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Extended-duration antibiotics are not associated with a reduction in surgical site infection in patients with ovarian cancer undergoing cytoreductive surgery with large bowel resection☆

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HIGHLIGHTS

- Extended post-operative ABX was not associated with reduced surgical site infection after large bowel resection.
- Extended post-operative ABX was not associated with reduced adverse postoperative outcomes.
- Prolonged post-operative antibiotics showed no impact on survival outcomes.
- Surgical site infection impacts PFS and OS in ovarian cancer patients undergoing large bowel resection.

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ABSTRACT

Objective(s). To evaluate whether extended dosing of antibiotics (ABX) after cytoreductive surgery (CRS) with large bowel resection for advanced ovarian cancer is associated with reduced incidence of surgical site infection (SSI) compared to standard intra-operative dosing and evaluate predictors of SSI.

Methods. A retrospective single-institution cohort study was performed in patients with stage III/IV ovarian cancer who underwent CRS from 2009 to 2017. Patients were divided into two cohorts: 1) standard intra-operative dosing ABX and 2) extended post-operative ABX. All ABX dosing was at the surgeon's discretion. The impact of antibiotic duration on SSI and other postoperative outcomes was assessed using univariate and multivariable Cox regression models.

Results. In total, 277 patients underwent cytoreductive surgery (CRS) with large bowel resection between 2009 and 2017. Forty-nine percent ($n = 137$) received standard intra-operative ABX and 50.5% ($n = 140$) received extended post-operative ABX. Rectosigmoid resection was the most common large bowel resection in the standard ABX (89.9%, $n = 124$) and extended ABX groups (90.0%, $n = 126$), respectively. No significant differences existed between age, BMI, hereditary predisposition, or medical comorbidities ($p > 0.05$). No difference was appreciated in the development of superficial incisional SSI between the standard ABX and extended ABX cohorts (10.9% vs. 12.9%, $p = 0.62$). Of patients who underwent a transverse colectomy, a larger percentage of patients developed a superficial SSI versus no SSI (21% vs. 6%, $p = 0.004$).

Conclusion(s). In this retrospective study of patients with advanced ovarian cancer undergoing CRS with LBR, extended post-operative ABX was not associated with reduced SSI, and prolonged administration of antibiotics should be avoided unless clinically indicated.

1. Introduction

Surgical site infections (SSIs) are a leading cause of healthcare-associated morbidity, accounting for up to 40% of nosocomial infections [1]. In patients with gynecologic cancer undergoing laparotomy, SSI

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rates as high as 35% have been reported, with longer hospital stays, readmission, reoperation, and increased healthcare costs [2–7]. Patients who are obese, malnourished, or undergo large bowel surgery are at the highest risk for SSI [3–9]. Notably, patients with gynecologic cancers who develop postoperative SSI have significantly worse progression-free survival (PFS) and overall survival (OS) [4–7].

In recent years, investigators have sought to identify modifiable risk factors and interventions to reduce infection rates. While individual measures, including suture closure [10], antimicrobial skin glue [11], closure trays [12,13], and immuno-nutrition [14–16] have consistently failed to improve infectious outcomes, studies demonstrate that implementing multi-point infection reduction bundles can reduce infectious morbidity [17–20]. In a prospective study by Lippitt et al., the implementation of a 5-point infection prevention bundle, which included skin and vaginal pre-operation with 4% chlorhexidine, preoperative antibiotic (ABX), mechanical bowel preparation, and appropriate timing of intra-operative ABX, led to significantly improved SSI rates [17]. Specifically, the bundle decreased the incidence of SSI from 20% to 3% in all patients and 33% to 7% in those who underwent colon resection [17].

One barrier to the evolution of surgical and perioperative care is the long-standing dogmatic practices that may not be rooted in high-quality evidence. While prophylactic antibiotics within 60 min of incision are the preoperative standard of care [21] owing to the substantial reduction in infectious morbidity, some surgeons may continue ABX post-operatively following cytoreductive surgery (CRS) with large bowel resection [22]. While the potential risks and benefits of prolonged perioperative ABX have not been explored in patients with gynecologic cancer, studies in patients following cardiac and colorectal surgery demonstrate no SSI reduction, increased rates of *C.Difficile* colitis, and acute kidney injury with this practice [23–25]. Additionally, newer retrospective data suggests that ABX use during chemotherapy is associated with worse oncologic outcomes in patients with ovarian cancer receiving platinum chemotherapy, as well as recurrent gynecologic cancers treated with immunotherapy [26–28]. Therefore, understanding how additional antibiotics during and after CRS with large bowel resection impact SSI will aid in implementing evidence-based strategies to improve infectious outcomes in patients with ovarian cancer. The objective of this study was to determine whether extended dosing of ABX after CRS with large bowel resection is associated with reduced incidence of SSI and other postoperative and oncologic adverse outcomes compared to standard intra-operative antibiotic dosing in patients with advanced ovarian cancer.

2. Methods

2.1. Study design

We performed an Institutional Review Board-approved, retrospective cohort study of patients with stage III and IV ovarian cancer who underwent CRS with large bowel resection followed by platinum chemotherapy between January 1st 2009-December 31st 2017. Participants were identified from the electronic medical record via ICD9 codes (183.0, 183.2, 183.8, 183.9), and charts were curated to identify patients >18 years diagnosed with high-grade ovarian cancer who underwent CRS with colorectal resection. Colorectal resection was defined as any large bowel resection and anastomosis (right hemicolectomy, transverse colectomy, left hemicolectomy, rectosigmoid resection) with or without stoma creation. Patients who did not receive surgery and front-line platinum chemotherapy were excluded. Further, patients with gross intra-abdominal contamination during bowel resection, according to the operative report, or who had preoperative bowel perforation/rupture were excluded. Patients were divided into two cohorts: 1) those who received standard prophylactic ABX prior to surgery with appropriate intra-operative re-dosing only and 2) those who received additional extended ABX, piperacillin/tazobactam, post-operatively. The duration of extended ABX was recorded.

