each hospital. It was administered jointly with MBP and the IAP mentioned above, as internationally recommended [19].

Readmission and mortality rates, whether directly attributable to SSI or not, and length of hospitalization were also recorded.

Microbiological studies

In patients with suspected SSI, microbiological samples (blood, wounds and/or peritoneal fluid or abscesses) were usually taken for culture.

Polymicrobial infection was defined as the isolation of ≥ 2 micro-organisms in the samples. If there were ≥ 3 micro-organisms, the laboratory reported the sample as polymicrobial without identifying the species of micro-organism isolated.

Antibiotic susceptibility was tested and interpreted using the microdilution method based on the Clinical and Laboratory Standards Institute (CLSI) guidelines [20]. Screening of multidrug-resistant (MDR) phenotypes including extended-spectrum β-lactamase (ESBL) and carbapenemase production was conducted according to the CLSI recommendations [21]. Selected isolates from each centre were characterized by polymerase chain reaction and DNA sequencing using established methods.

Multidrug-resistant Gram-negative bacilli (GNB) were defined as those resistant to at least three classes of antibiotics: carbapenems, ureidopenicillins, cephalosporins (ceftazidime and cefepime), monobactams, aminoglycosides, and fluoroquinolones. The following GNB were considered as MDR: (i) ESBL-producing Enterobacteriaceae, (ii) carbapenemase-producing Enterobacteriaceae, and (iii) MDR strains of *Pseudomonas aeruginosa*.

Statistical analysis

All statistics were calculated using SPSS version 20.0 (Chicago, IL, USA). Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U*-test as appropriate. Categorical variables were analysed using the χ^2-test or Fisher's exact test, as appropriate. The multivariate logistic regression model was performed using significant variables from the univariate analysis with $P \leq 0.05$. Adjusted odds ratio (OR) was calculated with 95% confidence interval (CI).

Ethical considerations

This study was approved by the Ethics Committee at Hospital Universitari de Bellvitge (reference: PR305/15).

Results

Overall, 3701 patients were included. Of these, 320 (8.6%) developed EO-SSI, 349 (9.4%) developed LO-SSI, and 3032 (81.9%) had no-SSI. Among the 669 (18.1%) patients with SSI, 333 (49.7%) had incisional (superficial and deep) SSI whereas 336 (50.2%) had OS-SSI.

Epidemiological and clinical characteristics

The comparison between the three groups (EO-SSI, LO-SSI, and no-SSI) is shown in Table I. Patients in the EO-SSI group were mostly males, underwent colon surgery, developed OS-SSI, and had longer hospitalization. Patients in the LO-SSI group more frequently received MBP, chemotherapy and radiotherapy, had incisional SSI and higher readmission rate.

Predictive factors

The distinctive predictive factors for EO-SSI and LO-SSI on univariate and multivariate regression analysis are shown in Tables II and III. Each cohort was compared with the no-SSI patient group. Compared with no-SSI, EO-SSI patients were mostly males, with an ASA score III–IV, had fewer laparoscopic procedures, less frequently received OAP and MBP and more frequently received a stoma. Patients with LO-SSI more frequently underwent rectal surgery, had prolonged operation time, had fewer laparoscopic procedures, less frequently received OAP and more frequently had received previous chemotherapy.

Aetiology of SSI

Of the 669 patients who developed SSI, 496 (74.1%) had positive surgical samples; 240 (48.4%) of these were polymicrobial. Blood cultures were performed in 238 (35.5%) of 669 patients, and they were positive in 34 out of 238 (14.3%). Concordance between blood cultures and abdominal samples was observed in 14 out of 34 (41.2%) cases. The most frequent isolates in surgical samples were *Escherichia coli* (229/496; 46.1%), *Enterococcus* spp. (23.3%) and *P. aeruginosa* (12.5%) (Table IV). There were no significant differences regarding aetiology between EO-SSI and LO-SSI, except *E. coli*, which was more frequently observed in EO-SSI than in LO-SSI (44.1% vs 25.2%; $P < 0.001$) and *Staphylococcus aureus*, which was more frequently observed in LO-SSI than in EO-SSI (6.3% vs 2.2%; $P = 0.009$). There were also no significant differences between groups in terms of MDR GNB, although there was a tendency for a higher proportion of MDR *P. aeruginosa* in LO-SSI than in EO-SSI.

Discussion

Our study revealed the different predictive factors for EO-SSI and LO-SSI after elective colorectal surgery. Male sex, ASA score III–IV, not receiving MBP, and stoma creation predicted EO-SSI, whereas rectal surgery, longer duration of surgery, and

Table I
Epidemiological and clinical characteristics of early-onset (EO-SSI), late-onset (LO-SSI), and no (No-SSI) surgical site infection patients

Variable	EO-SSI ($N = 320$)	LO-SSI ($N = 349$)	No-SSI ($N = 3032$)	P-value[a]
Age (years), mean (SD)	68.8 (12.4)	68.5 (11.6)	68.5 (12.1)	0.7
≥65 years	219 (68.4%)	236 (67.6%)	1980 (65.3%)	0.8
Male sex	243 (75.9%)	232 (66.5%)	1814 (59.8%)	0.007
ASA III–IV	159 (49.7%)	159 (45.6%)	1178 (38.9%)	0.3
NNIS 1–2	146 (45.6%)	168 (48.1%)	993 (32.8%)	0.5
Indication for surgery				
Neoplasia	300 (93.8%)	334 (95.7%)	2868 (94.6%)	0.2
IBD	11 (3.4%)	7 (2%)	73 (2.4%)	0.25
Other	8 (2.5%)	8 (2.3%)	87 (2.9%)	0.8
Type of surgery				0.007
Colon surgery	215 (67.2%)	199 (57%)	2104 (69.4%)	
Rectal surgery	105 (32.8%)	150 (43%)	928 (30.6%)	
Adequate antibiotic prophylaxis	264 (82.5%)	293 (84%)	2526 (83.3%)	0.6
Duration of surgery ≥75th percentile[b]	128 (40%)	161 (46.1%)	1163 (38.4%)	0.1
Laparoscopic surgery	156 (48.8%)	166 (47.6%)	1975 (65.1%)	0.7
Oral antibiotic prophylaxis	93 (29.1%)	122 (35%)	1352 (44.6%)	0.1
Mechanical bowel preparation	221 (70.2%)	283 (81.8%)	2283 (77.1%)	<0.001
Stoma	122 (38.2%)	125 (35.8%)	715 (23.6%)	0.5
Previous chemotherapy	52 (16.3%)	88 (25.2%)	471 (15.5%)	0.005
Previous radiotherapy	46 (14.4%)	80 (22.9%)	452 (14.9%)	0.005
Diagnosis of SSI during hospitalization	296 (92.5%)	185 (53%)	–	<0.001
Type of SSI				0.001
Incisional SSI	138 (43.1%)	195 (55.9%)	–	
Organ-space SSI	182 (56.9%)	154 (44.1%)	–	
Readmission	36 (11.2%)	96 (26.1%)	88 (2.9%)	<0.001
Readmission due to SSI	32 (10%)	85 (24.4%)	–	<0.001
Total length of stay, mean (SD) days	25.3 (27.6)	22.9 (17.4)	9 (7)	<0.001
Mortality	22 (6.9%)	13 (3.7%)	13 (0.4%)	0.07
Mortality attributed due to SSI	19 (5.9%)	12 (3.4%)	–	0.1

SD, standard deviation; ASA, American Society of Anesthesiologists' physical status; NNIS, National Nosocomial Infections Surveillance Risk Index; IBD, inflammatory bowel disease; SSI, surgical site infection.
[a] P-value refers to the comparison between EO-SSI and LO-SSI groups.
[b] Duration of surgery: 180 min.

previous chemotherapy predicted LO-SSI. This analysis identifies the specific predictive factors at each time-point (EO-SSI and LO-SSI), avoiding the bias of considering the most usual predictors of SSI.

Several distinctive predictive factors for EO-SSI were found. First, MBP was a protective factor in itself. The efficacy of MBP is questionable since a large body of evidence suggests that MBP has no beneficial effect in reducing SSI rates unless it is accompanied by an OAP [22,23]. The effect of MBP was probably influenced by the concomitant use of an OAP; however, MBP could also have had a beneficial effect in reducing patient morbidity since most EO-SSIs were OS.

Stoma creation appeared as the strongest risk factor for EO-SSI development. A previous study showed that stoma creation was a risk factor for superficial and deep incisional SSI, but that analysis did not include OS-SSI [24]. In our cohort, cases involving stoma creation were more complex and technically challenging, since surgery frequently involved the rectum and was performed due to pathologies such as IBD or diverticulosis rather than for neoplasia, therefore conferring a higher risk of SSI. These SSIs were equally distributed between incisional and OS-SSI. Another study examined the effect of stoma creation in rectal cancer patients after chemotherapy and radiotherapy, and showed results similar to ours: patients in the stoma group had greater comorbidities (higher ASA score, body mass index, or hypertension) than the other group [25]. This suggests that the need for stoma could be a marker of illness severity. Another study showed an increased anastomotic leakage rate in patients with a diverting stoma, although the stoma diminished the severity of the leakage [26]. Therefore the stoma is probably a marker of surgery with high risk of SSI.

Rectal surgery was an LO-SSI distinctive predictive factor. The rectal surgical technique usually requires incision through the perineum, which is a highly contaminated area. Manipulation of wounds in this area could increase the risk of incisional SSI (most frequent SSI type in this group), and such extensive surgery usually requires a long operation time: this was also an independent LO-SSI risk factor. We described higher rates of SSI associated with rectal surgery previously [27,28].

Chemotherapy was the strongest risk factor for developing LO-SSI. Chemotherapy with capecitabine or 5-fluorouracil is almost always administered in stage II–III rectal cancer to downstage tumour size and improve survival after surgery. Despite the beneficial effects of neoadjuvant therapy, it causes some degree of inflammation, necrosis, and fibrosis of surrounding tissue. This leads to an increased risk of

Table II
Univariate analysis of predictive factors associated with EO-SSI and LO-SSI (compared with 30 day no-SSI patients)

Variable	EO-SSI ($N = 320$)	No-SSI ($N = 3032$)	*P*-value	LO-SSI ($N = 349$)	No-SSI ($N = 3032$)	*P*-value
Age (years), mean (SD)	68.8 (12.4)	68.5 (12.1)	0.6	68.5 (11.5)	68.5 (12.2)	0.9
≥65 years	219 (68.4%)	1980 (65.3%)	0.26	113 (32.4%)	1052 (34.7%)	0.4
Male sex	243 (75.9%)	1814 (59.8%)	<0.001	232 (66.5%)	1814 (59.8%)	0.016
ASA III–IV	159 (49.7%)	1178 (38.9%)	<0.001	159 (45.6%)	1178 (38.9%)	0.015
NNIS 1–2	146 (45.6%)	993 (32.8%)	<0.001	168 (48.1%)	993 (32.8%)	<0.001
Indication for surgery						
Neoplasia	300 (93.8%)	2868 (94.6%)	0.5	334 (95.7%)	2868 (94.6%)	0.4
IBD	11 (3.4%)	73 (2.4%)	0.2	7 (2%)	73 (2.4%)	0.64
Other	8 (2.5%)	87 (2.9%)	0.7	8 (2.3%)	87 (2.9%)	0.53
Type of surgery			0.4			<0.001
Colon surgery	215 (67.2%)	2104 (69.4%)		199 (57%)	2104 (69.4%)	
Rectal surgery	105 (32.8%)	928 (30.6%)		150 (43%)	928 (30.6%)	
Adequate antibiotic prophylaxis	264 (82.5%)	2526 (83.3%)	0.7	293 (84%)	2526 (83.3%)	0.76
Duration of surgery ≥75th percentile[a]	128 (40%)	1163 (38.4%)	0.56	161 (46.1%)	1163 (38.4%)	0.005
Laparoscopic surgery	156 (48.8%)	1975 (65.1%)	<0.001	166 (47.6%)	1975 (65.1%)	<0.001
Oral antibiotic prophylaxis	93 (29.1%)	1352 (44.6%)	<0.001	122 (35%)	1352 (44.6%)	0.001
Mechanical bowel preparation	221 (70.2%)	2283 (77.1%)	0.006	283 (81.8%)	2283 (77.1%)	0.047
Stoma	122 (38.2%)	715 (23.6%)	<0.001	125 (35.8%)	715 (23.6%)	<0.001
Previous chemotherapy	52 (16.3%)	471 (15.5%)	0.7	88 (25.2%)	471 (15.5%)	<0.001
Previous radiotherapy	46 (14.4%)	452 (14.9%)	0.8	80 (22.9%)	452 (14.9%)	<0.001

EO-SSI, early-onset surgical site infection; No-SSI, no surgical site infection; LO-SSI, late-onset surgical site infection; SD, standard deviation; ASA, American Society of Anesthesiologists' physical status; NNIS, National Nosocomial Infections Surveillance Risk Index; IBD, inflammatory bowel disease.
[a] Duration of surgery: 180 min.

intraoperative bleeding, wound dehiscence, and wound infection [29].

We revealed laparoscopy and OAP as protective factors in both early and late SSI, as has been previously reported [30,31].

Escherichia coli was significantly more frequent in EO-SSI than in LO-SSI since the risk of anastomotic leakage and OS-SSI is the highest within the first few days after surgery. Conversely, *S. aureus* was significantly more frequent in LO-SSI than in EO-SSI. Since *S. aureus* colonizes human skin, wound manipulation or drains placed during hospitalization may increase the risk of wound infection [32]. Incisional SSI was the most frequent LO-SSI in our cohort. Although not significant, because of the small number of isolates, we found a tendency for a higher proportion of MDR *P. aeruginosa* in LO-SSI than in EO-SSI, probably related to antibiotic pressure.

In the outcome analyses, EO-SSI development increased LOS and mortality compared with LO-SSI or no-SSI. This was probably related to the fact that EO-SSI was predominantly OS, whereas LO-SSI was more frequently incisional. A previous

Table III
Multivariate analysis of predictive factors for EO-SSI and LO-SSI (significant variables of univariate analysis): logistic regression model

Variable	EO-SSI ($N = 320$)			LO-SSI ($N = 349$)		
	P-value	OR	95% CI	*P*-value	OR	95% CI
Male sex	<0.001	1.92	1.46–2.53	0.15	1.2	0.93–1.51
ASA III–IV	0.01	1.51	1.10–2.07	0.1	1.3	0.93–1.9
NNIS 1–2	0.25	1.24	0.85–1.83	0.7	1.1	0.70–1.74
Type of surgery						
Colon surgery						
Rectal surgery				0.03	1.43	1.03–1.97
Duration of surgery ≥75th percentile[a]				0.03	1.4	1.02–1.93
Laparoscopic surgery	<0.001	0.47	0.35–0.63	<0.001	0.44	0.30–0.60
Oral antibiotic prophylaxis	<0.001	0.5	0.44–0.76	<0.001	0.63	0.50–0.80
Mechanical bowel preparation	0.03	0.7	0.54–0.96	0.09	0.76	0.50–1.00
Stoma	<0.001	1.95	1.50–2.53	0.3	1.2	0.86–1.64
Previous chemotherapy				0.03	1.8	1.06–3.10
Previous radiotherapy				0.15	1.5	0.85–2.76

EO-SSI, early-onset surgical site infection; LO-SSI, late-onset surgical site infection; OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists' physical status; NNIS, National Nosocomial Infections Surveillance Risk Index.
[a] Greater than 75th percentile for the duration of surgery (180 min, 3 h).

Table IV
Aetiology of early-onset (EO-SSI) and late-onset (LO-SSI) surgical site infection

No. of patients	Overall ($N = 496$)	EO-SSI ($N = 253$)	LO-SSI ($N = 243$)	*P*-value
Gram-negative bacteria	324 (65.3%)	178 (70.4%)	146 (60.1%)	0.001
Escherichia coli	229 (46.2%)	141 (55.7%)	88 (36.2%)	<0.001
MDR *E. coli*	28 (5.6%)	16 (6.3%)	12 (4.9%)	0.5
Pseudomonas aeruginosa	62 (12.5%)	26 (10.3%)	36 (14.8%)	0.1
MDR *P. aeruginosa*	3 (0.6%)	0	3 (1.2%)	0.07
Klebsiella pneumoniae	30 (6%)	14 (5.5%)	16 (6.6%)	0.6
MDR *K. pneumoniae*	9 (1.8%)	4 (1.6%)	5 (2.1%)	0.6
Gram-positive bacteria	187 (28%)	87 (27.2%)	100 (28.7%)	0.6
Enterococcus faecalis	58 (11.7%)	33 (13%)	25 (10.3%)	0.3
Enterococcus faecium	58 (11.7%)	30 (11.9%)	28 (11.5%)	0.9
Staphylococcus aureus	28 (5.6%)	7 (2.8%)	21 (8.6%)	0.009
Anaerobes	32 (6.5%)	13 (5.1%)	19 (7.8%)	0.2
Bacteroides fragilis	14 (2.8%)	6 (2.4%)	8 (3.3%)	0.5
Yeast	19 (3.8%)	11 (4.3%)	8 (3.3%)	0.5
Candida albicans	15 (3%)	10 (4%)	5 (2.1%)	0.2
Polymicrobial	240 (48.4%)	123 (48.6%)	117 (48.1%)	0.9

EO-SSI, early-onset surgical site infection; LO-SSI, late-onset surgical site infection; MDR, multidrug-resistant.

study by our group has already shown the worst outcome associated with OS-SSI [33].

Among the strengths of this study is its multicentre nature, the large number of patients included, and the fact that data collection was uniformly performed by trained infection control staff members. This study also has some limitations. First, the number of variables was restricted since a multicentre surveillance system must collect limited but consistent variables. Second, the cut-off used to define EO-SSI and LO-SSI was arbitrary; however, it was established after the clinical observation of SSI.

In conclusion, we identified specific predictive factors for the development of EO-SSI and LO-SSI after elective colorectal surgery. The identification of these factors could help to establish targeted preventive measures for each infection type. Although further studies are needed, according to our results it seems appropriate to perform laparoscopic surgery whenever possible and give OAP combined with MBP. Special attention to patients with stoma creation should be paid to detect any sign of severe SSI. The duration of surgery should be shortened as much as possible.

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Conflicts of interest
None declared.

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Referencess

[1] European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012. Available at: www.ecdc.europa.eu [last accessed January 2018].
[2] Estudio de Prevalencia de las Infecciones Nosocomiales en España (EPINE). 2016. Available at: http://hws.vhebron.net/epine/Global/EPINEEPPS%202016%20Informe%20Global%20de%20España%20Resumen.pdf [last accessed January 2018]
[3] Shepard J, Ward W, Milstone A, Carlson T, Frederick J, Hadhazy E, et al. Financial impact of surgical site infections on hospitals. JAMA Surg 2013;148:907.
[4] Giard M, Lepape A, Allaouchiche B, Guerin C, Lehot JJ, Robert MO, et al. Early- and late-onset ventilator-associated pneumonia acquired in the intensive care unit: comparison of risk factors. J Crit Care 2008;23:27–33.
[5] Khan R, Al-Dorzi HM, Tamim HM, Rishu AH, Balkhy H, El-Saed A, et al. The impact of onset time on the isolated pathogens and outcomes in ventilator associated pneumonia. J Infect Public Health 2016;9:161–71.
[6] Garnacho-Montero J, Aldabó-Pallás T, Palomar-Martínez M, Vallés J, Almirante B, Garcés R, et al. Risk factors and prognosis of catheter-related bloodstream infection in critically ill patients: a multicenter study. Intensive Care Med 2008;34:2185–93.
[7] Chittick P, Azhar S, Movva K, Keller P, Boura JA, Band J. Early onset versus late onset peripherally inserted central venous catheter infections: an analysis of risk factors and microbiology. Infect Control Hosp Epidemiol 2013;34:980–3.
[8] Kok TW, Agrawal N, Sathappan SS, Chen WK. Risk factors for early implant-related surgical site infection. J Orthop Surg 2016;24:72–6.
[9] Guirao X, Juvany M, Franch G, Navinés J, Amador S, Badía JM. Value of C-reactive protein in the assessment of organ-space surgical site infections after elective open and laparoscopic colorectal surgery. Surg Infect (Larchmt) 2013;14:209–15.
[10] Petrosillo N, Drapeau CMJ, Nicastri E, Martini L, Ippolito G, Moro ML, et al. Surgical site infections in Italian hospitals: a prospective multicenter study. BMC Infect Dis 2008;8:34.

[11] Kirby A, Burnside G, Bretsztajn L, Burke D. Postoperative infections following colorectal surgery in an English teaching hospital. Infect Dis (London) 2015;47:825–9.
[12] VINCat. Generalitat de Catalunya. Available at: http://vincat.gencat.cat/ca/ [last accessed May 2016].
[13] Limón E, Shaw E, Badia JM, Piriz M, Escofet R, Gudiol F, et al. Postdischarge surgical site infections after uncomplicated elective colorectal surgery: impact and risk factors. The experience of the VINCat Program. J Hosp Infect 2014;86. 127–32.4.
[14] Centers for Disease Control and Prevention, Surgical site infection (SSI) event definition. Available at: http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf [last accessed May 2016].
[15] Tanner J, Khan D, Aplin C, Ball J, Thomas M, Bankart J. Postdischarge surveillance to identify colorectal surgical site infection rates and related costs. J Hosp Infect 2009;72:243–50.
[16] Harris AD, Samore MH, Lipsitch M, Kaye KS, Perencevich E, Carmeli Y. Control-group selection importance in studies of antimicrobial resistance: examples applied to *Pseudomonas aeruginosa*, Enterococci, and *Escherichia coli*. Clin Infect Dis 2002;34:1558–63.
[17] National Healthcare Safety Network (NHSN)/Centers for Disease Control and Prevention (CDC). Available from: http://www.cdc.gov/nhsn/ [last accessed October 2016].
[18] Horan TC, Emori G, Atlanta M. Definitions of key terms used in the NNIS System. Am J Infect Control 1997;25:112–6.
[19] De Jonge S, Atema JJ, Gans S, Boermeester MA, Gomes SM, Solomkin JS, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis 2016;16:e276–87.
[20] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; twenty-fifth informational supplement (M100–S22). Wayne, PA: CLSI; 2012.
[21] Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 10th edn. Wayne, PA: CLSI; 2015 (approved standard M07–A10).
[22] Dahabreh IJ, Steele DW, Shah N, Trikalinos TA. Oral mechanical bowel preparation for colorectal surgery: systematic review and meta-analysis. Dis Colon Rectum 2015;58:698–707.
[23] Murray ACA, Kiran RP. Bowel preparation: are antibiotics necessary for colorectal surgery? Adv Surg 2016;50:49–66.
[24] Ricciardi R, Roberts PL, Hall JF, Read TE, Francone TD, Pinchot SN, et al. What is the effect of stoma construction on surgical site infection after colorectal surgery? J Gastrointest Surg 2014;18:789–95.
[25] Messaris E, Connelly TM, Kulaylat AN, Miller J, Gusani NJ, Ortenzi G, et al. Is a diverting ostomy needed in mid-high rectal cancer patients undergoing a low anterior resection after neoadjuvant chemoradiation? An NSQIP analysis. Surgery 2015;158:686–91.
[26] Shiomi A, Ito M, Maeda K, Kinugasa Y, Ota M, Yamaue H, et al. Effects of a diverting stoma on symptomatic anastomotic leakage after low anterior resection for rectal cancer: a propensity score matching analysis of 1,014 consecutive patients. J Am Coll Surg 2015;220:186–94.
[27] Kwaan MR, Melton GB, Madoff RD, Chipman JG. Abdominoperineal resection, pelvic exenteration, and additional organ resection increase the risk of surgical site infection after elective colorectal surgery: an American College of Surgeons National Surgical Quality Improvement Program Analysis. Surg Infect 2015;16:675–83.
[28] Gomila A, Carratalà J, Camprubí D, Shaw E, Badia JM, Cruz A, et al. Risk factors and outcomes of organ-space surgical site infections after elective colon and rectal surgery. Antimicrob Resist Infect Control 2017;6:40.
[29] Li Y, Wang J, Ma X, Tan L, Yan Y, Xue C, et al. A review of neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Int J Biol Sci 2016;12:1022–31.
[30] Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined mechanical and oral antibiotic bowel preparation reduces incisional surgical site infection and anastomotic leak rates after elective colorectal resection: an analysis of colectomy-targeted ACS NSQIP. Ann Surg 2015;262:331–7.
[31] Kiran RP, El-Gazzaz H, Vogel JD, Remzi FH. Laparoscopic approach significantly reduces surgical site infections after colorectal surgery: data from National Surgical Quality Improvement Program. J Am Coll Surg 2010;211:232–8.
[32] Smith RL, Bohl JK, McElearney ST, Friel CM, Barclay MM, Sawyer RG, et al. Wound infection after elective colorectal resection. Ann Surg 2004;239:599–605. discussion 607.
[33] Gomila A, Badia JM, Carratalà J, Serra-Aracil X, Shaw E, Diaz-Brito V, et al. Current outcomes and predictors of treatment failure in patients with surgical site infection after elective colorectal surgery. A multicentre prospective cohort study. J Infect 2017;74:555–63.

6.3. Management and outcomes of surgical site infection after elective colorectal surgery

- Clinical and epidemiological characteristics of patients with incisional and OS-SSI
- Microbiological differences and presence of multidrug-resistant GNB in patients with incisional and OS-SSI
- Antimicrobial and surgical management of OS-SSI
- Predictive factors for treatment failure in patients with OS-SSI

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Current outcomes and predictors of treatment failure in patients with surgical site infection after elective colorectal surgery. A multicentre prospective cohort study

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KEYWORDS
Surgical site infections;
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Summary *Objective:* To determine current outcomes and predictors of treatment failure among patients with surgical site infection (SSI) after colorectal surgery.
Methods: A multicentre observational prospective cohort study of adults undergoing elective colorectal surgery in 10 Spanish hospitals (2011–2014). Treatment failure was defined as persistence of signs/symptoms of SSI or death at 30 days post-surgery.
Results: Of 3701 patients, 669 (18.1%) developed SSI; 336 (9.1%) were organ-space infections. Among patients with organ-space SSI, 81.2% required source control: 60.4% reoperation and 20.8% percutaneous/transrectal drainage. Overall treatment failure rate was 21.7%: 9% in incisional SSIs and 34.2% in organ-space SSIs ($p < 0.001$). Median length of stay was 15 days (IQR 9–22) for incisional SSIs and 24 days (IQR 17–35) for organ-space SSIs ($p < 0.001$). One hundred and twenty-seven patients (19%) required readmission and 35 patients died (5.2%). Risk factors for treatment failure among patients with organ-space SSI were age ≥65 years (OR 1.83, 95% CI: 1.07–1.83), laparoscopy (OR 1.7, 95% CI: 1.06–2.77), and reoperation (OR 2.8, 95% CI: 1.7–4.6).
Conclusions: Rates of SSI and treatment failure in organ-space SSI after elective colorectal surgery are notably high. Careful attention should be paid to older patients with previous laparoscopy requiring reoperation for organ-space SSI, so that treatment failure can be identified early.

Introduction

Surgical site infection (SSI) was the most common nosocomial infection in Europe in 2012, accounting for 19.6% of hospital-acquired infections among hospitalized patients.[1] It is also the most frequent postoperative complication and a major cause of morbidity and healthcare costs, due to increased length of stay (LOS) and drug consumption.[2–4]

The incidence of colorectal cancer (CRC) has fallen by almost 45% in the last three decades, and mortality by more than 50%, due to screening programs, but CRC remains the third most common cancer in men and the second most common cancer in women worldwide.[5,6] It is particularly worrisome that rates of SSI after elective colorectal surgery continue to be high, exceeding 20% in some institutions.[7,8] The introduction of laparoscopic surgery and the standardization of perioperative care have notably reduced SSI rates in colorectal surgery. Nevertheless, the clean-contaminated nature of this surgery and the increasingly complex nature of the procedures performed mean that infection rates remain high.

Although risk factors for SSI in colorectal surgery have been well established,[9–11] little is known about the frequency and predictors of treatment failure and poor outcomes in SSI. This is especially relevant in organ-space SSI, which is the most serious and life-threatening type of surgical infection. Previous studies have found an association between postoperative adverse events, including SSI, and certain patient-related risk factors such as higher American Society of Anesthesiologists (ASA) physical status classification, increased body mass index, or history of chronic obstructive pulmonary disease.[12,13] Preoperative chemoradiotherapy and poor compliance with an enhanced recovery program are also associated with higher readmission rates.[13] Furthermore, the emergence of multidrug-resistance, particularly extended-spectrum β-lactamase (ESBL) and carbapenemase production among Gram-negative bacilli (GNB) is a matter of particular concern[14,15] and may negatively impact treatment response in SSI.

At present, data regarding predictors of treatment failure or mortality in patients with SSI after colorectal surgery remain limited. Therefore, the aim of this large prospective multicentre cohort study of patients undergoing elective colorectal surgery was to assess the management and outcomes of patients with SSI, and to identify predictors of treatment failure in patients with an organ-space SSI.

Methods

Study design, patients and setting

We performed a multicentre observational study of a prospective cohort of adult patients (≥18 years old) undergoing elective colorectal surgery from 1st January 2011 to 31st December 2014 at 10 Spanish hospitals. Three of the hospitals were tertiary care university hospitals with more than 500 beds, five had between 200 and 500 beds, and two had fewer than 200 beds; all hospitals were participating in the VINCat program.[16] We included all consecutive patients hospitalized in any surgical department of the 10 participating hospitals. Trained infection control staff followed the patients up until 30 days after surgery. Patients with an existing infection at the surgical site at the time of surgery were excluded.

