

Feasibility of narrow-spectrum antimicrobial agents for postoperative intra-abdominal infections after gastrectomy

Running title; Narrow antibiotics for post-gastrectomy infections

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Keywords

Antimicrobial stewardship program, Broad-spectrum antibiotic, Cefmetazole, Complication, Post-gastrectomy, Surgical site infection

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Abbreviations: ICU, intensive care unit; RCT, randomized controlled trial; RR, relative risk ratio

Abstract

Introduction: Recently, antimicrobial resistance has received considerable attention.

Broad-spectrum antimicrobial agents are recommended as the initial therapy for postoperative intra-abdominal infections. However, at our institution, we have adopted a strategy of initially treating postoperative intra-abdominal complications with relatively narrow-spectrum antimicrobial agents, such as second-generation cephalosporins. In the current study, we aimed to retrospectively analyze the use of antimicrobial agents and the resulting treatment outcomes in patients with intra-abdominal complications after gastrectomy at our facility.

Methods: We conducted a retrospective observational study of patients treated with antibiotics for intra-abdominal infectious complications after gastrectomy between 2011 and 2021. We determined the proportion of "initial treatment failures" associated with the initial administration of antibiotics for postoperative intra-abdominal complications.

Results: Postoperative intra-abdominal infections were observed in 29 patients. Broad-spectrum antimicrobial agents were not administered. We successfully treated 19 patients. "Initial treatment failure" was observed in 10 patients, of whom five experienced failure due to bacterial resistance to the initial antimicrobial agent. All 10 patients who experienced "initial treatment failure" were discharged after drainage procedures or other treatments. There were no deaths due to postoperative complications. Cefmetazole was used as the initial antimicrobial agent in 27 of the 29 patients.

Conclusions: Considering that all patients with post-gastrectomy intra-abdominal infections were successfully treated using relatively narrow-spectrum antimicrobial agents, and "initial treatment failure" due to antimicrobial-resistant pathogens was

17.2%, the use of narrow-range antimicrobial agents for intra-abdominal infections after gastrectomy can be deemed appropriate.

1. Introduction

Postoperative surgical site infections are a crucial concern in terms of healthcare economics and patient prognosis,¹ underscoring the importance of appropriate treatment. Guidelines recommend carbapenems as the primary treatment option for postoperative intra-abdominal infections, regardless of the surgical approach.² However, in cases of postoperative intra-abdominal infections, appropriate bacterial culture results are frequently unavailable from specimens such as ascites fluid or drainage fluid cultures, leading to inappropriate de-escalation and prolonged use of broad-spectrum antimicrobials.^{3,4} Addressing these issues is necessary from the perspective of using the appropriate antimicrobial agent.

Gastrectomy, performed as a curative procedure for gastric cancer and other primary tumors of the stomach, has an annual incidence of more than 45,000 cases in Japan.⁵ Intra-abdominal infectious complications after gastrectomy include residual abscess, anastomotic leakage, and pancreatic fistula, with an incidence of 1.6–6.4 %.^{6,7} In contrast to the profile observed after colorectal surgery, upper gastrointestinal surgery results in a distinct microbial profile, justifying the use of narrow-spectrum antimicrobial agents as preventive measures against drug-resistant bacteria. At our institution, treatment of postoperative intra-abdominal infectious complications commences with relatively narrow-spectrum antimicrobial agents, such as second-generation cephalosporins, yielding favorable outcomes. In the current study, we aimed to retrospectively analyze the use of antimicrobial agents and the treatment outcomes of patients with intra-abdominal infections after gastrectomy at our hospital.

2. Patients and methods

2.1. Study design

We conducted a retrospective observational study assessing patients who underwent gastrectomy (excluding combined resection of the liver or pancreas) at the National Hospital Organization Kyoto Medical Center (Kyoto, Japan) between January 2011 and June 2021, and subsequently received antimicrobial therapy for intra-abdominal infectious complications after gastrectomy. We collected data from electronic medical records, including preoperative clinical information such as age, sex, American Society of Anesthesiologists physical status, body mass index, preoperative comorbidities (presence of diabetes, steroid use, preoperative chemotherapy, and assessment score obtained using the Charlson comorbidity index),⁸ surgical information (operative procedure, type of surgery [laparoscopic or open surgery], operative time, blood loss, and timing of surgery [elective or emergent]), type of postoperative intra-abdominal infection, and management. The determination of postoperative intra-abdominal infection retrospectively relied on the attending surgeon's documentation in the electronic medical records. The primary endpoint was the percentage of patients who experienced "initial treatment failure." "Initial treatment failure" was defined as either (1) unscheduled additional drainage after 24 h of antibiotic therapy that resulted in findings suggestive of infection, such as purulent drainage or gastrointestinal fluid, or (2) exacerbation of symptoms after completion of antimicrobial therapy, necessitating additional antibiotic therapy. Secondary endpoints included bacterial culture results and the course of treatment in cases of initial treatment failure.