2.2. Surgical procedures

Procedures were performed by nine attending gynecologic oncologists. The decision to prescribe additional ABX after surgery was at the discretion of the primary surgeon, without randomization. Each attending physician routinely prescribed either standard intra-operative ABX or extended post-operative ABX during the study period as part of their standard practice. Chlorhexidine alcohol-based scrub and betadine were used for preoperative abdominal and vaginal surgical-site preparation, respectively. All patients received the same preoperative and postoperative care, including pre and intraoperative antibiotic prophylaxis according to institutional guidelines. The standard institutional perioperative antibiotic regimen was per ACOG guidelines. Patients undergoing hysterectomy and/or laparotomy were to be given a single-dose of cefazolin or alternative antibiotic based off patient allergies. Antibiotics were adjusted for body mass index (BMI) and were re-dosed based off surgical time and blood loss. Patients who were re-dosed were not counted in the extended ABX group unless antibiotics were continued post-operatively. If bowel surgery was performed the institutional guideline was to administer additional antibiotics for extended coverage. Compliance in giving antibiotics within 1 h of surgical incision was not reviewed [29].

2.3. Data collection

Data was extracted for patient demographics, including age, BMI, race, hereditary genetic mutations, and American Society of Anesthesiologists score (ASA) at the time of CRS. Surgical variables collected included type of surgery (primary CRS or interval CRS following neoadjuvant chemotherapy), residual disease at CRS, and surgical procedures (small bowel and large bowel surgery, creation of an ileostomy or colostomy or upper abdominal surgery). Postoperative outcomes were also recorded. Specifically, the primary outcome was superficial incisional SSI within 30 days of surgery. Secondary outcomes were defined as deep incisional SSI, organ/space SSI, dehiscence, seroma, and hematoma, need for wound exploration or debridement, reoperation, readmission, ICU admission, urinary tract infection, pneumonia, bacteremia, bowel or urinary leak within 30 days of surgery. Infectious wound outcomes were defined using CDC definitions: superficial incisional SSI, deep incisional SSI, and organ/space infections [30]. Additional secondary outcomes were progression-free survival (PFS) and overall survival (OS). All collected patient information was stored electronically using REDCap (Research Electronic Data Capture) [31].

2.4. Statistical analysis

Categorical factors were reported with frequencies and percentages, and continuous measures summaries were reported as mean and standard deviation or medians and interquartile ranges. Continuous measures that show departure from normality and ordinal measures were summarized using medians and interquartile ranges or frequencies and percentages and compared using Wilcoxon rank sum tests. To compare patient and oncologic characteristics, Pearson chi-square tests, Fisher's Exact test, two sample *t*-tests, and Wilcoxon Rank Sum test were used for univariate analysis. PFS was defined as from surgery until date of disease recurrence and OS from surgery until the date of overall death, PFS and OS were censored at the last follow-up. Among all patients, there were only 4 deaths before recurrence, and they were all dead of other causes. They were all censored at the date of death for PFS, as a standard method of left-censored survival analysis. Survival month was defined as 30 days. Cox proportional hazards regression right-censored univariate and multivariable models were performed for PFS and OS, log-rank tests, and Cox univariate Wald tests were performed. All p values are two-sided, with 0.05 as the level of statistical significance and 95% CI. Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Patient demographics, oncologic and surgical details

In total, 277 patients underwent CRS with large bowel resection, followed by platinum chemotherapy between 2009 and 2017. Forty-nine percent ($n = 137$) received standard intra-operative ABX only and 50.5% ($n = 140$) received extended post-operative ABX. The duration of antibiotic administration in the extended antibiotic group was recorded. 1.4% ($n = 2$) of patients received <24 h of antibiotics, 47.1% ($n = 66$) received 24–48 h of antibiotics, 16.4% received 48–72 h, and 34.3% ($n = 48$) received >72 h of antibiotics. The patient demographics, oncology, and surgical characteristics of both groups are displayed in Table 1. There were no statistically significant differences in age, BMI, and medical comorbidities, including hypertension and diabetes, between the cohorts ($p > 0.05$). When comparing standard intra-operative ABX to extended ABX dosing, most patients were of white race (88.2% vs. 87.8%, $p = 0.94$) and had an ASA Score of 3 or 4 (83.1% vs. 81.9%; $p = 0.74$), respectively. Patients who received standard ABX were less likely to have undergone a mechanical bowel preparation than extended ABX patients (41.9% vs. 66.4%, $p < 0.001$). For both standard ABX and extended ABX patients, most had Stage III disease (78.1% vs. 80%, $p = 0.74$) and serous histology (89.8% vs. 90%, $p = 0.87$). Similarly, there were no differences in the rate of optimal resection, timing of CRS, procedures performed, or the number of bowel resections ($p > 0.05$). Surgical time was significantly shorter in patients who received standard ABX vs. extended ABX (270 vs 313 min, $p = 0.004$) (Table 1).