Surveillance program

The VINCat program is a healthcare-associated infection surveillance program in Spain, based on the National Healthcare Safety Network (NHSN) model.[17] The program prospectively collects data on preoperative demographics, comorbidities, procedure characteristics, microbiology, treatment, and 30-day postoperative outcomes for eligible surgical procedures.[18] The program provides regular feedback on results and benchmarking among hospitals and promotes preventive actions and scientific research.

Definitions

Surgical site infections were classified according to the Centers for Disease Control and Prevention (CDC)[19] criteria as superficial incisional, deep incisional, or organ-space infection. Surgical procedure categories were stratified (−1 to 3) according to risk of surgical infection as defined by the NHSN. Post-discharge surveillance of SSI was mandatory and consisted of review of electronic clinical records in primary and secondary care, checking readmissions and emergency visits, and reviewing microbiological and radiological data.[20]

Standardized data collection included age, sex, ASA score, mechanical bowel preparation, oral antibiotic prophylaxis, surgical risk index category according to the National Nosocomial Infections Surveillance (NNIS) system criteria,[21] adequate intravenous antibiotic prophylaxis, date and duration of surgery, laparoscopic surgery, wound classification, date of SSI, site of infection (superficial, deep incisional, or organ-space) and microbiology. Age, ASA score, NNIS risk index and site of infection were dichotomized for the analysis.

Intravenous antibiotic prophylaxis was considered adequate when the following three factors were all met: antibiotic administration according to local protocol at each hospital, completion of the infusion within 60 min of the surgical incision, and perioperative antibiotic redosing if indicated.

The initial antibiotic treatment was considered either empirical or targeted depending on the availability of microbiological sensitivity tests. The type and duration of antibiotic therapy was decided by the attending surgeon according to local protocol. Source control was defined as any procedure that resolved the infection focus or repaired anatomical derangements. It was classified as reoperation when a new surgical procedure was performed, regardless of whether drainages were inserted or not, and as drainage when percutaneous or transrectal drainage was done.

Microbiological studies

In patients with suspected SSI, microbiological samples from wounds and/or peritoneal fluid or abscesses were taken for culture in most cases. Blood cultures were also taken when indicated by the attending physician.

Polymicrobial infection was defined as isolation of $\geq$2 microorganisms in the samples. If there were $\geq$3 microorganisms, the laboratory reported the sample as polymicrobial without identifying the species of microorganisms isolated.

Antibiotic susceptibility was tested using the microdilution method following Clinical Laboratory Standard Institute (CLSI) guidelines. The antimicrobial susceptibility of isolates was interpreted according to current CLSI criteria.[22] Screening of multidrug-resistant phenotypes including ESBL and carbapenemase production was conducted according to CLSI recommendations.[23]

Enterobacteriaceae were identified using standard microbiological techniques at each participating centre. ESBL production was screened in all isolates with diminished susceptibility to cephalosporins and confirmed according to standard procedures. CLSI recommendations were used for susceptibility interpretation. Selected isolates from each centre were characterized by PCR and DNA sequencing using established methods.

The following GNB were considered to be multidrug-resistant (MDR): (i) ESBL-producing Enterobacteriaceae, (ii) carbapenemase-producing Enterobacteriaceae, and (iii) MDR strains of *Pseudomonas aeruginosa*. MDRGNB were defined as those resistant to at least three classes of antibiotics: carbapenems, ureidopenicillins, cephalosporins (ceftazidime and cefepime), monobactams, aminoglycosides and fluoroquinolones.

Primary and secondary outcomes

The primary study outcome was treatment failure, defined as persistence of any sign or symptom of SSI (signs of wound inflammation, suppuration from wounds or drainage sites and/or fever) or all-cause death, assessed at 30 days after the initial surgery.

Secondary outcomes were time to development of SSI, duration of antibiotic treatment, length of stay, readmission, and mortality, whether directly attributable to SSI or not.

Statistical analysis

Descriptive statistics were performed. Categorical variables were described as totals and frequencies; continuous variables were described as medians and interquartile ranges (IQR). Univariate comparisons were assessed for management and outcome variables between incisional and organ-space SSI populations applying the chi-square test or Fisher exact test for categorical variables and the *t* test or Mann–Whitney test for continuous variables. The final multivariate logistic model included significant variables identified from the univariate analysis. A *p*-value $\leq$0.05 was considered statistically significant for the final model. The final model's goodness of fit was assessed by the Hosmer–Lemeshow test. Data were analysed with IBM SPSS 20.0 (Chicago, Ill).

This study was approved by the Ethics Committee at Hospital Universitari de Bellvitge (reference: PR305/15).

Results

Clinical characteristics of patients

During the study period, a total of 3701 adult patients who had undergone elective colorectal surgery were prospectively reviewed, 68% after colon surgery and 32% after rectal surgery. Median age was 70 years, and 62% were male. Table 1 compares the characteristics of patients with no SSI, patients with incisional SSI (n = 333), and patients with an organ-space SSI (n = 336).

Microbiology

Cultures from surgical wounds and/or intraabdominal samples were performed in 533 of 669 cases (79.6%) and were

Table 1 Clinical characteristics of patients who developed an SSI.

	Non-SSI (n = 3032)	Incisional SSI (n = 333)	Organ-space SSI (n = 336)	*p*-value*
Age, median (IQR) years	69.6 (60.7–78)	70 (63–78)	69.5 (61–77)	0.2
≥65, *n* (%)	1980 (65.3)	231 (69.4)	224 (66.7)	0.4
Male sex, *n* (%)	1814 (59.8)	225 (67.6)	250 (74.4)	0.05
ASA III–IV, *n* (%)	1178 (38.9)	171 (51,7)	143 (43.8)	0.05
NNIS 1–2, *n* (%)	993 (32.8)	172 (52.7)	142 (42.3)	0.01
Indication for surgery, *n* (%):				
- Neoplasia	2868 (94.6)	319 (95.7)	315 (93.7)	0.2
- Inflammatory bowel disease	73 (2.4)	6 (1.8)	12 (3.6)	0.1
- Other	87 (2.9)	8 (2.4)	8 (2.4)	1
Type of surgery, *n* (%)				
- Colon	2104 (69.4)	214 (64.3)	200 (59.5)	0.2
- Rectum	928 (30.6)	119 (35.7)	136 (40.5)	
Adequate antibiotic prophylaxis, *n* (%)	2526 (83.3)	280 (84.1)	277 (82.4)	0.6
Duration of surgery, median (IQR) minutes	191.5 (80.2)	180 (125–255)	194 (140–274)	0.06
Laparoscopic surgery, *n* (%)	1975 (65.1)	146 (43.8)	176 (52.4)	0.03
Detection of infection during hospitalization, *n* (%)	0 (0)	218 (65.5)	263 (78.3)	<0.001
Oral antibiotic prophylaxis, *n* (%)	1352 (44.6)	113 (33.9)	102 (30.4)	0.3
Mechanical bowel preparation, *n* (%)	2283 (77.1)	250 (75.8)	254 (76.7)	0.8
Ostomy, *n* (%)	715 (23.6)	119 (35.7)	128 (38.2)	0.5
Previous chemotherapy, *n* (%)	471 (15.5)	72 (21.6)	68 (20.3)	0.6
Previous radiotherapy, *n* (%)	452 (14.9)	57 (17.1)	69 (20.6)	0.2

SSI: surgical site infection. **IQR**: interquartile range, **ASA**: American Society of Anesthesiologists physical status classification, **NNIS**: National Nosocomial Infections Surveillance Risk Index. **p*-value refers to comparison between incisional SSI and organ-space SSI.

positive in 496 (93%), as shown in Table 2. Blood cultures were performed in 238 of 669 (35.5%) patients, and they were positive in 34/238 (14.3%). Concordance between blood cultures and abdominal samples was observed in 14 of 34 (41.2%) cases. Patients with non-concordant samples had blood cultures with a different GNB in 3 cases, *Bacteroides* spp. in 5 cases, *Candida albicans* in 2 cases, coagulase-negative staphylococci in 4 cases and other isolates in 6 cases. The main causative agents of SSI were *Escherichia coli* (46.2%) followed by *Enterococcus* spp. (23.4%) and *P. aeruginosa* (12.5%). *Enterococcus faecalis* (11.7%) was equally distributed between incisional and organ-space infections, while *Enterococcus faecium* (11.7%) was almost three times more frequent in organ-space SSI than in incisional SSI. Polymicrobial infections were recorded in 50.6% of cases and anaerobes in 6.8% of cases, both being more frequent in organ-space SSI. Concerning multidrug-resistance among the clinically relevant GNB, there were 26 cases (11.3%) of *ESBL*-producing *E. coli* and 9 cases (30%) of *ESBL*-producing *Klebsiella pneumoniae*.

Management of organ-space SSI

Antimicrobial management varied depending on the type of SSI. While 237 (71.2%) of patients with incisional SSI received antibiotics, all 336 patients with organ-space SSI received antibiotic treatment, although type of antibiotic was recorded in only 313 cases. Initial antibiotic management of organ-space SSI is shown in Table 3. Empirical treatment had a median duration of 12 days (IQR 7–17.5), and was switched to targeted treatment in 124 (44.2%) cases. Targeted treatment, either initial or after an empirical regimen, had a median duration of 7 days (IQR 2–14). The most common antibiotics used were piperacillin–tazobactam (empirical in 34% of cases, targeted in 33%), followed by the antipseudomonal carbapenems meropenem or imipenem (empirical in 25%, targeted in 24%), and amoxicillin–clavulanic acid (empirical in 15.7%, targeted in 9.1%). A median of two antibiotic courses were given in patients with organ-space SSI (IQR 1–4). The rate of *Clostridium difficile* infection was 0.9% (6 of 669 patients).

Two hundred and seventy-three (81.2%) of the 336 patients underwent source control; 203 (60.4%) required reoperation due to suspected anastomotic leakage and 70 (20.8%) required insertion of a percutaneous or transrectal drain only. The other 63 (18.8%) were managed conservatively with antibiotic therapy due to the presence of small anastomotic leakages or abscesses with little clinical impact.

Primary and secondary outcomes

The outcomes of patients with SSI are shown in Table 4. Treatment failure was observed in 21.7% of cases, and was significantly more frequent in organ-space SSI than in incisional SSI (34.2% *vs* 9%, $p < 0.001$).

Median duration of antibiotic treatment for organ-space infections was 16 days (IQR 10–25), significantly longer than for incisional infections (10 days, IQR 7–15, $p < 0.001$). Median LOS including readmissions was 7 days (IQR 7–10) for

Table 2 Aetiology of SSI (nº of isolations from patients with positive cultures).

Group	Microorganism	Incisional SSI (n = 248) (%)	Organ-space SSI (n = 248) (%)	Overall (n = 496) (%)
GNB	*E. coli*	118 (47.5)	111 (44.7)	229 (46.2)
	P. aeruginosa	29 (11.7)	33 (13.3)	62 (12.5)
	K. pneumoniae	12 (4.8)	18 (7.2)	30 (6)
GPC	*E. faecalis*	28 (11.3)	30 (12)	58 (11.7)
	E. faecium	15 (6)	43 (17.3)	58 (11.7)
	S. aureus	24 (9.7)	5 (2)	29 (5.8)
Yeast	*C. albicans*	3 (1.2)	13 (5.2)	16 (3.2)
Anaerobes	*Bacteroides* spp.	15 (6)	14 (5.64)	29 (5.8)
	Clostridium spp.	1 (0.4)	4 (1.6)	5 (1)
Polymicrobial	≥2 microorganisms	108 (43.5)	143 (57.7)	251 (50.6)
Others		62 (25)	74 (29.8)	136 (27.4)

Multidrug-resistant Gram-negative bacilli			
	Susceptible, *n* (%)	ESBL, *n* (%)	CP, *n* (%)
E. coli (n = 229)	201 (87.7)	26 (11.3)	2 (0.9)
K. pneumoniae (n = 30)	20 (66.6)	9 (30)	1 (3.3)
	Susceptible, *n* (%)	MR, *n* (%)	CP, *n* (%)
P. aeruginosa (n = 62)	59 (95.1)	2 (3.2)	1 (1.6)

GNB: Gram-negative bacilli, **GPC**: Gram-positive cocci. **Others (nº of cases)**: *A. baumannii* (1), *A. hydrophila* (4), *C. diversus* (2), *C. freundii* (3), *E. aerogenes* (7), *E. cloacae* (7), *Enterococcus* spp. (2), *H. influenzae* (1), *K. oxytoca* (9), *M. morganii* (12), *P. mirabilis* (13), *P. vulgaris* (3), *S. marcescens* (1), *S. epidemidis* (6), coagulase-negative staphylococci (7), *S. maltophilia* (1), *S. agalactiae* (7), *S. anginosus* (8), *S. pneumoniae* (1), *S. viridans* group (16), *S. mitis* (1), Candida spp. (4), others (20). **ESBL**: extended spectrum β-lactamase, **CP**: carbapenemase, **MR**: multidrug-resistant.

Table 3 Initial antimicrobial management of organ-space SSI (n = 313).

Empirical (n = 280, 89.4%)			Targeted (n = 33, 10.5%)		
Antibiotic	*n* (%)	Duration (median, IQR)	Antibiotic	*n* (%)	Duration (median, IQR)
Piperacillin–tazobactam	95 (33.9)	9 (7–13)	Piperacillin–tazobactam	11 (33.3)	11 (10–16)
Meropenem/Imipenem	70 (25)	9 (6–14)	Meropenem/Imipenem	8 (24.2)	9.5 (5–18)
Amoxicillin–clavulanic acid	44 (15.7)	4 (2–7)	Amoxicillin–clavulanic acid	3 (9.1)	4 (1–4)
3GC plus metronidazole	23 (8.3)	8 (3–13)	Ertapenem	3 (9.1)	12 (1–12)
Ertapenem	13 (4.6)	5 (4–7)	Meropenem plus vancomycin	2 (6.1)	6.5
FQ plus metronidazole	10 (3.6)	6 (2–11)	FQ plus metronidazole	1 (3)	2
Other empirical antibiotics	25 (8.9)		Other targeted antibiotics	5 (15.1)	
Antifungal	*n* (%)	Duration (median, IQR)	Antifungal	*n* (%)	Duration (median, IQR)
Fluconazole	19 (82.6)	12 (5–15)	Fluconazole	10 (90.9)	15 (10–20)
Voriconazole	2 (9.5)	21 (21–21)	Voriconazole	1 (9.1)	2
Other empirical antifungal	2 (9.5)		Other targeted antifungal		

IQR: interquartile range, **3GC**: Third-generation cephalosporin, **FQ**: fluoroquinolone.

patients without SSI, 15 days (IQR 9–22) for patients with incisional SSI and 24 days (IQR 17–35) for patients with organ-space SSI. One hundred and twenty-seven patients (19%) required readmission, which was due to SSI in 117 patients (17.5%). Thirty-five out of 669 patients (5.2%) died; the mortality rate was significantly higher in organ-space infection than in incisional infection (8.9% *vs* 1.5%, $p < 0.001$). In 31 (4.6%) cases mortality was attributed to SSI.

Predictive factors of treatment failure

Table 5 refers to the univariate and multivariate analysis of predictive factors of treatment failure in organ-space SSI. The univariate study found age ≥65 years, ASA score III–IV, laparoscopic surgery, and reoperation to be significant risk factors. No particular antimicrobial resistance pattern or antibiotic treatment combinations were associated with treatment failure (not shown).

The analysis of patients undergoing laparoscopic surgery, compared to patients undergoing open surgery, is shown in Table 6.

Multivariate analysis identified age ≥65 years (OR 1.83, 95% CI 1.07–1.83), laparoscopic surgery (OR 1.7, 95% CI 1.06–2.77) and reoperation (OR 2.8, 95% CI 1.7–4.6) as independent predictive factors of treatment failure.

Table 4 Outcomes of patients with SSI.

	Incisional SSI (n = 333)	Organ-space SSI (n = 336)	Overall SSI (n = 669)	p-value
Time to development of SSI, median (IQR) days	9 (6–13)	7 (5–12)	8 (5–12)	<0.001
Duration of antibiotic treatment, median (IQR) days	10 (7–15)	16 (10–25)	13 (8–21)	<0.001
Length of stay (including readmission if there was), median (IQR) days	15 (9–22)	24 (17–35)	8 (6–14)	<0.001
Treatment failure rate, n (%)	30 (9)	115 (34.2)	145 (21.7)	<0.001
Readmission, n (%)	55 (16.5)	72 (21.4)	127 (19)	0.1
- Readmission attributable to SSI, n (%)	53 (15.9)	64 (19)	117 (17.5)	0.3
Mortality, n (%)	5 (1.5)	30 (8.9)	35 (5.2)	<0.001
- Mortality attributable to SSI, n (%)	4 (1.2)	27 (8)	31 (4.6)	<0.001

SSI: surgical site infection, **IQR**: interquartile range.

Discussion

This large, multicentre, prospective cohort study found that SSI rates and treatment failure among adult patients after elective colorectal surgery are notably high. It also identified that older age, laparoscopic surgery, and need for reoperation were independently associated with treatment failure.

We observed an overall SSI rate of 18.1%. Previous reported rates vary widely for a number of reasons. First of all, different definitions for SSI have been used: some include anastomotic leakage, while others do not. Second, the quality of data varies depending on whether there is underreporting and whether active post-discharge surveillance is performed to assess for SSI.[20,24] In 2009 the NHSN reported an SSI rate after colorectal surgery of as low as 5.6%,[25] even when post-discharge surveillance was performed. Other studies have reported rates similar to ours.[26–28]

Interestingly, we found a high proportion of *ESBL*-producing strains, particularly among *K. pneumoniae* and *E. coli*, probably reflecting an increased endogenous colonization by these microorganisms.[29] This finding coincides with those of a recent large study of antimicrobial susceptibility of GNB in intra-abdominal infections.[30] We found a high number of *P. aeruginosa* isolates, most of which (95.1%) were multidrug-susceptible. This high incidence of *P. aeruginosa* infection could be related to the fact that most patients had neoplasia.[31] The low resistance rate could be attributed to the fact that all these patients were electively admitted to hospital. Regarding the incidence of other pathogens, *Enterococcus* spp. were the most frequent Gram-positive microorganisms identified, as has previously been reported.[32] Interestingly, *E. faecium*, which is of

Table 5 Univariate and multivariate analysis of risk factors for treatment failure in organ-space SSI.

Variable	Univariate		Multivariate	
	Treatment failure	p-value	OR	95% CI
Sex: male/female (%)	34.8/32.6	0.7		
Age: <65/≥65 years (%)	25/38.8	0.01	**1.83**	**1.07–1.83**
Colon/rectal surgery (%)	34/34.6	0.9		
ASA I–II/III–IV (%)	29.6/40.1	0.04	1.4	0.84–2.24
Laparoscopic surgery, No/Yes (%)	28.7/39.2	0.04	**1.7**	**1.06–2.77**
Detection of infection during hospitalization, No/Yes (%)	26/36.5	0.09		
Neoplasia, No/Yes (%)	33.3/34.3	0.9		
Inflammatory bowel disease, No/Yes (%)	34.6/25	0.7		
Chemotherapy, No/Yes (%)	32.6/41.2	0.2		
Radiotherapy, No/Yes (%)	32/43.5	0.07		
Multidrug-resistance, No/Yes (%)	33.7/41.7	0.4		
Combined initial treatment, No/Yes (%)	33.6/37	0.6		
Reoperation, No/Yes (%)	21.1/42.9	<0.001	**2.8**	**1.7–4.6**
Drainage, No/Yes (%)	36.1/27.1	0.16		

Bold numbers indicate the results with statistical significance in multivariate analysis.
OR: Odds Ratio, **95% CI**: 95% confidence interval. **ASA**: American Society of Anesthesiologists physical status classification.

Table 6 Comparison of patients with organ-space SSI who had undergone laparoscopic and open surgery.

	Laparoscopic surgery (n = 176)	Open surgery (n = 160)	p-value
Age ≥ 65, *n* (%)	109 (61.9)	115 (71.9)	0.05
Male sex, *n* (%)	132 (75)	118 (73.8)	0.7
ASA III–IV, *n* (%)	69 (39.2)	78 (48.8)	0.07
NNIS 1–2, *n* (%)	40 (22.7)	102 (63.7)	<0.001
Type of surgery, *n* (%)			
- Colon	88 (50)	112 (70)	
- Rectum	88 (50)	48 (30)	<0.001
Adequate antibiotic prophylaxis, *n* (%)	139 (79)	138 (86.2)	0.08
Duration of surgery, median (IQR) minutes	196 (160–270)	150 (120–230)	<0.001
Detection of infection during hospitalization, *n* (%)	131 (74.4)	132 (82.5)	0.07
Oral antibiotic prophylaxis, *n* (%)	52 (29.5)	50 (31.2)	0.7
Mechanical bowel preparation, *n* (%)	137 (78.7)	117 (74.5)	0.3
Ostomy, *n* (%)	77 (43.8)	51 (32.1)	0.03
Previous chemotherapy, *n* (%)	45 (25.6)	23 (14.5)	0.01
Previous radiotherapy, *n* (%)	49 (27.8)	20 (12.6)	0.001
Time to development of SSI, median (IQR) days	8 (5–13)	9 (6–14)	0.4
Reoperation or drainage due to SSI, *n* (%)	147 (83.5)	126 (78.8)	0.2
Duration of antibiotic treatment, median (IQR) days	17 (12–27)	15 (9–24)	0.009
Length of stay (including readmission if there was), median (IQR) days	23 (16–36)	26 (18–34)	0.8
Treatment failure rate, *n* (%)	69 (39.2)	46 (28.7)	0.04
Readmission, *n* (%)	43 (24.4)	29 (18.1)	0.1
Mortality, *n* (%)	13 (7.4)	17 (10.6)	0.3

ASA: American Society of Anesthesiologists physical status classification, **NNIS**: National Nosocomial Infections Surveillance Risk Index, **IQR**: interquartile range, **SSI**: surgical site infection.

growing concern due to its resistance pattern, was almost three times more frequent in organ-space SSI than in incisional SSI. This is important because the empirical treatment frequently used in organ-space infections, such as carbapenems or piperacillin–tazobactam, does not offer effective coverage against this microorganism.

In this study, patients with organ-space SSI had a long duration of therapy, with a median exceeding 15 days. In addition, empirical treatment was rarely switched to a targeted option based on microbiological results. A recent clinical trial comparing a long antibiotic course of 10 days with a short course of 4 days for the treatment of intra-abdominal infections demonstrated that, in the presence of adequate control of the infectious source, the short course was equally as safe as the long course in terms of patient outcomes.[33] This could be a good opportunity to improve antimicrobial stewardship programs in those hospitals with higher antibiotic consumption. We found that most patients with an organ-space SSI underwent reoperation due to suspected anastomotic leakage or needed percutaneous or transrectal drainage. Thus, the duration of antibiotic therapy could have been shorter in those patients with adequate source control. Despite this, the rate of *C. difficile* infection was quite low in our cohort.

Length of stay was significantly longer in patients with organ-space SSI compared to those with incisional SSI. This is an important finding because other investigators revealed that SSI increased mean LOS by 9.7 days and mean cost of treatment by 20,842 dollars.[3] We found high readmission and mortality rates: both were substantially higher than previously reported[10,13,34] and in most cases were due to SSI. In fact, the mortality rate in organ-space SSI reached almost 9%, which emphasizes the seriousness of this infection.

This is the first study investigating predictive factors of treatment failure in an elective colorectal surgery population. We found that 21.7% of patients who developed an SSI had treatment failure within 30 days of surgery. This figure was nearly four times higher in organ-space SSI than in incisional SSI. This means that more than one third of patients who developed an organ-space SSI still had an active infection 30 days after the initial surgery.

We found that the only independent risk factors for treatment failure were older age (≥65 years), laparoscopic surgery, and reoperation. Neither type of surgery (colon *vs* rectum) nor the presence of multidrug-resistant GNB influenced outcome. Older age and higher ASA score have been associated with poorer outcomes in previous studies,[12] probably reflecting patients' frailty.

Although laparoscopic surgery is regarded as a protective factor against incisional SSI,[35] we found that it was an independent risk factor for 30-day treatment failure. Patients with an organ-space SSI who underwent laparoscopic surgery were younger, with lower NNIS modified Risk Index,

lower ASA score, they had more frequently received chemotherapy and radiotherapy and were more frequently diagnosed after discharge than those with open surgery. It can be hypothesized that because patients with previous laparoscopy had less comorbidities, they were discharged earlier than those with previous laparotomy, and then they presented with a more severe infection that contributed to treatment failure.

In our study, reoperation was found to be a risk factor for treatment failure, although it was probably a surrogate marker of illness severity rather than a risk factor itself. Reoperation is required in most cases of anastomotic leakage in order to achieve a clinical cure, but a longer postoperative period is needed to resolve the infection. Among the patients who died, 13.3% had undergone reoperation compared with 1.2% in those who had not died ($p = 0.001$), a finding that reinforces the idea that reoperation is a marker of illness severity.

Among the strengths of the study are its multicentre nature, the large number of patients included, and the fact that data collection was uniformly performed by trained infection control staff. Nevertheless, the study has a number of limitations that should be acknowledged. Firstly, it is a retrospective analysis of prospectively collected data. Therefore, as with any observational study, there is potential for residual confounding. Secondly, it is possible that some factors that might be associated with treatment failure were not recorded, such as the adequacy of initial antibiotic treatment.

In conclusion, the present study provides important and current data on the most prevalent microbiology of SSI after elective colorectal surgery that may help physicians when choosing prophylactic and empirical treatments. Treatment failure is a frequent problem among patients with organ-space SSI and can be underestimated. This complication is associated with high readmission and mortality rates and prolonged antibiotic therapy and LOS. Source control of the infection focus is crucial and allows to shorten the antibiotic treatment and avoid side effects. Careful attention should be paid to older patients with previous laparoscopy who require reoperation for organ-space SSI, so that treatment failure can be recognised early. Moreover, effective preventive strategies are urgently needed.

Conflict of interest disclosures

None reported.

