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The Clinical Importance of Preoperative Rectal Swabs in Patients after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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Keywords

Surgical site infections · Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · Multidrug-resistant bacteria · Hospital-acquired infection

Abstract

Background: Surgical site infections are among the most common healthcare-associated infections, especially in patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The aim of this retrospective study was to examine postoperative infectious complications according to preoperative screening findings of nasal and rectal swabs. ***Methods:*** Two hundred four consecutive patients received nasal and rectal swab examination for multidrug-resistant (MDR) bacteria within 30 days before the operation in patients where CRS and HIPEC were planned. Inclusion criteria were as follows: confirmed peritoneal metastases (histologically and/or cytologically); age under 85 years; adequate renal, liver, and bone marrow function; no sign of infection preoperatively; resectable disease; and CRS and HIPEC procedure. If surgical site infection occurred, the microbial spectrum of the site was assessed. One hundred twenty-one patients (63 female [52.1%] and 58 male [47.9%]) met the criteria and were further analyzed retrospectively. Statistical correlations between postoperative complications and risk factors were investigated by univariate and multivariate analysis. ***Results:*** Postoperative complications in total were observed in 57 patients (47.1%) with major complications (Clavien-Dindo grades 3–4) in 15 patients (12.4%) and infectious complications in 37 (30.6%) patients. The overall prevalence of nasal MRSA carriage was 3.28%, and the overall prevalence of rectal MDR bacteria carriage was 10.7%. In propensity score analysis, colonized patients compared to noncolonized patients showed increased total complications (CD1–5, $p = 0.025$), infectious complications ($p = 0.028$), surgical site infections ($p = 0.022$) as well as pneumonia ($p = 0.016$). Multivariate analysis showed that in addition to preoperative rectal colonization, American Society of Anesthesiologists score was a risk factor for postoperative complications. ***Conclusions:*** Preoperative 3-MRGN and vancomycin-resistant enterococcus colonization were associated with increased complications and surgical site infections. Special antimicrobial treatment pathways are necessary for these patients to reduce postoperative complications due to colonization.

Introduction

In the course of gynecological and gastrointestinal metastatic disease, peritoneal metastases are often considered not operable [1, 2], the role of surgery in these patients is often solely to alleviate tumor-related complications. The introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) offered these patients a potentially curative approach. The number of centers conducting CRS and HIPEC procedures is increasing, in part, because of the dramatically enhanced result and quality of life of patients with various tumor entities following CRS and

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HIPEC. Such complex surgical procedures, given the promising outcomes, are often associated with a high rate of postoperative complications and high perioperative mortality, limiting the broad implementation of these procedures [3, 4]. Studies often report surgical and HIPEC-related complications but few concentrate on postoperative infectious complications [2, 5–7]. To prevent transmission of multidrug-resistant (MDR) bacteria, as well as reduce perioperative complications, it is necessary to recognize the bacterial reservoir, so that preventative measures such as contact isolation of the patient and any decolonization measures can be instituted as soon as possible.

Currently, preventative measures for perioperative infectious complications include the use of screening tests to identify colonized patients and subsequent perioperative antibiotic prophylaxis. However, no algorithm for the treatment or decolonization of HIPEC patients exists. Whether perioperative prophylaxis should include coverage for pathogens detected in the preoperative swab is unclear. This depends on many factors including the pathogen, its antimicrobial susceptibility profile, the host, the planned procedure, and other risk factors for postoperative infection [8]. We analyzed the clinical record of the patients receiving CRS and HIPEC for peritoneal metastases in our hospital to evaluate the associations between potential prognostic variables including preoperative colonization with MDR microbes and postoperative infectious complications.