3.2. Postoperative outcomes

Postoperative outcomes are outlined in Table 2. SSIs were stratified by superficial incisional, deep incisional, and organ or space, according to the CDC guidelines [30]. There was no difference in the rate of superficial incisional SSI between standard ABX and extended ABX (10.9 vs. 12.9%, $p = 0.62$). The organ/space infection rate was lower in the standard ABX patients versus extended ABX (4.4% vs. 10.7%, $p = 0.046$). Postoperative complications, including reoperation, readmission, ICU admission, and anastomotic leak, were not statistically significant across both ABX regimen cohorts ($p > 0.05$). The rate of *C. difficile* colitis in the postoperative period was 3.6% ($n = 5$) in the extended ABX patients compared to 1.5% ($n = 2$) of the standard ABX patients ($p = 0.45$). Similarly, no difference was appreciated in postoperative complications, according to the Clavien Dindo score, length of stay, or time to chemotherapy between standard ABX or extended ABX patients ($p > 0.05$).

3.3. Univariate analysis for predictors of surgical site infection

Table 3 outlines the univariate analysis for patients with either a superficial or any SSI. Of 277 patients, 33 (12%) patients experienced a superficial SSI, and 48 (17%) patients experienced any SSI. Patients with superficial SSI were older than those without superficial SSI (median 65.5 vs. 62.0 years, $p = 0.01$), but there was no difference in age for any SSI versus no SSI (median 63.7 vs. 62.2 years, $p = 0.35$). There were no significant differences between BMI, race, ASA scores, or medical comorbidities for patients who experienced a superficial or any SSI vs. no SSI, $p > 0.05$. The majority of patients who experienced a superficial or any SSI were stage III (66.7% and 66.8%) with serous histology (93.9% and 91.7%). Stage and histology did not impact the development of a superficial or any SSI, $p > 0.05$. Over half of patients who developed both a superficial SSI (57.6%) or any SSI (54.2%) received mechanical bowel preparation. Receipt of mechanical bowel preparation, oral antibiotic prep, or both was not associated with an increased risk of developing either a superficial SSI or any SSI, $p > 0.05$. Intraperitoneal chemotherapy recipients did not have higher rates of superficial or any SSI, $p = 0.34$ and $p = 0.28$, respectively. Timing of CRS (primary vs interval CRS) and the extent of residual disease did not impact the development of SSI, $p > 0.05$. Of patients who underwent a transverse colectomy, a larger percentage of patients developed a superficial SSI

Table 1
Patient demographics, oncologic & surgical details.

	sABX	eABX	P value
	($N = 137$)	($N = 140$)	
Patient Details			
Age (years)	63.2 ± 9.8	61.6 ± 10.4	0.19
BMI (kg/m^2)	27.7 ± 6.3	26.5 ± 5.7	0.11
Race			0.94
Caucasian	120 (88.2)	122 (87.8)	
Black	10 (7.4)	12 (8.6)	
Indian	1 (0.74)	1 (0.72)	
Middle Eastern	1 (0.74)	0 (0.0)	
Asian	2 (1.5)	3 (2.2)	
Other	2 (1.5)	1 (0.72)	
Genetic Mutation			
BRCA1	9 (8.7)	16 (16.8)	0.082
BRCA2	8 (5.9)	6 (6.3)	0.53
Other (BRIP1, RAD51C/D)	10 (9.6)	6 (6.3)	0.39
Medical Comorbidities			
HTN	57 (41.6)	52 (37.1)	0.45
DM	16 (11.7)	10 (7.1)	0.20
CKD	9 (6.6)	4 (2.9)	0.14
CAD	17 (12.4)	17 (12.1)	0.95
ASA Score			0.79
1/2	23 (16.9)	25 (18.1)	
3/4	113 (83.1)	113 (81.9)	
Bowel Preparation			**<0.001**
Mechanical	57 (41.9)	93 (66.4)	
Antibiotic	1 (0.74)	1 (0.71)	
Both	9 (6.6)	10 (7.1)	
None	69 (50.7)	36 (25.7)	
Oncologic Details			
Stage			0.74
III	107 (78.1)	112 (80.0)	
IV	29 (21.2)	27 (19.3)	
Histology			0.87
Serous	123 (89.8)	126 (90.0)	
Endometrioid	1 (0.73)	2 (1.4)	
Clear Cell	7 (5.1)	6 (4.3)	
Carcinosarcoma	4 (2.9)	6 (4.3)	
Mucinous	1 (0.73)	0 (0.0)	
Other	1 (0.73)	0 (0.0)	
IP chemotherapy	15 (10.9)	15 (10.8)	0.97
Surgical Details			
Timing of CRS			0.12
Primary CRS	102 (74.5)	115 (82.1)	
Interval CRS	35 (25.5)	25 (17.9)	
Residual Disease			0.22
Optimal (Complete)	63 (46.7)	48 (34.3)	
Optimal (<1 cm)	9 (6.6)	17 (12.1)	
Optimal (<0.5 cm)	34 (24.8)	39 (27.9)	
Optimal (NOS)	17 (12.4)	22 (15.7)	
Suboptimal	13 (9.5)	14 (10.0)	
Procedures			
Small Bowel Resection	18 (13.0)	18 (12.9)	0.36
Right Hemicolectomy	12 (8.7)	12 (8.6)	0.53
Transverse Colectomy	12 (8.7)	12 (8.6)	0.87
Left Hemicolectomy	21 (15.2)	21 (15.0)	0.23
Rectosigmoid Resection	124 (89.9)	126 (90.0)	0.65
Splenectomy	25 (18.1)	25 (17.9)	0.28
Liver Resection	7 (5.1)	7 (5.0)	0.81
Diaphragm Stripping/Resection	16 (11.6)	16 (11.4)	0.66
Ileostomy	15 (10.9)	16 (11.4)	0.90
End/Loop Colostomy	8 (5.8)	6 (4.3)	0.56
Number of Bowel Resections	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	0.09
Surgical Time (minutes)	270.3 ± 90.8	313.7 ± 125.7	**0.004**

Statistics presented as Mean ± SD, Median [P25, P75], N (column %).
ABX, antibiotics; BMI, body mass index; ECOG, Eastern Co-operative Oncology Group; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CAD, coronary artery disease; VTE, venous thromboembolism; CRS, cytoreductive surgery; IP, intraperitoneal; R0 – no gross residual disease; NOS – not otherwise specified.