Information on previous presentation

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References

1. European Center for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012. www.ecdc.europa.eu.
2. Owens CD, Stoessel K. Surgical site infections: epidemiology, microbiology and prevention. *J Hosp Infect* 2008;**70**(Suppl. 2):3–10. http://dx.doi.org/10.1016/S0195-6701(08)60017-1.
3. de Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence and impact on hospital utilization and treatment costs. *Am J Infect Control* 2009;**37**(5):387–97. http://dx.doi.org/10.1016/j.ajic.2008.12.010.
4. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR, Guideline for Prevention of Surgical Site Infection, 1999. Centers for disease control and prevention (CDC) hospital infection control practices advisory committee. *Am J Infect Control* 1999;**27**(2):97–132. quiz 133–4; discussion 96.
5. Welch HG, Robertson DJ. Colorectal cancer on the decline – why screening can't explain it all. *N Engl J Med* 2016;**374**(17):1605–7. http://dx.doi.org/10.1056/NEJMp1600448.
6. Aran V, Victorino AP, Thuler LC, Ferreira CG. Colorectal cancer: epidemiology, disease mechanisms and interventions to reduce onset and mortality. *Clin Colorectal Cancer* 2016. http://dx.doi.org/10.1016/j.clcc.2016.02.008.
7. Tanner J, Khan D, Aplin C, Ball J, Thomas M, Bankart J. Post-discharge surveillance to identify colorectal surgical site infection rates and related costs. *J Hosp Infect* 2009;**72**(3):243–50. http://dx.doi.org/10.1016/j.jhin.2009.03.021.
8. Kirby A, Burnside G, Bretsztajn L, Burke D. Postoperative infections following colorectal surgery in an English teaching hospital. *Infect Dis (Lond)* 2015;**47**(11):825–9. http://dx.doi.org/10.3109/23744235.2015.1055584.
9. Baucom RB, Phillips SE, Ehrenfeld JM, Muldoon RL, Poulose BK, Herline AJ, et al. Association of perioperative hypothermia during colectomy with surgical site infection. *JAMA Surg* 2015;**150**(6):570–5. http://dx.doi.org/10.1001/jamasurg.2015.77.
10. Bakker IS, Grossmann I, Henneman D, Havenga K, Wiggers T. Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. *Br J Surg* 2014;**101**(4):424–32. http://dx.doi.org/10.1002/bjs.9395. discussion 432.
11. Biondo S. Prevention of surgical site infection: still an important challenge in colorectal surgery. *Tech Coloproctol* 2014;**18**(10):861–2. http://dx.doi.org/10.1007/s10151-014-1206-0.
12. Kohut AY, Liu JJ, Stein DE, Sensenig R, Poggio JL. Patient-specific risk factors are predictive for postoperative adverse events in colorectal surgery: an American College of Surgeons National Surgical Quality Improvement Program-based

analysis. *Am J Surg* 2015;**209**(2):219—29. http://dx.doi.org/10.1016/j.amjsurg.2014.08.020.
13. Francis NK, Mason J, Salib E, Allanby L, Messenger D, Allison AS, et al. Factors predicting 30-day readmission after laparoscopic colorectal cancer surgery within an enhanced recovery programme. *Colorectal Dis* 2015;**17**(7):O148—54. http://dx.doi.org/10.1111/codi.13002.
14. Ho J, Tambyah PA, Paterson DL. Multiresistant Gram-negative infections: a global perspective. *Curr Opin Infect Dis* 2010;**23**(6):546—53. http://dx.doi.org/10.1097/QCO.0b013e32833f0d3e.
15. Khan AS, Dancer SJ, Humphreys H. Priorities in the prevention and control of multidrug-resistant Enterobacteriaceae in hospitals. *J Hosp Infect* 2012;**82**(2):85—93. http://dx.doi.org/10.1016/j.jhin.2012.06.013.
16. VINCat. Generalitat de Catalunya. Available from: http://vincat.gencat.cat/ca/. [Accessed 8 October 2016].
17. National Healthcare Safety Network (NHSN)|Centers for Disease Control and Prevention (CDC). Available from: http://www.cdc.gov/nhsn/. [Accessed 8 October 2016].
18. Pujol M, Limón E, López-Contreras J, Sallés M, Bella F, Gudiol F. Surveillance of surgical site infections in elective colorectal surgery. Results of the VINCat Program (2007—2010). *Enferm Infecc Microbiol Clin* 2012;**30**(Suppl. 3):20—5. http://dx.doi.org/10.1016/S0213-005X(12)70092-7.
19. CDC Surgical Site Infection (SSI) Event definition. Available from: http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf.
20. Limón E, Shaw E, Badia JM, Piriz M, Escofet R, Gudiol F, et al. Post-discharge surgical site infections after uncomplicated elective colorectal surgery: impact and risk factors. The experience of the VINCat Program. *J Hosp Infect* 2014;**86**(2):127—32. http://dx.doi.org/10.1016/j.jhin.2013.11.004.
21. Horan TC, Emori G, Atlanta MS. Definitions of key terms used in the NNIS System. *Am J Infect Control* 1997;**25**(2):112—6. http://dx.doi.org/10.1016/S0196-6553(97)90037-7.
22. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing; twenty-fifth informational supplement (M100-S22)*. Wayne, PA, USA: CLSI; 2012.
23. Clinical and Laboratory Standards Institute. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically*. 10th ed. (Approved Standard M07-A10). Wayne, PA, USA: CLSI; 2015.
24. Tanner J, Padley W, Kiernan M, Leaper D, Norrie P, Baggott R. A benchmark too far: findings from a national survey of surgical site infection surveillance. *J Hosp Infect* 2013;**83**(2):87—91. http://dx.doi.org/10.1016/j.jhin.2012.11.010.
25. Edwards JR, Peterson KD, Mu Y, Banerjee S, Allen-Bridson K, Morrell G, et al. National healthcare safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control* 2009;**37**:783—805. http://dx.doi.org/10.1016/j.ajic.2009.10.001.
26. Staszewicz W, Eisenring MC, Bettschart V, Harbarth S, Troillet N. Thirteen years of surgical site infection surveillance in Swiss hospitals. *J Hosp Infect* 2014;**88**(1):40—7. http://dx.doi.org/10.1016/j.jhin.2014.06.003.
27. Hennessey DB, Burke JP, Ni-Dhonochu T, Shields C, Winter DC, Mealy K. Risk factors for surgical site infection following colorectal resection: a multi-institutional study. *Int J Colorectal Dis* 2016;**31**(2):267—71. http://dx.doi.org/10.1007/s00384-015-2413-5.
28. Serra-Aracil X, Espin-Basany E, Biondo S, Guirao X, Orrego C, Sitges-Serra A, et al. Surgical site infection in elective operations for colorectal cancer after the application of preventive measures. *Arch Surg* 2011;**146**(5):606. http://dx.doi.org/10.1001/archsurg.2011.90.
29. Betteridge T, Merlino J, Natoli J, Cheong EYL, Gottlieb T, Stokes HW. Plasmids and bacterial strains mediating multidrug-resistant hospital-acquired infections are coresidents of the hospital environment. *Microb Drug Resist* 2013;**19**(2):104—9. http://dx.doi.org/10.1089/mdr.2012.0104.
30. Chen YH, Hsueh PR, Badal RE, Hawser SP, Hoban DJ, Bouchillon SK, et al. Antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region according to currently established susceptibility interpretive criteria. *J Infect* 2011;**62**(4):280—91. http://dx.doi.org/10.1016/j.jinf.2011.02.009.
31. Rolston KV, Nesher L, Tarrand JT. Current microbiology of surgical site infections in patients with cancer: a retrospective review. *Infect Dis Ther* 2014;**3**:245—56. http://dx.doi.org/10.1007/s40121-014-0048-4.
32. Augustin P, Kermarrec N, Muller-Serieys C, Lasocki S, Chosidow D, Marmuse J-P, et al. Risk factors for multidrug resistant bacteria and optimization of empirical antibiotic therapy in postoperative peritonitis 2010. *Crit Care* 2010;**14**:R20. http://dx.doi.org/10.1186/cc8877.
33. Sawyer RG, Claridge JA, Nathens AB, Rotstein D, Duane TM, Evans HL, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* 2015;**372**(21):1996—2005. http://dx.doi.org/10.1056/NEJMoa1411162.
34. Eagye KJ, Nicolau DP. Deep and organ/space infections in patients undergoing elective colorectal surgery: incidence and impact on hospital length of stay and costs. *Am J Surg* 2009;**198**:359—67. http://dx.doi.org/10.1016/j.amjsurg.2008.11.030.
35. Aimaq R, Akopian G, Kaufman HS. Surgical site infection rates in laparoscopic versus open colorectal surgery. *Am Surg* 2011;**77**(10):1290—4.

6.4 Analysis of the health cost of organ-space surgical site infection in elective colorectal surgery

- Characteristics of the 10 participating hospitals
- Clinical characteristics, crude LOS and mortality rates in patients developing incisional SSI, OS-SSI and in those not developing SSI
- Estimation of the excess LOS, the possibility of being discharged alive and the risk of mortality in patients with OS-SSI and in those with incisional SSI or without SSI
- Predictive factors of increased LOS in patients with OS-SSI

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Multistate modelling to estimate excess length of stay and risk of death associated with organ/space infection after elective colorectal surgery

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SUMMARY

Background: Accounting for time-dependency and competing events are strongly recommended to estimate excess length of stay (LOS) and risk of death associated with healthcare-associated infections.

Aim: To assess the effect of organ/space (OS) surgical site infection (SSI) on excess LOS and in-hospital mortality in patients undergoing elective colorectal surgery (ECS).

Methods: A multicentre prospective adult cohort undergoing ECS, January 2012 to December 2014, at 10 Spanish hospitals was used. SSI was considered the time-varying exposure and defined as incisional (superficial and deep) or OS. Discharge alive and death were the study endpoints. The mean excess LOS was estimated using a multistate

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model which provided a weighted average based on the states patients passed through. Multivariate Cox regression models were used to assess the effect of OS-SSI on risk of discharge alive or in-hospital mortality.

Findings: Of 2778 patients, 343 (12.3%) developed SSI: 194 (7%) OS-SSI and 149 (5.3%) incisional SSI. Compared to incisional SSI or no infection, OS-SSI prolonged LOS by 4.2 days (95% confidence interval (CI): 4.1–4.3) and 9 days (8.9–9.1), respectively, reduced the risk of discharge alive (adjusted hazard ratio (aHR): 0.36 (95% CI: 0.28–0.47) and aHR: 0.17 (0.14–0.21), respectively), and increased the risk of in-hospital mortality (aHR: 8.02 (1.03–62.9) and aHR: 10.7 (3.7–30.9), respectively).

Conclusion: OS-SSI substantially extended LOS and increased risk of death in patients undergoing ECS. These results reinforce OS-SSI as the SSI with the highest health burden in ECS.

Introduction

Surgical site infections (SSIs) are one of the most severe and dreaded healthcare-associated infections (HCAIs) in elective colorectal surgery (ECS). These infections increase morbidity and mortality, and prolong length of stay (LOS), thereby increasing patient and health costs [1,2]. Among SSIs, organ/space (OS)-SSI has been associated with the worst outcomes [3–5].

Since colorectal surgery is a cornerstone of treatment for colorectal cancer – the third most common cancer diagnosed in developed countries – avoiding these HCAIs is an urgent matter. Multiple strategies have been shown to be successful in preventing SSIs; however, recent studies still show high rates of OS-SSI associated with colorectal surgery [6–13].

Measuring the health cost of OS-SSI accurately can facilitate joint efforts by all stakeholders to implement targeted prevention strategies. Currently, from the hospital perspective, the cost of HCAIs is mostly due to extending patient LOS, which determines missed new hospital admissions [14,15]. When estimating LOS due to HCAIs, applying statistical models that consider the time-dependent nature of the infection has been recommended. This approach permits a better control of time-dependent bias and avoids overestimation of excess LOS [16,17].

To date, studies reporting the effect of SSI on LOS in colorectal surgery have not considered time-dependent bias [1,4,12]. The purpose of the present study is therefore to assess the health costs of OS-SSI measured in terms of excess LOS and risk of death during the hospital stay in a prospective cohort of patients undergoing ECS, taking into account timing of infection and competing events.

Methods

Setting and study design

This was a multicentre prospective cohort study of adult (aged ≥18 years) patients who underwent ECS from January 2012 to December 2014, at 10 hospitals in Catalonia, Spain. The hospital characteristics are shown in Table I. All these hospitals routinely report data to the regional surveillance programme for HCAIs: VINCat [5,18]. All patients hospitalized for ECS at the different hospitals were followed up until discharge or death. Patients with pre-existing infection at the time of surgery or with SSIs diagnosed after discharge were excluded.

Outcomes

The main outcomes were excess LOS and in-hospital mortality of patients who acquired an OS-SSI during their stay for ECS. Risk factors associated with the longest excess LOS due to OS-SSI defined as excess LOS >75th percentile (p75) were also assessed.

Table I
Characteristics of acute hospitals participating in the study, 2012–2014

Hospital	Type	Acute beds	Admissions	ECS	Bed-days[a]
1	University hospital	760	87,899	449	4430
2	University hospital	518	50,004	454	3347
3	Medium-sized teaching hospital	295	36,123	214	1742
4	Medium-sized teaching hospital	431	58,945	408	2904
5	Community hospital	121	17,077	220	1407
6	Medium-sized teaching hospital	200	23,796	159	1419
7	University hospital	450	46,495	233	2040
8	Medium-sized teaching hospital	283	39,037	295	2217
9	Community hospital	130	38,332	127	965
10	Medium-sized teaching hospital	276	28,177	219	1340
Total		3464	425,885	2778	21,811

ECS, elective colorectal surgery.
[a] Bed-days related to patients undergoing elective colorectal surgery in each hospital.

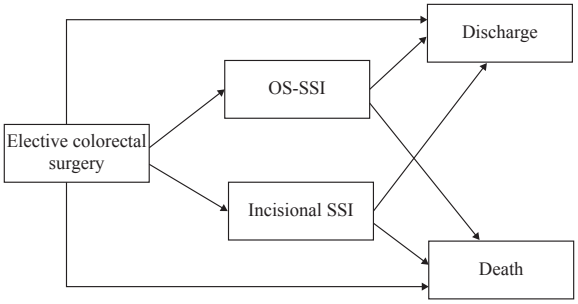

Figure 1. Multistate model adopted for the analysis of excess length of stay of patients with surgical site infection. Patients discharged without infection underwent post-discharge surveillance for up to 30 days after surgery. In all, 115 patients developed an SSI after discharge (71 incisional SSIs and 44 organ/space (OS)-SSIs). Of the patients who developed SSIs, 18 patients with incisional SSI and 40 with OS-SSI required readmission (these patients were not included in the analysis).

Independent variables

Age, sex, American Society of Anesthesiologists' (ASA) physical status, type of procedure (colon/rectal), laparoscopic approach, adequacy of intravenous antibiotic prophylaxis (IAP), and primary diagnosis (cancer, inflammatory bowel disease (IBD) or other) were considered as potential baseline confounders [19]. Age (<65 and ≥65 years) and ASA (I–II and III–IV) were dichotomized for the analysis.

Definitions

SSIs were defined according to the Centers for Disease Control and Prevention criteria and divided, for the purpose of this study, into incisional (superficial or deep) and OS infection [20].

Adequate antibiotic prophylaxis was considered when the following three conditions were met: antibiotics administered according to the local evidence-based protocol at each hospital, completion of the infusion within 60 min before the surgical incision, and perioperative antibiotic redosing if indicated.

Data collection

Data were obtained from the VINCat database, based on standardized protocols, which prospectively collects information related to demographics, comorbidities, perioperative characteristics, and 30-day postoperative outcomes for eligible surgical procedures [18,21].

Statistical analysis

Incidence densities in the cohort were calculated by dividing the number of events by the number of patient-days at risk per 1000. To estimate excess LOS, we used a multistate modelling as outlined by Beyersmann *et al.* [22]. Patients entered the initial state after the ECS and exited by entering one of the two competing states: death or discharge alive, with or without acquiring an SSI, which was the time-dependent exposure of interest. This approach allowed us to estimate the mean excess LOS of patients with SSI (OS-SSI or incisional SSI) with respect to uninfected patients. The multistate model provides a weighted average of the LOS based on the path followed by patients (Figure 1). Patients who were still in hospital 30 days after surgery were artificially right-censored to avoid the influence of outliers on LOS.

Proportional hazards models were established for the time to mortality during admission and the time to discharge alive, with a set of risk factors including the SSI indicators. The results are shown as hazard ratio (HR) and the corresponding confidence intervals for the univariate and multivariate models. HRs were obtained from the cause-specific hazard models for mortality or for discharge alive. In each model, 'hospital' was introduced as strata variable to take into account potential differences in death or discharge alive between hospitals.

To characterize patients with the longest excess LOS, a binary indicator of excess LOS >p75 (>16 days) was computed. Thus, $Y = 1$ was assigned for values with the highest excess LOS (>p75), and $Y = 0$ was assigned otherwise. We established a generalized linear model for the response variable Y with demographic and clinical characteristics as covariates. The sample size used for this model was 2629, since patients with incisional SSI were excluded. The results are shown as odds ratios (ORs) and the corresponding confidence intervals (CIs) for the univariate and multivariate models.

Multivariate models included covariates of the univariate models with $P < 0.10$ and relevant variables from a clinical point of view.

All the results were obtained with SAS v9.4, SAS Institute, Inc. (Cary, NC, USA) and R v3.4.4 (etm package).

Ethics

This study was approved by the Ethics Committee of Hospital Universitari de Bellvitge (reference: PR092/16).

Results

A total of 2778 patients were included in the cohort; cancer was the main cause of surgery 2623 (94%). During the hospital stay, 343 patients (12.3%) developed SSI. Of those, 194 (7%) had OS-SSI and 149 (5.3%) incisional SSI. The incidence density of overall SSI was 15.7 per 1000 patient-days at risk; 8.9 and 6.8 per 1000 patient-days at risk for OS-SSI and incisional SSI, respectively. Infection occurred in a median time of six days after surgery for both OS-SSI and incisional SSI. The median LOS for patients without infection was six days (interquartile range: 5–9); and 24 days (18–36) and 15 days (10–22) for patients with OS-SSI and incisional SSI, respectively. Baseline patient characteristics are shown in Table II.

Excess of length of stay

At the end of the study, 2649 patients (95.4%) were discharged, 22 died (0.8%), and 107 (3.8%) remained in hospital. Compared to patients who did not develop an infection or who had an incisional SSI, OS-SSI increased LOS an average of 9 days (95% CI: 8.9–9.1) and 4.2 days (4.1–4.3), respectively. The risk of discharge alive decreased in patients with OS-SSI (aHR: 0.17;

Table II
Baseline, perioperative characteristics, and crude length of stay and mortality rates of patients in the cohort

Variable	Non-SSI	Incisional SSI	OS-SSI
	(*N* = 2 435)	(*N* = 149)	(*N* = 194)
Sex, male	1469 (60.3%)	106 (71.1%)	149 (76.8%)
Age (years), median (IQR)	64.5 (60.7–77.7)	70.9 (62.2–79.1)	70.3 (61.1–78.7)
ASA class ≥III	958 (39.3%)	79 (53.0%)	91 (46.9%)
Primary diagnosis			
Cancer	2303 (94.6%)	142 (95.3%)	178 (91.7%)
Inflammatory bowel disease	58 (2.4%)	4 (2.6%)	8 (4.1%)
Other	74 (3.0%)	3 (2.0%)	8 (4.1%)
Type of procedure			
Colon	1675 (68.8%)	88 (59.1%)	116 (59.8%)
Rectal	760 (31.2%)	61 (40.9%)	78 (40.2%)
Laparoscopic approach	1634 (67.1%)	77 (51.7%)	101 (52.0%)
Adequate intravenous prophylaxis	1983 (81.4%)	121 (81.2%)	156 (80.4%)
Operating time >75th percentile[a]	979 (40.2%)	58 (38.9%)	87 (44.8%)
NNIS risk index ≥1	796 (32.7%)	73 (48.9%)	88 (45.4%)
Length of stay (days), median (IQR)	6 (5–9)	15 (10–22)	24 (18–36)
Days from surgery to infection, median (IQR)		6 (5–10)	6 (4–9)
Days from infection to discharge, median (IQR)		8 (4–13)	18 (11–28)
In-hospital mortality	5 (0.2%)	1 (0.7%)	16 (8.2%)

SSI, surgical site infection; OS, organ/space; IQR, interquartile range; ASA, American Society of Anesthesiologists' physical status; IBD, inflammatory bowel disease; NNIS, National Nosocomial Infections Surveillance.
[a] Duration of operative procedure >180 min.

95% CI: 0.14–0.21) and with incisional SSI (aHR: 0.46; 0.39–0.55), although the greatest effect was associated with OS-SSI (Table III).

Risk factors associated with the longest excess LOS due to OS-SSI were receiving inadequate IAP (aOR: 1.10; 95% CI: 1.01–1.20; $P = 0.03$) and non-laparoscopic approach (1.06; 0.99–1.15; $P = 0.08$) (Table IV).

In-hospital mortality

Of the 22 patients who died during their hospital stay, five were uninfected, one had incisional SSI, and 16 had OS-SSI. After accounting for demographics and perioperative characteristics, patients with OS-SSI had a higher risk of death than patients with incisional SSI (aHR: 8.02; 95% CI: 1.03–62.9) or without infection (10.7; 3.7–30.9) (Table III).

Discussion

This study shows that, among SSIs, OS-SSI had the greatest burden on LOS and mortality in patients undergoing ECS in a large cohort of patients. The results are consistent with those reported in the literature; however, previous studies frequently used matching designs to estimate excess LOS, a type of design that overestimates LOS, since they do not consider time-dependency of the infection [1,4,23–26].

Excess LOS attributed to SSI varies from 4.1 to 15 days, although most studies reporting these data include a small number of surgeries and evaluate data on patients undergoing different types of surgical procedure [1,4,23]. Our study is the first using multistate modelling to estimate excess LOS in ECS. Patients with OS-SSI stayed an average of nine additional days in hospital, a period greater than the median stay of patients without infection in the cohort. Since ECS is currently a high-volume procedure worldwide due to the incidence of cancer, improving efforts to avoid this preventable complication would free up hospital capacity to treat additional patients [27].

There is a paucity of studies exploring factors that predispose to a prolonged stay in colorectal surgery. In such studies, age, comorbidities, open surgery approach, prolonged ileus, or infection are associated with the longest hospital stays [28–30]. Our results suggest that the longest admissions occurred in patients receiving inadequate IAP or undergoing an open surgery. In contrast, no associations with age, the highest ASA score, type of procedure or primary diagnosis were observed. Since adequate IAP and laparoscopic access to the abdominal cavity prevent postoperative complications, these factors may act as surrogate marker for confounders that could influence LOS, such as prolonged ileus. Unfortunately, a lack of data prevented us exploring this subject further [31,32].

ECS is considered a safe procedure since it is associated with low mortality rates, ranging from 0.9% to 4% [33,34]. In our study, the mortality rate was <1% in patients with incisional SSI or those who did not have an infection; but for patients with OS-SSI, the risk of death during admission was 10 times higher than the risk for uninfected patients. Interestingly, a recent study conducted in the UK found that, among postoperative infections in ECS, OS-SSI was the only infection associated with an increase in one-year mortality [35].

The strength of the present study is that we have considered the time-dependent nature of SSI and competing risk events, to obtain a more precise estimation of extra LOS and risk of mortality in a large prospective cohort of patients. Notably, the analysis enables us to show that incisional SSI has a slight effect on LOS and no effect on mortality. This reinforces the idea that OS-SSI in ECS is the SSI carrying the greatest health burden.

Table III
Estimated excess length of stay (LOS) and hazards models for discharge or death

Comparison	Excess LOS (days), mean (95% CI)	Hazard ratio of discharge alive		Hazard ratio of death[a]	
		Model 1 HR (95% CI)	Model 2 aHR (95% CI)	Model 1 HR (95% CI)	Model 2 aHR (95% CI)
Incisional SSI vs uninfected	2.9 (2.8–3.0)	0.45 (0.38–0.53)	0.46 (0.39–0.55)	–[b]	–[b]
OS-SSI vs uninfected	9 (8.9–9.1)	0.18 (0.15–0.22)	0.17 (0.14–0.21)	8.14 (2.73–24.23)	10.77 (3.75–30.89)
OS-SSI vs incisional SSI	4.2 (4.1–4.3)	0.38 (0.29–0.49)	0.36 (0.28–0.47)	6.69 (0.86–52.14)	8.02 (1.03–62.89)

aHR, adjusted hazard ratio; CI, confidence interval; SSI, surgical site infection; OS, organ/space.
Model 1: univariate analysis. Model 2: Model 1 adjusted for age, sex, American Society of Anesthesiologists' physical status, type of procedure, laparoscopic approach, and adequate intravenous antibiotic prophylaxis.
[a] Includes mortality during the hospital stay.
[b] As only one patient died during the stay, in the incisional SSI group the hazard for mortality has not been calculated.

Table IV
Univariate and multivariate analysis of risk factors for the longest length of stay due to OS-SSI

Risk factor	OR (95% CI)	aOR (95% CI)	*P*-value
Age ≥65 years	1 (0.94–1.07)	1 (0.94–1.07)	0.96
Male sex	0.95 (0.90–1.02)	0.95 (0.89–1.02)	0.15
ASA class ≥III	0.99 (0.93–1.07)	1 (0.93–1.07)	0.97
Type of procedure, colon	0.99 (0.93–1.07)	0.99 (0.92–1.07)	0.87
Non-laparoscopic approach	1.06 (0.99–1.14)	1.06 (0.99–1.15)	0.08
Inadequate intravenous antibiotic prophylaxis	1.10 (1.01–1.20)	1.10 (1.01–1.20)	0.03
Primary diagnosis			
Cancer	0.91 (0.77–1.07)		
IBD	1.20 (0.93–1.56)		
Other	1.06 (0.85–1.32)		

OS-SSI, organ/space surgical site infection; OR, odds ratio; aOR, adjusted odds ratio; ASA, American Society of Anesthesiologists' physical status; IBD, inflammatory bowel disease.
Longest length of stay = excess length of stay >p75.
The analysis included 2629 patients (incisional SSIs were excluded). Of these, 895 patients had an excess length of stay >p75 (>16 days), 105 had OS-SSIs.

The major limitation of this work is that it only included infections detected during hospitalization. Since more than 20% of SSIs are detected post discharge if we included those patients in the analysis, the real effect of OS-SSIs on LOS may be miscalculated [36]. To include patients with OS-SSIs diagnosed post discharge in the analysis, two approaches could be proposed: including a new path from discharge to infection in the multistate model; or using models for multivariate survival and recurrent events. A further limitation is the unadjusted nature of the excess LOS analysis; although to overcome that, we computed a binary indicator of excess LOS and adopted a generalized linear model. However, unmeasured information on postoperative details or on time-varying covariates, such as ICU admission, might be confounding the results [37].

In summary, accounting for time-dependency and competing events, OS-SSI substantially extends LOS and increases risk of mortality. These results reinforce the notion that OS-SSI is the SSI with the highest health burden in ECS. Hence, OS-SSI prevention should be a priority for all healthcare providers.

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References

[1] Kirkland KB, Briggs JP, Trivette SL, Wilkinson WL, Sexton DJ. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol 1999;20:725–30.
[2] Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P. Adverse impact of surgical site infections in English hospitals. J Hosp Infect 2005;60:93–103.

[3] Blumetti J, Luu M, Sarosi G, Hartless K, McFarlin J, Parker B, et al. Surgical site infections after colorectal surgery: do risk factors vary depending on the type of infection considered? Surgery 2007;142:704–11.
[4] Eagye KJ, Nicolau DP. Deep and organ/space infections in patients undergoing elective colorectal surgery: incidence and impact on hospital length of stay and costs. Am J Surg 2009;198:359–67.
[5] Gomila A, Badia JM, Carratalà J, Serra-Aracil X, Shaw E, Diaz-Brito V, et al. Current outcomes and predictors of treatment failure in patients with surgical site infection after elective colorectal surgery. A multicentre prospective cohort study. J Infect 2017;74:555–63.
[6] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics. CA Cancer J Clin 2012;65:87–108.
[7] Wick EC, Hobson DB, Bennett JL, Demski R, Maragakis L, Gearhart SL, et al. Implementation of a surgical comprehensive unit-based safety program to reduce surgical site infections. J Am Coll Surg 2012;215:193–200.
[8] Tanner J, Padley W, Assadian O, Leaper D, Kiernan M, Edmiston C. Do surgical care bundles reduce the risk of surgical site infections in patients undergoing colorectal surgery? A systematic review and cohort meta-analysis of 8,515 patients. Surgery 2015;158:66–77.
[9] Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. Oral antibiotic bowel preparation significantly reduces surgical site infection rates and readmission rates in elective colorectal surgery. Ann Surg 2015;261:1034–40.
[10] Allegranzi B, Bischoff P, de Jonge S, Kubilay NZ, Zayed B, Gomes SM, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis 2016;16:e276–87.
[11] Zywot A, Lau CSM, Stephen Fletcher H, Paul S. Bundles prevent surgical site infections after colorectal surgery: meta-analysis and systematic review. J Gastrointest Surg 2017;21:1915–30.
[12] Hennessey DB, Burke JP, Ni-Dhonochu T, Shields C, Winter DC, Mealy K. Risk factors for surgical site infection following colorectal resection: a multi-institutional study. Int J Colorectal Dis 2016;31:267–71.
[13] Gomila A, Carratalà J, Camprubí D, Shaw E, Badia JM, Cruz A, et al. Risk factors and outcomes of organ-space surgical site infections after elective colon and rectal surgery. Antimicrob Resist Infect Control 2017 21;6:40.
[14] Graves N, Weinhold D, Tong E, Birrell F, Doidge S, Ramritu P, et al. Effect of healthcare-acquired infection on length of hospital stay and cost. Infect Control Hosp Epidemiol 2007;28:280–92.
[15] Graves N, Harbarth S, Beyersmann J, Barnett A, Halton K, Cooper B. Estimating the cost of health care-associated infections: mind your p's and q's. Clin Infect Dis 2010;50:1017–21.
[16] Barnett AG, Beyersmann J, Allignol A, Rosenthal VD, Graves N, Wolkewitz M. The time-dependent bias and its effect on extra length of stay due to nosocomial infection. Value Health 2011;14:381–6.
[17] Stewardson AJ, Allignol A, Beyersmann J, Graves N, Schumacher M, Meyer R, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and *Staphylococcus aureus* in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill 2016;21.
[18] VINCat. Generalitat de Catalunya. Available from: http://catsalut.gencat.cat/ca/proveidors-professionals/vincat/ [last accessed 1 Oct 2018].
[19] Owens WD, Felts JA, Spitznagel Jr EL. ASA physical status classifications: a study of consistency of ratings. Anesthesiology 1978;49:239–43.
[20] CDC Surgical Site Infection (SSI) Event definition. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf [last accessed 1 Oct 2018].
[21] Pujol M, Limón E, López-Contreras J, Sallés M, Bella F, Gudiol F, VINCat Program. Surveillance of surgical site infections in elective colorectal surgery. Results of the VINCat Program (2007–2010). Enferm Infecc Microbiol Clin 2012;30(Suppl 3):20–5.
[22] Beyersmann J, Wolkewitz M, Allignol A, Grambauer N, Schumacher M. Application of multistate models in hospital epidemiology: advances and challenges. Biometric J 2011;53:332–50.
[23] Jenks PJ, Laurent M, McQuarry S, Watkins R. Clinical and economic burden of surgical site infection (SSI) and predicted financial consequences of elimination of SSI from an English hospital. J Hosp Infect 2014;86:24–33.
[24] Ohno M, Shimada Y, Satoh M, Kojima Y, Sakamoto K, Hori S. Evaluation of economic burden of colonic surgical site infection at a Japanese hospital. J Hosp Infect 2018;99:31–5.
[25] De Angelis G, Murthy A, Beyersmann J, Harbarth S. Estimating the impact of healthcare-associated infections on length of stay and costs. Clin Microbiol Infect 2010;16:1729–35.
[26] Heister T, Wolkewitz M, Kaier K. Estimating the additional costs of surgical site infections: length bias, time-dependent bias, and conditioning on the future. J Hosp Infect 2018;99:103–4.
[27] Favoriti P, Carbone G, Greco M, Pirozzi F, Pirozzi RE, Corcione F. Worldwide burden of colorectal cancer: a review. Updates Surg 2016;68:7–11.
[28] Reddy KM, Meyer CE, Palazzo FF, Conaghan P, Blunt MC, Stebbings WS, et al. Postoperative stay following colorectal surgery: a study of factors associated with prolonged hospital stay. Ann R Coll Surg Engl 2003;85:111–4.
[29] Faiz O, Haji A, Burns E, Bottle A, Kennedy R, Aylin P. Hospital stay amongst patients undergoing major elective colorectal surgery: predicting prolonged stay and readmissions in NHS hospitals. Colorectal Dis 2011;13:816–22.
[30] Ahmed Ali U, Dunne T, Gurland B, Vogel JD, Kiran RP. Actual versus estimated length of stay after colorectal surgery: which factors influence a deviation? Am J Surg 2014;208:663–9.
[31] Ho VP, Barie PS, Stein SL, Trencheva K, Milsom JW, Lee SW, et al. Antibiotic regimen and the timing of prophylaxis are important for reducing surgical site infection after elective abdominal colorectal surgery. Surg Infect (Larchmt) 2011;12:255–60.
[32] Kang CY, Chaudhry OO, Halabi WJ, Nguyen V, Carmichael JC, Stamos MJ, et al. Outcomes of laparoscopic colorectal surgery: data from the Nationwide Inpatient Sample 2009. Am J Surg 2012;204:952–7.
[33] Cone MM, Herzig DO, Diggs BS, Dolan JP, Rea JD, Deveney KE, et al. Dramatic decreases in mortality from laparoscopic colon resections based on data from the nationwide inpatient sample. Arch Surg 2011;146:594–9.
[34] Billeter AT, Polk Jr HC, Hohmann SF, Qadan M, Fry DE, Jorden JR, et al. Mortality after elective colon resection: the search for outcomes that define quality in surgical practice. J Am Coll Surg 2012;214:436–43.
[35] Kirby A, Burnside G, Bretsztajn L, Burke D. Postoperative infections following colorectal surgery in an English teaching hospital. Infect Dis (Lond) 2015;47:825–9.
[36] Limón E, Shaw E, Badia JM, Piriz M, Escofet R, Gudiol F, et al. Post-discharge surgical site infections after uncomplicated elective colorectal surgery: impact and risk factors. The experience of the VINCat program. J Hosp Infect 2014;86:127–32.
[37] Pouwels KB, Vansteelandt S, Batra R, Edgeworth JD, Smieszek T, Robotham JV. Intensive care unit (ICU)-acquired bacteraemia and ICU mortality and discharge: addressing time-varying confounding using appropriate methodology. J Hosp Infect 2018;99:42–7.

