






BMJ Open Study protocol of REpeat versus Single ShoT Antibiotic prophylaxis in major Abdominal Surgery (RESISTAAS I): a prospective observational study of antibiotic prophylaxis practice for patients undergoing major abdominal surgery

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ABSTRACT

Introduction Surgical site infections (SSIs) are among the most common complications after abdominal surgery and develop in approximately 20% of patients. These patients suffer a 12% increase in mortality, underlying the need for strategies reducing SSI. Perioperative antibiotic prophylaxis is paramount for SSI prevention in major abdominal surgery. Yet, intraoperative redosing criteria are subjective and whether patients benefit from it remains unclear.

Methods and analysis The REpeat versus Single ShoT Antibiotic prophylaxis in major Abdominal Surgery (RESISTAAS I) study is a single-centre, prospective, observational study investigating redosing of antibiotic prophylaxis in 300 patients undergoing major abdominal surgery. Adult patients scheduled for major abdominal surgery will be included. Current practice of redosing regarding number and time period will be recorded. Postoperative SSIs, nosocomial infections, clinically relevant infection-associated bacteria, postoperative antibiotic treatment, in addition to other clinical, pharmacological and economical outcomes will be evaluated. Differences between groups will be analysed with analysis of covariance.

Ethics and dissemination RESISTAAS I will be conducted in accordance with the Declaration of Helsinki and internal, national and international standards of GCP. The Medical Ethics Review Board of Heidelberg University has approved the study prior to initiation (S-404/2021). The study has been registered on 7 February 2022 at German Clinical Trials Register, with identifier DRKS00027892. We plan to disseminate the results of the study in a peer-reviewed journal.

Trial registration German Clinical Trials Register (DRKS): DRKS00027892.

INTRODUCTION

Nosocomial infections, including surgical site infections (SSIs), are among the most common complications after abdominal surgery. SSI occurs in up to 20% of patients

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Since antibiotic half-life is often the driver behind the decision whether to repeat the perioperative antibiotic prophylaxis, this study will measure the antibiotic concentration before redosing and directly before the final suture to increase objectivity in the comparison.
- ⇒ Only major abdominal surgeries will be evaluated thus focusing on visceral surgery and reducing bias.
- ⇒ A subgroup analysis based on contamination degree of the major abdominal surgery will be performed to reduce bias.
- ⇒ As this is not a blinded study, a performance bias from healthcare providers cannot be excluded.

and increase mortality risk by 12%.¹ In addition, SSIs are associated with an increasing morbidity and healthcare cost.²

As the skin barrier is pierced during the operation, the skin bacteria, a part of the normal skin flora, are inevitably carried into the surgical field. In order to avoid clinically significant complications by this spread, standard hygiene measures must be adhered to.³ In addition to decontamination and disinfection measures, perioperative antibiotic prophylaxis is given in major abdominal surgery to prevent postoperative infections. Ideally, this prophylaxis is given no longer than 120 min before the incision.⁴ Despite standards for hygiene, operations lasting longer than 3 hours, those associated with high blood loss and blood transfusions, or requiring a long period of anaesthesia are a major risk factor for postoperative infections.³ Moreover, length of stay on the intensive care unit, as well as the total length of hospital stay,

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Ability to give informed consent	Allergy to internal standard perioperative antibiotics
Adults (≥ 18 years old)	Antibiotic treatment at time of inclusion
Planned elective major abdominal surgery	Obvious Infection at time of inclusion
	Off-label-use of antibiotics
	Inability to give informed consent

*Major abdominal surgery defined as operations creating any gastrointestinal anastomosis or involving parenchymal resection of the liver or pancreas.

systemic comorbidities, previous antibiotic therapy and the degree of contamination of the operation are all risk factors for SSIs.⁵