Table 2
Post-operative outcomes.

	sABX	eABX	P value
	(*N* = 137)	(*N* = 140)	
Infectious Wound Outcomes			
Superficial Incisional SSI	15 (10.9)	18 (12.9)	0.62
Deep Incisional SSI	0 (0.0)	0 (0.0)	---
Organ or Space SSI	6 (4.4)	15 (10.7)	**0.046**
Postoperative Complications			
Reoperation	3 (2.2)	8 (5.7)	0.13
Readmission	8 (5.8)	12 (8.6)	0.38
ICU Admission	19 (13.9)	20 (14.3)	0.92
Anastomotic Leak	5 (3.6)	5 (3.6)	0.99
UTI	13 (9.5)	10 (7.1)	0.48
C Difficile	2 (1.5)	5 (3.6)	0.45
DVT	3 (2.2)	2 (1.4)	0.68
Pulmonary Embolism	1 (0.73)	1 (0.71)	0.99
Blood Transfusion	66 (49.3)	67 (49.3)	0.99
Length of Stay (days)	7.0 [5.5, 10.0]	8.0 [6.0, 10.0]	0.73
Clavien Dindo Post-operative Complications Score			0.99
0	24 (17.6)	24 (17.1)	
I	25 (18.4)	26 (18.6)	
II	57 (41.9)	59 (42.1)	
III	11 (8.1)	14 (10.0)	
IV	19 (14.0)	17 (12.1)	
Time to Chemotherapy (days)	35.0 [29.0, 45.0]	36.5 [29.0, 46.0]	0.83

Statistics presented as Median [P25, P75], N (column %).
ABX, antibiotics.

versus no SSI (21% vs. 6%, $p = 0.004$). Liver resections ($n = 14$) were also statistically correlated with the development of superficial SSI (12.1% vs. 3.7%, $p = 0.032$) and any SSI (10.4% vs. 3.5%, $p = 0.039$) compared to no SSI. There was no difference in surgical time for patients who developed a superficial SSI versus no SSI (346.2 ± 185.7 vs. 284.2 ± 96.0 min, $p = 0.16$) and any SSI versus no SSI (332.1 ± 167.0 vs. 283.5 ± 95.6, $p = 0.10$).

3.4. Oncologic outcomes

Table 4 compares oncologic outcomes for patients who received extended ABX following surgery as well as patients who developed SSI. There were no significant differences in PFS (median 26.7 months vs. 31.7 months, HR 0.98 95% CI 0.75–1.28, $p = 0.89$) or OS (median 68.6 months vs. 70.5 months, HR 0.96 95% CI 0.70–1.31, $p = 0.80$) for patients who received extended ABX following surgery on both univariate and multivariable analysis. Lastly, we examined SSI (both superficial and any) and its impact on PFS and OS. On univariate analysis patients who experienced a superficial SSI had both a decreased PFS (median15.7 months vs 21.5 months, HR 1.57 95% CI 1.05–2.34, $p = 0.02$) and OS (median 50.0 months vs 72.3 months, HR 1.66 95% CI 1.07–2.56, $p = 0.022$) compared to patients with no superficial SSI. These results were similar when comparing any SSI to no SSI group; any SSI group demonstrated a statistically significant decrease in PFS (median 15.8 months vs. 21.9 months, HR 1.53 95% CI 1.08–2.15, $p = 0.015$) and OS (median 55.3 months vs 72.7 months, HR 1.57 95% CI 1.08–2.27, $p = 0.017$) (Figs. 1 and 2). After controlling for cytoreductive status at the time of surgery neither PFS (HR 1.40 95% CI 0.94–2.10, $p = 0.10$) or OS (HR 1.51 95% CI 0.97–2.34, $p = 0.067$) were significantly impacted by superficial SSI. This also applied for the combined SSI group when controlling for cytoreductive status with the following PFS (HR 1.39 95% CI 0.98–1.97, $p = 0.063$) and OS (HR 1.40, 95% CI 0.96–2.05, $p = 0.081$).

4. Discussion

While current evidence does not support the routine use of extended post-operative ABX after CRS with large bowel resection in gynecologic oncology, many surgical practices that may not be rooted in high-quality data persist. This study aimed to determine whether extended ABX dosing after CRS with large bowel resection is associated with a reduced incidence of SSI versus standard intra-operative ABX in patients undergoing surgery for ovarian cancer. In this single-institution, retrospective evaluation of 277 patients with ovarian cancer undergoing CRS, approximately one-half received additional/extended antibiotics following surgery. Notably, extended ABX was not associated with a reduction in SSI after CRS with large bowel resection. Patients who received extended ABX did not experience any difference in PFS or OS compared to those who did not. SSI did impact PFS and OS in our cohort, underscoring the importance of infection prevention in patients with ovarian cancer.