6.5. An organism of special interest in colorectal surgery: *Pseudomonas aeruginosa*

- Clinical and epidemiological characteristics of patients with SSI caused either by *P. aeruginosa* or by other microorganisms
- Concomitant microbiology of SSIs due to *P. aeruginosa* or to other microorganisms and prevalence of multidrug-resistance
- Antimicrobial management of *P. aeruginosa* SSIs
- Outcomes in patients with *P. aeruginosa* SSI and patients with SSI due to other pathogens

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RESEARCH ARTICLE Open Access

Preoperative oral antibiotic prophylaxis reduces *Pseudomonas aeruginosa* surgical site infections after elective colorectal surgery: a multicenter prospective cohort study

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Abstract

Background: Healthcare-associated infections caused by *Pseudomonas aeruginosa* are associated with poor outcomes. However, the role of *P. aeruginosa* in surgical site infections after colorectal surgery has not been evaluated. The aim of this study was to determine the predictive factors and outcomes of surgical site infections caused by *P. aeruginosa* after colorectal surgery, with special emphasis on the role of preoperative oral antibiotic prophylaxis.

Methods: We conducted an observational, multicenter, prospective cohort study of all patients undergoing elective colorectal surgery at 10 Spanish hospitals (2011–2014). A logistic regression model was used to identify predictive factors for *P. aeruginosa* surgical site infections.

Results: Out of 3701 patients, 669 (18.1%) developed surgical site infections, and 62 (9.3%) of these were due to *P. aeruginosa*. The following factors were found to differentiate between *P. aeruginosa* surgical site infections and those caused by other microorganisms: American Society of Anesthesiologists' score III–IV (67.7% vs 45.5%, $p = 0.001$, odds ratio (OR) 2.5, 95% confidence interval (95% CI) 1.44–4.39), National Nosocomial Infections Surveillance risk index 1–2 (74.2% vs 44.2%, $p < 0.001$, OR 3.6, 95% CI 2.01–6.56), duration of surgery ≥75thpercentile (61.3% vs 41.4%, $p = 0.003$, OR 2.2, 95% CI 1.31–3.83) and oral antibiotic prophylaxis (17.7% vs 33.6%, $p = 0.01$, OR 0.4, 95% CI 0.21–0.83). Patients with *P. aeruginosa* surgical site infections were administered antibiotic treatment for a longer duration (median 17 days [interquartile range (IQR) 10–24] vs 13d [IQR 8–20], $p = 0.015$, OR 1.1, 95% CI 1.00–1.12), had a higher treatment failure rate (30.6% vs 20.8%, $p = 0.07$, OR 1.7, 95% CI 0.96–2.99), and longer hospitalization (median 22 days [IQR 15–42] vs 19d [IQR 12–28], $p = 0.02$, OR 1.1, 95% CI 1.00–1.17) than those with surgical site infections due to other microorganisms. Independent predictive factors associated with *P. aeruginosa* surgical site infections were the National Nosocomial Infections Surveillance risk index 1–2 (OR 2.3, 95% CI 1.03–5.40) and the use of oral antibiotic prophylaxis (OR 0.4, 95% CI 0.23–0.90).

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Conclusions: We observed that surgical site infections due to *P. aeruginosa* are associated with a higher National Nosocomial Infections Surveillance risk index, poor outcomes, and lack of preoperative oral antibiotic prophylaxis. These findings can aid in establishing specific preventive measures and appropriate empirical antibiotic treatment.

Keywords: Healthcare-associated infection, Surgical site infection, Colorectal surgery, Colorectal cancer, Spain

Background

Currently, surgical site infections (SSIs) are the most frequent healthcare-associated infections (HAI) in acute-care hospitals in Europe and the US, accounting for 20% of all HAIs [1]. The development of an SSI lengthens patients' hospital stay and increases readmission and mortality rates 2–11 times [2]. In particular, colorectal surgery is associated with high rates of SSI due to increased possibility of contamination during the procedure, although findings of SSI rates from studies considerably vary due to differences in the surveillance criteria used and the quality of data collection [3, 4].

Pseudomonas aeruginosa is one of the main causes of HAIs worldwide. Overall, it is considered to be the fourth leading cause of HAIs [1]; *P. aeruginosa* is frequently detected in patients with serious underlying conditions, and is associated with poor prognosis and high mortality [5]. Therapeutic options for *P. aeruginosa* infections are limited due to its intrinsic resistant pattern and its capacity to develop multiple drug resistance, necessitating the second-order or multiple antibiotic treatment [6, 7].

Despite the prevalence of SSIs among HAIs [1], the risk factors for *P. aeruginosa* in intraabdominal SSIs have not been examined in detail. Given the high frequency of elective colorectal surgery and the potential serious outcomes associated with *P. aeruginosa* infections, it is essential to determine the predictive factors of *P. aeruginosa* SSIs after colorectal surgery. The aim of this study involving a large, multicenter, prospective cohort of patients undergoing elective colorectal surgery was to identify specific predictive factors of *P. aeruginosa* SSIs, with special focus on the role of preoperative oral antibiotic prophylaxis, in order to propose specific preventive measures and appropriate empirical antibiotic treatment.

Methods

Setting and study patients

This was an observational, prospective cohort study of 3701 consecutive patients (age ≥ 18 years) who underwent elective colorectal surgery between January 2011 and December 2014 at 10 Spanish hospitals belonging to the VINCat Program [8]. VINCat is an HAI surveillance program based on the National Healthcare Safety Network (NHSN) model [9]. According to this program, hospitals submit information regarding patients' demographics and comorbidities, procedure characteristics, microbiological and treatment data, as well as 30-day postoperative outcomes [10]. Post-discharge surveillance of SSIs until 30 days after surgery is mandatory and consists of a review of the electronic clinical records in primary and secondary care, checking of readmissions and emergency visits, and reviewing microbiological and radiological data [11]. For the purpose of this study, data prospectively collected from patients undergoing elective colorectal surgery and who developed SSI caused by *P. aeruginosa* and by other aetiologies were analysed. Patients with pre-existing infection at the surgical site at the time of surgery were excluded from the surveillance.

Study variables

Variables included in this study are described elsewhere [12]. These variables included age, sex, American Society of Anesthesiologists' (ASA) physical status, administration of mechanical bowel preparation (MBP), oral antibiotic prophylaxis (OAP), surgical risk index category based on the National Nosocomial Infections Surveillance (NNIS) modified system criteria [13], adequacy of the intravenous antibiotic prophylaxis, length of surgery (prolonged surgery was considered as the duration of surgery ≥75th percentile of the procedure), laparoscopic surgery, wound classification, date of SSI, site of infection (superficial and deep incisional SSI or organ-space (OS)-SSI, underlying disease (including neoplasia, inflammatory bowel disease and others), microbiology, and antibiotic treatment. Age, ASA score, and NNIS modified risk index were dichotomized for the analysis.

Study outcomes included duration of antibiotic treatment, length of stay (LOS), overall readmission, and overall mortality within 30 days of initial surgery. Readmission, if any, was included in the LOS.

Definitions

SSIs were defined according to the Centers for Disease Control and Prevention (CDC) [14] into incisional (superficial and deep) and OS, and were stratified into categories of surgical procedures (– 1 to 3) according to the risk of surgical infection as defined by NHSN. Superficial and deep incisional SSI were considered together because the nature and management of these two types of infection is similar, in contrast to OS-SSI, which

significantly differs. SSI due to *P. aeruginosa* was defined as the isolation of this microorganism from surgical samples.

The NNIS modified risk index predicts the risk of SSIs in colorectal surgery and range from − 1 to 2, depending on the presence of one or more of the following factors: ASA score III–V (1 point), contaminated or dirty-infected surgery (1 point), length of surgery ≥75th percentile of the procedure (1 point), and laparoscopic surgery (− 1 point) [15]. This risk was calculated for all patients in our cohort.

The intravenous antibiotic prophylaxis included second-generation cephalosporin plus metronidazole administration, in accordance with the last consensus international guidelines on antimicrobial prophylaxis [16]. The treatment was deemed adequate, only when the antibiotics were administered according to the local protocol at each hospital, if the infusion was completed within 60 min of the surgical incision, and perioperative redosing administered (if indicated).

Administration of oral antibiotics in 2–3 doses a day before surgery was considered as OAP. In addition, patients received MBP and the intravenous antibiotic prophylaxis mentioned above. The use of OAP was not mandatory but based on the local protocol at each hospital. OAP included a combination of aminoglycoside (neomycin 1 g, gentamicin 80 mg, or kanamycin 1 g) with 1 g of metronidazole or 1 g of erythromycin [17].

The initial antibiotic treatment was either empirical or targeted, depending on the availability of microbiological sensitivity tests. The type and duration of antibiotic therapy was decided by the attending surgeon according to the local protocol. Source control was defined as any procedure which resolved the infection focus or repaired anatomical derangements. It was classified as reoperation when a new surgical procedure was performed, regardless of whether drainages were inserted or not. Drainage was considered when percutaneous or transrectal drainage was performed.

Treatment failure was defined as the persistence of clinical and/or radiological symptoms/signs of SSIs or all-cause mortality evaluated at 30 days post initial surgery.

Microbiological studies

Surgical samples were collected in most patients (533/669) with suspected SSIs, and blood cultures were performed when indicated by the attending physician. Polymicrobial infection was defined as isolation of ≥2 microorganisms in surgical samples; however, with ≥3 microorganisms isolated, identification was not performed.

The microdilution method, according to the Clinical Laboratory Standard Institute (CLSI) guidelines, was used to test and interpret antibiotic susceptibility [18]. Multidrug-resistant phenotypes were screened according to the CLSI recommendations [19] and characterized by PCR and DNA sequencing. The multidrug-resistant gram-negative bacteria suspected were: (i) extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae; (ii) carbapenemase-producing Enterobacteriaceae; and (iii) multidrug-resistant strains of *P. aeruginosa*, resistant to at least three of the following classes of antibiotics: carbapenems, ureidopenicillins, cephalosporins (ceftazidime and cefepime), monobactams, aminoglycosides, or fluoroquinolones.

Statistical analysis

Categorical variables were described as totals and frequencies while continuous variables were described as medians and interquartile ranges (IQR). Univariate analyses comparing patients with SSIs caused by *P. aeruginosa* and patients with SSIs caused by other microorganisms were performed using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. A multivariate logistic regression analysis which included statistically significant and clinically relevant variables in the univariate analysis was performed to determine independent predictive factors of *P. aeruginosa* SSI. A p value of < 0.05 was considered to be statistically significant. Results were given as odds ratios (OR) and 95% confidence intervals (95% CI). The final model's goodness-of-fit was assessed by the Hosmer–Lemeshow test. Data were analyzed using the IBM SPSS 20.0 (Chicago, Ill., USA).

Results

Over the entire study period, 3701 patients were enrolled, and 669 (18%) developed SSIs. Of the 669 SSIs, there were 62 (9.3%) *P. aeruginosa* SSIs, 29 incisional SSIs, and 33 OS-SSIs. The number of *P. aeruginosa* SSIs remained stable over the 4-year study period, as shown in Fig. 1.

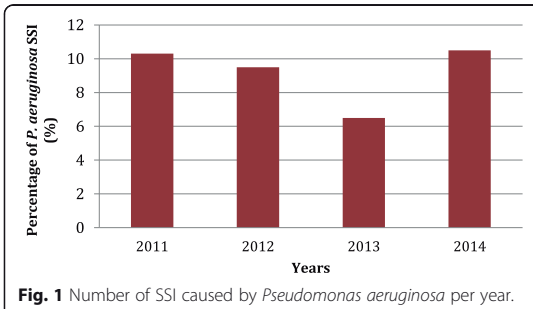

Fig. 1 Number of SSI caused by *Pseudomonas aeruginosa* per year. *P. aeruginosa*: *Pseudomonas aeruginosa,* SSI: surgical site infections. (%): percentage. This figure shows the percentage of surgical site infections caused by *Pseudomonas aeruginosa* after elective colorectal surgery in the whole cohort of patients

Risk factor analysis

Patients with *P. aeruginosa* SSIs had higher ASA score III–IV (67.7% vs 45.5%, $p = 0.001$, OR 2.5, 95% CI 1.44–4.39), NNIS risk index 1–2 (74.2% vs 44.2%, $p < 0.001$, OR 3.6, 95% CI 2.01–6.56), longer duration of surgery (61.3% vs 41.4%, $p = 0.003$, OR 2.2, 95% CI 1.31–3.83), and less frequently received OAP (17.7% vs 33.6%, $p = 0.01$, OR 0.4, 95% CI 0.21–0.83) compared to patients with SSIs due to other organisms, as shown in Table 1.

Microbiological features

The comparison between patients with SSIs caused by *P. aeruginosa* and those with SSIs caused by other microorganisms is shown in Table 2. Of the 62 *P. aeruginosa* SSI cases, two had concomitant bacteremia (one case of *P. aeruginosa* and *Bacteroides fragilis,* and one of *Bacteroides spp)*. The SSIs caused by *P. aeruginosa* were more frequently polymicrobial (67.7% vs 33.4%, $p < 0.001$, OR 4.2, 95% CI 2.39–7.30) and less frequently accompanied by gram-positive organisms (16.1% vs 29.2%, $p = 0.02$, OR 0.4, 95% CI 0.23–0.94) than SSIs caused by other microorganisms. Multidrug-resistant *P. aeruginosa* was detected in three cases (4.8%). There were no differences in the number of multidrug-resistant *Enterobacteriaceae* isolated between patients with *P. aeruginosa* SSIs and those with SSIs due to other organisms.

Treatment

Among patients, 19 (65.5%) of 29 patients with *P. aeruginosa* incisional SSIs received antibiotic treatment, while all 33 patients (100%) with *P. aeruginosa* OS-SSIs received antibiotics. The initial antibiotic management of *P. aeruginosa* SSIs is shown in Table 3. Empirical treatment had a median duration of 10 (IQR 6–16) days and was switched to a targeted treatment in 33.3% of cases. In 13 cases (28.8%), there was no further treatment after empirical antibiotic. Targeted treatment, either initial or after the empirical regimen, had a median duration of 11 (IQR 7–18) days. Of the 33 patients with

Table 1 Risk factors analysis of patients with *P. aeruginosa* SSI and SSI due other organisms

Epidemiological characteristics	Non-SSI ($n = 3032$)	*P. aeruginosa* SSI ($n = 62$)	Other SSI ($n = 607$)	*P-value	OR (95% CI)
Age, median (IQR), years	69.6 (60.7–78)	71.3 (64.9–80)	69.9 (61.4–77)	0.1	1.0 (0.97–1.12)
Male sex, *n* (%)	1814 (59.8)	44 (71)	431 (71)	0.9	1.0 (0.56–1.78)
ASA III-IV, *n* (%)	1178 (38.9)	42 (67.7)	276 (45.5)	0.001	2.5 (1.44–4.39)
NNIS 1–2, *n* (%)	993 (32.8)	46 (74.2)	268 (44.2)	< 0.001	3.6 (2.01–6.56)
Indication for surgery, *n* (%):					
- Neoplasia	2868 (94.6)	57 (91.9)	577 (95.1)	0.3	0.5 (0.22–1.58)
- Inflammatory bowel disease	73 (2.4)	3 (4.8)	15 (2.5)	0.3	2.0 (0.56–7.13)
- Other	87 (2.9)	2 (3.2)	14 (2.3)	0.6	1.4 (0.31–6.36)
Type of surgery, *n* (%)				0.2	1.3 (0.81–2.33)
- Colon	2104 (69.4)	34 (54.8)	380 (62.6)		
- Rectum	928 (30.6)	28 (45.2)	227 (37.4)		
Adequate antibiotic prophylaxis, *n* (%)	2526 (83.3)	55 (88.7)	502 (82.7)	0.2	1.6 (0.73–3.37)
Duration of surgery ≥75th p[a], *n* (%)	1163 (38.4)	38 (61.3)	251 (41.4)	0.003	2.2 (1.31–3.83)
Laparoscopic surgery, *n* (%)	1975 (65.1)	25 (40.3)	297 (48.9)	0.2	0.7 (0.41–1.29)
Detection of SSI during hospitalization, *n* (%)	_	46 (74.2)	435 (71.7)	0.6	1.1 (0.65–1.93)
Oral antibiotic prophylaxis, *n* (%)	1352 (44.6)	11 (17.7)	204 (33.6)	0.01	0.4 (0.21–0.83)
Mechanical bowel preparation, *n* (%)	2283 (77.1)	50 (80.6)	454 (75.8)	0.4	1.3 (0.69–2.56)
Ostomy, *n* (%)	715 (23.6)	29 (46.8)	218 (36)	0.09	1.5 (0.92–2.64)
Previous chemotherapy, *n* (%)	471 (15.5)	15 (24.2)	125 (20.6)	0.5	1.2 (0.66–2.26)
Previous radiotherapy, *n* (%)	452 (14.9)	14 (22.6)	112 (18.5)	0.4	1.3 (0.68–2.41)
Type of SSI, *n* (%):				0.6	1.1 (0.67–1.92)
- Incisional	_	29 (46.8)	304 (50.1)		
- Organ-space	_	33 (53.2)	303 (49.9)		

P. aeruginosa: Pseudomonas aeruginosa, *SSI:* surgical site infection, *IQR:* interquartile range, *ASA:* American Society of Anaesthesiologists' physical status, *NNIS:* National Nosocomial Infections Surveillance Risk Index

**P*-value refers to comparison between *P. aeruginosa* SSI and other SSI

[a]Length of surgery greater than the 75th percentile of the procedure

Table 2 Microbiological features of SSI with or without *Pseudomonas aeruginosa*

Microorganisms	*P. aeruginosa* SSI ($n = 62$)	Other SSI ($n = 607$)	*P*-value	OR (95% CI)
Polymicrobial infection, *n* (%)	42 (67.7)	203 (33.4)	< 0.001	4.2 (2.39–7.30)
Gram-negative bacteria, *n* (%)	28 (45.2)	262 (43.2)	0.7	1.1 (0.64–1.83)
- *E. coli*	17 (27.4)	212 (34.9)	0.2	0.7 (0.39–1.26)
• *E. coli* MDR[a]	4 (6.5)	24 (4)	0.3	1.6 (0.56–4.99)
- *K. pneumoniae*	3 (4.8)	27 (4.4)	0.8	1.1 (0.32–3.70)
• *K. pneumoniae* MDR[a]	1 (1.6)	8 (1.3)	0.8	1.2 (0.51–9.97)
Gram-positive bacteria, *n* (%)	10 (16.1)	177 (29.2)	0.02	0.4 (0.23–0.94)
- Enterococcus spp	6 (9.7)	111 (18.3)	0.08	0.4 (0.20–1.13)
• *E. faecalis*	4 (6.5)	54 (8.9)	0.5	0.7 (0.24–2.02)
• *E. faecium*	2 (3.2)	56 (9.2)	0.1	0.3 (0.07–1.37)
- *S. aureus*	3 (4.8)	26 (4.3)	0.8	1.1 (0.33–3.86)
- *Coagulase negative staphylococci*	1 (1.6)	12 (2)	0.8	0.8 (0.1–6-35)
Fungus, *n* (%)	1 (1.6)	19 (3.1)	0.5	0.5 (0.06–3.85)
- *C. albicans*	1 (1.6)	15 (2.5)	0.6	0.6 (0.08–4.98)
Anaerobes, *n* (%)	1 (1.6)	33 (5.4)	0.2	0.3 (0.03–2.12)
- *B. fragilis*	0 (0)	16 (2.6)	0.1	0.9 (0.88–0.92)
- *C. perfringens*	0 (0)	3 (0.5)	0.6	0.9 (0.88–0.92)

P. aeruginosa: Pseudomonas aeruginosa, SSI: surgical site infection, *MDR*: multidrug-resistant, *E. Coli: Escherichia coli, K. pneumoniae: Klebsiella pneumoniae, A. baumannii: Acinetobacter baumannii, E. faecalis: Enterococcus faecalis, E. faecium: Enterococcus faecium, S. aureus: Staphylococcus aureus, C. albicans: Candida albicans, B. fragilis: Bacteroides fragilis, C. perfringens: Clostridium perfringens*

[a]*E. coli* MDR *and K. pneumoniae* MDR are included in the box above referring to the organism group

OS-SSI, 28 (84.8%) underwent source control of the infectious focus, 19 underwent reoperation due to significant anastomotic leakages while 9 underwent percutaneous drainage due to small leakages or abscesses.

Outcomes

Patients with *P. aeruginosa* SSIs underwent a longer duration of antibiotic treatment (median 17 [IQR 10–24] vs 13 [IQR 8–20] days, $p = 0.015$, OR 1.1, 95% CI 1.00–1.12), higher LOS (22 [IQR 15–42] vs 19 [IQR 12-28] days, $p = 0.02$, OR 1.1, 95% CI 1.00–1.17), and higher treatment failure rate (30.6% vs 20.8%, $p = 0.07$, OR 1.7, 95% CI 0.96–2.99) than patients with SSIs due to other organisms, as shown in Table 4. There was no difference in the mortality rate between the two groups.

Predictive factors

Multivariate logistic regression analysis of predictive factors for *P. aeruginosa* SSIs based on significant factors at the univariate analysis level is shown in Table 5. ASA

Table 3 Initial antimicrobial management of *P. aeruginosa* SSI

Empirical	($n = 45$, 72.5%)	Targeted	($n = 7$, 11.3%)
Antibiotic	*n* (%)	Antibiotic	*n* (%)
Amoxicillin-clavulanic acid	15 (33.3)	Piperacillin-tazobactam	2 (28.5)
Meropenem/Imipenem	13 (28.8)	Meropenem	1 (14.2)
Piperacillin-tazobactam	9 (20)	3GC plus metronidazole	1 (14.2)
3GC	2 (4.4)	FQ	1 (14.2)
FQ plus metronidazole	2 (4.4)	3GC	1 (14.2)
Aminoglycoside plus metronidazole	1 (2.2)	FQ plus metronidazole	1 (14.2)
3GC plus metronidazole	1 (2.2)		
Piperacillin-tazobactam plus cotrimoxazole	1 (2.2)		
Antifungal			
Fluconazole	1 (2.2)		

SSI: Surgical site infection, *3GC*: Third-generation cephalosporin, *FQ*: fluoroquinolone

Table 4 Outcome of patients with and without *P. aeruginosa* SSI

Outcomes	Non-SSI (*n* = 3032)	*P. aeruginosa* SSI (*n* = 62)	Other SSI (*n* = 607)	*P-value	OR (95% CI)
Duration of treatment, median (IQR), days	_	17 (10–24)	13 (8–20)	0.015	1.1 (1.00–1.12)
Treatment failure, *n* (%)	_	19 (30.6)	126 (20.8)	0.07	1.7 (0.96–2.99)
Readmission, *n* (%)	88 (2.9)	10 (16.1)	117 (19.3)	0.5	0.8 (0.39–1.63)
Length of readmission, median (IQR), days	(*n* = 88) 5 (3–9)	(*n* = 10) 11 (7–15)	(*n* = 117) 10 (7–15)	0.8	1.0 (0.91–1.06)
Length of stay, median (IQR), days	7 (5–10)	22 (15–42)	19 (12–28)	0.02	1.1 (1.00–1.17)
Mortality, *n* (%)	13 (0.4)	4 (6.5)	31 (5.1)	0.6	1.28 (0.43–3.75)

P. aeruginosa: *Pseudomonas aeruginosa*, *SSI*: surgical site infection, *IQR*: interquartile range
*P-value refers to comparison between *P. aeruginosa* SSI and other SSI

score and duration of surgery, that were significantly associated with *P. aeruginosa* SSI in the univariate analysis, were not included in the multivariate analysis due to their association with NNIS risk index. The independent predictive factors for *P. aeruginosa* SSIs were NNIS risk index (OR 2.3, 95% CI 1.03–5.40) and preoperative OAP (OR 0.4, 95% CI 0.23–0.90).

Discussion

To the best of our knowledge, this is the first study to identify the clinical characteristics and risk factors of *P. aeruginosa* SSIs in a large cohort of patients undergoing elective colorectal surgery. The main findings are that NNIS modified risk index and OAP are associated with the risk of development of SSIs caused by *P. aeruginosa*.

Majority of the patients in our cohort had colorectal cancer. The intestinal microbiota of these patients present specific characteristics, showing an increased proportion of gram-negative bacteria, especially Enterobacteriaceae [20, 21]. However, *P. aeruginosa* does not seem to play a relevant role in the intestinal microbiota of patients, even with colorectal cancer. For this reason, we did not expect to detect a high rate of *P. aeruginosa* SSIs; however, we observed a rate of almost 10% in our cohort. A partial explanation could be that the systemic antimicrobial prophylaxis produced a selective antibiotic pressure leading to overgrowth of *P. aeruginosa*. Furthermore, tissue trauma and blood loss following a major surgery as well as the use of drugs (such as opioids) are associated with significant loss of diversity and abundance of the gut normal microbiota. This leads to an increase in the number and virulence of low-abundance collagenase-producing intestinal microorganisms, such as *Enterococcus faecalis* or *P. aeruginosa,* which may favor SSI and ileus by modulating the immune response of the host [22, 23]. OAP has been associated with good postoperative outcomes, nevertheless, the underlying changes in the gut microbiota are not completely known.

Table 5 Multivariate analysis of predictive factors of *P. aeruginosa* SSI

	P. aeruginosa SSI/ Other SSI	*P*-value	OR (95% CI)
NNIS 1–2, %	74.2/44.2	0.04	2.3 (1.03–5.40)
Rectal surgery, %	45.2/37.4	0.3	1.4 (0.70–2.70)
Oral antibiotic prophylaxis, %	17.7/33.6	0.02	0.4 (0.23–0.90)
Ostomy, %	46.8/36	0.5	1.2 (0.60–2.30)

P. aeruginosa: *Pseudomonas aeruginosa*, *SSI*: surgical site infection, *OR*: Odds Ratio, *95% CI*: 95% confidence interval, *ASA*: American Society of Anaesthesiologists' physical status. *NNIS*: National Nosocomial Infections Surveillance Risk Index

Previous studies have reported rates of *P. aeruginosa* SSI similar to those observed in the present study, despite the differences in patient characteristics (including emergency surgery, intensive care unit admission, and prior use of broad-spectrum antibiotics) [24, 25]. Patients with *P. aeruginosa* SSIs in our cohort had higher ASA score and NNIS risk index, longer duration of surgery, and lower levels of OAP. The study conducted by Montravers et al. [26], which involved more than 300 patients with community-acquired and nosocomial intraabdominal infections, revealed that *P. aeruginosa* was more frequently isolated in nosocomial cases (in more severely ill patients).

It should be noted that *P. aeruginosa* SSIs were more frequently polymicrobial in nature than SSIs caused by other organisms, as previously observed [24, 25]. It is possible that the interaction of *P. aeruginosa* with other gram-negative bacteria led to this clinical impact. We observed a very low rate of multidrug-resistant *P. aeruginosa*, explained by the short hospital stay of patients before surgery and the absence of prior long-term antibiotic therapy.

Among patients with *P. aeruginosa* SSIs, the most frequently used empiric antibiotic treatment failed to target the organism. This suggests that the attending physicians might not have considered *Pseudomonas* as the causative agent. The role of the empiric antibiotic treatment in the outcome of patients with intraabdominal infections has been widely discussed [24, 26]; however, as we noted previously [12], it is generally accepted that the control of the source of infection is the cornerstone of management in

severe cases [27, 28]. Most patients with *P. aeruginosa* OS-SSIs in our cohort underwent source control.

Patients with *P. aeruginosa* SSIs had a longer antibiotic treatment, higher treatment failure, and longer hospitalization than patients with SSIs caused by other organisms. This reinforces the idea that *P. aeruginosa* affects patients with more serious underlying diseases and implies worse prognoses. However, we did not observe differences in mortality rates between patients with *P. aeruginosa* SSIs and SSIs caused by other organisms, probably due to our low overall mortality rate, neither did they observe differences, in studies previously cited [24, 26]. As reported previously, treatment failure among patients with the most serious SSIs in our cohort was not associated with any microbiological etiology, including *P. aeruginosa* [12].