Continuation of antibiotics after surgical procedures shows no advantages and is associated with an increase in wound infections.^{6,7} Additionally, postoperative continuation of antibiotic prophylaxis is associated with a multitude of non-infectious complications.⁸ Most analysis on perioperative antibiotic prophylaxis investigate patients after elective orthopaedic interventions—procedures that fundamentally differ in the degree of contamination and hygiene regulations in comparison to visceral surgical operations. Only few studies analyse the association between antibiotic prophylaxis and duration of surgery without differentiation between abdominal, traumatic, gynaecological or cardiovascular procedures.^{9,10} The contamination classes of the operation—clean-not contaminated, clean-contaminated, contaminated or in a manifestly infected region—are also not considered. However, this distinction is essential for assessing postoperative infection rates.¹¹

The WHO guideline advocates for the use of perioperative antibiotic prophylaxis while emphasising the need for further studies on the optimal time of administration and redosing.¹² Due to lack of objective criteria for redosing and scarcity of evidence, REpeat versus SIngle ShoT Antibiotic prophylaxis in major Abdominal Surgery (RESISTAAS I) study was developed to investigate intraoperative redosing of antibiotic prophylaxis in patients undergoing major abdominal surgery and its effect on SSIs.

METHODS AND ANALYSIS

Study design

The RESISTAAS I study is a single-centre, prospective, observational study investigating redosing of antibiotic prophylaxis in 300 patients undergoing major abdominal surgery.

Study population

Inclusion and exclusion criteria

Inclusion criteria consist of elective major abdominal surgery for any indication. Major abdominal surgery is defined as operations creating any gastrointestinal anastomosis or involving parenchymal resection of the liver or pancreas.

Subjects who are unable to provide written informed consent, have had previous laparotomy in the last 3 months or receive antibiotic treatment at time of initial assessment are excluded from the study. A detailed overview of the eligibility criteria is provided in [table 1](#).

Recruitment strategy

Participants admitted to the Department of Surgery at the University of Heidelberg will be screened for eligibility starting February 2022 and recruited by an investigator of the clinical research centre for surgery. After the index operation, the patients' clinical course will be followed prospectively until the 30th postoperative day (POD). The study aims to recruit 300 patients within 6 months.

Study flow

Study procedure starts the day before scheduled elective major abdominal surgery with the screening of patients for eligibility and informed consent of potential participants. After informed consent is obtained, an investigator will record baseline information of the participants. Baseline information consists of biometric characteristics (age, gender, weight, height, body mass index (BMI), body surface area (BSA), nutritional status, activity level), comorbidities (chronic diseases including heart, kidney, liver, metabolic diseases, immunologic disorders, allergies, history of alcohol, drug or nicotine overindulgence, previous surgeries, history of malignancy, current medication, Charlson comorbidity index, ASA score) and initial routine preoperative laboratory (electrolytes, kidney and liver function parameters, blood glucose, leucocyte blood count, haemoglobin, CRP, INR, platelets and PTT) values.

On the day of operation, perioperative information on antibiotic schedule (time of initiation, duration, type of perioperative antibiotic and redosing if applicable) surgical information (antiseptic for skin preparation, surgical procedure and organ involvement: colon, small intestines, stomach, liver, pancreas resections with extent of resections, gastrointestinal anastomoses, multivisceral resections; intraoperative contamination from colon, small intestines, stomach or gall bladder perforation, intraoperative blood loss, contamination degree as defined by the Centers for Disease Control and Prevention (CDC): clean, clean-contaminated, contaminated or dirty/infected¹³; duration of operation),

volume management (transfusions, volume substitution with crystalloids or colloids, blood loss, urine output) and initial postoperative course (transfer to the Post-Anesthesia Care Unit (PACU), Intensive Care Unit (ICU), Intermediate Care (IMC), extubation timepoint, vasopressor use) will be recorded. During surgery, a vial of serum will be taken before redosing and before the final suture and immediately processed to estimate antibiotic concentration by a validated high-performance liquid chromatography assay with ultraviolet detection for beta-lactams and cephalosporins (online supplemental figure 1). Free drug concentration will be measured for high protein-bound drugs. Total drug concentrations will be measured for low to moderately protein-bound drugs like ampicillin.¹⁴