Surgical site infections have been consistently associated with increased morbidity and mortality in patients with gynecologic cancers. In this population, SSIs were associated with extended duration of hospital stays, increased rate of re-operation, and wound dehiscence [4–7]. Factors associated with SSI include higher BMI, increased surgical complexity, and advanced-stage disease. Although many factors implicated in SSI are non-modifiable, in recent years, research efforts have prioritized multi-modality infection reduction efforts. Schiavone et al. investigated the effects of an intervention bundle, including preoperative oral antibiotics with optional mechanical bowel preparation, skin preparation, and the use of a separate surgical tray, and found a significant reduction in 30-day SSIs in patients following CRS with large bowel resection [19]. Subsequently, Bruce et al. examined the effectiveness of an abdominal closure bundle in a gynecologic oncology patient population undergoing laparotomy. This bundle included changing surgical gowns and gloves, repeat surgical scrub, and usage of new instruments for closure of fascia. Although they found the bundle to be easily implemented, they did not find significant reductions in SSIs in this population [13]. In a similar study, an abdominal closure protocol was enacted for patients undergoing total abdominal hysterectomy by a gynecologic oncologist. In both univariate and multivariate analyses, bowel resection was a risk factor for developing SSI, which correlates with our findings. Although potential risk factors were identified, the abdominal closure protocol in this study did not decrease SSI [32]. It is unclear whether adjusting surgical techniques and using SSI-reducing bundles effectively decreases SSIs, leaving surgeons searching for additional solutions.

Broadening or extending perioperative antibiotics has been studied as a strategy to reduce SSIs in gynecologic cancer patients. Kuznicki et al. implemented dual-antibiotic surgical prophylaxis of cefazolin and metronidazole for all gynecologic oncology patients undergoing hysterectomy. In this population, a 58% reduction in SSIs was observed. The dual-agent SSI bundle cohort also experienced significantly lower readmission rates [33]. However, historical studies across surgical disciplines have found that multi-dose, expanded antibiotic regimens and prolonged prophylaxis can be detrimental [23–25]. In a multicenter retrospective cohort study of patients undergoing colorectal surgical procedures, prolonged perioperative antimicrobial prophylaxis was associated with an increased risk of acute kidney injury and *C. difficile* colitis and did not lead to a reduction in SSI [34]. Within oncologic surgical disciplines, extended antibiotic regimens have also been associated with increased risk of *C. difficile* [35]. More recently, Nusrath et al. performed an open-label randomized clinical trial in India of patients undergoing major oncological clean-contaminated surgeries. Patients were randomized to single-dose vs. extended ABX dose groups. In their study, the overall SSI rate of the single-dose group was not significantly different from that of the extended group (11.3% vs. 14.7%, $p = 0.40$) [36]. Our findings are consistent with these prior results, suggesting that extended ABX after CRS with large bowel resection is not associated with reducing SSI risk in ovarian cancer patients and should, therefore, be avoided.

Consistent with prior studies, PFS and OS were impacted in our cohort by the development of SSI post-operatively. In a retrospective

Table 3
Univariate analysis for surgical site infection.