2.2. Statistical analysis and ethical approval

Stata/SE® (version 18.0; StataCorp, College Station, TX, USA) was used for the statistical analysis, and statistical significance was set at $p < 0.05$. Risk factors were examined using Fisher's exact test, and 95% confidence intervals (CIs) for relative risk

ratios were calculated. Student T-test was used to compare the duration of initial antibiotic therapy. To ensure ethical compliance, a summary of the study, including its purpose, content, and contact information, was posted on the hospital's website, allowing participants to opt out of the study. The Kyoto Medical Center Ethics Review Committee approved this study (Approval number: 21-030). This work conforms to the provisions of the Declaration of Helsinki (The Code of Ethics of the World Medical Association) for experiments involving humans, and the manuscript has been prepared in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.

3. Results

A patient flowchart is shown in **Figure 1**. In total, 701 gastrectomies (excluding combined resection of liver or pancreas) were performed between January 2011 and June 2021. Among patients who underwent gastrectomies, 29 (4.1 %) were treated with antibiotics for intra-abdominal infections.

Table 1 summarizes the 29 identified cases. Patient age ranged from 44 to 86 years.

Except for one case of a neuroendocrine tumor, gastric cancer was the most prevalent ailment. Among the 29 patients, 18 underwent distal gastrectomy, nine underwent total gastrectomy, and two underwent completion gastrectomy. One case of emergency surgery for gastric cancer perforation was included in the open distal gastrectomy group, although no antimicrobial therapy was administered immediately post-procedure.

Table 2 summarizes details of the postoperative intra-abdominal infectious complications. Complications included anastomotic leakage (n=10), pancreatic fistulae (n=16), residual abscesses (n=9), and remnant gastric necrosis (n=1) (including multiple complications). Cefmetazole was the primary antibacterial agent used in 27 cases,

whereas ampicillin–sulbactam and cefazolin were employed in one case each. One patient who received ampicillin–sulbactam was switched to clindamycin immediately after receiving ampicillin–sulbactam following an allergic reaction. Notably, none of the patients was administered broad-spectrum antibacterial agents, such as carbapenems, which are recommended by the guidelines. Except for one patient who was already in the intensive care unit (ICU) owing to postoperative anastomotic bleeding, antimicrobial therapy was initiated in the surgical ward for the remaining 28 patients. Over 40% of the patients either exhibited suspected infection in the drainage fluid (purulent drainage or gastrointestinal contents) or drainage was performed as treatment within 24 h of initiating antimicrobial therapy; these have been used as inclusion criteria for clinical evaluation of antimicrobial agents in intra-abdominal infections.⁹

“Initial treatment failure” was documented in 10 patients (33 %). **Table 3** presents a list of cases of "initial treatment failure." In three of the "initial treatment failure" cases, the pathogen remained unidentified. In five cases of "initial treatment failure" (17.2 % of 29 cases), pathogens detected were resistant to the initial antimicrobial agent. Moreover, additional drainage procedures or other forms of invasive treatment were required for all "initial treatment failure" cases, and the patients subsequently recovered and were discharged.

The results of the risk factor analysis are presented in **Table 4**. Patients with infectious drainage at the start of antimicrobial therapy were at a high risk of "initial treatment failure" (relative risk ratio [RR], 3.83; 95% confidence interval, 1.63–9.00; $p = 0.01$). The point estimate of the RR for laparoscopic surgery to open surgery was 2.85 (95% confidence interval, 1.04–7.80; $p = 0.05$). The mean duration of initial antibiotic therapy was 8.7 days in cases of “initial treatment failure” and 8.3 days in other cases, and no

significant difference was detected between the two groups (mean difference, 0.4 days; 95% confidence interval, -2.6–3.5 days; $p = 0.77$).

Our institution's antibiogram data are listed in **Supplementary Tables 1 and 2**. Data before 2015 could not be obtained; thus, average values from 2016 to the first half of 2021 are presented.