Follow-up visits 3 (POD5), 4 (POD14) and 5 (POD30) will focus on documentation of the postoperative course, postoperative complications and microbial findings through direct assessment, questioning and case note review. SSI as defined by CDC will be recorded as dichotomous values as well as categorical¹³:

1. Superficial incisional SSI—infection within 30 days after surgery involving skin subcutaneous tissue of incision and fulfilling one of the following criteria:
 - i. Purulent secretion at the site of superficial incision
 - ii. Cultural detection of pathogens from an aseptically removed wound exudate or tissue from the superficial incision
 - iii. Any of the following signs: pain or tenderness, localised swelling, redness or overheating, and the surgeon is deliberately opening the superficial incision. However, this criterion does not apply in the presence of a negative microbiological culture from the superficial incision.
 - iv. Diagnosis by the attending physician
2. Postoperative deep incisional SSI—infection within 30 days of surgery and infection appears to be related to surgery and involves fascia and muscle tissue and one of the following criteria applies:
 - i. Purulent secretion from the depth of the incision, but not from the operated organ or body cavity, as such infections would then belong to the (SSI-O) category.
 - ii. Spontaneously or deliberately opened by the surgeon if the patient has at least one of the following symptoms: fever ($>38^{\circ}\text{C}$), localised pain or tenderness. However, this criterion does not apply if there is a negative microbiological culture from the depth of the incision.
 - iii. Abscess or other signs of infection affecting the deeper layers can be seen during the clinical examination, during the next operation, during the histopathological examination or during radiological examinations
 - iv. Diagnosis by the attending physician
3. Organ/space SSI—infection within 30 days after surgery, and infection appears to be related to surgery and involves organs or body cavities that were opened

or tampered with during surgery and any of the following criteria applies:

- i. Purulent secretion from a drain that has access to the organ or body cavity in the operating area
- ii. Cultural detection of pathogens from an aseptically removed wound secretion or tissue from an organ or the body cavity in the operating area
- iii. Abscess or other sign of an infection of the organ or body cavity in the operating area can be seen on clinical examination, during the next operation, on histopathological examination or during radiological examination
- iv. Diagnosis by the attending physician

For all SSIs, timing of occurrence, microbial findings and treatments will be recorded.

Remote infections (pneumonia, bacteraemia, sepsis, phlebitis, urinary tract infections, cholangitis, gastrointestinal infections as diagnosed by attending clinician based on national guidelines) with timing of occurrence, location, microbial findings and treatments will be documented.^{15–17} General postoperative complications will also be recorded (postoperative bleeding, wound dehiscence, seromas, lymphatic fistulas, suture insufficiency, mortality). Dynamics of postoperative laboratory values will be documented (electrolytes, kidney and liver function parameters, blood glucose, leucocyte blood count, haemoglobin, CRP, INR, platelets and PTT). Additional postoperative diagnostics (ultrasound, CT, MRI, endoscopy) or interventions (postoperative abdominal drainage placement, bronchoscopy, re-laparotomy, organ replacement therapy) will be documented for each patient. Additionally, organ-specific complications will be recorded:

1. Gastrointestinal: anastomosis insufficiency, time to first bowel movement, infections and treatment.
2. Hepatic: postoperative liver failure as defined by the ISGLS,¹⁸ postoperative bleeding, biliary leakage/biloma and treatment.
3. Renal: insufficiency as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) Foundation¹⁹ and treatment.
4. Pancreatic: fistula, pancreatitis, insufficiency and treatment.

All complications will be classified according to the Clavien-Dindo classification and Comprehensive Complication Index will be calculated for each patient.²⁰ Bacterial resistance to antibiotics will be documented based on a susceptibility analysis of cultures as performed by the clinical microbiology laboratory. The response to antibiotic will be classified as susceptible, intermediate and resistant, as defined by the most recent EUCAST recommendation.²¹

Treatment cost will be extracted from the internal patient data system and analysed based on perioperative antibiotic prophylaxis strategy. Based on the German reimbursement system (diagnosis-related group, G-DRG), the total treatment cost for the hospital stay, specific treatment costs for antibiotics and complication-associated costs will be analysed and compared between groups.