Materials and Methods

In a 2-year period from January 2017 to January 2019, 204 patients with peritoneal metastases from multiple primary cancers were treated with CRS and HIPEC at our hospital. We selected 121 patients from a prospectively managed database who fulfilled the inclusion criteria. Inclusion criteria were as follows: confirmed peritoneal metastases (histologically and/or cytologically); age under 85 years; adequate renal, liver, and bone marrow function; no sign of infection preoperatively. Testing for MDR was performed via either nasal or rectal swab. Nasal swabs were performed as a standard procedure in all patients, while rectal swabs were performed in cases of risk factors for colonization or history of perioperative complications. We excluded 83 patients for incomplete records as no perioperative screening was performed in these cases due to technical reasons. All patients were admitted for surgery between 4 and 6 weeks after the end of the last chemotherapy regimen and after having proven their preoperative immune competency by blood tests. Due to the high-risk nature of the patient collective undergoing CRS and HIPEC (i.e., multiple previous operations), it is a part of our protocol to routinely test all patients undergoing CRS and HIPEC in order to detect clinically inapparent MRSA and MRE colonization early. This testing is part of the standard and was routinely administered upon admission at the Charité during this time. In the case of a positive nasal swab with Gram-negative bacteria, selective oral decontamination is performed with approximately 0.5 g of a paste containing colistin, tobramycin, and amphotericin B each in a 2% concentration. In case of positive screening in the preoperative rectal smear, a selective bowel decontamination (SDD) with 10 mL suspension with 100 mg colistin, 122 mg tobramycin, and 500 mg amphotericin B is applied. Our decolonization protocol against MRSA includes nasal decolonization with turixin ointment and mouthwashes (all over a period of 5 days) in addition to general decontaminative measures (patient whole body wash preoperatively with chlorhexidine washcloths). Postoperative microbiological analysis was performed only when clinically indicated, i.e., when bacterial infection is suspected. Postoperative infection was defined by the presence of fever, dyspnea, dysuria, a purulent surgical wound, or purulent drain secretion as well as an elevated leucocyte count and elevated C-reactive protein (CRP). Complications were documented and classified according to the Clavien-Dindo Classification for Postoperative Complications, requiring interventional endoscopy or CT scan/ultrasound-guided procedures, surgery, or readmission to the intensive care unit. In all symptomatic patients with suspect infection, blood cultures were obtained, and a sample from the central venous line tip, biological fluids like those from intestinal drainage, and urinary cultures were cultivated. No additional microbial studies were performed in asymptomatic patients. Reported postoperative adverse events and classified as infectious or other (including medical and operation-related). In the case of infectious complications, the location of infection and results of microbial analysis were reported.

Surgical Procedure

All patients received thoracic X-ray, ECG, and pulmonary function exam prior to surgery. Colonoscopy and gastroscopy were performed depending on clinic and concomitant diseases. In case of rectal colonization in preoperative hygiene screening, colon irrigation was performed as selective intestinal decontamination. All patients were treated with an antibiotic prophylaxis 30 min before incision; they received 2 g i.v. ceftriaxone and 500 mg i.v. metronidazole. Treatment with metronidazole was repeated every 4 h during the operation. Patients were provided with thromboembolic prophylaxis with low molecular heparin postoperatively and pneumatic compression stockings during the operation. The degree of peritoneal disease and cytoreduction was graded according to the peritoneal cancer index (PCI) [9]. At the end of the procedure, residual disease was scored according to completeness of cytoreduction classification (CC) (no residual disease: CC-0; residual disease <2.5 mm: CC-1; residual disease of 2.5 mm to 2.5 cm: CC-2; and residual disease >2.5 cm: CC3) [3]. The goal of surgery was to eradicate all macroscopic tumor tissue. En bloc partial or total visceral resections and peritonectomies were performed according to the tumor-involved organs and/or peritoneal surfaces. Intestinal anastomoses were performed before HIPEC application. HIPEC application either included mitomycin and cisplatin (CDDP) or oxaliplatin and intravenous chemotherapy with 5 fluorouracil and leucovorin for a duration of either 60 or 90 min. Patients were admitted to the intensive care unit for a minimum of 24 h postoperatively.