4. Discussion

Even when postoperative intra-abdominal infections were treated using relatively narrow-spectrum antimicrobial agents, "initial treatment failure" owing to antimicrobial-resistant bacteria was detected in 17.2% (5/29 cases), and all patients showing "initial treatment failure" required drainage or other treatment before being discharged after satisfactory recovery. There were no mortalities related to postoperative complications. Therefore, our findings suggest that the use of narrow-spectrum antimicrobial agents in patients with intra-abdominal infectious complications post-gastrectomies seems to be justifiable.

Guidelines recommend the use of broad-spectrum antibacterial agents such as carbapenems as initial therapy for postoperative intra-abdominal infections². An adverse effect of broad-spectrum antimicrobial agents is the increased prevalence of antimicrobial-resistant bacteria. For example, the long-term use of carbapenems has been reported to increase the prevalence of carbapenem-resistant bacteria by approximately three times after 30 days of hospitalization.¹⁰ The odds ratio of death increases by more than 3-fold in cases of infection with carbapenem-resistant organisms compared with that in individuals infected with carbapenem-susceptible organisms.¹¹

Intra-abdominal infections are often challenging to treat using a de-escalation strategy,¹² which is a fundamental approach to treating infectious diseases, owing to frequently

undetectable bacterial culture specimens, as shown in the study. Given the increased prevalence of antimicrobial-resistant bacteria owing to prolonged antimicrobial therapy, long-term administration of broad-spectrum antimicrobial agents should be avoided, and the current study provides substantial evidence to support this hypothesis. CMZ was
5 mainly used in this study because of its narrow-spectrum activity against enterobacteriaceae, including ESBL-producing species.¹³ More than one-third of the causal organisms of SSI following upper gastrointestinal surgery are enterobacteriaceae, and CMZ has a more than 90% susceptible rate against the bulk of these species, *Escherichia coli* and *Klebsiella pneumoniae*.¹⁴ Our antibiograms showed similar
10 susceptible rates, which validate our choice of antimicrobial agents.

In the field of internal medicine, the effect of monotherapy using beta-lactams on 90-day mortality in patients with pneumonia was found to be non-inferior to that of therapy using beta-lactams combined with macrolides or new quinolones,¹⁵ with a 90-day mortality rate of approximately 10%; however, the 90-day mortality rate was 0% in the
15 current study. Given that no deaths were observed despite diverse infection etiologies, the use of narrow-spectrum antimicrobial agents for intra-abdominal infectious complications is justifiable.

To the best of our knowledge, the use of narrow-spectrum antimicrobial drugs has not been reported for intra-abdominal complications. This is the only study focused on the
20 types of antibiotics used to treat postoperative intra-abdominal infections after gastrectomy. Although the effects of antimicrobial agents on intra-abdominal infections have been compared previously, the only study conducted to determine the types of antimicrobial agents administered to treat postoperative intra-abdominal infections was a randomized controlled trial (RCT) by Wang et al., comparing the effects of
25 meropenem and tigecycline.¹⁶ The authors reported the non-inferiority of the effects of

tigecycline to those of meropenem; however, the limitations were as follows:
tigecycline is not widely used in Japan; the non-inferiority margin of 20% was
substantially large; de-escalation was executed in less than 30% of patients in both
groups; and most importantly, the study included patients who underwent hepatobiliary
and colorectal surgeries in addition to gastrectomy.

Risk factor analysis revealed that the risk of "initial treatment failure" was higher in
patients who exhibited infectious drainage at the initiation of antimicrobial therapy (RR,
3.83; 95 % confidence interval, 1.63–9.00; $p = 0.01$) than that in those who did not
exhibit infectious drainage. These cases are regarded as instances where complications
emerged while the drain was still in position, and the drainage malfunction persisted
even after drain adjustment, requiring additional unscheduled intervention.

Patients who underwent open surgery had a higher RR than those who did not. A recent
meta-analysis of RCTs comparing the effects of open surgery with those of laparoscopic
gastrectomy for gastric cancer reported a reduced incidence of intra-abdominal
abscesses in the laparoscopic surgery group (RR, 0.67; 95% confidence interval, 0.46–
0.97; $p = 0.038$).¹⁷ Nevertheless, to the best of our knowledge, no previous study has
explored laparotomy and laparoscopy as factors associated with "initial treatment
failure" for intra-abdominal infectious complications. In the current study, the rationale
underlying the identification of open surgery as a risk factor for "initial treatment
failure" may be attributed to the fact that surgeons treating the laparoscopic surgery
group were more experienced in handling intra-abdominal infections than those treating
the open surgery group, possibly leading to appropriate treatment in the laparoscopic
surgery group. This is further supported by the fact that open surgery was performed
relatively earlier (i.e, until 2017) than laparoscopic surgery. Accordingly, because of
prior experience with intra-abdominal infectious complications, in the laparoscopic

surgery group, "initial treatment failure" was reduced owing to proper drain placement during surgery and initial infection management via drainage.