	Superficial SSI ($N = 33$)	No superficial SSI ($N = 244$)	P value	Any SSI ($N = 48$)	No SSI ($N = 229$)	P value
Patient Details						
Age (years)	65.5 ± 6.5	62.0 ± 10.4	0.010	63.7 ± 8.8	62.2 ± 10.3	0.35
BMI (kg/m^2)	27.4 ± 5.5	27.1 ± 6.1	0.78	26.8 ± 5.3	27.1 ± 6.2	0.74
Race			0.019			<0.001
Caucasian	30 (90.9)	212 (87.6)		44 (91.7)	198 (87.2)	
Black	0 (0.00)	22 (9.1)		0 (0.00)	22 (9.7)	
Indian	1 (3.0)	1 (0.41)		1 (2.1)	1 (0.44)	
Middle Eastern	0 (0.00)	1 (0.41)		0 (0.00)	1 (0.44)	
Asian	0 (0.00)	5 (2.1)		0 (0.00)	5 (2.2)	
Other	2 (6.1)	1 (0.41)		3 (6.3)	0 (0.00)	
Medical Comorbidities						
HTN	14 (42.4)	95 (38.9)	0.70	21 (43.8)	88 (38.4)	0.49
DM	4 (12.1)	22 (9.0)	0.57	4 (8.3)	22 (9.6)	0.78
CKD	1 (3.0)	12 (4.9)	0.63	1 (2.1)	12 (5.2)	0.35
CAD	6 (18.2)	28 (11.5)	0.27	9 (18.8)	25 (10.9)	0.13
ASA Score			0.91			0.60
1/2	6 (18.2)	42 (17.4)		7 (14.9)	41 (18.1)	
3/4	27 (81.8)	199 (82.6)		40 (85.1)	186 (81.9)	
Bowel Preparation			0.76			0.74
Mechanical	19 (57.6)	131 (53.9)		26 (54.2)	124 (54.4)	
Oral Antibiotics	0 (0.00)	2 (0.82)		0 (0.00)	2 (0.88)	
Both	1 (3.0)	18 (7.4)		2 (4.2)	17 (7.5)	
None	13 (39.4)	92 (37.9)		20 (41.7)	85 (37.3)	
Oncologic Details						
Stage			0.27			0.16
III	22 (66.7)	197 (80.7)		33 (66.8)	186 (81.2)	
IV	11 (33.3)	45 (18.4)		15 (31.3)	41 (17.9)	
IP chemotherapy	2 (6.1)	28 (11.5)	0.34	3 (6.4)	27 (11.8)	0.28
Surgical Details						
Timing of CRS			0.61			0.36
Primary CRS	190 (77.9)	27 (81.1)		40 (83.3)	177 (77.3)	
Interval CRS	54 (22.1)	6 (18.2)		8 (16.7)	52 (22.7)	
Residual Disease			0.17			0.063
Optimal (Complete)	7 (21.2)	105 (43.0)		11 (22.9)	101 (44.1)	
Optimal (<1 cm)	4 (12.1)	22 (9.0)		6 (12.5)	20 (8.7)	
Optimal (<0.5 cm)	10 (30.3)	63 (25.8)		14 (29.2)	59 (25.8)	
Optimal (NOS)	7 (21.2)	32 (13.1)		9 (18.8)	30 (13.1)	
Suboptimal	5 (15.2)	22 (9.0)		8 (16.7)	19 (8.3)	
Procedures						
Small Bowel Resection	8 (24.2)	33 (13.5)	0.10	11 (22.9)	30 (13.1)	0.082
Right Hemicolectomy	3 (9.1)	18 (7.3)	0.73	4 (8.3)	17 (7.4)	0.83
Transverse Colectomy	7 (21.2)	16 (6.6)	**0.004**	7 (14.6)	16 (7.0)	0.083
Left Hemicolectomy	4 (12.1)	31 (12.7)	0.92	6 (12.5)	29 (12.7)	0.98
Rectosigmoid Resection	27 (81.8)	220 (90.2)	0.15	39 (81.3)	208 (90.8)	0.052
Splenectomy	5 (15.2)	38 (15.6)	0.95	10 (20.8)	33 (14.4)	0.26
Liver Resection	4 (12.1)	9 (3.7)	**0.032**	5 (10.4)	8 (3.5)	**0.039**
Diaphragm Stripping/Resection	3 (9.1)	31 (12.7)	0.55	6 (12.5)	28 (12.2)	0.96
Ileostomy	5 (15.2)	26 (10.7)	0.44	7 (14.6)	24 (10.5)	0.41
End/Loop Colostomy	2 (6.1)	12 (4.9)	0.78	4 (8.3)	10 (4.4)	0.25
Number of Bowel Resections	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	0.15[d]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	0.55
Surgical Time (minutes)	346.2 ± 185.7	284.2 ± 96.0	0.16	332.1 ± 167.0	283.5 ± 95.6	0.10

Statistics presented as Mean ± SD, Median [P25, P75], N (column %).
ABX, antibiotics; BMI, body mass index; ECOG, Eastern Co-operative Oncology Group; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CAD, coronary artery disease; VTE, venous thromboembolism; CRS, cytoreductive surgery; IP, intraperitoneal; R0 – no gross residual disease; NOS – not otherwise specified.

Table 4
Oncologic outcomes.

	PFS				OS			
Variable	Median months (95% CI)	3-year PFS (95% CI)	HR (95% CI)	P value	Median months (95% CI)	3-year OS (95% CI)	HR (95% CI)	P value
Additional ABX ($n = 138$)	20.8 (17.2–23.8)	26.7 (19.2, 34.3)	---	0.81	57.4 (45.7–68.8)	68.8 (60.9, 76.6)	---	0.57
No Additional ABX ($n = 135$)	17.8 (16.3–24.4)	31.7 (23.7,39.6)	0.97 (0.74,1.26)		58.6 (47.0–74.7)	70.5 (62.7,78.8)	0.91 (0.67, 1.25)	
Superficial SSI (n = 33)	15.7 (13.3–20.8)	9.8 (0.0,20.4)	---	**0.02**	37.3 (24.6–65.1)	50.0 (32.7, 67.4)	---	**0.022**
No Superficial SSI ($n = 243$)	21.5 (17.6–24.3)	31.7 (25.8, 37.7)	1.57 (1.05,2.34)		58.6 (51.6–70.8)	72.3 (66.5, 78.0)	1.66 (1.07,2.56)	
Any SSI (n = 48)	15.8 (13.7–21.4)	11.0 (1.9, 20.1)	---	**0.015**	44.1 (28.7–65.1)	55.3 (41.1, 69.6)	---	**0.017**
No SSI ($n = 228$)	21.9 (17.6–24.7)	33.0 (26.8, 39.2)	1.53 (1.08,2.15)		59.9 (52.3–70.8)	72.7 (66.7, 78.6)	1.57 (1.08, 2.27)	

CI: confidence interval, HR: hazard ratio.