Patient Demographics and Histopathological Data

We reported demographic, clinical, and pathological data for each patient: age, sex, comorbidities, primary tumor etiology, American Society of Anesthesiologists (ASA) score, previous abdominal operations, previous chemotherapy, preoperative chemotherapy, method of surgical procedures, PCI and CC score, perioperative complications, Clavien-Dindo classification as well as results from microbiological testing preoperatively and in case of infection.

Table 1. Demographics and patient characteristics

Characteristic	*N* (%)
Recipient age	56.3 (23.0–84.0)
Male gender	58 (47.9)
Female gender	63 (52.1)
ASA ≥ 3	76 (62.8)
Previous operation	80 (66.1)
Etiology	
Gastric	36 (29.7)
Ovarian	7 (5.7)
Colorectal	29 (24.0)
Mesothelioma	24 (19.8)
Peritoneal/CUP/unknown	23 (19.0)
Other	2 (1.7)
Resected organs (mean)	1.37 (1–6)
GI intervention	80 (66.1)
Splenectomy	7 (5.8)
PCI (mean)	13.59 (1–39)
HIPEC agent	
Cisplatin	93 (76.9)
Oxaliplatin	24 (19.8)
Preoperative nasal swab	121 (100.0)
Positive nasal swab	4 (3.3)
Preoperative rectal swab	65 (53.7)
Positive rectal swab	13 (10.7)
Both positive nasal and rectal	2 (1.7)

HIPEC, hyperthermic intraperitoneal chemotherapy; GI, gastrointestinal; PCI, peritoneal carcinomatosis index; ASA, American Society of Anesthesiologists; CUP, cancer of unknown primary.

Statistical Analysis

SPSS 11.5 software (SPSS, Chicago, IL, USA) was used for data analysis. Propensity score analysis was used to match patients who has a positive rectal swab in preclinical examination with a cohort of patients who had no history of rectal colonization. A 1:1 PSM was performed using a logistic regression model with a match tolerance of 0.1 based on the following matching parameters: patient age and ASA score.

Patient characteristics and postoperative outcomes were compared between the matched cohorts. Qualitative variables were compared using the Pearson χ^2 test or Fisher's exact test, as appropriate. Quantitative variables were compared using the Mann-Whitney U test or the student *t* test, as appropriate. Multivariate analysis was used to determine factors independently associated with postoperative infectious complication. The statistical significance was set at $p < 0.05$.

Results

The mean age was 56.3 years (23.05–83.95), and clinical characteristics are reported in Table 1. In our cohort, 58 (47.9%) patients were male and 63 (52.1%) were female. Seventy-six patients had an ASA score of over 3 (62.8%), and 80 patients had a history of previous operation (66.1%). The etiology of the primary malignancy was gastric cancer in 36 (29.7%) patients, ovarian cancer in 7 (5.7%), colorectal cancer in 29 (24.0%) patients, mesothelioma in 24 (19.8%) patients, while primary malignancy was unknown in 23 (19.0%) patients. The mean number of resected organs was 1.37 (1–6). Gastrointestinal intervention occurred in 80 (66.1%) patients, and splenectomy was performed in 7 (5.8%) patients. The mean PCI was 13.59 (1–39). Ninety-eight patients had received neoadjuvant chemotherapy regimens preoperatively (81.0%). A total of 13 (10.7%) positive results were collected from rectal swab, and 4 (3.3%) positive results were collected from the nasal swab. Two of these patients had both a positive nasal and rectal swab.

In the total study population, an uncomplicated recovery was observed in 64 cases (52.9%), while postoperative complications were observed in 57 patients (47.1%) with major complications (Clavien-Dindo grades 3–4) occurring in 15 patients (12.4%). Out of the 121 patients, 37 (30.6%) had an infectious complication perioperatively, 35 (28.9%) of the 121 patients had ≥2 complications. Out of the 13 colonized patients, 11 (84.6%) showed a complication (CD1–5) postoperatively, while nosocomial infections were present in 10 (76.9%) colonized patients. The perioperative 90-day mortality rate was 2.5% in our cohort.