This study had some limitations. First, this was a retrospective, single-center, observational study. The limitation of the single-center setting arises from the use of drains after gastrectomy at our institution. Patients who did not receive a drain immediately after surgery were excluded from this study. The effectiveness of routine drain placement during gastrectomy has not been proven in the latest meta-analysis,¹⁸ and in some institutions, drains are not placed routinely during laparoscopic procedures.¹⁹ In the current study, only 20.7% of the patients (six patients) exhibited drainage contamination, indicating effective drain function in a small subset of cases when complications arose. Overall, the external validity of cases without a drain was established to some extent.

Second, the regional specificity of the antimicrobials used needs to be considered. Cefmetazole, the narrow-spectrum antimicrobial agent predominantly used in the current study, is currently restricted to East Asia, with limited reports on its effectiveness.^{13,20} Consequently, the results of this study may not be valid in Western countries.

Third, the electronic medical records lacked vital sign data at the time of infection.

Therefore, we were unable to determine the severity of the intra-abdominal infections at the onset. Nevertheless, the fact that only one patient in our study required antimicrobial medication in the ICU implies that a small number of patients were in a severe condition. This study suggests that clinically stable individuals may be suitable candidates for narrow-spectrum antimicrobial therapy.

Finally, the statistical analysis undertaken also presented a limitation. This was a small study with only 29 patients, and the 95% confidence interval for RR in the risk factor

analysis was notably wide. Owing to the limited number of primary outcomes, only univariate analysis was conducted, whereas multivariate risk factor analysis, which accounts for confounding variables, was not performed.

5 **5. Conclusions**

Despite these limitations, this study has substantial value as a descriptive study, considering the absence of articles reporting the outcomes in patients with postoperative intra-abdominal infections treated using narrow-spectrum antimicrobial drugs. In future, multicenter trials and prospective investigations are required to address the limitations of this study.

In conclusion, narrow-spectrum antimicrobial therapy is appropriate in patients with intra-abdominal infections following gastrectomy.

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Authorship statement:

KG and HH conceived and designed the study. KG and KD performed data collation and analysis. KG drafted the manuscript. KG and HH participated in manuscript preparation and critical revision. All authors have read and approved the manuscript. All authors meet the ICMJE authorship criteria.

25 Declarations of interest:

None.

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References

1. World Health Organization. Global guidelines for the prevention of surgical site infection; 2018. Available from <https://apps.who.int/iris/bitstream/handle/10665/250680/9789241549882-eng.pdf>. [last
5 accessed 10/02/2023].
2. Mazuski JE, Tessier JM, May AK, et al. The surgical infection society revised guidelines on the management of intra-abdominal infection. *Surg Infect (Larchmt)* 2017;18:1–76; doi: 10.1089/sur.2016.261.
3. Robinson ED, Volles DF, Kramme K, et al. Collaborative antimicrobial stewardship
10 for surgeons. *Infect Dis Clin North Am* 2020;34:97–108; doi:
10.1016/j.idc.2019.11.002.
4. Delaplain PT, Kaafarani HMA, Benedict LAO, et al. Different surgeon, different duration: Lack of consensus on the appropriate duration of antimicrobial prophylaxis and therapy in surgical practice. *Surg Infect (Larchmt)* 2022;23:232–47; doi:
15 10.1089/sur.2021.323.
5. Marubashi S, Takahashi A, Kakeji Y, et al. Surgical outcomes in gastroenterological surgery in Japan: Report of the national clinical database 2011–2019. *Ann Gastroenterol Surg* 2021;5:639–58;doi: 10.1002/ags3.12462.
6. Watanabe M, Miyata H, Gotoh M, et al. Total gastrectomy risk model: Data from
20 20,011 Japanese patients in a nationwide internet-based database. *Ann Surg*
2014;260:1034–9;doi: 10.1097/SLA.0000000000000781.
7. Kurita N, Miyata H, Gotoh M, et al. Risk model for distal gastrectomy when treating gastric cancer on the basis of data from 33,917 Japanese patients collected using a nationwide web-based data entry system. *Ann Surg* 2015;262:295–303; doi:
25 10.1097/SLA.0000000000001127.

8. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987;40:373–83; doi: 10.1016/0021-9681(87)90171-8.
9. U.S. Department of Health and Human Services Food and Drug Administration
5 Center for Drug Evaluation and Research (CDER). Complicated intraabdominal infections: Developing drugs for treatment guidance for industry; 2018. Available from <https://www.fda.gov/media/84691/download>. [last accessed 10/02/2023]
10. Rungsitsathian K, Wacharachaisurapol N, Nakaranurack C, et al. Acceptance and outcome of interventions in a meropenem de-escalation antimicrobial stewardship program in pediatrics. *Pediatr Int* 2021;63:1458–65; doi:10.1111/ped.14703.
11. Martin A, Fahrbach K, Zhao Q, et al. Association between carbapenem resistance and mortality among adult, hospitalized patients with serious infections due to *Enterobacteriaceae*: Results of a systematic literature review and meta-analysis. *Open Forum Infect Dis* 2018;5:ofy150; doi: 10.1093/ofid/ofy150.
- 15 12. Schuts EC, Hulscher MEJL, Mouton JW, et al. Current evidence on hospital antimicrobial stewardship objectives: A systematic review and meta-analysis. *Lancet Infect Dis* 2016;16:847–56; /doi: 10.1016/S1473-3099(16)00065-7.
- 20 13. Fukuchi T, Iwata K, Kobayashi S, et al. Cefmetazole for bacteremia caused by ESBL-producing enterobacteriaceae comparing with carbapenems. *BMC Infect Dis* 2016;16:427; doi: 10.1186/s12879-016-1770-1.
14. Takesue Y, Kusachi S, Mikamo H, et al. Antimicrobial susceptibility of pathogens isolated from surgical site infections in Japan: Comparison of data from nationwide surveillance studies conducted in 2010 and 2014-2015. *J Infect Chemother* 2017;23(6):339-348, doi: 10.1016/j.jiac.2017.03.010

15. Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med* 2015;372:1312–23; doi: 10.1056/NEJMoa1406330.
16. Wang HJ, Xing XZ, Qu SN, et al. A randomized controlled trial comparing the efficacy of tigecycline versus meropenem in the treatment of postoperative complicated intra-abdominal infections. *Ann Palliat Med* 2021;10:1262–75; doi: 10.21037/apm-20-907.
17. Lou S, Yin X, Wang Y, et al. Laparoscopic versus open gastrectomy for gastric cancer: A systematic review and meta-analysis of randomized controlled trials. *Int J Surg* 2022;102:106678; doi: 10.1016/j.ijssu.2022.106678.
18. Wang Z, Chen J, Su K, et al. Abdominal drainage versus no drainage post-gastrectomy for gastric cancer. *Cochrane Database Syst Rev* 2015;2015:CD008788; doi: 10.1002/14651858.CD008788.pub3.
19. Shimoike N, Akagawa S, Yagi D, et al. Laparoscopic gastrectomy with and without prophylactic drains in gastric cancer: A propensity score-matched analysis. *World J Surg Oncol* 2019;17:144; doi: 10.1186/s12957-019-1690-9.
20. Hiranuma M, Kobayashi D, Yokota K, et al. Chi-square automatic interaction detector decision tree analysis model: Predicting cefmetazole response in intra-abdominal infection. *J Infect Chemother* 2023;29:7–14; doi: 10.1016/j.jiac.2022.09.002.

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Tables

Table 1

Clinical characteristics of 29 patients with intra-abdominal infections

		All cases (n = 29)
Age (mean ± SD)		71 ± 9.7
Sex	Male	22 (75.9%)
	Female	7 (24.1%)
Body mass index (mean ± SD)		23.4 ± 3.7
CCI	Medium (CCI: 1–2)	15 (51.7%)
	High (CCI: 3–4)	12 (41.4%)
	Very high (CCI: ≥ 5)	2 (6.9%)
Diabetes mellitus		6 (20.7%)
Steroid use		1 (3.4%)
Preoperative chemotherapy		3 (10.3%)
ASA-PS	1	2 (6.9%)
	2	22 (75.9%)
	3	5 (17.2%)
Surgical disease	Gastric cancer	28 (96.6%)
	Neuroendocrine tumor	1 (3.4%)
Surgical approach	Open surgery	10 (34.5%)
	Laparoscopic surgery	19 (65.5%)
Timing of surgery	Emergent	1 (3.4%)
	Elective	28 (96.6%)
Surgical procedure	Distal gastrectomy	18 (62.1%)
	Total gastrectomy	9 (31%)
	Completion gastrectomy	2 (6.9%)
Operative time (min)		285 [237–340]
Intraoperative bleeding (min)		50 [20–155]

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Abbreviations: SD, standard deviation; CCI, Charlson comorbidity index; ASA-PS, American Society of Anesthesiologists physical status

Operative time and intraoperative bleeding are shown as medians and interquartile ranges.