The administration of OAP was a strong protective factor against the development of *P. aeruginosa* SSIs. Two previous outstanding studies [29, 30] based on the large American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, showed a significant decrease in the rates of postoperative incisional SSI, anastomotic leakage, ileus, and 30-day mortality in patients undergoing elective colorectal procedures who received MBP and OAP (compared to patients who had received MBP or OAP alone, or those who had not received any preparation). We also showed a reduction in the OS-SSI rate with the use of MBP combined with OAP [31]. Some authors have however suggested the same benefit in the use of OAP without MBP [32], but this need to be validated in further large multicenter randomized controlled trials.

The most appropriate combination of oral antibiotics has not been clearly stated. In our study, the most frequently used aminoglycoside was neomycin, since its poor absorption in the digestive tract allows all its effects to be concentrated in the intestinal lumen. This specific characteristic, which also rules it out for the treatment of systemic infections, may justify its good activity against *P. aeruginosa*. Although the use of OAP in elective colorectal surgery has been recommended in recent World Health Organization guidelines [33, 34], many hospitals have abandoned this practice over the last decade since MBP has been shown to be ineffective [35]. Since OAP is administered together with MBP, the use of OAP was also abandoned. Although evaluation of OAP was not an objective in our study, our results reinforce the use of OAP combined with MBP in reducing *P. aeruginosa* SSI rates.

This study has some limitations. First, the hospitals in our study differed in terms of size, characteristics, levels of activity, and type of preoperative oral preparation. As previously mentioned OAP was not administered in a uniform manner but according to local protocols that did not depend on the baseline characteristics of patients. However, all hospitals followed the VINCat recommendations and CLSI microbiological guidance. Second, because of the nature of our study, we could not exclude bias related to risk factors not included in the study. However, the large number of patients and the consistent collection of the data by expert infection control staffs, support the results.

Conclusions

SSIs due to *P. aeruginosa* after elective colorectal surgery mainly occur in patients with a high NNIS risk index and in those who do not receive OAP. We recommend empirical antibiotic treatment covering the multi-susceptible *P. aeruginosa* in more severely ill patients who develop SSIs but do not receive OAP. We observed worse outcomes in patients with *P. aeruginosa* SSIs, as demonstrated by the need for longer antibiotic treatments, higher treatment failure, and higher LOS. Further studies are needed to prove the effectiveness of OAP in the prevention of *P. aeruginosa* SSIs after colorectal surgery.

Abbreviations

95% CI: 95% confidence interval; ACS-NSQIP: American College of Surgeons National Surgical Quality Improvement Program; ASA: American Society of Anaesthesiologists; CDC: Centers for Disease Control and Prevention; CLSI: Clinical Laboratory Standard Institute; ESBL: Extended-spectrum beta-lactamase; HAI: Healthcare-associated infection; IBM SPSS: International Business Machines Corp. Statistical Package for the Social Sciences; IQR: Interquartile range; LOS: Length of stay; MBP: Mechanical bowel preparation; NHSN: National Healthcare Safety Network; NNIS: National Nosocomial Infection Surveillance; OAP: Oral antibiotic prophylaxis; OR: Odds ratio; OS-SSI: Organ-space surgical site infection; SSI: Surgical site infection; USA: United States of America

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AG, JC, and MP conceived and designed the study; AG analyzed and interpreted the patient data regarding surgical site infections after colon and rectal surgery. AG, JC, JMB and MP were major contributors in writing the manuscript. All other authors (ES, DC, MPi, VDB, EE, CN, MB, RP, AL, AC, SB, DF, EL and FG) collected the patient data, read, and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee at Hospital Universitari de Bellvitge (reference: PR305/15). As this study analysed data that is part of the

VINCat program registry, and no individual data is published as well as no intervention is performed to patients, no individual consent to participate was required by the Ethics Committee at our institution. This study conformed to the ORION guidelines for reporting cohort studies [36].

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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References
1. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf. Accessed 8 Oct 2016.
2. Anderson DJ, MD, MPH, Podgorny DNP, MS, RN, Berríos-Torres SI, MD, Bratzler DW, DO, MPH, Dellinger EP, MD, Greene L, RN, MPS, CIC, et al. Strategies to Prevent Surgical Site Infections in Acute Care Hospitals: 2014 Update. Infect Control Hosp Epidemiol. 2014;35(6):605–27.
3. Petrosillo N, Drapeau CMJ, Nicastri E, Martini L, Ippolito G, Moro ML, et al. Surgical site infections in Italian hospitals: a prospective multicenter study. BMC infect Dis. 2008;8:34.
4. Keenan JE, Speicher PJ, Thacker JKM, Walter M, Kuchibhatla M, Mantyh CR. The preventive surgical site infection bundle in colorectal surgery: an effective approach to surgical site infection reduction and health care cost savings. JAMA Surg. 2014;149:1045–52.
5. Gellatly SL, Hancock RE. Pseudomonas aeruginosa: new insights into pathogenesis and host defenses. Pathog Dis. 2013;67(3):159–73.
6. Livermore DM. Multiple mechanisms of antimicrobial resistance in Pseudomonas aeruginosa: our worst nightmare? Clin Infect Dis. 2002;34:634–40.
7. Kim YJ, Jun YH, Kim YR, Park KG, Park YJ, Kang JY, et al. Risk factors for mortality in patients with Pseudomonas aeruginosa bacteremia; retrospective study of impact of combination antimicrobial therapy. BMC infect Dis. 2014;14:161.
8. VINCat. Generalitat de Catalunya. Available from: http://catsalut.gencat.cat/ca/inici. Accessed 8 Oct 2016.
9. National Healthcare Safety Network (NHSN) | Centers for Disease Control and Prevention (CDC). Available from: http://www.cdc.gov/nhsn/. Accessed 8 Oct 2016.
10. Pujol M, Limón E, López-Contreras J, Sallés M, Bella F, Gudiol F. Surveillance of surgical site infections in elective colorectal surgery. Results of the VINCat Program (2007–2010). Enferm. Infecc. Microbiol. Clin. 2012;30(Suppl 3):20–5.
11. Limón E, Shaw E, Badia JM, Piriz M, Escofet R, Gudiol F, et al. Post-discharge surgical site infections after uncomplicated elective colorectal surgery: impact and risk factors. The experience of the VINCat program. J Hosp Infect. 2014;86:127–32.
12. Gomila A, Badia JM, Carratalà J, Serra-Aracil X, Shaw E, Diaz-Brito V, et al. Current outcomes and predictors of treatment failure in patients with surgical site infection after elective colorectal surgery. A multicentre prospective cohort study. J Inf Secur. 2017;74:555–63.
13. Horan TC, Emori G, Atlanta M. Definitions of key terms used in the NNIS system. Am J Infect Control. 1997;25:112–6.
14. CDC Surgical Site Infection (SSI) Event definition. Available from: http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf. Accessed 8 Oct 2016.
15. Gaynes RP, Culver DH, Horan TC, Edwards JR, Richards C, Tolson JS. Surgical site infection (SSI) rates in the United States, 1992–1998: the National Nosocomial Infections Surveillance System Basic SSI risk index. Clin Infect Dis. 2001;33:S69–77.
16. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. ASHP RePoRt antimicrobial prophylaxis clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Heal Pharm. 2013;70:195–283.
17. Khubchandani IT, Karamchandani MC, Sheets JA, Stasik JJ, Rosen L, Riether RD. Metronidazole vs. erythromycin, neomycin, and cefazolin in prophylaxis for colonic surgery. Dis Colon Rectum. 1989;32:17–20.
18. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement (M100-S22). Wayne, PA: CLSI; 2012.
19. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; 10th edn (approved standard M07-A10). Wayne: CLSI; 2015.
20. Gao R, Gao Z, Huang L, Qin H. Gut microbiota and colorectal cancer. Eur J Clin Microbiol Infect Dis. 2017;36:757–69.
21. Rapozo DCM, Bernardazzi C, de HSP S. Diet and microbiota in inflammatory bowel disease: the gut in disharmony. World J Gastroenterol. 2017;23:2124–40.
22. Alverdy JC, Hyoju SK, Weigerinck M, Gilbert JA. The gut microbiome and the mechanism of surgical infection. Br J Surg. 2017;104:e14–23.
23. Guyton K, Alverdy JC. The gut microbiota and gastrointestinal surgery. Nat Rev Gastroenterol Hepatol. 2017;14(1):43–54.
24. Augustin P, Tran-Dinh A, Valin N, Desmard M, Crevecoeur MA, Muller-Serieys C, et al. Pseudomonas aeruginosa post-operative peritonitis: clinical features, risk factors, and prognosis. Surg. Infect (Larchmt). 2013;14:297–303.
25. Miller B, Popejoy MW, Hershberger E, Steenbergen JN, Alverdy J. Characteristics and outcomes of complicated intra-abdominal infections involving Pseudomonas aeruginosa from a randomized, double-blind, phase 3 Ceftolozane-Tazobactam study. Antimicrob Agents Chemother. 2016;60:4387–90.
26. Montravers P, Lepape A, Dubreuil L, Gauzit R, Pean Y, Benchimol D, et al. Clinical and microbiological profiles of community-acquired and nosocomial intra-abdominal infections: results of the French prospective, observational EBIIA study. J Antimicrob Chemother. 2009;63:785–94.
27. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N. Engl. J. Med. 2015;372:1996–2005.
28. Sartelli M, Catena F, Abu-Zidan FM, Ansaloni L, Biffl WL, Boermeester MA, et al. Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference. World. J Emerg Surg. 2017;12:22.
29. Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined mechanical and Oral antibiotic bowel preparation reduces incisional surgical site infection and anastomotic leak rates after elective colorectal resection: an analysis of colectomy-targeted ACS NSQIP. Ann Surg. 2015;262:331–7.
30. Kiran RP, Murray ACA, Chiuzan C, Estrada D, Forde K. Combined preoperative mechanical bowel preparation with Oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. Ann Surg. 2015;262:416–25.
31. Gomila A, Carratalà J, Camprubí D, Shaw E, Badia JM, Cruz A, et al. Risk factors and outcomes of organ-space surgical site infections after elective colon and rectal surgery. Antimicrob. Resist. Infect Control. 2017;6:40.
32. Koullouros M, Khan N, Aly EH. The role of oral antibiotics prophylaxis in prevention of surgical site infection in colorectal surgery. Int J Color Dis. 2016;32(1):1–18.
33. De Jonge S, Atema JJ, Gans S, Boermeester MA, Gomes SM, Solomkin JS, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet infect Dis. 2016;16:e276–87.
34. Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, et al. New WHO recommendations on intraoperative and postoperative measures

for surgical site infection prevention: an evidence-based global perspective. Lancet infect Dis. 2016;16:e288–303.
35. Jung B, Påhlman L, Nyström P-O, Nilsson E. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg. 2007;94:689–95.
36. Stone SP, Cooper BS, Kibbler CC, Cookson BD, Roberts JA, Medley GF, Duckworth G, Lai R, Ebrahim S, Brown EM, Wiffen PJ, Davey PG. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. Lancet Infect Dis. 2007;7(4):282-8.

7. DISCUSSION

Our investigation aimed to identify the predictive factors and to define adequate management of SSI occurring after elective colorectal surgery. We also analysed the effect of different preventive measures of SSI, specifically preoperative OAP.

Our first observational prospective cohort study showed differences in the predictive factors and outcomes of OS-SSI in colon and rectal surgery. In our cohort, patients undergoing colon surgery had higher mortality than patients undergoing rectal surgery, probably because they were older and had more comorbidities. In contrast, although patients undergoing rectal surgery were younger they had higher rates of SSI, probably due to the increased complexity the procedure the risk of contamination and the length of the surgery, which frequently involves excision of additional organs.

Male sex was found to be a common risk factor for OS-SSI in colon and rectal surgery. Interestingly, the administration of OAP was a common protective factor in both surgeries. In view of this finding, the VINCat Program applied a bundle of preventive measures for SSI in elective colon and rectal surgeries, including the administration of OAP combined with MBP the day before surgery.

In the second study involving the same cohort of 10 Spanish hospitals participating in the VINCat Program, our aim was to analyze certain factors involved in the development of EO-SSI (SSI occurring within the first week of surgery) and LO-SSI (SSI occurring from the 8th to 30th day), and the possible differences in outcome between these two infections.

Our results showed that, among the 669 patients who developed SSI, approximately half developed EO-SSI and the other half

LO-SSI. We found that patients with EO-SSI underwent colon surgery and developed OS-SSI on more occasions, while the number of cases of incisional SSI and the readmission rates were higher in patients with LO-SSI. Unlike other HAIs, there were no significant differences regarding etiology and the presence of multidrug-resistance between EO-SSI and LO-SSI, suggesting that the antibiotic empiric coverage does not need to be adjusted depending on the timing of the development of the SSI. The multivariate analysis identified the following distinctive predictive factors of EO-SSI: male sex, ASA score III-IV, receiving MBP and stoma creation. In contrast, predictive factors of LO-SSI were longer duration of surgery, having received chemotherapy, or rectal surgery. Patients who received an stoma had complicated surgeries which usually involved the rectum, or complex pathologies such as inflammatory bowel disease or diverticulosis that involve a higher risk of infection. Stoma creation may well have acted as a marker of illness severity. Chemotherapy is usually administered in stage II-III rectal tumors to downstage tumor size and improve survival. This treatment causes a degree of inflammation and necrosis, increasing the risk of wound infection when an incision is performed. Laparoscopy and OAP were protective factors in both groups, as previously reported. Mortality was significantly higher in EO-SSI than in LO-SSI, due to the fact that most EO-SSIs were OS-SSIs, the most serious SSIs.

In our third study we aimed to analyse the current antimicrobial treatment and surgical management of OS-SSIs after colon and rectal surgery, in order to find predictive factors of treatment failure that could help prevent these infections. We found

that, overall, 21.7% of patients who developed SSI had treatment failure, and this rate reached 34.2% in patients with OS-SSI, a figure almost 4 times higher than in patients with incisional SSIs. When management of OS-SSI was analysed, we found that all patients with OS-SSI received antibiotic for a median period of more than 15 days, although surprisingly this was not associated with a high rate of *Clostridium difficile* infection. Moreover, 81.2% of these patients required either reoperation or insertion of percutaneous drainage as interventions to control the infection source. In these cases in which source control was achieved, duration of the antibiotic treatment could possibly have been shorter.

We found that the only independent risk factors associated with treatment failure in patients with OS-SSI were older age (≥ 65 years), laparoscopic surgery and reoperation. While the first factor was to be expected, the other two were not. The reason why laparoscopic surgery could be associated with higher treatment failure in this population is that patients who underwent laparoscopy were younger and had less comorbidity, and also the diagnosis was frequently done after discharge. Therefore, since their previous risk was lower, they were discharged earlier than those who underwent laparotomy and their surveillance was not so intensive. In any case, we would recommend the performance of laparoscopic surgery whenever possible due to efficacy in reducing SSI rates, but close follow-up of patients after surgery is mandatory, especially in young patients. Reoperation was found to be a risk factor for treatment failure. Since it usually indicates a more serious OS-SSI, in which a longer postoperative period is required to recover, it was used as a surrogate

marker of illness severity.

In the fourth study we analysed the health costs of developing SSI after elective colorectal surgery, in terms of excess LOS and in-hospital mortality. We were particularly interested in evaluating the health costs of developing OS-SSI compared to the costs of developing incisional SSI or not developing SSI. Our study was the first to use multistate modelling in this type of surgery, which avoids overestimating LOS by not considering the moment of development of SSI. The median LOS in OS-SSI patients was 9 days higher than in patients who did not develop SSI and was 4.2 days higher in those who developed incisional SSI. This is an important finding since this excess of hospital stay reduces the hospital's capacity to admit new patients for surgery and increases the waiting lists for elective surgery. Interestingly, the development of an OS-SSI meant a tenfold increase in the adjusted risk of in-hospital mortality compared to patients who did not develop SSI, and an eightfold increase compared to those who developed incisional SSI. This result underlines the severity of OS-SSI and stresses the necessity of avoiding this complication of elective surgery.

The only independent risk factors associated with the excess LOS in patients with OS-SSI were administration of inadequate IAP and not performing laparoscopic surgery. Adequate IAP and laparoscopic surgery have been associated with a reduction in the risk of postoperative complications, such as ileus or infection; therefore, OS-SSI developing under these conditions would probably be less severe and require a shorter hospital stay than other SSIs. Therefore, these factors may act as confounders of excess LOS attributed to OS-SSI.

The fifth study focused on the analysis of SSI caused by *P. aeruginosa* after elective surgery of the colon and rectum. Almost 10% of the total SSIs were caused by *P. aeruginosa*, a surprisingly high rate given that this agent is not a usual microorganism of the human gut microbiota. However, both the application of intravenous antibiotic prophylaxis (which does not cover *P. aeruginosa*) and the stress produced by the surgery could have contributed to its overgrowth. Surprisingly, most *P. aeruginosa* isolates were multidrug-susceptible, probably because patients had been hospitalized for a very short period previous to surgery. Patients with *P. aeruginosa* SSI had higher ASA score and NNIS modified risk index, which indicates a more serious baseline status than other patients. This could have contributed to lengthening both the antibiotic treatment and the hospitalization after surgery, and to increasing the treatment failure rate compared with SSI caused by other etiologies. This rate was significantly high, around 30%.

Interestingly, we found that the only independent predictive factors for *P. aeruginosa* SSI were higher NNIS risk index and the lack of administration of preoperative OAP. The protective effect of OAP was even higher in patients with *P. aeruginosa* SSI than in patients with SSI due to other etiologies. This is probably because in most cases the oral antibiotic administered included neomycin, an aminoglycoside with poor absorption in the digestive tract and very good profile against *P. aeruginosa*. Although the evaluation of the effectiveness of OAP was not an objective of our study, our results support its use in combination with MBP, but future multicenter trials are needed to confirm these results.

7.1. Specific characteristics and surgical approach in colon and rectal surgery

This large multicentre cohort study found significant differences in the incidence, predictive factors and outcomes of OS-SSI after elective colon and rectal surgery. This suggests that the two procedures should be considered as different surgical interventions.

The separation of procedures according to patients' characteristics may allow more accurate assessment of their specific risk factors. Comparing colon and rectal populations, we found that they had different characteristics in terms of risk factors for SSI. Patients undergoing colon surgery were older, had more inflammatory bowel disease and less laparoscopy, factors related to SSI. On the other hand, patients undergoing rectal surgery were younger but had more rate of malignancy; more frequently received chemoradiotherapy and had longer surgery duration. The surgical techniques were also different, something inherent to the anatomical location of the disease, in special with more ostomies performed in rectal resections. These factors, associated with the fact that the rectum has higher bacterial contamination load, conferred it greater risk of SSI. Accordingly, overall SSI and OS-SSI rates were higher in rectal surgery than in colon surgery. Although these rates were high, they were similar to these reported in previous studies (Serra-Aracil et al. 2011) (Hennessey et al. 2016). Data from surveillance systems in Europe an US vary widely ("Surveillance of surgical site infections in NHS hospitals in England," 2015) (Young et al. 2012), being in most

cases lower than ours, though postdischarge surveillance is not always performed.

We found significant differences in the predictive factors for developing an OS-SSI in colon and rectal surgeries. In colon surgery, independent risk factors predisposing to OS-SSI were male sex and ostomy creation, while laparoscopic surgery and OAP were protective factors. In rectal surgery, independent risk factors for OS-SSI were male sex and longer duration of surgery, whereas OAP was the only protective factor. Male sex was a common risk factor for developing OS-SSI in both colon and rectal surgeries; this association is well established (Morikane et al. 2014) (Tang et al. 2001) (Bakker et al. 2014), although the reasons are not known.

Ostomy creation was a strong risk factor for the development of OS-SSI in colon surgery but not in rectal surgery, as previously reported elsewhere (Serra-Aracil et al. 2011). Ostomies are normally used to divert the faecal stream from a newly created immature anastomosis, or to definitively disconnect the gastrointestinal tract in some extensive colorectal surgeries. Nevertheless, ostomies have been associated with increased rates of SSI in previous studies (Konishi et al. 2006) (Morikane et al. 2014) (Blumetti et al. 2007) (Ho et al. 2011) because they allow organisms from the air, contaminated hands, or skin flora to reach the subcutaneous fat and the wound, and eventually the intraabdominal cavity (Fraccalvieri et al. 2012). In our study, patients with colon surgery who received an ostomy more frequently underwent laparotomy due to complex pathology like inflammatory bowel disease or diverticulitis. These diseases have been

associated with OS-SSI (Eskicioglu et al. 2014), and ostomy creation may act, in part, as a marker of this complex pathology.

The laparoscopic approach significantly reduced SSI rates in several large-database studies and also offered other benefits such as faster recovery of pulmonary function, less pain and shorter postoperative stay (Aimaq et al. 2011) (Kiran et al. 2010). In our study it served as an independent protective factor for the development of OS-SSI in colon surgery, but not in rectal surgery. Probably, the beneficial effect of laparoscopy was exceeded by the higher frequency of risk factors for SSI inherent in rectal surgery.

Importantly, we found that OAP was a protective factor for the development of OS-SSI in both colon and rectal surgeries, although the impact was higher in rectal surgery, probably because the rectum has a higher level of bacterial contamination. During the study period there was not a national or regional recommendation for the application of OAP, and for this reason the use of the measure was decided by each participating hospital (it was only applied in 4 of the 10 hospitals). The findings of the present study lead to a change in the clinical practice of hospitals participating in the VINCat program and in 2016 the use of OAP was institutionally recommended. The OAP combined with intravenous prophylaxis and MBP significantly reduces SSI rates after colon and rectal surgery by decreasing the intraluminal bacterial load (Morris et al. 2015) (Scarborough, Mantyh, Sun, & Migaly 2015) (Machuca et al. 2016); in a previous meta-analysis of randomized controlled trials comparing the effectiveness of OAP plus intravenous antibiotic prophylaxis vs intravenous antibiotic prophylaxis alone, the association of OAP was estimated to reduce the

incidence of SSI by 43% (Bellows, Mills, Kelly, & Gagliardi 2011). Nevertheless, the use of MBP has been widely questioned, due to its unpleasant gastrointestinal effects, and in many studies it has failed to reduce SSI rates (Dahabreh et al. 2015). Currently, since almost all studies that demonstrate the effectiveness of OAP have been performed in combination with MBP, the use of MBP will have to be raised again. Last World Health Organization (WHO) recommendations on preoperative measures for surgical site infection prevention suggest using OAP with MBP in all adults undergoing elective colorectal surgery (De Jonge et al. 2016) (Allegranzi et al. 2016).

Longer duration of surgery was an independent risk factor for the development of an OS-SSI in rectal surgery. This association has often been described in the colorectal surgery population (Hennessey et al. 2016) (Gervaz et al. 2012) (Watanabe et al. 2015), and it also favours other risk factors for SSI like the hyperglycaemia or hypothermia (Allegranzi et al. 2016). Given the capacity of this parameter to predict SSI, it was included as one of the components of the NNIS risk index. Rectal tumours close to the anal verge usually require extensive surgery with additional organ resection, requiring longer operative time and causing greater bleeding, factors that have been associated with an increased risk of SSI (Bakker et al. 2014) (Kwaan, Melton, Madoff, & Chipman 2015). Moreover, in these prolonged surgeries, antibiotic redosing is not always administered correctly.

Significantly, mortality of patients with organ-space SSI after colon surgery was higher than after rectal surgery. The fact that

patients in the colon group were older and more frequently had complicated diseases other than neoplasia could explain this result.

Among the strengths of the study is its multicentre nature, the large number of patients included and the fact that all data were collected by trained infection control staff. However, the study has a number of limitations that should be acknowledged. Firstly, the retrospective analysis of prospectively collected data may lead to bias and is unable to control for confounding factors. Secondly, certain risk factors that have been linked to SSI such as perioperative hyperglycaemia, hypothermia and blood transfusion were not recorded here.

In conclusion, we found differences in the incidence, risk factors and outcomes of overall SSI and OS-SSI between colon and rectal surgery, suggesting that they could be considered as different surgical procedures. These differences should be borne in mind for the purpose of surveillance and for the implementation of preventive strategies. Administration of OAP would be an important measure to reduce the OS-SSI rate in both colon and rectal surgeries.

7.2. Timing of the development of surgical site infection in elective colorectal surgery

The most significant finding of our multicenter study involving a large number of patients was that predictive factors of EO-SSI and LO-SSI after elective colorectal surgery were different. Predictive factors for EO-SSI were male sex, ASA score III-IV, not receiving MBP and stoma creation, while predictive factors of LO-SSI were rectal surgery, longer

duration of surgery and previous chemotherapy.

Regarding SSI aetiology, *E. coli* was significantly more frequent in EO-SSI than in LO-SSI since the risk of anastomotic leakage and organ-space SSI is the highest within the first days after surgery. Conversely, *S. aureus* was significantly more frequent in LO-SSI than in EO-SSI, since manipulation of wounds during hospitalization increases the risk of wound infection (Smith et al. 2004). Accordingly, incisional SSI was more frequent in the late period in our cohort. Although not significant because of the small number of isolates, we found a tendency to a higher proportion of multidrug-resistant *P. aeruginosa* in LO-SSI compared to EO-SSI, probably related to antibiotic pressure.

We found several distinctive predictive factors for EO-SSI. Firstly, MBP was a protective factor in itself. There is increasing controversy about the efficacy of MBP since a large body of evidence suggests that MBP has no beneficial effect in reducing SSI rates unless it is accompanied by OAP (Dahabreh et al. 2015)' (Murray & Kiran 2016). We agree with that opinion, and probably the effect of MBP was influenced by that of concomitant OAP, but it could also have had a beneficial effect in reducing patient morbidity since most EO-SSIs were organ-space.

Stoma creation was found to be the strongest risk factor for the development of EO-SSI. One previous study (Ricciardi et al. 2014) found that stoma creation was a risk factor for superficial and deep incisional SSI, but that analysis did not include OS-SSI. In our cohort, cases involving stoma creation were more complex and technically challenging, since surgery was frequently performed due to pathologies like IBD or diverticulosis rather than for neoplasia,

therefore conferring a higher risk of SSI. Another study (Messaris et al. 2015) that analyzed the effect of stoma creation in rectal cancer patients after chemotherapy and radiotherapy found results similar to ours: patients in the stoma group had greater comorbidities (higher ASA score, body mass index or hypertension) than the other group. This suggests that need for stoma could be a marker of illness severity. One last study (Shiomi et al. 2015) found that the anastomotic leakage rate was increased in the group of patients with a diverting stoma, but that the stoma diminished the severity of the leakage.

Regarding distinctive predictive factors for LO-SSI, we found that rectal surgery was a risk factor. The rectal surgical technique usually requires incision through the perineum, which is a highly contaminated area. Manipulation of wounds could increase the risk of incisional SSI, the most frequent type of SSI in this group. Extensive surgery in this area usually requires a long operation time (Kwaan et al. 2015), which was also an independent risk factor for LO-SSI. We formerly described higher rates of SSI associated with rectal surgery (Gomila et al. 2017).

Chemotherapy was the strongest risk factor for developing LO-SSI. Chemotherapy with capecitabine or 5-fluoruracil is almost always administered in stage II-III rectal cancer to downstage tumor size and improve survival after surgery. Despite the beneficial effects of the neoadjuvant therapy, it causes some degree of inflammation, necrosis and fibrosis of surrounding tissue. This leads to increased risk of intraoperative bleeding, wound dehiscence and wound infection (Li et al. 2016).

Regarding common predictive factors of SSI, we found that laparoscopy and OAP were protective factors in both early and late SSI, as has been previously reported (Morris et al. 2015) (Kiran et al. 2010).

When outcomes were analyzed, we found that the development of EO-SSI increased LOS and mortality compared to LO-SSI or no-SSI. This was probably related to the fact that EO-SSI was predominantly organ-space, while LO-SSI was more frequently incisional. A previous study by our group already showed the worst outcome associated with OS-SSI (Gomila et al. 2017).

Among the strengths of the study is its multicenter nature, the large number of patients included and the fact that data collection was uniformly performed by trained infection control staff. This study has some limitations that should be acknowledged. First, the number of variables was restricted because a multicenter surveillance system must collect limited but consistent variables. Second, the cut-off used to define EO-SSI and LO-SSI was arbitrary, though it was established after clinical observation of SSI.

In conclusion, we found some specific predictive factors for the development of EO-SSI and LO-SSI after elective colorectal surgery. The identification of these factors could help to establish targeted preventive measures for each infection type. According to our results, it seems appropriate to perform laparoscopic surgery whenever possible and give MBP combined with OAP in all cases. Stoma creation should be done only when necessary in colon surgery, and duration of surgery should be shortened as much as possible in rectal surgery.

7.3. Management and outcomes of surgical site infection after elective colorectal surgery

This large, multicentre, prospective cohort study found that SSI rates and treatment failure among adult patients after elective colorectal surgery are notably high. It also identified that older age, laparoscopic surgery, and need for reoperation were independently associated with treatment failure.