Perioperative complications were evaluated among colonized and noncolonized patients via propensity score analysis. Eight patients (53.3%) without preoperative rectal colonization, while 11 patients (84.6) with a positive preoperative rectal swab had perioperative complications ($p = 0.025$). There was no difference between the incidence of major complications (CD grades 3–4). Major complications occurred in 6 (46.2%) colonized patients and 2 (13.3%) noncolonized ($p = 0.114$). The type and grade of perioperative complications are reported in Table 2. Patients with a positive preoperative rectal swab showed significantly increased rates of surgical site infection (2 [13.3%] vs. 8 [61.5%] $p = 0.022$) and pneumonia (2 [13.3%] vs. 5 [38.5%] $p = 0.016$). Despite the increased rates of surgical site infection, the rate of surgical site infection with MDR bacteria (1 [6.7%] vs. 4 [30.8%] $p = 0.161$) did not vary between the groups.

The most common bacteria isolated in preoperative swabs were 3 MRGN *Escherichia coli* and *Enterococcus faecalis* (Table 3). In the 37 patients with infectious complications, we collected positive cultures as reported in Table 4. *Enterococcus faecalis* and *Escherichia coli* were the most frequent species isolated, followed by *Klebsiella* and *Pseudomonas aeruginosa*. In 2 patients with 3 MRGN *Escherichia coli* in preoperative rectal swabs, 3 MRGN *Escherichia coli* was also found in postoperative cultures after surgical site infection. No further patients with positive swabs showed similar organisms in postoperative cultures.

Table 2. Perioperative complications shown among colonized and noncolonized patients

	Total (n = 13)	%	Colonized (n = 13)	%	Sig.
Patients with complications	8	53.3	11	84.6	**0.025**
Patients with infectious complications	6	40.0	10	76.9	**0.028**
Patients with major complications (CD ≥ 3)	2	13.3	6	46.2	0.114
Sepsis	1	6.7	3	23.1	0.076
Central line-associated	0	0.0	3	23.1	0.076
Surgical site infection	2	13.3	8	61.5	**0.022**
Surgical site infection with MDR bacteria	1	6.7	4	30.8	0.161
Pneumonia	2	13.3	5	38.5	**0.016**
Peritonitis	3	20.0	2	15.4	0.930
Urinary tract infection	2	13.3	4	30.8	0.409
Pleural effusion	2	13.3	4	30.8	0.161
Acute renal failure	4	26.7	2	15.4	0.588
Pulmonary embolism	1	6.7	0	0.0	0.343
Anastomotic dehiscence	1	6.7	0	0.0	0.343
Postoperative hemorrhage	1	6.7	0	0.0	0.343
Gastric perforation	2	13.3	0	0.0	0.172

CD, Clavien-Dindo; MDR, multidrug-resistant. Bold values denote statistical significance at the $p < 0.05$ level.

Logistic regression analysis was performed to correlate risk factors for adverse events including perioperative complications and infectious complications. Univariate analysis showed that ASA score ($p = 0.001$), positive preoperative rectal screening ($p = 0.016$) were factors significantly influencing postoperative complications (Table 5). Univariate analysis of factors affecting infectious complications also identified ASA score ($p = 0.002$) and positive preoperative rectal screening ($p = 0.002$) as significant. Both parameters were also significant upon multivariate analysis. ASA score ($p = 0.004$) and positive preoperative rectal screening (colonization rectal, $p = 0.004$) were identified as independent variables significantly associated with postoperative infectious complications (Table 5).