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Table 2

Details of intra-abdominal infectious complications

		All cases (n = 29)
Intra-abdominal infections*	Residual abscess	9 (31.0%)
	Anastomotic leakage	10 (34.5%)
	Pancreatic fistula	16 (55.2%)
	Remnant gastric necrosis	1 (3.4%)
C-D grades of intra-abdominal infections	Grade II	13 (44.8%)
	Grade IIIa	12 (41.4%)
	Grade IIIb	4 (13.8%)
Days from surgery to initiation of antibiotics		7 [6–9]
Initial antibiotics	CMZ	27 (93.1%)
	CEZ	1 (3.4%)
	ABPC/SBT**	1 (3.4%)
Duration of initial antibiotic therapy (days)		8 [5–10]
Location of initial antimicrobial administration	Intensive care unit	1 (3.4%)
	Surgical ward	28 (96.6%)
Case status at antimicrobial therapy initiation	Cases with drainage and suspected infection	6 (20.7%)
	Cases in which drainage began within 24 hours of antimicrobial initiation	10 (34.5%)
	Cases that fit one of the above two categories	13 (44.8%)

Abbreviations: C-D, Clavien-Dindo; CMZ, cefmetazole; CEZ, cefazolin; ABPC/SBT, ampicillin/sulbactam

* There was some overlap.

** Changed to clindamycin owing to allergy.

Days from surgery to initiation of antimicrobial therapy and duration of initial antibiotic therapy are shown as medians and interquartile ranges.

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Table 3

Cases of “initial treatment failure”

Case No.	Intra-abdominal infections	Initial antibiotics	Pathogens detected at the start of antibiotics	Additional therapy	Pathogens detected at additional therapy
1	Pancreatic fistula Residual abscess	CMZ	Not detected	Additional drainage (local anesthesia) Resumption of antibiotics (LVFX)	<i>Klebsiella pneumoniae</i> (ESBL producing) <i>Citrobacter species</i>
2	Anastomotic leakage	CMZ	Not detected	Additional drainage (laparotomy) Resumption of antibiotics (CAZ)	<i>Pseudomonas aeruginosa</i> , <i>Serratia marcescens</i>
3	Pancreatic fistula	CMZ	Not detected	Resumption of antibiotics (CMZ)*	<i>Klebsiella pneumoniae</i> (ESBL producing)
4	Pancreatic fistula Remnant gastric necrosis	CMZ	Not detected	Residual gastrectomy	Not detected
5	Anastomotic leakage	CMZ	Not detected	Additional drainage (local anesthesia)	Not detected
6	Residual abscess	CMZ	Not detected	Additional drainage (local anesthesia)	Not detected
7	Residual abscess	CMZ	<i>Klebsiella pneumoniae</i> (ESBL producing) <i>Lactobacillus species</i>	Additional drainage (local anesthesia) Resumption of antibiotics (CMZ)	Not detected
8	Pancreatic fistula	CMZ	<i>Aeromonas hydrophila</i>	Drain position change** Resumption of antibiotics (CTX)	Not detected
9	Pancreatic fistula	CMZ	<i>Staphylococcus haemolyticus</i>	Drain position change	<i>Staphylococcus haemolyticus</i>

		<u>(methicillin resistance)</u>	<u>(methicillin resistance)</u>
		<u>Enterococcus faecalis</u>	
10	Pancreatic fistula CMZ	<u>Klebsiella pneumoniae</u>	Additional drainage (local anesthesia) <u>Enterococcus faecalis</u>

Abbreviations: CAZ, Ceftazidime; CMZ, cefmetazole; CTX, Cefotaxime; ESBL, extended-spectrum β -lactamase; LVFX, Levofloxacin;

Pathogens that were not responsive to the first antibiotic dose are underlined.

5 “Not detected” refers to the condition in which cultures were sent, but there was no growth.