We observed an overall SSI rate of 18.1%. Previous reported rates vary widely for a number of reasons. First of all, different definitions for SSI have been used: some include anastomotic leakage, while others do not. Second, the quality of data varies depending on whether there is underreporting and whether active post-discharge surveillance is performed to assess for SSI (Limón et al. 2014) (Tanner et al. 2013). In 2009 the NHSN reported an SSI rate after colorectal surgery of as low as 5.6% (Edwards et al. 2009), even when post-discharge surveillance was performed. Other studies have reported rates similar to ours (Staszewicz, Eisenring, Bettschart, Harbarth, & Troillet 2014), (Hennessey et al. 2016) (Serra-Aracil et al. 2011). Interestingly, we found a high proportion of ESBL-producing strains, particularly among *K. pneumoniae* and *E. coli*, probably reflecting an increased endogenous colonization by these microorganisms (Betteridge et al. 2013). This finding coincides with those of a recent large study of antimicrobial susceptibility of GNB in intra-abdominal infections (Chen et al. 2011). We found a high number of *P. aeruginosa* isolates, most of which (95.1%) were multidrug-susceptible. This high incidence of *P. aeruginosa* infection could be

related to the fact that most patients had neoplasia (Rolston, Nesher, & Tarrand, 2014). The low resistance rate could be attributed to the fact that all these patients were electively admitted to hospital. Regarding the incidence of other pathogens, Enterococcus spp. were the most frequent Gram-positive microorganisms identified, as has previously been reported (Augustin et al. 2010). Interestingly, *E. faecium*, which is of growing concern due to its resistance pattern, was almost three times more frequent in OS-SSI than in incisional SSI. This is important because the empirical treatment frequently used in OS-SSIs, such as carbapenems or piperacillin-tazobactam, does not offer effective coverage against this microorganism.

In this study, patients with OS-SSI had a long duration of therapy, with a median exceeding 15 days. In addition, empirical treatment was rarely switched to a targeted option based on microbiological results. A recent clinical trial comparing a long antibiotic course of 10 days with a short course of 4 days for the treatment of intraabdominal infections demonstrated that, in the presence of adequate control of the infectious source, the short course was equally as safe as the long course in terms of patient outcomes (Sawyer et al. 2015). This could be a good opportunity to improve antimicrobial stewardship programs in those hospitals with higher antibiotic consumption. We found that most patients with an OS-SSI underwent reoperation due to suspected anastomotic leakage or needed percutaneous or transrectal drainage. Thus, the duration of antibiotic therapy could have been shorter in those patients with adequate source control. Despite this, the rate of *C. difficile* infection was quite low in our cohort.

Length of stay was significantly longer in patients with OS-SSI compared to those with incisional SSI. This is an important finding because other investigators revealed that SSI increased mean LOS by 9.7 days and mean cost of treatment by 20,842 dollars (de Lissovoy et al. 2009). We found high readmission and mortality rates: both were substantially higher than previously reported (Bakker et al. 2014) (Francis et al. 2015) (Eagye & Nicolau 2009) and in most cases were due to SSI. In fact, the mortality rate in OS-SSI reached almost 9%, which emphasizes the seriousness of this infection.

This is the first study investigating predictive factors of treatment failure in an elective colorectal surgery population. We found that 21.7% of patients who developed an SSI had treatment failure within 30 days of surgery. This figure was nearly four times higher in OS-SSI than in incisional SSI. This means that more than one third of patients who developed an OS-SSI still had an active infection 30 days after the initial surgery.

We found that the only independent risk factors for treatment failure were older age (≥ 65 years), laparoscopic surgery, and reoperation. Neither type of surgery (colon vs rectum) nor the presence of multidrug-resistant GNB influenced outcome. Older age and higher ASA score have been associated with poorer outcomes in previous studies (Kohut et al. 2015), probably reflecting patients' frailty.

Although laparoscopic surgery is regarded as a protective factor against incisional SSI (Aimaq et al. 2011), we found that it was an independent risk factor for 30-day treatment failure. Patients with an OS-SSI who underwent laparoscopic surgery were younger, with

lower NNIS modified Risk Index, lower ASA score, they had more frequently received chemotherapy and radiotherapy and were more frequently diagnosed after discharge than those with open surgery. It can be hypothesized that because patients with previous laparoscopy had less comorbidities, they were discharged earlier than those with previous laparotomy, and then they presented with a more severe infection that contributed to treatment failure.

In our study, reoperation was found to be a risk factor for treatment failure, although it was probably a surrogate marker of illness severity rather than a risk factor itself. Reoperation is required in most cases of anastomotic leakage in order to achieve a clinical cure, but a longer postoperative period is needed to resolve the infection. Among the patients who died, 13.3% had undergone reoperation compared with 1.2% in those who had not died ($p< 0.001$), a finding that reinforces the idea that reoperation is a marker of illness severity.

Among the strengths of the study are its multicentre nature, the large number of patients included, and the fact that data collection was uniformly performed by trained infection control staff. Nevertheless, the study has a number of limitations that should be acknowledged. Firstly, it is a retrospective analysis of prospectively collected data. Therefore, as with any observational study, there is potential for residual confounding. Secondly, it is possible that some factors that might be associated with treatment failure were not recorded, such as the adequacy of initial antibiotic treatment.

In conclusion, the present study provides important and current data on the most prevalent microbiology of SSI after elective

colorectal surgery that may help physicians when choosing prophylactic and empirical treatments. Treatment failure is a frequent problem among patients with OS-SSI and can be underestimated. This complication is associated with high readmission and mortality rates and prolonged antibiotic therapy and LOS. Source control of the infection focus is crucial and allows shortening the antibiotic treatment and avoiding side effects. Careful attention should be paid to older patients with previous laparoscopy who require reoperation for OS-SSI, so that treatment failure can be recognised early. Moreover, effective preventive strategies are urgently needed.

7.4. Analysis of the health cost of organ-space surgical site infection in elective colorectal surgery.

This study shows that amongst SSIs, OS-SSIs had the greatest burden on LOS and mortality in patients undergoing elective colorectal surgery in a large cohort of patients. The results are consistent with those reported in the literature; however, previous studies commonly used matching designs to estimate excess LOS (Kirkland et al. 1999) (Eagye & Nicolau 2009) (Jenks, Laurent, McQuarry, & Watkins 2014) (Ohno et al. 2018), a type of design that overestimate LOS, since they do not consider time-dependency of the infection (De Angelis, Murthy, Beyersmann, & Harbarth 2010) (Heister, Wolkewitz, & Kaier 2018).

Excess LOS attributed to SSI varies from 4.1 to 15 days, although most studies which report these data include a small number of surgeries and evaluate data on patients undergoing different types of surgical procedures (Kirkland et al. 1999) (Eagye & Nicolau 2009)

(Jenks et al. 2014). Our study is the first using multistate modelling to estimate excess LOS in elective colorectal surgery. Patients with OS-SSI stayed an average of nine additional days in hospital, a period greater than the median stay of patients without infection in the cohort. Since elective colorectal surgery is currently a high-volume procedure worldwide due to the incidence of cancer (Favoriti et al. n.d.), improving efforts to avoid this preventable complication would free up hospital capacity to treat additional patients.

There is a paucity of studies exploring factors that predispose to a prolonged stay in colorectal surgery. In such studies, age, comorbidities, open surgery approach, prolonged ileus or infection are associated with the longest hospital stays (Reddy et al. 2003) (Faiz et al. 2011) (Ahmed et al. 2014). Our results suggest that the longest admissions occurred in patients receiving inadequate IAP or undergoing an open surgery. In contrast, no associations with age, the highest ASA score, type of procedure or primary diagnosis were observed. Since adequate IAP and laparoscopic access to the abdominal cavity prevent postoperative complications (Ho et al. 2011) (Kang et al. 2012), these factors may actually act as surrogate markers for confounders that could influence LOS, such as prolonged ileus. Unfortunately, a lack of data prevented us explore this subject further.

Elective colorectal surgery is considered a safe procedure since it is associated with low mortality rates, ranging from 0.9% to 4 % (Cone et al. 2011), (Billeter et al. 2012). In our study, the mortality rate was lower than 1% in patients with incisional SSI or those who did not have an infection; but for patients with OS-SSI, the risk of death during admission was 10 times higher than the risk for uninfected patients.

Interestingly, a recent study conducted in the UK found that among postoperative infections in elective colorectal surgery, OS-SSI was the only infection associated with an increase in 1-year mortality (Kirby et al. 2015).

The strength of the present study is that we have considered the time-dependent nature of SSI and competing risk events, to obtain a more precise estimation of extra LOS and risk of mortality in a large prospective cohort of patients. Notably, the analysis enables us to show that incisional SSI has a slight effect on LOS and no effect on mortality. This reinforces the idea that OS-SSI in elective colorectal surgery is the SSI which carries the highest health burden.

The major limitation of this work is that it only included infections detected during hospitalisation. Since more than 20% of SSIs are detected post-discharge (Limón et al., 2014), the real effect of OS-SSI on overall LOS must therefore be miscalculated. To include patients with OS-SSIs diagnosed post-discharge in the analysis, two approaches could be proposed: including a new path from discharge to infection in the multistate model, or using models for multivariate survival and recurrent events. A further limitation is the unadjusted nature of the excess LOS analysis; although to overcome that, we computed a binary indicator of excess LOS and adopted a generalised linear model. However, unmeasured information on postoperative details or on time-varying covariates, such as ICU admission, might be confounding (Pouwels et al., 2018).

In summary, accounting for time-dependency and competing events, OS-SSI substantially extends LOS and increases risk of mortality. These results reinforce the notion that OS-SSI is the SSI with

the highest health burden in elective colorectal surgery. Hence, OS-SSI prevention should be a priority for all healthcare providers.

7.5. An organism of special interest in colorectal surgery: *Pseudomonas aeruginosa*

This is the first study to analyse the risk factors and clinical characteristics of SSI caused by *P. aeruginosa* in a large cohort of patients undergoing elective colorectal surgery. The main findings are that factors included in the NNIS modified risk index and OAP play a major role in the development of SSI caused by *P.aeruginosa*.

The majority of patients in our cohort had colorectal cancer. The intestinal microbiota of these patients presents certain specific characteristics, showing an increased proportion of GNB, especially Enterobacteriaceae (Gao, Gao, Huang, & Qin 2017) (Rapozo, Bernardazzi, & de Souza 2017). Nevertheless, *P. aeruginosa* does not seem to play a relevant role in this setting. For this reason, we did not expect to find a high rate of *P. aeruginosa* SSI; nevertheless, we observed a rate of almost 10%. The standard intravenous antibiotic prophylaxis we used consisted in a combination of a second-generation cephalosporin plus metronidazole, in accordance with the latest international guidelines (Bratzler et al. 2013). This systemic antimicrobial prophylaxis was able to produce a selective antibiotic pressure leading to overgrowth of *P. aeruginosa*.

Previous research has found rates of *P.aeruginosa* SSI similar to those observed in the present study (Montravers et al. 2009) (Miller, Popejoy, Hershberger, Steenbergen, & Alverdy 2016), in spite of the

difference in patient characteristics, since they included emergency surgery and prior use of broad-spectrum antibiotics. The study by Montravers et al. (Montravers et al. 2009), which dealt with more than 300 patients with community-acquired and nosocomial intraabdominal infection, found that *P. aeruginosa* was more frequently isolated in the nosocomial cases, who were more severely ill. Nevertheless, when analysing mortality, *P. aeruginosa* was not associated with higher death rates. In the study by Augustin et al. (Augustin et al. 2013), which analysed *P. aeruginosa* postoperative peritonitis, mortality was associated with higher APACHE II score and organ dysfunction, but not with the presence of *P. aeruginosa*.

Patients with *P. aeruginosa* SSI in our cohort had higher ASA score and NNIS risk index, longer duration of surgery and lower levels of OAP administration. Moreover, they had longer antibiotic treatment, higher treatment failure and longer hospitalization than patients with SSI caused by other organisms. This reinforces the idea that *P. aeruginosa* affects patients with more serious underlying diseases and implies worse prognosis. Nonetheless, we did not observe differences in the mortality rate between patients with *P. aeruginosa* SSI and other SSI, probably due to our low overall mortality rate. As we have reported previously, treatment failure among patients with the most serious SSI in our cohort was not associated with any microbiological aetiology, including *P. aeruginosa* (Gomila et al. 2017).

It should be noted that *P. aeruginosa* SSI was more frequently polymicrobial than SSI caused by other organisms, as previously observed (Augustin et al. 2013) (Miller et al. 2016). It may be the

interaction of this organism with other GNB that has the clinical impact. We found a very low rate of multidrug-resistant *P. aeruginosa*, explained by the short hospital stay of patients before surgery and the absence of prior antibiotic therapy for a long period.

Among patients with *P. aeruginosa* SSI, the most frequently used empiric antibiotic did not cover the organism. This suggests that the attending physicians did not expect it as aetiology. Even so, most patients with inadequate empiric antibiotic had incisional SSI, which has mild consequences. The role of the empiric antibiotic in the outcome of patients with intraabdominal infections has been widely discussed (Augustin et al. 2013) (Montravers et al. 2009), but it is generally accepted that control of the infectious focus is the cornerstone of management in severe cases (Sawyer et al. 2015) (Sartelli et al. 2017), as we noted in previous work (Gomila et al. 2017).

Importantly, the administration of OAP was a strong protective factor against the development of *P. aeruginosa* SSI. Many studies have analysed the effect of different antibiotic combinations in the prevention of SSI after colorectal surgery (Morris et al. 2015) (Bellows et al. 2011) (Scarborough et al. 2015) (Gomila et al. 2017), but none of them have analysed their effectiveness against the specific causative organisms of SSI. In our study, the most frequently used aminoglycoside was neomycin, since its poor absorption in the digestive tract allows all its effect to be concentrated in the intestinal lumen. This specific characteristic, which also rules it out for the treatment of systemic infections, may justify its good activity against *P. aeruginosa*. Although the use of OAP in elective colorectal surgery has been recommended by the recent World Health Organization

guidelines (De Jonge et al. 2016) (Allegranzi et al. 2016), many hospitals have abandoned this practice over the last decade since MBP has been shown to be ineffective (Jung, Påhlman, Nyström, & Nilsson 2007). Our results support the use of OAP combined with MBP to reduce the SSI rates.

This study has some limitations. First, the hospitals included differed in terms of size, characteristics and levels of activity; nevertheless, all of them followed the VINCat recommendations and CLSI microbiological guidance. Second, as it was an observational study, data were retrospectively analysed after prospective collection, which may have led to bias. However, the large number of patients included and the fact that data were consistently collected by expert infection control staff lend support to the results.

In conclusion, SSI due to *P. aeruginosa* after elective colorectal surgery is frequent and occurs mainly in patients with comorbidities and in those who do not receive OAP. We observed worse outcome in patients with *P. aeruginosa* SSI, represented by the need for longer antibiotic treatment, higher treatment failure and higher LOS. Our results support the use of preoperative OAP in all patients undergoing elective colorectal surgery.

7.6. Limitations of the studies

The studies included present certain limitations that should be acknowledged.

Firstly, all the studies were conducted in a cohort of patients from 10 Spanish hospitals from the same region in Catalonia and the

extrapolation of our results to other settings should be made with caution. Also, the participating hospitals differed in terms of size, activity, characteristics and type of preoperative preparation; this may have led us to overestimate or underestimate the differences found between surgeries, types of SSI, and the effect of certain predictive factors. Nevertheless, all the studies follow the VINCat guidance on HAI preventive measures.

Second, all the studies reported are observational; despite our efforts to adjust for confounders by multivariate analysis, we were not able to eliminate unmeasured confounders between groups.

Related to these first two limitations, we should mention a further one: the inability to properly evaluate the administration of preoperative OAP, which was a measure that seemed to play a significant role in all our analysis. The application of this measure was not controlled in the studies, and it was administered heterogeneously in accordance with local protocols. While some hospitals applied only MBP, others administered MBP together with OAP. Therefore, we were unable to definitively establish any causal relationship between the apparent protective effect of OAP and the risk of development of SSI.

Fourth, certain risk factors that have been linked to SSI, among them perioperative hyperglycaemia, hypothermia, body mass index and blood transfusions, were not recorded in our database. This was because a multicenter surveillance Program such as the VINCat must collect limited but consistent and robust variables to maintain a standard of data quality collection. It is probable that our rates of SSI

after elective colorectal surgery, which are notably high compared to other surveillance programs, are due to this high standard of quality.

In the study of the timing of development of SSI, the cut-off used to define EO-SSI and LO-SSI was applied arbitrarily after observation of the clinical evolution of SSI. We thought that 7 days, which was the median period of development of SSI, would be long enough to distinguish between the types and outcomes of SSI.

In the study of the management and predictors of treatment failure for OS-SSI, the adequacy of the initial antibiotic treatment was not recorded: we only recorded whether it was an empirical or targeted treatment. This made it more difficult to assess the possible effect of the antimicrobial therapy on patients' outcomes.

In our calculation of the health costs of SSI, we could not adjust the excess LOS for factors that might have influenced it (except for SSI itself, which was introduced in the multistate model). For instance, other time-dependent variables such as intensive care unit admission or details on severity of infection could not be controlled due to a lack of data.

8. CONCLUSIONS

8.1. Specific characteristics and surgical approach in colon and rectal surgery

- Colon and rectal surgery differed in incidence, risk factors and outcomes of overall SSI and OS-SSI. These findings suggest that from the point of view of surveillance they should be considered as different surgical procedures. Rectal surgery had higher SSI rates, although colon surgery was associated with higher mortality.
- The administration of OAP would be an important measure to reduce the OS-SSI rate in both colon and rectal surgeries, although prospective randomized controlled trials are needed to confirm these data.

8.2. Timing of the development of surgical site infection in elective colorectal surgery

- We identified specific predictive factors for the development of EO-SSI and LO-SSI after elective colorectal surgery. The identification of these factors could help establish targeted preventive measures for each infection type.
- Although further studies are needed, it seems appropriate to perform laparoscopic surgery and administer OAP combined with MBP whenever possible.
- Stoma creation, either lateral or terminal, appears as predictor of EO-SSI. Therefore, special attention should be paid to patients

with stoma creation in order to detect any sign of serious SSI.

- The duration of surgery should be shortened as much as possible since it has been associated with increased risk of LO-SSI.

8.3. Management and outcomes of surgical site infection after elective colorectal surgery

- We found a significant prevalence of ESBL-production among *E. coli* and especially, *K. pneumoniae* isolates. In contrast, most *P. aeruginosa* isolates were multidrug-susceptible.
- Patients in our cohort received prolonged antibiotic treatment even when the infection focus was adequately controlled. Source control is crucial and usually allows a reduction in the antibiotic treatment and avoids side effects.
- Treatment failure is a frequent complication in patients who develop SSI after elective colorectal surgery, especially in those with OS-SSIs. In these cases treatment failure affected more than one third of patients, and it was associated with high readmission and mortality rates and prolonged therapy and LOS.
- Independent risk factors for treatment failure in patients with OS-SSIs were age (≥ 65 years), the performance of laparoscopic surgery and the need for reoperation. Careful attention should be paid to older patients with previous laparoscopy who require reoperation for OS-SSI, so that treatment failure can be recognised promptly.

8.4. Analysis of the health cost of organ-space surgical site infection in elective colorectal surgery.

- Patients with OS-SSI presented significant increases in LOS compared to patients who developed incisional-SSI and those who did not develop SSI.
- Risk factors associated with excess LOS in patients with OS-SSI were the administration of IAP and not performing laparoscopic surgery, although no further analysis of these issues can be made.
- In-hospital mortality in patients with OS-SSI was eight times higher than mortality of patients with incisional-SSI and 10 times higher than in those who did not develop SSI.

8.5. An organism of special interest in colorectal surgery: *Pseudomonas aeruginosa*

- Surgical site infection due to *P. aeruginosa* after elective colorectal surgery accounted for almost 10% of cases and occurred mainly in patients with high NNIS risk index (which is indicative of a more serious baseline status) and in those who did not receive OAP.
- We found a very low rate of multidrug-resistant *P. aeruginosa* strains (4.8%). Therefore, we recommend empirical antibiotic treatment to cover the multidrug-susceptible *P. aeruginosa* in more severely ill patients who develop SSI but who do not receive OAP.

- We observed worse outcomes in patients with *P. aeruginosa* SSI, characterized by the need for longer antibiotic treatments, higher treatment failure and higher LOS than patients with SSI due to other etiologies.
- Future studies are needed to assess the effectiveness of OAP in the prevention of *P. aeruginosa* SSI after elective colorectal surgery.

9. REFERENCES

Ali, U., Dunne, T., Gurland, B., Vogel, JD., Kiran, RP. (2014). Actual versus estimated length of stay after colorectal surgery: which factors influence a deviation? *The American Journal of Surgery*, *208*(4), 663–669.

Aimaq, R., Akopian, G., Kaufman HS. (2011). Surgical site infection rates in laparoscopic versus open colorectal surgery. *The American Surgeon*, *77*(10), 1290–1294.

Allegranzi, B., Zayed, B., Bischoff, P., et al. (2016). New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *The Lancet Infectious Diseases*, *16*(12), e288–e303.

Anderson, D.J., Podgorny, K., Berríos-Torres, S.I., et al. Strategies to Prevent Surgical Site Infections in Acute Care Hospitals: 2014 Update. *Infect Control Hosp Epidemiol*. 2014 Sep;35 Suppl 2:S66-88.

Aran, V., Victorino, A.P., Thuler, L.C., Ferreira, C.G. (2016). Colorectal Cancer: Epidemiology, Disease Mechanisms and Interventions to Reduce Onset and Mortality. *Clinical Colorectal Cancer*. 15(3):195-203.

Augustin, P., Kermarrec, N., Muller-Serieys, C., et al. (2010). Risk factors for multidrug resistant bacteria and optimization of empirical antibiotic therapy in postoperative peritonitis. *Critical Care*, *14*(R20).

Augustin, P., Tran-Dinh, A., Valin, N., et al. (2013). Pseudomonas aeruginosa Post-Operative Peritonitis: Clinical Features, Risk Factors, and Prognosis. *Surgical Infections*, *14*(3), 297–303.

Bakker, I. S., Grossmann, I., Henneman, D., Havenga, K., Wiggers, T.

(2014). Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. *The British Journal of Surgery*, *101*(4), 424–32; discussion 432.

Barnett, A. G., Beyersmann, J., Allignol, A., Rosenthal, V. D., Graves, N., Wolkewitz, M. (2011). The Time-Dependent Bias and its Effect on Extra Length of Stay due to Nosocomial Infection. *Value in Health*, *14*(2), 381–386.

Baucom, R. B., Phillips, S. E., Ehrenfeld, J. M., et al. (2015). Association of Perioperative Hypothermia During Colectomy With Surgical Site Infection. *JAMA Surgery*, *150*(6), 570–5.

Bellows, C. F., Mills, K. T., Kelly, T. N., Gagliardi, G. (2011). Combination of oral non-absorbable and intravenous antibiotics versus intravenous antibiotics alone in the prevention of surgical site infections after colorectal surgery: a meta-analysis of randomized controlled trials. *Techniques in Coloproctology*, *15*(4), 385–95.

Betteridge, T., Merlino, J., Natoli, J., Cheong, E. Y.-L., Gottlieb, T., Stokes, H. W. (2013). Plasmids and Bacterial Strains Mediating Multidrug-Resistant Hospital-Acquired Infections Are Coresidents of the Hospital Environment. *Microbial Drug Resistance*, *19*(2), 104–109.

Beyersmann, J., Wolkewitz, M., Allignol, A., Grambauer, N., Schumacher, M. (2011). Application of multistate models in hospital epidemiology: Advances and challenges. *Biometrical Journal*, *53*(2), 332–350.

Billeter, A. T., Polk, H. C., Hohmann, S. F., et al. (2012). Mortality after Elective Colon Resection: The Search for Outcomes that Define Quality in Surgical Practice. *Journal of the American College of*

Surgeons, *214*(4), 436–443.

Biondo, S. (2014). Prevention of surgical site infection: still an important challenge in colorectal surgery. *Techniques in Coloproctology*, *18*(10), 861–2.

Blumetti, J., Luu, M., Sarosi, G., et al. (2007). Surgical site infections after colorectal surgery: Do risk factors vary depending on the type of infection considered? *Surgery*, *142*, 704–11.

Bratzler, D. W., Dellinger, E. P., Olsen, K. M., et al. (2013). Antimicrobial prophylaxis Clinical practice guidelines for antimicrobial prophylaxis in surgery. *American Journal Health-System Pharmacy*, *70*(70), 195–283.

Chen, Y. H., Hsueh, P. R., Badal, R. E., et al. (2011). Antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region according to currently established susceptibility interpretive criteria. *Journal of Infection*, *62*(4), 280–291.

Chittick, P., Azhar, S., Movva, K., Keller, P., Boura, J. A., Band, J. (2013). Early onset versus late onset peripherally inserted central venous catheter infections: an analysis of risk factors and microbiology. *Infection Control and Hospital Epidemiology*, *34*(9), 980–3.

Coello, R., Charlett, A., Wilson, J., Ward, V., Pearson, A., Borriello, P. (2005). Adverse impact of surgical site infections in English hospitals. *Journal of Hospital Infection*, *60*(2), 93–103.

Cone, M. M., Herzig, D. O., Diggs, B. S., et al. (2011). Dramatic decreases in mortality from laparoscopic colon resections based on data from the Nationwide Inpatient Sample. *Archives of*

Surgery (Chicago, Ill. : 1960), *146*(5), 594–9.

Dahabreh, I. J., Steele, D. W., Shah, N., Trikalinos, T. A. (2015). Oral Mechanical Bowel Preparation for Colorectal Surgery: Systematic Review and Meta-Analysis. *Diseases of the Colon and Rectum*, *58*(7), 698–707.

De Angelis, G., Murthy, A., Beyersmann, J., Harbarth, S. (2010). Estimating the impact of healthcare-associated infections on length of stay and costs. *Clin Microbiol Infect*, *16*, 1729–1735.

De Jonge, S., Atema, J. J., Gans, S., Boermeester, M. A., Gomes, S. M., Solomkin, J. S. (2016). New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *The Lancet Infectious Diseases*, *16*, e276–e287.

de Lissovoy, G., Fraeman, K., Hutchins, V., Murphy, D., Song, D., Vaughn, B. B. (2009). Surgical site infection: incidence and impact on hospital utilization and treatment costs. *American Journal of Infection Control*, *37*(5), 387–97.

Eagye, K. J., Nicolau, D. P. (2009). Deep and organ/space infections in patients undergoing elective colorectal surgery: incidence and impact on hospital length of stay and costs. *The American Journal of Surgery*, *198*, 359–367.

Edwards, J. R., Peterson, K. D., Mu, Y., et al. (2009). National Healthcare Safety Network (NHSN) report: Data summary for 2006 through 2008, issued December 2009. *American Journal of Infection Control*, *37*, 783–805.

Eskicioglu, C., Nelson, J., Roberts, P. L., et al. (2014). Is Patient Diagnosis a Risk Factor for Organ Space Infection After Colorectal

Resections? *Diseases of the Colon & Rectum*, *57*(6), 733–739.

Faiz, O., Haji, A., Burns, E., Bottle, A., Kennedy, R., Aylin, P. (2011). Hospital stay amongst patients undergoing major elective colorectal surgery: predicting prolonged stay and readmissions in NHS hospitals. *Colorectal Disease*, *13*(7), 816–822.

Favoriti, P., Carbone, G., Greco, M., et al. (2016). Worldwide burden of colorectal cancer: a review. *Updates in Surgery*, *68*. (1):7-11.

Centers for Disease Control and Prevention. (2016). National and State Healthcare Associated Infections Progress Report 2016. Available at: https://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf

Fraccalvieri, D., Biondo, S., Saez, J., et al. (2012). Management of colorectal anastomotic leakage: differences between salvage and anastomotic takedown. *American Journal of Surgery*, *204*, 671–676.

Francis, N. K., Mason, J., Salib, E., et al. (2015). Factors predicting 30-day readmission after laparoscopic colorectal cancer surgery within an enhanced recovery programme. *Colorectal Diseases,* 17(7):O148-54

Frasson, M., Granero-Castro, P., Ramos Rodriguez, J. L., et al. (2016). Risk factors for anastomotic leak and postoperative morbidity and mortality after elective right colectomy for cancer: results from a prospective, multicentric study of 1102 patients. *International Journal of Colorectal Disease*, *31*(1), 105–114.

Gao, R., Gao, Z., Huang, L., Qin, H. (2017). Gut microbiota and colorectal cancer. *European Journal of Clinical Microbiology & Infectious Diseases*, *36*(5), 757–769.

Garnacho-Montero, J., Aldabó-Pallás, T., Palomar-Martínez, M., et al. (2008). Risk factors and prognosis of catheter-related bloodstream infection in critically ill patients: a multicenter study. *Intensive Care Medicine*, *34*, 2185–2193.

Gaynes, R. P., Culver, D. H., Horan, T. C., Edwards, J. R., Richards, C., Tolson, J. S. (2001). Surgical Site Infection (SSI) Rates in the United States, 1992–1998: The National Nosocomial Infections Surveillance System Basic SSI Risk Index. *Clinical Infectious Diseases*, *33*(s2), S69–S77.

Gervaz, P., Bandiera-Clerc, C., Buchs, N. C., et al. (2012). Scoring system to predict the risk of surgical-site infection after colorectal resection. *British Journal of Surgery*, *99*(4), 589–595.

Giard, M., Lepape, A., Allaouchiche, B., et al. (2008). ,Early-and late-onset ventilator-associated pneumonia acquired in the intensive care unit: comparison of risk factors. *Journal of Critical Care*, *23*, 27–33.

Gomila, A., Badia, J. M., Carratalà, et al. (2017). Current outcomes and predictors of treatment failure in patients with surgical site infection after elective colorectal surgery. A multicentre prospective cohort study. *Journal of Infection*, *74*(6), 555–563.

Gomila, A., Carratalà, J., Camprubí, D., et al. (2017). Risk factors and outcomes of organ-space surgical site infections after elective colon and rectal surgery. *Antimicrobial Resistance & Infection Control*, *6*(1), 40.