Table 3. Microorganisms identified in rectal swabs

Microorganism	Positive preoperative rectal swab
3 MRGN *Escherichia coli*	8
E. faecium VRE	3
3 MRGN *Enterobacter cloacae*	2
Total	13

Discussion

Colonization with MDR bacteria in patients undergoing CRS and HIPEC is of particular concern. The morbidity and mortality rates after cytoreduction and HIPEC are commonly reported to be high [2, 10, 11]. Patients undergoing CRS and HIPEC are likely to have greater risk factors for perioperative problems (prior procedures, chemotherapy, multiple organ resections, preoperative colonization) and therefore require more extensive preventive measures. Colonization with MDR bacteria is a significant risk factor for perioperative infection in these patients [12, 13].

In particular, patients with a positive preoperative rectal swab showed significantly increased rates of surgical site infection in our study. The majority of SSIs following colorectal surgery are caused by endogenous bacteria from the digestive tract [12, 13]. Therefore, SDD has been suggested as a potential strategy for the reduction of perioperative complications. G.S.A. Abis demonstrated that SDD decreases the load of Proteobacteria, Enterobacteriaceae, and *E. coli* in an experimental setting. However, colonization with multiresistant microbes presents an even higher risk for postoperative complications, and little is known about the efficacy of SDD in these cases [14]. Our results suggest that SDD is not effective in patients with MDR colonization after CRS and HIPEC.

In 52.5% of patients, we reported an uneventful postoperative course, while 58 patients encountered complications. These results are supported by those reported in the literature. For the few reports that recorded infectious symptoms, rates between 24 and 45% were found, with mortality correlated with infection being 1–2%. In 209 peritonectomies, Kusamura et al. [15] recorded 3.4% infectious disease levels observed by HIPEC, and in Grade III adverse incidents, Sugarbaker registered 42% infection rates and grade IV adverse incident rates of 5% [16].

Table 4. Microorganisms isolated from cultures

	Infections, *n*					
	surgical site	abdominal drain	catheter	pulmonary	urinary	bloodstream
Escherichia coli	2	3	0	0	5	2
3MRGN	2	0	0	0	0	0
ESBL	1	0	0	0	0	0
Klebsiella pneumoniae	1	1	2	8	0	
Staphylococcus aureus	2	2	0	0	0	1
Enterococcus faecalis	6	1	6	0	3	3
Pseudomonas aeruginosa	1	2	1	0	0	1
Staphylococcus haemolyticus	0	1	0	0	0	0
Staphylococcus epidermidis	2	0	4	0	0	0
Bacteroides Vulgatus	1					
Bacteroides Fragilis	1	0	0	0	0	0
Streptococcus dysgalactiae	1	0	0	0	0	0

Table 5. Analysis of risk factors for infectious complications after CRS and HIPEC

	N (%)	Perioperative complications		Perioperative infectious complications	
		p value	*p* value	*p* value	*p* value
Recipient age	56.4 (19.5–78.8)	0.190		0.181	
Male gender	58 (47.9)	0.995		0.529	
ASA ≥ 3	43 (35.5)	**0.001**	**0.025**	**0.002**	**0.004**
Previous operation	74 (61.2)	0.981		0.277	
Resected organs (mean)	1.44 (1–6)	0.135		0.518	
Colorectal resection	32 (26.4)	0.776		0.549	
Splenectomy	7 (5.7)	0.053		0.770	
PCI	143 (73.0)	0.172		0.211	
Colonization rectal	13 (10.7)	**0.016**	**0.029**	**0.002**	**0.004**

HIPEC, hyperthermic intraperitoneal chemotherapy; GI, gastrointestinal; PCI, peritoneal carcinomatosis index; ASA, American Society of Anesthesiologists. Bold values denote statistical significance at the $p < 0.05$ level.