* Eventually, laparotomy was required owing to bleeding pseudoaneurysm.

** Eventually required transcatheter arterial embolization owing to bleeding pseudoaneurysm.

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Table 4

Risk factor analysis for “initial treatment failure”

		“Initial treatment failure” case/total (%)	RR	RR 95 % CI	p-value
Sex	Men	7/22 (31.8%)	Ref	Ref	0.66
	Women	3/7 (42.9%)	1.35	0.47–3.86	
Age	≥ 70 years old	5/16 (31.3%)	Ref	Ref	0.71
	< 70 years old	5/13 (38.5%)	1.23	0.45–3.35	
ASA-PS score	3	1/5 (20%)	Ref	Ref	0.63
	1,2	9/24 (37.5%)	1.88	0.30–11.7	
Surgical approach	Laparoscopic	4/19 (21.1%)	Ref	Ref	0.05
	Open	6/10 (60%)	2.85	1.04–7.8	
Surgical procedure	Distal	4/18 (22.2%)	Ref	Ref	0.11
	Other	6/11 (54.5%)	2.45	0.89–6.8	
Body mass index	≥ 25	3/12 (25%)	ref	ref	0.45
	< 25	7/17 (41.2%)	1.65	0.53–5.11	
Infectious drainage	No	5/23 (21.7%)	Ref	Ref	0.01
	Yes	5/6 (83.3%)	3.83	1.63–9	
Additional drainage	No	6/19 (31.6%)	Ref	Ref	0.48
	Yes	4/10 (40%)	1.27	0.46–3.47	
CCI	Medium (CCI: 1–2)	5/15 (33.3%)	Ref	Ref	1
	High/Very high (CCI: ≥ 3)	5/14 (35.7%)	1.07	0.39–2.92	
Residual abscess	No	7/20 (35%)	Ref	Ref	1
	Yes	3/9 (33.3%)	0.95	0.32–2.86	
Anastomotic leakage	No	8/19 (42.1%)	Ref	Ref	0.41
	Yes	2/10 (20%)	0.48	0.12–1.83	
Pancreatic fistula	No	4/13 (30.8%)	Ref	Ref	1
	Yes	6/16 (37.5%)	1.22	0.43–3.42	

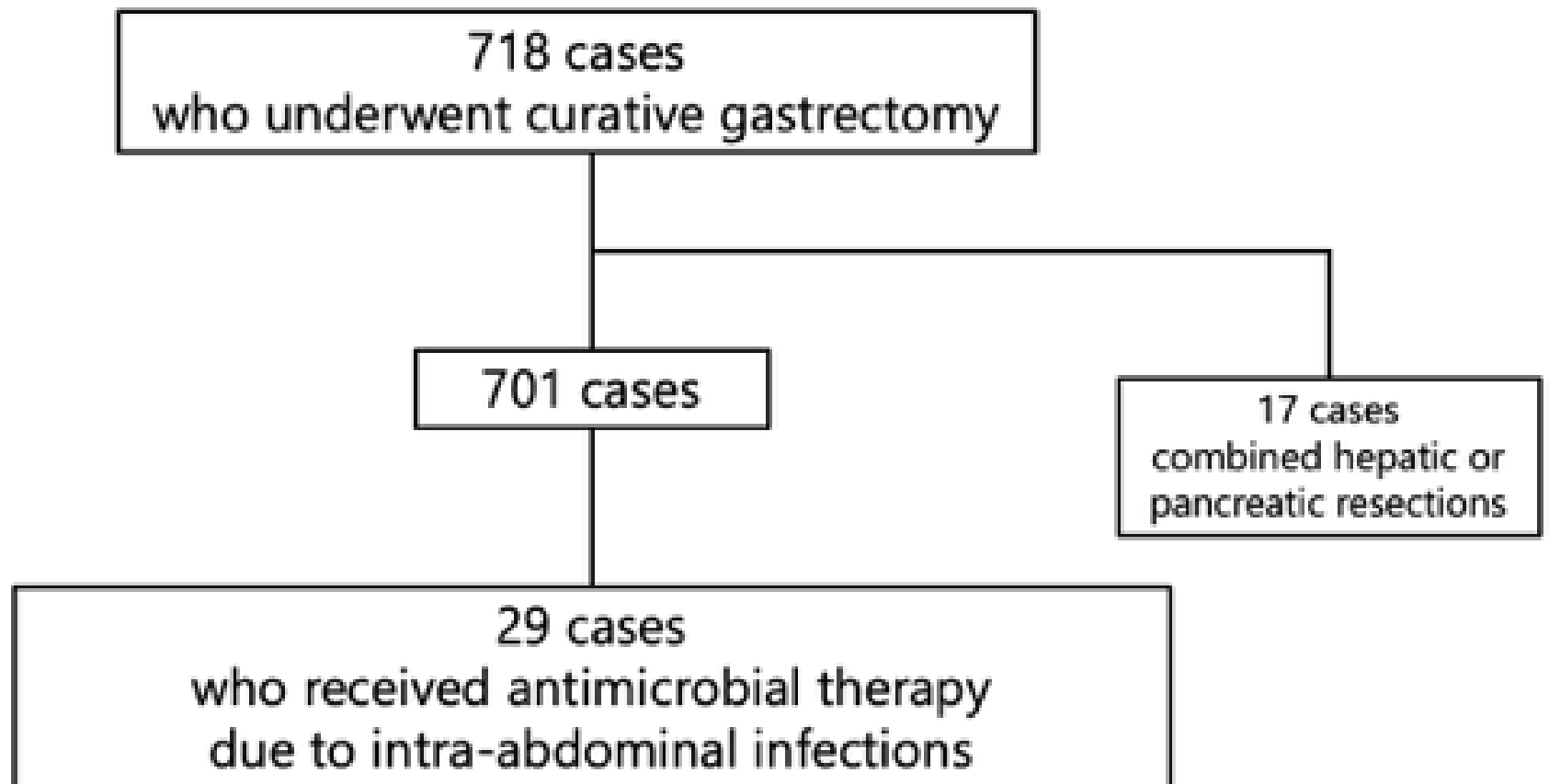
Abbreviations: RR, relative risk ratio; CI, confidence interval; ASA-PS, American Society of Anesthesiologists physical status; ref, reference; NA, not applicable; CCI, Charlson comorbidity index