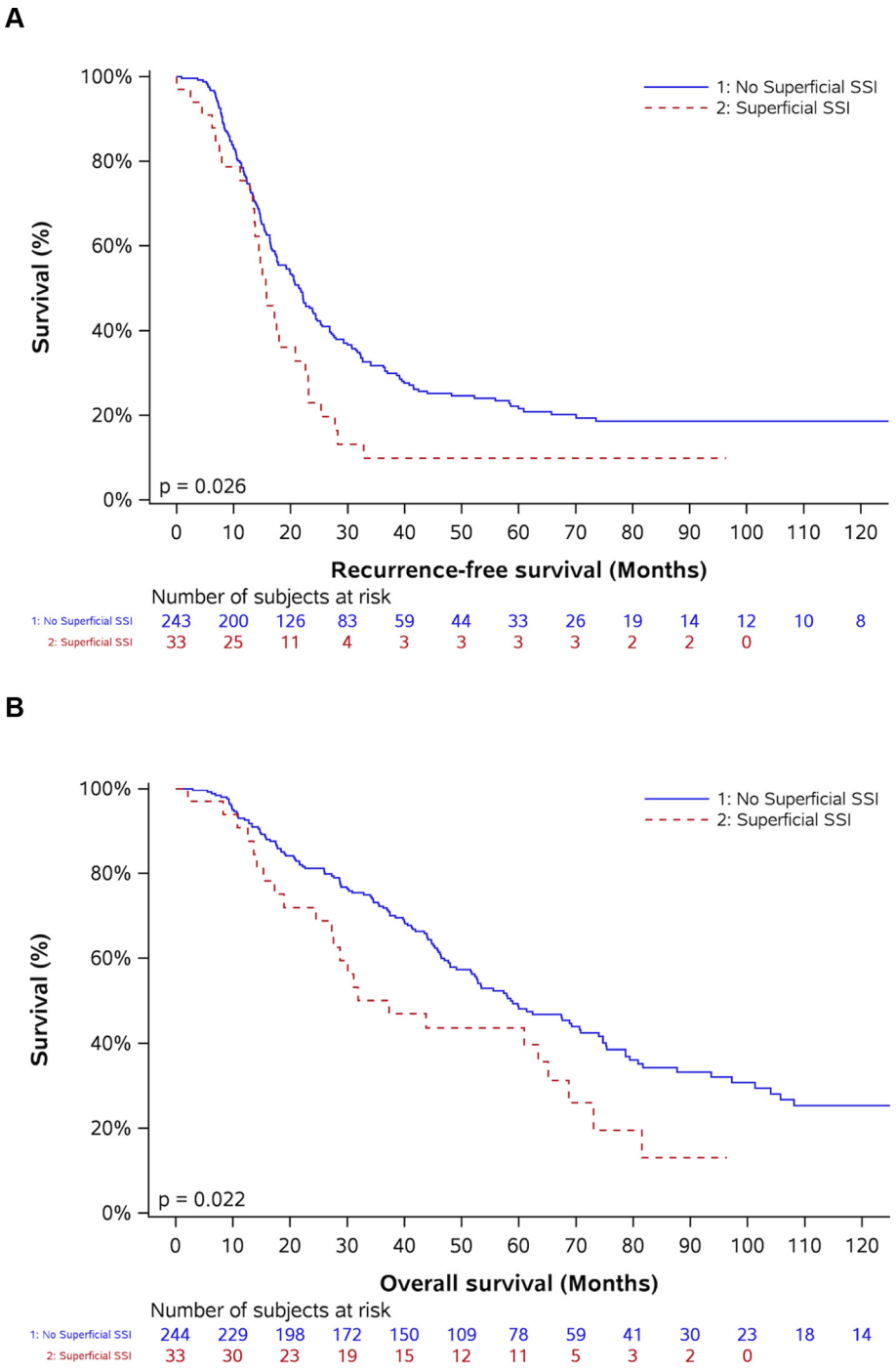

Fig. 1. Progression-free survival (A) and overall survival (B) of superficial SSI vs. No superficial SSI.

review of 888 patients who experienced SSI following ovarian cancer primary surgery, the occurrence of superficial or organ/space SSI was independently associated with worse OS (HR 1.69 and 1.46, respectively). SSI occurrence was not associated with decreased disease-free survival [4]. More broadly, perioperative infectious disease, defined as a positive microbiology result obtained within a 6-week postoperative period, is an independent risk factor for survival in patients with ovarian cancer. Patients with perioperative infectious disease demonstrated shorter median PFS (8.4 vs 17.6 months; $p < 0.001$) and decreased overall survival (29.0 vs 51.8 months; $p = 0.011$) [37]. Perioperative infections were associated with increased surgical mortality, delay in chemotherapy treatment, and decreased chemotherapy response, which would explain poor oncologic outcomes in this cohort.

In our study, extended ABX was not associated with PFS or OS detriment in ovarian cancer patients. However this is important to consider as recent evidence suggests antibiotic treatment during cancer therapy may impact survival, response, and recurrence. In a study performed by Chambers et al., patients with newly diagnosed stage III/IV ovarian cancer receiving platinum chemotherapy who received antibiotics for >48 h demonstrated a significant decrease in PFS and OS [26]. Retrospective studies in various other disciplines have also demonstrated the relationship between antibiotics, the microbiome, and clinical