Throughout our study, surgical site infections and central line-associated bloodstream infections were the most frequent complications in the category 1–2. The most common complications of Clavien-Dindo grades 3–4 were sepsis, pneumonia, and peritonitis. We therefore consider preoperative colonization as a risk factor for perioperative major complications as well as infectious complications after undergoing CRS and HIPEC. Cytoreductive surgical procedures often require several bowel resections in the effort to achieve a CC-0 score. In addition to MDR colonization, our findings classify colorectal resections as a factor affecting the risk of postoperative infection. However, the extent and type of operation were accounted for in our cohort, suggesting MDR colonization is an independent risk factor. Other potential confounders for the group with detected MRE include antibiotic pretreatment, previous stays in hospitals or nursing facilities, nutrition, etc. One weakness of this study is that not all of these confounders were considered.

Preoperative colonization may necessitate tailored perioperative antibiotic medication and decolonization regimens. However, the treatment algorithms in the case of positive rectal swab remain unclear. The administration of tailored antibiotic prophylaxis and SDD regimens for MDR bacteria carriers appears reasonable. Active screening and targeted prophylaxis may be considered in certain situations despite the limited evidence. The MRE discovered in screening was not responsible for the infections, with the exception of 3MRGN *E. coli* and SSIs, where 3MRGN *E. coli* is found in SSIs in two of eight colonized individuals. Interestingly, no 3MRGN *E. coli* is detected in bloodstream infections or urinary tract infec-

tions. MRSA, VRE, and 3MRGN *E. cloacae* do not show in the infections as pathogens. In this respect, the results suggest that MRE detection may be a surrogate parameter for an insufficient immunological response. While it is unknown whether the eradication of MREs may result in a significant reduction in infection rates, it is reasonable to employ an aggressive antibiotic approach in MRE carriers if an infection is suspected.

The current study is limited by its retrospective nature and as a nonrandomized study with a relatively small sample size. However, it is one of the very few studies that addresses specific decolonization strategies for patients colonized with MDR bacteria undergoing treatment with HIPEC. Finally, we used a single rectal swab followed by conventional culture in chromogenic screening medium to detect persistent intestinal colonization which may have been too insensitive or resulted in a selection bias favoring the inclusion of patients with high titers [17]. Further, whereas colistin and paromomycin have been used in diverse SDD, the efficacy of alternatives such as rifaximin in decolonization regimens as an option in patients colonized with MDR bacteria undergoing CRS and HIPEC is yet to be assessed. Important aspects like resistance development of Enterobacteriaceae under decolonization treatment, achievability of sustained decolonization, identification of colonized patients that are at greatest risk of infection, and the impact of the intestinal microbiome need to be addressed in future studies.

Conclusions

Patients colonized with MDR bacteria have a higher risk of infection, and the *E. coli* ESBL are the most commonly active infectious agents. Individual decolonization strategies must be discussed and performed in an earlier preoperative setting. Also, it seems reasonable to adapt prophylaxis in certain, individual selected cases, especially when risk factors other than colonization exist such as patients undergoing high-risk procedures like CRS and HIPEC, particularly those with colorectal interventions. A suitable antibiotic strategy for these cases needs to be evaluated. Further studies which show that an individual broad perioperative antibiotic prophylaxis reduces these infections so as not to lead to an inflation of antibiotic applications with reserve antibiotics are needed. Alternatively, targeted (early) decolonization procedures should be considered for these patients. The variables identified to significantly affect the risk of postoperative infectious complications in patients in our cohort of patients with peritoneal metastases undergoing CRS and HIPEC were tumor load (PCI score), ASA score, and bowel resection.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin, approval number EA2/037/12. Written informed consent was not required as per the Ethics Committee of the Charité – Universitätsmedizin Berlin, approval number EA2/037/12.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: Philippa Seika and Beate Rau; data collection: Philippa Seika; analysis and interpretation of results and draft manuscript preparation: Philippa Seika, Beate Rau, and Susanne Marz. Christine Geffers, Thomas Adam, Linda Feldbrügge, Maximilian Jara, and Johann Pratschke critically revised the manuscript for important intellectual content. All authors reviewed the results and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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