Graves, N., Harbarth, S., Beyersmann, J., Barnett, A., Halton, K., Cooper, B. (2010). Estimating the Cost of Health Care–Associated Infections: Mind Your p's and q's. *Clinical Infectious Diseases*,

50(7), 1017–1021.

Graves, N., Weinhold, D., Tong, E., et al. (2007). Effect of Healthcare-Acquired Infection on Length of Hospital Stay and Cost. *Infection Control & Hospital Epidemiology*, *28*(03), 280–292.

Guirao, X., Juvany, M., Franch, G., Navinés, J., Amador, S., Badía, J. M. (2013). Value of C-reactive protein in the assessment of organ-space surgical site infections after elective open and laparoscopic colorectal surgery. *Surgical Infections*, *14*(2), 209–15.

Haley, R. W., Culver, D. H., White, J. W., et al. (1985). The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. *American Journal of Epidemiology*, *121*(2), 182–205.

Harris, A. D., Samore, M. H., Lipsitch, M., Kaye, K. S., Perencevich, E., Carmeli, Y. (2002). Control-group selection importance in studies of antimicrobial resistance: examples applied to Pseudomonas aeruginosa, Enterococci, and Escherichia coli. *Clinical Infectious Diseases*, *34*(12), 1558–63.

Heister, T., Wolkewitz, M., Kaier, K. (2018). Editor Estimating the additional costs of surgical site infections: length bias, time-dependent bias, and conditioning on the future. *The Journal of Hospital Infection*. 2018 May;99(1):103-104.

Hennessey, D. B., Burke, J. P., Ni-Dhonochu, T., Shields, C., Winter, D. C., Mealy, K. (2016). Risk factors for surgical site infection following colorectal resection: a multi-institutional study. *International Journal of Colorectal Disease*, *31*(2), 267–71.

Ho, J., Tambyah, P. A., Paterson, D. L. (2010). Multiresistant Gram-negative infections: a global perspective. *Current Opinion in*

Infectious Diseases, *23*(6), 546–53.

Ho, V. P., Barie, P. S., Stein, S. L., et al. (2011). Antibiotic Regimen and the Timing of Prophylaxis Are Important for Reducing Surgical Site Infection after Elective Abdominal Colorectal Surgery. *Surgical Infections*, *12*(4), 255–260.

Ho, V. P., Stein, S. L., Trencheva, K., et al. (2011). Differing risk factors for incisional and organ/space surgical site infections following abdominal colorectal surgery. *Diseases of the Colon and Rectum*, *54*(7), 818–25.

Jenks, P. J., Laurent, M., McQuarry, S., Watkins, R. (2014). Clinical and economic burden of surgical site infection (SSI) and predicted financial consequences of elimination of SSI from an English hospital. *Journal of Hospital Infection*, *86*(1), 24–33.

Jung, B., Påhlman, L., Nyström, P.-O., Nilsson, E. (2007). Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. *British Journal of Surgery*, *94*(6), 689–695.

Kang, C. Y., Chaudhry, O. O., Halabi, W. J., et al. (2012). Outcomes of laparoscopic colorectal surgery: data from the Nationwide Inpatient Sample 2009. *The American Journal of Surgery*, *204*(6), 952–957.

Khan, A. S., Dancer, S. J., Humphreys, H. (2012). Priorities in the prevention and control of multidrug-resistant Enterobacteriaceae in hospitals. *Journal of Hospital Infection*, *82*(2), 85–93.

Khan, R., Al-Dorzi, H. M., Tamim, H. M., et al. (2016). The impact of onset time on the isolated pathogens and outcomes in ventilator associated pneumonia. *Journal of Infection and Public Health*, *9*,

161–171.

Kiran, R. P., El-Gazzaz, G. H., Vogel, J. D., Remzi, F. H. (2010). Laparoscopic approach significantly reduces surgical site infections after colorectal surgery: Data from national surgical quality improvement program. *Journal of the American College of Surgeons*, *211*(2), 232–238.

Kirby, A., Burnside, G., Bretsztajn, L., Burke, D. (2015). Postoperative infections following colorectal surgery in an English teaching hospital. *Infectious Diseases (London, England)*, *47*(11), 825–9.

Kirkland, K. B., Briggs, J. P., Trivette, S. L., Wilkinson, W. E., Sexton, D. J. (1999). The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. *Infection Control and Hospital Epidemiology*, *20*(11), 725–30.

Kirkland, K. B., Briggs, J. P., Trivette, S. L., Wilkinson, W. E., Sexton, D. J. (1999). The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. *Infection Control and Hospital Epidemiology*, *20*(11), 725–30.

Kohut, A. Y., Liu, J. J., Stein, D. E., Sensenig, R., Poggio, J. L. (2015). Patient-specific risk factors are predictive for postoperative adverse events in colorectal surgery: an American College of Surgeons National Surgical Quality Improvement Program-based analysis. *American Journal of Surgery*, *209*(2), 219–29.

Konishi, T., Watanabe, T., Kishimoto, J., Nagawa, H. (2006). Elective colon and rectal surgery differ in risk factors for wound infection: results of prospective surveillance. *Annals of Surgery*, *244*(5),

758–63.

Kwaan, M. R., Melton, G. B., Madoff, R. D., Chipman, J. G. (2015). Abdominoperineal Resection, Pelvic Exenteration, and Additional Organ Resection Increase the Risk of Surgical Site Infection after Elective Colorectal Surgery: An American College of Surgeons National Surgical Quality Improvement Program Analysis. *Surgical Infections (Larchmt)*, *16*(6), 675–83.

Li, Y., Wang, J., Ma, X., et al. (2016). A Review of Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer. *International Journal of Biological Sciences*, *12*(8), 1022–31.

Limón, E., Shaw, E., Badia, J. M., et al. (2014). Post-discharge surgical site infections after uncomplicated elective colorectal surgery: impact and risk factors. The experience of the VINCat Program. *Journal of Hospital Infection*, *86*(2), 127–32.

M07-A10. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; 10th edition (2015).

M100-S25. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. (2015).

Machuca, I., Gutiérrez-Gutiérrez, B., Pérez-Cortés, S., et al. Oral decontamination with aminoglycosides is associated with lower risk of mortality and infections in high-risk patients colonized with colistin-resistant, KPC-producing *Klebsiella pneumoniae*. *Journal of Antimicrobial Chemotherapy*, *71*(11), 3242–3249.

Magill, S. S., Edwards, J. R., Bamberg, et al. (2014). Multistate Point-Prevalence Survey of Health Care–Associated Infections. *New*

England Journal of Medicine, *370*(13), 1198–1208.

Mandell, G. L., Bennet, J. E., Dolin, R. (2014). *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th edition*. Elsevier Health Science, ed.

Messaris, E., Connelly, T. M., Kulaylat, et al. (2015). Is a diverting ostomy needed in mid-high rectal cancer patients undergoing a low anterior resection after neoadjuvant chemoradiation? An NSQIP analysis. *Surgery*, *158*(3), 686–691.

Miller, B., Popejoy, M. W., Hershberger, E., Steenbergen, J. N., Alverdy, J. (2016). Characteristics and Outcomes of Complicated Intra-abdominal Infections Involving Pseudomonas aeruginosa from a Randomized, Double-Blind, Phase 3 Ceftolozane-Tazobactam Study. *Antimicrobial Agents and Chemotherapy*, *60*(7), 4387–90.

Montravers, P., Lepape, A., Dubreuil, L., et al. (2009). Clinical and microbiological profiles of community-acquired and nosocomial intra-abdominal infections: results of the French prospective, observational EBIIA study. *Journal of Antimicrobial Chemotherapy*, *63*(4), 785–794.

Morikane, K., Honda, H., Yamagishi, T., Suzuki, S., Aminaka, M. (2014). Factors associated with surgical site infection in colorectal surgery: the Japan nosocomial infections surveillance. *Infection Control and Hospital Epidemiology*, *35*(6), 660–6.

Morris, M. S., Graham, L. A., Chu, D. I., Cannon, J. A., Hawn, M. T. (2015). Oral Antibiotic Bowel Preparation Significantly Reduces Surgical Site Infection Rates and Readmission Rates in Elective Colorectal Surgery. *Annals of Surgery*, *261*(6), 1034–40.

Murray, A. C. A., Kiran, R. P. (2016). Bowel Preparation: Are Antibiotics

Necessary for Colorectal Surgery? *Advances in Surgery*, *50*(1), 49–66.

National Healthcare Safety Network | Centers for Disease Control and Prevention. (n.d.). Available at: http://www.cdc.gov/nhsn/

Ohno, M., Shimada, Y., Satoh, M., Kojima, Y., Sakamoto, K., Hori, S. (2018). Evaluation of economic burden of colonic surgical site infection at a Japanese hospital. *Journal of Hospital Infection*, *99*, 31–35.

Owens, C. D., Stoessel, K. (2008). Surgical site infections: epidemiology, microbiology and prevention. *The Journal of Hospital Infection*, *70 Suppl 2*, 3–10.

Penel, N., Neu, J.-C., Clisant, S., Hoppe, H., Devos, P., Yazdanpanah, Y. (2007). Risk factors for early catheter-related infections in cancer patients. *Cancer*, *110*(7), 1586–1592.

Petrosillo, N., Drapeau, C. M. J., Nicastri, E., et al. (2008). Surgical site infections in Italian Hospitals: a prospective multicenter study. *BMC Infectious Diseases*, *8*, 34.

Pouwels, K. B., Vansteelandt, S., Batra, R., Edgeworth, J. D., Smieszek, T., Robotham, J. V. (2018). Intensive care unit (ICU)-acquired bacteraemia and ICU mortality and discharge: addressing time-varying confounding using appropriate methodology. *Journal of Hospital Infection*, *99*(1), 42–47.

Pronovost, P. (2008). Interventions to decrease catheter-related bloodstream infections in the ICU: the Keystone Intensive Care Unit Project. *American Journal of Infection Control*, *36*(10), S171.e1-5.

Rapozo, D. C. M., Bernardazzi, C., de Souza, H. S. P. (2017). Diet and

microbiota in inflammatory bowel disease: The gut in disharmony. *World Journal of Gastroenterology*, *23*(12), 2124–2140.

Reddy, K. M., Meyer, C. E. R., Palazzo, et al. (2003). Postoperative stay following colorectal surgery: a study of factors associated with prolonged hospital stay. *Annals of the Royal College of Surgeons of England*, *85*(2), 111–4. 4

Resar, R., Pronovost, P., Haraden, C., Simmonds, T., Rainey, T., Nolan, T. (2005). Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. *Joint Commission Journal on Quality and Patient Safety*, *31*(5), 243–8.

Ricciardi, R., Roberts, P. L., Hall, J. F., et al. (2014). What Is the Effect of Stoma Construction on Surgical Site Infection After Colorectal Surgery? *Journal of Gastrointestinal Surgery*, *18*(4), 789–795.

Rolston, K. V. I., Lior, N., Tarrand, J. T. (2014). Current Microbiology of Surgical Site Infections in Patients with Cancer: A Retrospective Review. *Infectious Diseases Therapy*, 3(2):245-56.

Rosenberger, L. H., Politano, A. D., Sawyer, R. G. (2011). The surgical care improvement project and prevention of post-operative infection, including surgical site infection. *Surgical Infections*, *12*(3), 163–8.

Sartelli, M., Catena, F., Abu-Zidan, F. M., et al. (2017). Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference. *World Journal of Emergency Surgery*, *12*, 22.

Sawyer, R. G., Claridge, J. a., Nathens, A. B., et al. (2015). Trial of short-course antimicrobial therapy for intraabdominal infection. *The*

New England Journal of Medicine, *372*(21), 1996–2005.

Scarborough, J. E., Mantyh, C. R., Sun, Z., Migaly, J. (2015). Combined Mechanical and Oral Antibiotic Bowel Preparation Reduces Incisional Surgical Site Infection and Anastomotic Leak Rates After Elective Colorectal Resection: An Analysis of Colectomy-Targeted ACS NSQIP. *Annals of Surgery*, *262*(2), 331–7.

Serra-Aracil, X., Espin-Basany, E., Biondo, et al. (2011). Surgical Site Infection in Elective Operations for Colorectal Cancer After the Application of Preventive Measures. *Archives of Surgery*, *146*(5), 606.

Shiomi, A., Ito, M., Maeda, K., et al. (2015). Effects of a Diverting Stoma on Symptomatic Anastomotic Leakage after Low Anterior Resection for Rectal Cancer: A Propensity Score Matching Analysis of 1,014 Consecutive Patients. *Journal of the American College of Surgeons*, *220*(2), 186–194.

Smith, R. L., Bohl, J. K., McElearney, et al. (2004). Wound infection after elective colorectal resection. *Annals of Surgery*, *239*(5), 599-605; discussion 605-607.

Staszewicz, W., Eisenring, M.-C., Bettschart, V., Harbarth, S., Troillet, N. (2014). Thirteen years of surgical site infection surveillance in Swiss hospitals. *The Journal of Hospital Infection*, *88*(1), 40–7.

Stewardson, A. J., Allignol, A., Beyersmann, J., et al. (2016). The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. *Euro Surveillance*, *21*(33), 30319.

Elgohari, S., Lamagni, T., Harrington, P., et al. Surveillance of surgical site infections in NHS hospitals in England. (2015). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/666465/SSI_annual_report_NHS_hospitals_2016-17.pdf

Tang, R., Chen, H. H., Wang, Y. L., Changchien, C. R., Chen, J.-S. (2001). Risk Factors For Surgical Site Infection After Elective Resection of the Colon and Rectum : A Single-Center Prospective Study of 2 , 809 Consecutive Patients. *Annals of Surgery*, *234*(2), 181–189.

Tanner, J., Padley, W., Assadian, O., Leaper, D., Kiernan, M., Edmiston, C. (2015). Do surgical care bundles reduce the risk of surgical site infections in patients undergoing colorectal surgery? A systematic review and cohort meta-analysis of 8,515 patients. *Surgery*, *158*(1), 66–77.

Tanner, J., Padley, W., Kiernan, M., Leaper, D., Norrie, P., Baggott, R. (2013). A benchmark too far: Findings from a national survey of surgical site infection surveillance. *Journal of Hospital Infection*, *83*(2), 87–91.

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., Jemal, A. (2015). Global cancer statistics, 2012. *CA: A Cancer Journal for Clinicians*, *65*(2), 87–108.

VINCat Program. Generalitat de Catalunya. (n.d.). Available at: http://catsalut.gencat.cat.

Waits, S. A., Fritze, D., Banerjee, M., et al. (2014). Developing an argument for bundled interventions to reduce surgical site infection in colorectal surgery. *Surgery*, *155*(4), 602–6.

Watanabe, M., Suzuki, H., Nomura, S., et al. (2015). Performance

Assessment of the Risk Index Category for Surgical Site Infection after Colorectal Surgery. *Surgical Infections*, *16*(1), 84–89.

Kok, W. K. T., Agrawal, N., Sathappan, S., Kelven Chen, W. (2016). Risk factors for early implant-related surgical site infection. *Journal of Orthopaedic Surgery*, *24*(1), 72–6.

Welch, H. G., Robertson, D. J. (2016). Colorectal Cancer on the Decline - Why Screening Can't Explain It All. *The New England Journal of Medicine*, *374*(17), 1605–1607.

Young, H., Knepper, B., Moore, E. E., Johnson, J. L., Mehler, P., Price, C. S. (2012). Surgical site infection after colon surgery: National healthcare safety network risk factors and modeled rates compared with published risk factors and rates. *Journal of the American College of Surgeons*. 2012 May;214(5):852-9.

Zarb, P., Coignard, B., Griskeviciene, J., et al. (2012). Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Available at: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf.

Zywot, A., Lau, C. S. M., Stephen Fletcher, H., Paul, S. (2017). Bundles Prevent Surgical Site Infections After Colorectal Surgery: Meta-analysis and Systematic Review. *Journal of Gastrointestinal Surgery*, *21*(11), 1915–1930.

10. ANNEXES

FULL EXPLICATIU PER A OMPLIR LA BASE DE DADES

A la base de dades hem ocultat tots els camps previs excepte nom i cognom del pacient, NHC, data de la IQ, si ha tingut infecció o no i el microorganisme aïllat com a informacióNo us espanteu per la quantitat de variables (columnes) que hi ha ja que la majoria, en els casos en que no hi ha infecció, no s'han d'omplir.

A) Dades del pacient:

- Malaltia de base que el porta a la cirurgia:
- Si es tracta de neoplàsia → 1
- Si és malaltia inflamatòria intestinal → 2
- Si és una altra causa → 3. Hi ha una columna de camp obert al costat per posar quina és la malaltia en aquest cas. La poliposi colònica familiar entraria en aquest apartat.
- Quimioteràpia prèvia a la cirurgia (setmanes, mesos): En cas afirmatiu → 1, si no → 0.
- Radioteràpia prèvia a la cirurgia (setmanes, mesos): En cas afirmatiu→ 1, si no → 0.

B) Dades de la cirurgia:

- Profilaxis antibiòtica endovenosa: Hem realitzat un llistat (al final) amb els fàrmacs més freqüentment utilitzat/s en la profilaxis endovenosa i posarem el número corresponent al fàrmac/s (fins a 2 màxim) en les columnes de profilaxis (Prof ATB 1, Prof ATB 2).
- En la profilaxis oral posem inicialment si es fa o no: Si → 1, no → 0. Si no es fa, les següents columnes (ATB oral 1, ATB oral 2) les deixem en blanc. Si es fa, posem el número/s corresponent/s al fàrmac utilitzat, que també estan posats en la taula del final.
- Profilaxis mecànica: posem si es fa o no: Si → 1, no → 0. En cas que es faci, llavors indiquem amb la numeració corresponent si es fa via anteròg rada o oral (1), retròg rada o en enemes (2) o les dues (3).
- Si s'ha realitzat una ostomia durant la cirurgia (ja sigui ileostomia o colostomia) posem: Si → 1, No → 0.

C) <u>Dades de la infecció de localització quirúrgica, EN CAS QUE N'HI HAGI</u>:

En els casos en que no hi ha infecció, deixem les columnes que fan referència a la infecció en blanc.

En els casos en que hi ha infecció, recollim:

- **Microbiologia:**

- Si s'han obtingut cultius: Si→ 1, No → 0.
- En cas de que **NO** s'hagin obtingut cultius, les següents columnes a fins al tractament queden en blanc.
- En cas de que **SI** s'hagin obtingut cultius: si són positius (inclou els cultius polimicrobians on no predomina cap microorganisme) posem →1. Si són negatius → 0.
- En cas que siguin positius, després recollim si s'ha obtingut creixement d'algun d'aquests 3 microorganismes: *E. Coli*, *K. pneumoniae* o *P. aeruginosa*. Si → 1, no → 0.
- Si s'ha obtingut algun d'aquests microorganismes, en les següents columnes indiquem si és multiresistent: BLEE: Si → 1, no → 0. Carbapenemassa: Si→ 1, no → 0. Multirresistent (per a *P. aeruginosa*): Si → 1, no → 0.
- Si no s'ha obtingut el microorganisme en concret, després de la columna amb el 0 deixem les columnes del mecanisme de resistència en blanc.

*** Hem definit els microorganismes multiresistents com:** aquells informats com a resistents (o amb sensibilitat intermitja) a 3 o més classes d'antimicrobians. Dintre d'això:

- <u>*E. coli, K. pneumoniae* BLEE</u> : resistència a cefalosporines de 3ª generació (se sol informar cefotaxima, ceftazidima i cefepime) i aztreonam també.
- <u>*E. coli, K. pneumoniae* carbapenemasa</u>: resistència a carbapenems, sent Ertapenem el principalment afectat. Després els altres, Imipenem i Meropenem.

- *P. aeruginosa* multirresistent: resistent a 3 o més famílies d'antipseudomònics. L'antibiograma sol mostrar sensibilitat únicament a amikacina i colistina.
- *P. aeruginosa* carbapenemasa: Té els mateixos criteris que l'anterior però l'antibiograma sol tenir sensibilitat també a aztreonam.

- **Tractament de la infecció:**

- Reintervenció quirúrgica: cirurgia electiva o urgent per infecció d'òrgan i espai posterior a la cirurgia inicial. Si → 1, No → 0.
- Tractament antibiòtic: En cas que en rebi → 1, en cas que no en rebi (alguns casos d'infecció de ferida superficial) → 0. En aquest cas deixem les següents (ATB 1, ATB 2, ATB 3.. etc, en blanc).
- En els casos en que SI que es tracta, recollim tots els antibiòtics que ha portat el pacient, la via d'aministració (IV→ intravenosa o VO → oral), la seva indicació (E→ empíric o D → dirigit) i la data d'inici i final de cadascun. Hem posat fins a 7 opcions d'antibiòtic, pel que apareixen moltes columnes, però sabem que en la majoria no se n'utilitzen tants.

* Les definicions que prenem per a tractament empíric i dirigit són:
  - Empíric: El que s'inicia quan hi ha sospita d'infecció però no està confirmada.
  - Dirigit: El que s'inicia quan hi ha un cultiu positiu amb antibiograma del microorganisme.

  En els casos en que s'afegeix metronidazol a un tractament dirigit assumint que també hi ha anaerobis encara que no s'hagin aïllat, el posarem com a empíric.

- **Evolució de la infecció:** Als 30 dies de la intervenció quirúrgica. Posem el número corresponent a la columna:

1. Curació clínica: resolució dels símptomes i signes de la infecció de localització quirúrgica (dolor, febre..). No tenim en compte resultats de proves d'imatge. Pot tenir símptomes per una altra infecció (urinària, respiratòria..) que no tindrem en compte.

2. Persistència de la infecció: continuen els signes (supuració..) i símptomes d'infecció de localització de cirurgia de colon.
3. Mort: per qualsevol causa. En l'apartat següent especifiquem si és atribuïda a la infecció de localització quirúrgica o no.

D) Dades d'evolució clínica generals (de tots els pacients):

- Reintervenció quirúrgica per causes diferents a la ILQ: SI →1, no → 0.
- Data d'alta d'hospitalització: de l'ingrés de la cirurgia**.** Sabem que en molts casos ja s'havia recollit aquesta dada, però en molts casos ens falta, pel que us la tornaríem a demanar.
- Reingrés: dintre dels 30 dies posterios a la IQ. Si → 1, no → 0. En els casos en que hi ha reingrés, posarem la data del reingrés i la de l'alta del reingrés i definirem la causa:
  1. Per la infecció de la cirurgia del colon.
  2. Per altres causes (inclou infeccions d'altres tipus).
- Mortalitat: Dintre dels 30 dies posteriors a la IQ o posteriorment si és durant l'ingrés. Si → 1, no → 0.

En cas afirmatiu, posarem la data de la mort en la següent columna i després si és mortalitat atribuïda a la ILQ o no: inclou mortalitat per complicació de la cirurgia com perforació/dehiscència de sutura, on considerem que queda implícita la infecció.

TAULA DE FÀRMACS (profilaxis antibiòtica endovenosa i oral, i tractament)

* Hem utilitzat els mateixos números/codis de fàrmacs per a la profilaxis endovenosa i per als tractaments. La profilaxis oral té una codificació diferent.

Profilaxis endovenosa i tractaments (IV i VO)	**Profilaxis oral**
Ciprofloxacino → 1	Metronidazol VO → 1
Metronidazol → 2	Eritromicina/Azitromicina VO → 2
Amoxicil·lina- àcid clavulànic → 3	Neomicina VO → 3
Piperacil·lina- tazobactam → 4	Altres ATB VO→ 4
Ertapenem → 5	
Meropenem/ Imipenem → 6	
Cefuroxima/ Ceftriaxona → 7	
Cotrimoxazol → 8	
Aztreonam → 9	
Gentamicina/amikacina/tobramicina → 10	
Ampicil·lina → 11	
Ceftazidima → 12	
Cefepime → 13	
Clindamicina → 14	
Daptomicina → 15	
Vancomicina → 16	
Teicoplanina → 17	
Linezolid → 18	
Tigeciclina → 19	
Colistina → 20	
Altres → 21	

Tractament combinat:

0 → ciprofloxacino + metronidazol

1 → P/T + cotrimoxazol

2 → meropenem + teicoplanina

3 → aztreonam + teicoplanina

4 → aztreonam + metronidazol

5 → meropenem + vancomicina

6 → P/T + linezolid

7 → P/T + tigeciclina

8 → ceftriaxona + metronidazol

9 → aminoglicòsid + clindamicina

10 → P/T + vancomicina

11 → Aminoglicòsid + metronidazol

12 → metronidazol + clindamicina

13 → ciprofloxacino + clindamicina

14 → meropenem + colistina

15 → metronidazol + altres

FULL RECOLLIDA DE DADES CIRURGIA COLON-RECTE VINCat (2011-2014)

A) PACIENT : Nom NHC

Malaltia de base: 1. Neoplàsia 2. M. Inflamatòria intestinal 3. Altres: _____

Quimioteràpia prèvia: SI (1) / NO (0)

Radioteràpia prèvia: SI (1) / NO (0)

B) CIRURGIA

Profilaxis antibiòtica endovenosa: 1. _____ 2. _____

Profilaxis antibiòtica oral: SI (1) / NO (0) Quina: 1. _____ 2. _____

Profilaxis mecànica: SI (1) / NO (0) Tipus: 1. Anteròg rada 2. Retròg rada 3. Ambdues

Ostomia post-cirurgia: SI (1) / NO (0)

C) En els casos d'INFECCIÓ DE LOCALITZACIÓ QUIRÚRGICA:

- **Microbiologia:**

Obtenció cultius: SI (1) / NO (0)

Cultius obtinguts positius: SI (1) / NO (0)

- *E. Coli*: SI (1) / NO (0)
  - EC BLEE: SI (1) / NO (0)
  - EC carbapenemasa: SI (1) / NO (0)
- *K. pneumoniae*: SI (1) / NO (0)
  - KP BLEE: SI (1) / NO (0)
  - KP carbapenemasa: SI (1) / NO (0)
- *P. aeruginosa*: SI (1) / NO (0)
  - PA multiR: SI (1) / NO (0)
  - PA carbapenemasa: SI (1) / NO (0)

- **Tractament de la infecció:**

Reintervenció quirúrgica: SI (1) / NO (0)

Tractament antibiòtic: SI (1) / NO (0)

- En cas que SI, quin:

Antibiòtic	Via (IV / VO)	Indicació (E / D)	Data inici	Data final

* E: empíric / D: dirigit

- **Evolució de la infecció (als 30 dies de la IQ):**

1. Curació clínica 2. Persistència de la infecció 3. Mort

D) EVOLUCIÓ CLÍNICA

Reintervenció quirúrgica per altres causes a infecció: SI (1) / NO (0)

Reingrés (en els 30 dies posteriors a la IQ):

- NO (0)
- SI (1) → Data reingrés: Data alta reingrés:
  → Causa: 1. ILQ colorectal 2. Altres

Mortalitat (en els 30 dies posteriors a la IQ o en qualsevol moment durant l'ingrés):

- NO (0)
- SI (1) → Data:
  Mortalitat atribuïda a la ILQ colorectal: SI (1) / NO (0)

11. CATALAN SUMMARY (RESUM EN CATALÀ)

Aquesta tesi s'ha centrat en l'anàlisi de les taxes i resistències d'infecció, el factors de risc i l'evolució dels pacients intervinguts de cirurgia de colon i recte amb infecció de localització quirúrgica (ILQ).

Introducció

Les ILQs són les infeccions relacionades amb l'assistència sanitària més freqüents en els hospitals d'aguts d'arreu d'Europa, Estats Units i Espanya segons les últimes enquestes de prevalença. El desenvolupament de les ILQs augmenta de forma significativa la morbi-mortalitat dels pacients, la seva estada hospitalària, afavoreix els reingressos i augmenta de forma molt significativa els costos hospitalaris. Per aquest motiu, és especialment rellevant la seva prevenció.

En aquest context, les ILQs després de cirurgia de colon i recte tenen un paper especialment rellevant, ja que degut a la naturalesa inherentment contaminada d'aquest tipus de cirurgia, les taxes d'infecció acostumen a ser més elevades que a la resta de cirurgies, tot i aplicar mesures preventives com la profilaxis antibiòtica endovenosa o la cirurgia laparoscòpica. A més, cada vegada es practiquen tècniques quirúrgiques més complexes que afavoreixen la infecció.

Per altra banda, el càncer colorectal, la principal indicació d'aquest tipus de cirurgia, continua sent un dels tipus de càncer més freqüents tant en homes com en dones actualment, tot i les campanyes de detecció precoç.

La preparació mecànica del colon abans de la cirurgia s'ha deixat d'utilitzar en molts hospitals en els últims anys ja que no

semblava tenir una utilitat clara i a més provocava importants efectes desagradables en els pacients, com nàusees i vòmits. A la vegada que es va abandonar la preparació mecànica també es va deixar d'utilitzar la profilaxis amb antibiòtics orals no absorbibles, com macròlids i aminoglicòsids, una mesura que sí semblava tenir eficàcia.

A més, el desenvolupament en els últims anys de resistències antimicrobianes múltiples per part de les bactèries gramnegatives, principal flora intestinal junt amb les bactèries anaeròbies, suposa una amenaça important a tot el món. Existeixen casos d'infeccions causades per bactèries gramnegatives multiresistents en les quals no es disposa d'opcions terapèutiques. I aquestes infeccions han demostrat augmentar de forma significativa la morbimortalitat dels pacients.

Afegit a això està el fet de que en les infeccions intraabdominals és important no només l'adequació de l'antibiòtic sinó aconseguir un bon control del focus d'infecció, ja sigui mitjançant reoperació per dehiscència anastomòtica o mitjançant drenatge percutani d'abscés degut a contaminació intraquirúrgica. El fet de realitzar o no aquestes maniobres influirà de forma significativa en el pronòstic dels pacients postoperats.