“Infectious drainage” implies cases with drainage and suspected infections.

“Additional drainage” implies cases in which drainage began within 24 h of antimicrobial therapy initiation.

Figure legends

Figure 1. Flowchart of patients in the present study.



Supplementary table 1

GNR Antibiograms in Kyoto Medical Center (2016-2021)

Species	ABPC	ABPC/ SBT	TAZ/ PIPC	CEZ	CTM	CMZ	CTX	CAZ	MEPM	LVFX
<i>Escherichia coli</i>	55%	64%	99%	62%	72%	99%	76%	77%	100%	68%
<i>Klebsiella pneumoniae</i>	0%	76%	91%	73%	79%	98%	84%	84%	99%	93%
<i>Enterobacter cloacae</i>	0%	0%	74%	0%	1%	1%	56%	63%	100%	96%
<i>Klebsiella oxytoca</i>	0%	55%	81%	26%	80%	99%	88%	90%	100%	88%
<i>Pseudomonas aeruginosa</i>	NA	0%	87%	NA	NA	NA	NA	86%	90%	87%
<i>Haemophilus influenzae</i>	35%	57%	NA	NA	NA	NA	NA (CTRX: 100%)	NA	100%	100%

※All species include ESBL (Extended-spectrum β -lactamase)-producing species.

Abbreviations: GNR, Gram-Negative Rods;

ABPC, Ampicillin; ABPC/SBT, Ampicillin/sulbactam; TAZ/PIPC, Tazobactam/ piperacillin;

CEZ, Cefazolin; CTM, Cefotiam; CMZ, Cefmetazole; CTX, Cefotaxime; CTRX, Ceftriaxone;

CAZ, Ceftazidime; Meropenem, MEPM; LVFX, Levofloxacin; NA, not available

Supplementary table 2

GPC Antibigrams in Kyoto Medical Center (2016-2021)

Species	ABPC	ABPC/SBT	CEZ	CLDM	VCM	LVFX
MSSA	35%	100%	100%	80%	100%	84%
MRSA	0%	0%	0%	19%	100%	19%
<i>Enterococcus faecalis</i>	100%	NA	0%	0%	100%	83%

Abbreviations: GPC, Gram-positive cocci;

MSSA, Methicillin-Susceptible *Staphylococcus Aureus*; MRSA, Methicillin-Resistant *Staphylococcus Aureus*;

ABPC, Ampicillin; ABPC/SBT, Ampicillin/sulbactam; CEZ, Cefazolin; CLDM, Clindamycin; VCM, Vancomycin;

LVFX, Levofloxacin; NA, not available