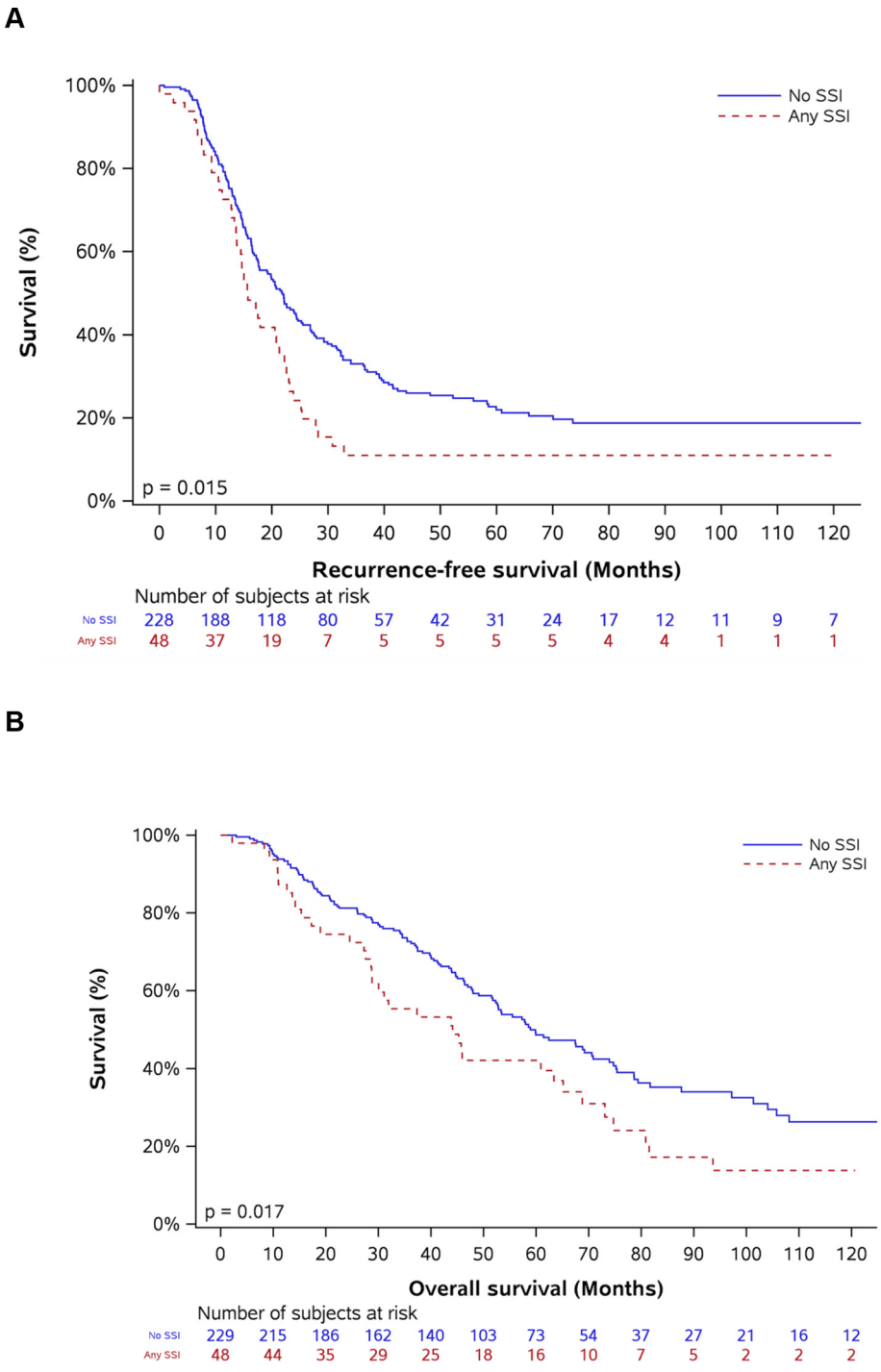

Fig. 2. Progression-free survival (A) and overall survival (B) of any SSI vs. No superficial SSI.

response [38–41]. These studies demonstrate it is essential to balance improving polymicrobial coverage, promoting antibacterial stewardship, and considering the evolving understanding of the gut microbiome and its impact on oncologic outcomes.

There are several key limitations to this study that should be considered. Primarily, this was a single-institution, retrospective, non-randomized study where the decision for extended ABX after surgery was made at the discretion of the primary surgeon. Due to this, we cannot conclude whether ABX duration or specific surgeon practices directly impacted outcomes, and the possibility of selection bias must be factored in. Our analysis intentionally excluded patients from the study where the surgeon reported gross fecal contamination of the operative field during colorectal resection, which introduces bias and may not have been reported uniformly in operative results. The exclusion of this group was intentional, as gross spillage known to be a risk factor for postoperative complications [42]. We realize that there may also be cases where gross spill occurred and was not reported, particularly in the extended ABX group. Additionally due to the length of the study period and changing practices we did not identify the amount of surgeons who utilized standard ABX vs. extended ABX dosing, or if there was a length of time in practice differences. It was not collected whether each surgeon only picked one strategy or the other for all their patients. Additionally, a scoring system based upon surgical complexity and number of surgical procedures performed per patient was

not recorded. Despite these limitations, our study reports on a large cohort of patients with ovarian cancer undergoing CRS with large bowel resection. It demonstrates that the extended ABX administration is not associated with a decreased incidence of SSI.

In this retrospective cohort of patients with stage III and IV ovarian cancer undergoing CRS with large bowel resection, we conclude that extended ABX post-operatively was not associated with a decreased incidence of SSI or adverse postoperative outcomes. Prolonged antibiotics showed no impact on survival outcomes, but the presence of any SSI did significantly worsen PFS and OS in patients with ovarian cancer. Innovative strategies to decrease SSIs in our patient population are needed. However, prolonged antibiotics following routine colorectal resection in CRS may not be beneficial. We must continue challenging anecdotal, often dogmatic, surgical practices and provide guideline-concordant care to promote the best outcomes for patients with ovarian cancer.

CRediT authorship contribution statement

Julia Chalif: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Laura M. Chambers:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Meng Yao:** Data curation, Writing – original draft, Writing – review & editing. **Michelle Kuznicki:** Data curation, Writing – original draft, Writing – review & editing. **Robert DeBernardo:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing. **Peter G. Rose:** Data curation, Writing – original draft, Writing – review & editing. **Chad M. Michener:** Data curation, Writing – original draft, Writing – review & editing. **Roberto Vargas:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration, Supervision.

Declaration of competing interest

All authors have no relevant conflicts of interest to disclose.

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