En aquest context general hi ha situacions específiques en relació a la definició dels factors de riscs i maneig de les ILQ en cirurgia colorectal que s'han abordat en aquest projecte:

1. <u>Característiques específiques de la cirurgia del colon i del recte</u>

S'ha suggerit que les cirurgies del colon i recte tenen diferent risc d'infecció quirúrgica degut al diferent abordatge quirúrgic i al grau de

contaminació de cadascuna. Tot i així, la majoria d'estudis han avaluat aquestes dues cirurgies de forma conjunta. A més a més, els dos tipus d'infecció de localització quirúrgica, la incisional (superficial i profunda) i la d'òrgan-espai, tenen factors de risc i mecanismes patogènics diferents, el que suggereix que probablement requereixen també una avaluació de forma separada. Generalment, el desenvolupament d'una infecció d'òrgan-espai te conseqüències més greus que el desenvolupament d'una incisional i requereix reintervenció en molts casos. A més, la majoria d'avanços fets fins ara en cirurgia colorectal, com ara la cirurgia mínimament invasiva han disminuït principalment les taxes d'infecció incisional, mantenint les taxes d'infecció d'òrgan-espai elevades.

L'objectiu del nostre primer estudi era comparar la incidència, factors de risc i evolució de la infecció de localització quirúrgica en la cirurgia electiva del colon i el recte de forma diferencial.

2. Moment del desenvolupament de la ILQ en cirurgia electiva colorectal

En algunes infeccions relacionades amb l'assistència sanitària com és la bacterièmia de catèter o la pneumònia associada a ventil·lació s'ha vist que tant els factors de risc com la patogènia, la microbiologia i el pronòstic poden variar en funció del moment en què es desenvolupi la infecció. Tot i la importància de la ILQ actualment com a principal causa d'infecció relacionada amb l'assistència sanitària, no s'ha fet una avaluació diferencial en funció del moment de desenvolupament de la infecció. I tenint en compte que la cirurgia colorectal te les taxes més altes d'infecció de totes les cirurgies electives, l'objectiu del nostre

segon estudi era definir els factors predictius i l'evolució de la ILQ desenvolupada immeditadament després de la cirurgia i de forma tardana, per tal d'establir mesures preventives adequades en el casos en que sigui possible.

3. Maneig i pronòstic de la ILQ en cirurgia electiva colorectal

Com s'ha comentat, la infecció d'òrgan-espai és la més greu de les ILQs i comporta elevada morbimortalitat i costos. Així i tot, els factors relacionats amb el fracàs terapèutic en pacients que pateixen aquest tipus d'infecció no han estat avaluats. Per altra banda, com també s'ha comentat, el desenvolupament de multiresistència per part de les bactèries gram-negatives te un impacte negatiu significatiu en aquest tipus d'infecció i pot dificultar el maneig.

Per aquest motiu, l'objectiu d'aquest estudi va ser avaluar el maneig, els factors predictors de persistència de la infecció i de mortalitat (fracàs terapèutic) en pacients amb infecció d'òrgan-espai post-operats de cirurgia electiva de colon i recte.

4. Anàlisi dels costs en salut del desenvolupament d'infecció d'òrgan-espai en cirurgia electiva colorectal

Tot i que en diverses ocasions s'han analitzat les conseqüències en termes de costs de salut del desenvolupament de ILQs després de cirurgia colorectal, en cap moment s'ha fet un anàlisi que tingui en compte el moment en què es desenvolupa la infecció. Si no es te en compte aquesta variable, és probable que es produeixi una sobreestimació de la durada hospitalària atribuïble a la infecció.

Les infeccions d'òrgan-espai, com ja s'ha comentat són més

greus i estan associades a major morbimortalitat. Analitzar els costos de salut de la infecció d'òrgan-espai, tot comparant-los amb els costos de la infecció incisional o al fet de no desenvolupar infecció, permetrà mesurar de forma acurada les conseqüències de la infecció d'òrgan-espai per tal d'intentar establir mesures preventives adequades.

5. Un microorganisme d'especial rellevància en cirurgia colorectal: *Pseudomonas aeruginosa*

Pseudomonas aeruginosa és un dels principals microorganismes causals d'infeccions nosocomials o relacionades amb l'assistència sanitària. Tot i així, els factors de risc per desenvolupar infeccions intraabdominals per aquest microorganisme han estat poc avaluats.

Per altra banda, *P. aeruginosa* normalment afecta pacients amb major comorbiditats, implicant un pitjor pronòstic. A més, la seva major resistència intrínseca comparada amb d'altres bactèries gramnegatives, dificulta encara més el tractament de les infeccions on hi està implicada. Per aquest motiu, l'objectiu d'aquest estudi va ser definir els factors predictius i pronòsitc de la ILQ causada per *P. aeruginosa* en aquesta població, per tal d'establir les mesures preventives i tractament adequats.

Objectius

- Avaluar les diferències en prevalença d'infecció, factors de risc i pronòstic de les ILQ en cirurgia de colon i cirurgia de recte. I més concretament, les infeccions d'òrgan-espai.
- Comparar els factors de risc, el tipus d'infecció més prevalent, la microbiologia i resistències antimicrobianes, i el pronòstic de les

ILQs desenvolupades de forma immediata i de forma tardana després de cirurgia electiva colorectal.

- Definir el maneig antimicrobià i quirúrgic dels pacients amb ILQ d'òrgan-espai després de cirurgia electiva colorectal i determinar els factors predictors de fracàs terapèutic en aquesta població.
- Determinar de forma acurada els costos de salut del desenvolupament d'una infecció d'òrgan-espai, comparant-los amb els costos de desenvolupar infecció incisional i de no desenvolupar cap infecció.
- Determinar els factors de risc, el maneig i el pronòstic de les ILQs causades per *P. aeruginosa* en pacients postoperats de cirurgia de colon i recte.

Metodologia

Aquest estudi va incloure tots els pacients adults (≥ 18 anys) sotmesos a cirurgia electiva colorectal des de l'1 de Gener de 2011 al 31 de Desembre de 2014 en 10 hospitals catalans. Tres hospitals eren hospitals terciaris universitaris (Hospital Universitari de Bellvitge, Consorci Sanitari Parc Taulí, Hospital Universitari Mútua de Terrassa), 5 tenien entre 200 i 500 llits (Hospital General de Granollers, Hospital Universitari Sant Joan de Reus, Consorci Sanitari de Terrassa, Consorci Sanitari de l'Anoia, Fundació Althaïa) i 2 tenien menys de 200 llits (Parc Sanitari Sant Joan de Déu, Hospital de Viladecans). Es van incloure consecutivament tots els pacients hospitalitzats en qualsevol des serveis quirúrgics dels 10 hospitals. Els pacients amb una ILQ prèvia a la cirurgia es van excloure.

Tots els hospitals eren participants del Programa VINCat, programa de vigilància epidemiològica de les infeccions relacionades amb l'assistència sanitària a Catalunya, creat al 2006 com a ampliació del programa VINICS. El Programa està basat en el model del National Healthcare Safety Network (NHSN) i pel que fa a la vigilància de les ILQs, recull dades demogràfiques, de característiques de la cirurgia i microbiologia de les ILQs. A propòsit d'aquest projecte es van afegir dades referents a les comorbiditats dels pacients, tractament i pronòstic, amb un seguiment igual de 30 dies postoperatoris.

Tots els estudis inclosos en aquesta memòria són estudis observacionals prospectius de cohort. Després d'analitzar les característiques epidemiològiques, microbiològiques, de resistència antimicrobiana i evolució, es van realitzar diferents anàlisi multivariants amb les variables pertinents per a determinar els factors predictius de la variable pronòstic en cada estudi.

La recollida de dades estandarditzada dels pacients va incloure edat, gènere, la puntuació de l'American Society of Anaesthesiologists' (ASA), preparació mecànica intestinal, profilaxis antibiòtica oral, la puntuació de risc quirúrgic d'acord amb el National Nosocomial Infections Surveillance (NNIS), l'adequació de la profilaxis antibiòtica endovenosa, la data i durada de la cirurgia, la cirurgia laparoscòpica, classificació de la ferida quirúrgica, data la de ILQ, tipus de ILQ (incisional superficial o profunda, d'òrgan-espai), la microbiologia, estada hospitalària, reingrés i mortalitat.

Les diferents definicions de variables es descriuen a l'apartat de metodologia d'aquesta memòria.

L'anàlisi de mostres microbiològiques es va fer en el laboratori

local de cada hospital d'acord amb els criteris del Clinical Laboratory Standard Institute (CLSI).

Pel que fa a l'anàlisi estadístic, les variables categòriques es van descriure com a totals i freqüències. Les variables contínues es van descriure com a medianes i rangs interquartils (RIQ) o mitjana i desviació estàndard (DE) segons l'adequació. Per detectar diferències significatives entre grups, es va utilitzar la prova Chi-quadrat o la prova exacta de Fisher per a variables categòriques, i la prova t de Student o la prova de Mann-Whitney per a variables contínues, segons adequació. La significació estadística es va establir en $\alpha = 0,05$. Tots els p-valors informats són de doble cua. Els anàlisis multivariants es van realitzar mitjançant regressió logística binària en els estudis 1,2,3 i 5. A l'estudi 4 es va utilitzar regressió multivariant de Cox per analitzar el risc de ser donat d'alta viu o mort i la regressió lineal general per analitzar els factors de risc associats a major estada hospitalària en pacients amb infecció d'òrgan-espai. Els resultats de l'anàlisi multivariant s'han mostrat com a Odds Ratio (OR) o Hazard ratio ajustat (aHR) i intervals de confiança del 95% (IC95%). La prova de qualitat del model final va ser avaluada per la prova de Hosmer-Lemeshow. L'excés d'estada hospitalària atribuït a la infecció en l'estudi 4 es va calcular mitjançat un model multiestat en el qual la ILQ era la variable temps-dependent.

L'estudi va ser aprovat pel Comitè d'Ètica de l'Hospital Universitari de Bellvitge (referencia: PR305/15).

Resultats

1. Característiques especifiques de la cirurgia del colon i del recte

En el primer estudi vam observar que la taxa total de ILQ en cirurgia de colon va ser 16.4% i la taxa d'ILQ d'òrgan-espai va ser del 7,9%, mentre que en la cirurgia rectal, la taxa global era del 21,6% i la d'òrgan-espai del 11,5%. Els factors de risc independents per LQ d'òrgan-espai en la cirurgia de colon van ser el sexe masculí (OR: 1,57; IC95%: 1,14 a 2,15) i la creació d'ostomia (OR: 2.65; IC95%: 1.8 a 3.92) mentre que laparoscòpia (OR: 0.5; IC95%: 0.38-0.69) i la profilaxis antibiòtica oral combinada amb la preparació mecànica del colon (i la profilaxi d'antibiòtica intravenosa aplicada en tots els casos) (OR: 0,7; IC95%: 0.51-0.97) van ser factors protectors. En la cirurgia rectal, els factors de risc independents per a la ILQ d'òrgan-espai van ser el sexe masculí (OR: 2,11, 95%CI: 1.34-3.31) i una cirurgia més prolongada (OR: 1,49; IC del 95%: 1,03-2,15), mentre que la profilaxis antibiòtica oral (OR: 0.49; IC95%: 0.32-0.73) va ser factor de protecció. Entre els pacients amb ILQ d'òrgan-espai, es va observar una diferència significativa en quant a la mortalitat, sent major en cirurgia de colon que en cirurgia rectal (11.5% vs. 5.1%, p = 0.04).

2. Moment de desenvolupament de la ILQ en cirurgia electiva colorectal

Dels 3701 pacients inclosos, 320 (8,6%) van desenvolupar infecció immediata (≤ 7 dies) i 349 (9,4%) van desenvolupar infecció tardana (entre 8 i 30 dies). La resta no va desenvolupar infecció. Els pacients amb ILQ immediata eren majoritàriament homes, que s'havien sotmès

a cirurgia del colon i van desenvolupar ILQ d'òrgan-espai més freqüentment, mentre que els pacients amb ILQ tardana van rebre freqüentment quimioteràpia o radioteràpia i van desenvolupar ILQ incisional.

Els factors predictors de ILQ immediada van ser el sexe masculí (OR: 1.92; P <0,001), el ASA > 2 (OR: 1.51; P= 0.01), l'administració de preparació mecànica intestinal (OR: 0,7; P= 0.03) i la creació d'estoma (OR: 1.95; P <0,001). Els factors predictors d'ILQ tardana van ser la cirurgia rectal (OR: 1.43; P= 0,03), prolongació de la cirurgia (≥ al percentil 75 estipulat per al procediment) (OR: 1.4; P= 0.03) i la quimioteràpia prèvia a la cirurgia (OR: 1.8; P= 0.03).

3. Maneig i pronòstic de la ILQ en cirurgia electiva colorectal

Dels 669 (18.1%) pacients que van desenvolupar ILQ, 496 van tenir cultius positius. El 50% de les infeccions van ser polimicrobianes, amb predomini de bactèries gram-negatives i enterococ. Es va objectivar un 11.3% de *Escherichia coli* i un 30% de *Klebsiella pneumoniae* productors de betalactamassa d'expectre estès. De totes les infeccions, 336 (9.1%) van ser infeccions d'òrgan-espai. Entre els pacients amb ILQ òrgan-espai el 81.2% va requerir intervencionisme per a control del focus d'infecció; en el 60.4% van consistir en una reoperació per dehiscència significativa i en el 20.8% en drenatge percutani/transrectal de la col·lecció. El 100% dels pacients amb infecció d'òrgan-espai van rebre antibioteràpia, amb una durada mitjana superior a 15 dies. La taxa de fracàs terapèutic global, és a dir de persistència de la infecció o mort en els 30 dies posteriors a la IQ, va ser del 21.7%: del 9% en la ILQ incisional i del 34.2% en la ILQ

d'òrgan-espai (p <0,001). La durada mitjana de l'estada va ser de 15 dies (RIQ 9-22) per les ILQ incisionals i de 24 dies (RIQ 17-35) per les ILQ d'òrgan-espai (p <0,001). Vint-i-set pacients (19%) van requerir reingrés i 35 pacients van morir (5.2%) dintre dels 30 dies posteriors a la cirurgia.

En l'anàlisi dels factors predictius independents del fracàs terapèutic en pacients amb infecció d'òrgan-espai, vam observar que l'edat superior a 65 anys (OR 1.83, IC95%: 1.07-1.83), la laparoscòpia (OR 1.7, IC95%: 1.06-2.77) i la reoperació (OR 2.8, IC95%: 1.7-4.6) van resultar predictors.

4. Anàlisi dels costs en salut del desenvolupament d'infecció d'òrgan-espai en cirurgia electiva colorectal

Dels 2778 pacients inclosos en aquest estudi, 343 (12.3%) van desenvolupar ILQ; 194 (7%) infecció d'òrgan-espai i 149 (5.3%) infecció incisional. El desenvolupament d'infecció d'òrgan-espai va allargar l'estada hospitalària en 4.2 dies (IC95% 4.1-4.3) comparat amb els pacients amb infecció incisional i en 9 dies (IC95% 8.9-9.1) comparat amb els pacients que no van desenvolupar infecció. Els pacients amb infecció d'òrgan-espai van tenir menys probabilitat de ser donats d'alta vius respecte a pacients amb infecció incisional (aHR 0.36, IC95% 0.28-0.47) i respecte a pacients sense infecció (aHR 0.17, IC95% 0.14-0.21). El risc de mortalitat va ser major en pacients amb infecció d'òrgan-espai comparat amb pacients amb infecció incisional (aHR 8.02, IC95% 1.03-62.8) i respecte a pacients que no van desenvolupar infecció (aHR: 10.7, IC95% 3.7-30.8).

5. Un microorganisme d'especial rellevància en cirurgia colorectal: *Pseudomonas aeruginosa*

Dels 669 (18.1%) pacients que van desenvolupar ILQ, 62 (9.3%) van ser degudes a *P. aeruginosa*. Els pacients amb ILQ deguda a *P. aeruginosa* tenien amb major freqüència un índex ASA de III-IV (67.7% vs 45.5%, p = 0.001, OR 2.5, IC95% 1.44-4.39), un index NNIS 1-2 (74.2% vs 44.2%, p <0.001, OR 3.6, IC95% 2.01-6.56), una major proporció de pacients amb durada de la cirurgia superior al percentil 75 del procediment (61.3 % vs 41.4%, p= 0.003, OR 2.2; IC95%: 1.31-3.83) i amb menys freqüència rebien profilaxis antibiòtica oral (17.7% vs 33.6%, p= 0.01, OR 0.4; IC95%: 0.21-0.83) que els pacients amb infeccions causades per altres microorganismes.

Les ILQ causades per *P. aeruginosa* van ser més freqüentment polimicrobianes que les causades per altres microorganismes però amb menys freqüència acompanyades per gram positius. El percentatge d'infecció per *P. aeruginosa* multiresistent va ser del 4.8%.

Els pacients amb ILQ causada per *P. aeruginosa* van rebre tractament antibiòtic de forma més perllongada (mitjana 17 dies [IQR 10-24] vs 13d [IQR 8-20], p= 0.015, OR 1.1, IC95% 1.00 -1.12), van tenir major taxa de fracàs terapèutic (30.6% vs 20.8%, p= 0.07, OR 1.7, IC95% 0.96-2.99) i una hospitalització més perllongada (mitjana 22 dies [RIQ 15-42] vs 19d [RIQ 12 -28], p= 0.02, OR 1.1, IC95%: 1.00-1.17) que aquells amb ILQ causada per altres microorganismes. Els factors predictors independents de ILQs degudes a *P. aeruginosa* van ser l'índex NNIS 1-2 (OR 2.3, IC95%: 1.03-5.40) com a factor de risc i l'ús de

la profilaxi antibiòtica oral (OR 0.4; IC95%: 0.23-0.90) com a factor protector.

Discussió

El nostre estudi s'ha focalitzat en la definició dels factors de risc i protecció així com en el maneig de les ILQs en cirurgia electiva colorectal. En aquesta memòria es descriu el resultat de l'aplicació de diferents mesures de prevenció de la ILQ, focalitzant en l'aplicació preoperatòria de la profilaxis antibiòtica oral no absorbible.

En el primer estudi vam analitzar els factors de risc diferencials i el pronòstic de la ILQ després de cirurgia de colon i de cirurgia de recte. Vam observar que els pacients sotmesos a cirurgia de colon eren més grans i tenien majors comorbiditats, i això anava associat a una major mortalitat global als 30 dies de la cirurgia. Per altra banda, els pacients sotmesos a cirurgia de recte eren més joves i van presentar taxes substancialment més altes d'ILQ. Això probablement es relaciona amb el tipus de cirurgia més complexa i amb major contaminació bacteriana que implica la localització rectal. A més, la cirurgia rectal implica en alguns casos de lesions localment avançades, la necessitat d'excisió addicional d'altres òrgans pèlvics, la qual cosa també implica major risc d'infecció.

Com a factor de risc comú d'ILQ en cirurgia de colon i recte es va objectivar el sexe masculí, mentre que l'administració de profilaxis oral va resultar factor protector comú. Els resultats d'aquest estudi, junt amb la resta d'evidència a la literatura que demostra l'eficàcia de la profilaxis antibiòtica oral pre-operatòria junt amb la preparació mecànica intestinal, han impulsat la recomanació

institucional per part del VINCat a tots els hospitals que en formen part d'un paquet de mesures per-operatòries que han mostrat eficàcia reduint les taxes d'ILQ en cirurgia colorectal, entre les quals hi ha es troba la profilaxis oral de forma fonamental.

En el segon estudi, en el qual vam analitzar les diferències en quant a la naturalesa i evolució de les ILQs desenvolupades immediatament (primera setmana) després de la cirurgia colorectal o de forma tardana (a partir de la primera setmana i fins a un mes), es va observar que els pacients infectats de forma immediata tenien principalment infecció profunda, d'òrgan-espai després de cirurgia de colon, mentre que els que la desenvolupaven de forma tardana tenien amb major proporció infecció incisional després de cirurgia de recte. A diferència d'altres infeccions relacionades amb l'assistència sanitària, no hi van haver diferències en quant a la microbiologia i la presència de multiresistència segons el moment de desenvolupament de la ILQ, el que suggereix que no és necessària un tractament empíric específic en cada cas. Els pacients amb infecció immediata tenien una situació basal més greu, mesurada de forma independent per una major puntuació ASA, i se'ls va realitzar amb major freqüència una ostomia, un reflex, probablement, d'aquest major risc quirúrgic i de dehiscència anastomòtica durant la cirurgia. En canvi, factors de risc independents per infecció tardana van ser una major durada de la cirurgia, relacionat amb la cirurgia rectal i la seva major complexitat i haver rebut quimioteràpia prèviament. Aquesta s'aplica amb freqüència en pacients amb tumors rectals localment avançats prèviament a la cirurgia per tal de reduir-ne la mida, però també fa que els teixits

siguin més friables i sagnin amb major facilitat, un factor de risc per ILQ.

La cirurgia laparoscòpica i l'haver administrat profilaxis antibiòtica oral van protegir de la ILQ tant immediatament després de la cirurgia com de forma tardana.

Com era d'esperar pel tipus d'infecció, la ILQ immediata va comportar major mortalitat que la tardana, donat que es tracta d'una infecció més profunda i greu.

El tercer estudi es va focalitzar en l'anàlisi del maneig antimicrobià i quirúrgic de la ILQ d'òrgan-espai i en els factors de risc de fracàs terapèutic en aquesta població. El fracàs terapèutic global als 30 dies de la cirurgia dels pacients amb ILQ va ser del 21.7%, però aquesta va ser quatre vegades major en la infecció d'òrgan-espai que en la incisional. En pacients amb infecció d'òrgan-espai, la durada del tractament antibiòtic va ser major als 15 dies, una durada probablement excessiva si tenim en compte que en el 81.2% dels casos es va fer control del focus d'infecció. En aquests casos la literatura demostra que una durada de 4-5 dies és suficient. Sorprenentment, aquesta durada perllongada no es va associar amb una incidència important d'infecció per *Clostridium difficile*.

Els únics factors que es van associar amb el fracàs terapèutic en pacients amb infecció d'òrgan-espai va ser l'edat superior a 65 anys, la cirurgia laparoscòpica i la reoperació. Mentre que el primer és explicable, els segons van resultar més incomprensibles inicialment. Analitzant els casos intervinguts per laparoscòpia, vam objectivar que eren pacients més joves i amb menys comorbilitats que els operats per laparotomia, i el diagnòstic es va fer més freqüentment després de

l'alta. És probable que degut a que tenien un menor risc quirúrgic "a priori", es donessin d'alta abans, passant desapercebuda la complicació. La reoperació és interpretable com un marcador de severitat de la infecció més que un factor de risc per si mateixa. És demostrat que els casos en que hi ha una dehiscència o abscés, són necessàries les maniobres per controlar i drenar el focus infecció per tal de curar la infecció. En aquests casos és necessari avaluar el resultat a més llarg termini.

El quart article és un anàlisi dels costos de salut de la infecció d'òrgan-espai, expressats en termes d'excés d'estada hospitalària i probabilitat de mort intrahospitalària degut a la infecció d'òrgan-espai, comparada amb els costos de la infecció incisional o al fet de no desenvolupar infecció. L'estudi mostra que una infecció d'òrgan-espai augmenta l'estada hospitalària 4.2 dies respecte l'estada de pacients amb infecció incisional i 9 dies respecte als que no desenvolupen infecció. Això te un impacte significatiu a nivell poblacional, ja que disminueix de forma significativa la capacitat quirúrgica dels hospitals degut a que aquest excés de dies d'ingrés impedeix l' ingrés i tractament de nous pacients que ho requereixen, per tant endarrerint cirurgies electives necessàries. Els factors associats a aquest excés d'estada hospitalària en pacients amb infecció d'òrgan-espai van ser la profilaxis antibiòtica inadequada i la cirurgia oberta, encara que aquests són factors associats a altres complicacions postoperatòries com l'ili paralític i el distrés respiratori.

Per altra banda, l'estudi mostra també que el risc de mortalitat intrahospitalària en pacients amb infecció d'òrgan-espai és 8 vegades superior al risc de pacients amb infecció incisional i més de 10 vegades

superior al risc de pacients que no desenvolupen infecció. Això reforma encara més la idea de la gravetat de la infecció d'òrgan-espai i la necessitat d'investigar mesures per a la seva prevenció.

En el cinquè article vam focalitzar-nos en l'anàlisi de les ILQs causades per *P. aeruginosa* en la mateixa població. Aquestes infeccions van suposar un 10% del total aproximadament, un resultat no menyspreable tenint en compte que *P. aeruginosa* no és un microorganisme habitual de la flora colònica normal. És probable que la profilaxis aplicada, que no inclou cobertura per aquest microorganisme, i l'estrès produït per la cirurgia, permetin el sobrecreixement d'aquest microorganisme. La majoria d'aïllaments van ser multisensibles. Els pacients amb ILQ deguda a *P. aeruginosa* estaven més debilitats basalment (major puntuació ASA i NNIS), i van rebre tractament antibiòtic més perllongat. També van tenir major durada de l'hospitalització i major fracàs terapèutic que els pacients amb infeccions causades per altres microoganismes.

Els únics factors que es van relacionar de forma independent amb el risc d'ILQ per *P. aeruginosa* van ser el NNIS, indicador d'un estat basal debilitat, i la profilaxis antibiòtica oral com a factor protector. L'efecte protector de la profilaxis oral va ser en aquest cas major que en el cas d'ILQs causades per altres microorganismes. Això probablement està relacionat amb el fet que en molts casos la combinació d'antibiòtics orals administrada va incloure la neomicina, un aminoglicòsid amb potent efecte antipseudomònic que al no ser absorbible a nivell sistèmic, concentra tot el seu efecte a nivell intestinal i presenta poques resistències antimicrobianes per aquest mateix motiu.

Conclusions

- La cirurgia del colon i del recte difereixen en les seves taxes i factors de risc d'infecció així com en el pronòstic, pel que s'haurien de considerar de forma diferencial de cara a la vigilància epidemiològica i l'aplicació de mesures preventives.

- La profilaxis antibiòtica oral va mostrar reduir les taxes d'ILQ d'òrgan-espai tant en cirurgia de colon com de recte, encara que es necessiten estudis prospectius randomitzats per confirmar aquests resultats.

- La ILQ desenvolupada de forma immediata després de la cirurgia és més habitualment d'òrgan-espai i greu, mentre que la desenvolupada de forma tardana és més freqüentment incisional i més lleu. La microbiologia i taxes de resistència antibiòtica no va diferir de forma significativa. La cirurgia laparoscòpica i la profilaxis antibiòtica oral van ser factors protectors comuns dels dos moments d'infecció.

- Es va observar una proporció significativa d'Enterobactèries productores de betalactamasses d'espectre estès. La durada antibiòtica dels pacients amb infecció d'òrgan-espai va ser perllongada, probablement excessiva, tenint en compte que en la majoria de casos es va assolir un adequat control del focus d'infecció.

El fracàs terapèutic és freqüent en pacients sotmesos a cirurgia electiva colorectal que desenvolupen ILQ, sobretot en aquells que presenten infecció d'òrgan-espai. Aquesta infecció s'associa a major reingrés, estada hospitalària i mortalitat.

- Els factors predictors de fracàs terapèutic en pacients amb infecció d'òrgan-espai van ser l'edat igual o superior a 65 anys, la cirurgia laparoscòpica i la necessitat de reoperació. En pacients intervinguts per laparoscòpia i que requereixen reoperació per dehiscència,

s'hauria de fer un seguiment estret per detectar de forma precoç els signes de fracàs terapèutic.

- La infecció d'òrgan-espai s'associa a un excés d'estada hospitalària significatiu comparat amb la infecció incisional o amb el no desenvolupament d'infecció calculat amb un model multiestat que inclou la variable infecció com a temps-depenent i evita la sobreestimació de l'estada hospitalària.
- La mortalitat intrahospitalària dels pacients amb infecció d'òrgan-espai va ser 8 vegades superior a la dels pacients amb infecció incisional i 10 vegades superior a la dels pacients que no van desenvolupar infecció.
- Les ILQs causades per *P. aeruginosa* suposen el 10% del total aproximadament i es donen amb major freqüència en pacients amb més comorbiditats i en aquells que no reben profilaxis antibiòtica oral. S'associen a pitjor pronòstic, representat per major durada de l'antibioteràpia, major fracàs terapèutic i major durada hospitalària. Recomanaríem la cobertura empírica per *P. aeruginosa* multisensible en pacients més severament malalts que no han rebut profilaxis antibiòtica oral i desenvolupen ILQ.

12. ABBREVIATIONS

SSI: Surgical site infection

OS-SSI: organ-space surgical site infection

HAI: Healthcare-associated infection

US: United States

CDC's: Centres for Diseases Control and Prevention

NHSN: National Healthcare Safety Network

CRC: Colorectal cancer

MBP: Mechanical bowel preparation

OAP: Oral antibiotic prophylaxis

ESBL: Extended-spectrum betalactamase

GNB: Gram-negative bacteria

SENIC: Study on the efficacy of Nosocomial Infection Control

SCIP: Surgical Care Improvement Project

VINCat: Vigilància Infeccions Nosocomials a Catalunya

LOS: Length of stay

EO-SSI: Early-onset surgical site infection

LO-SSI: Late-onset surgical site infection

ASA: American Society of Anaesthesiologists'

APACHE II: Acute Physiology and Chronic Health Evaluation II

ICS: Institut Català de la Salut

NNIS: National Nosocomial Infections Surveillance

CLSI: Clinical Laboratory Standard Institute

HR: Hazard Ratio

UK: United Kingdom

13. ACKNOWLEDGEMENTS