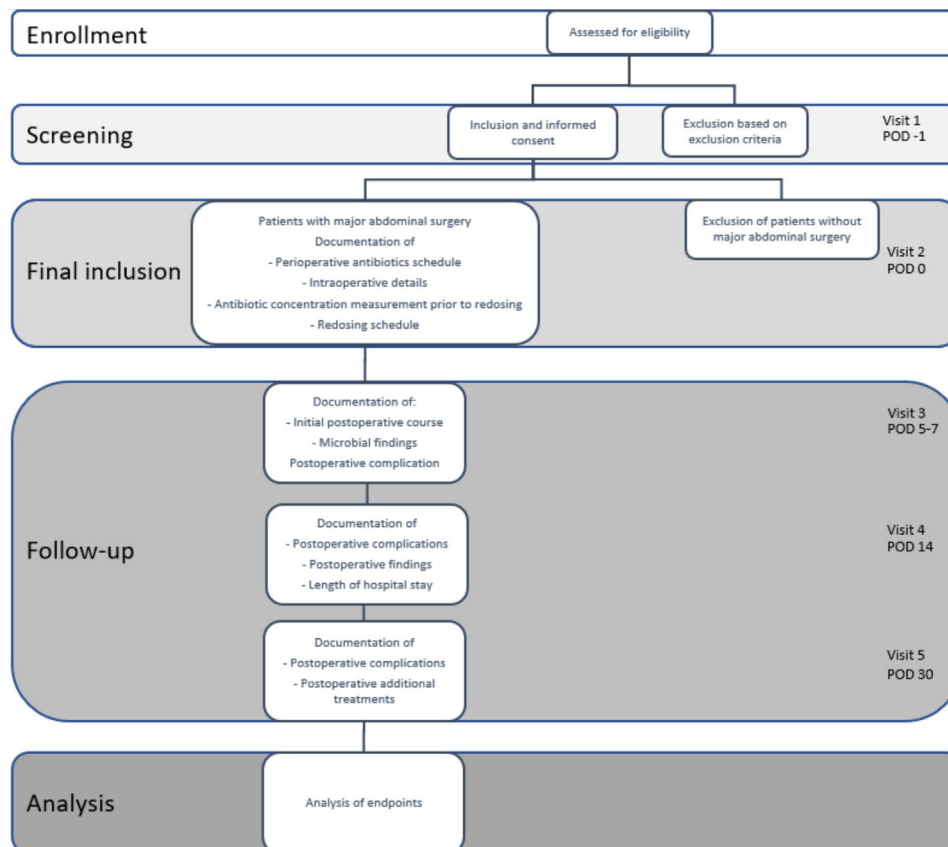


Figure 1 Study process or the flow of the study. POD, postoperative day.

Furthermore, hospital-specific costs of included cases will be compared with the cost-matrix of the Institute for the Remuneration System in Hospitals, which analyses data of the average treatment costs on G-DRG basis.²²

An overview of the study flow is depicted in [figure 1](#).

Endpoints

The primary endpoint examines the occurrence of SSI after major abdominal surgery in association with frequency and timing of redosing. The antibiotic plasma concentration prior to redosing and before closure of the abdominal wound will be measured and compared among redosing schedules for the endpoint SSI.

SSIs are defined in accordance with CDC criteria and will be analysed as dichotomous outcomes and as categorical variables: superficial incisional, deep incisional and organ/space SSI.¹³

Remote infections, postoperative antibiotic use, perioperative volume management, occurrence of resistant bacteria, general and organ-specific complications, additional diagnostics and interventions, length of hospital stay and treatment cost analysis comprise secondary endpoints that will be compared among redosing schedules.

Additionally, a subgroup analysis will be performed for groups based on contamination classification.

[Table 2](#) provides an overview of major endpoints of RESISTAAS I study.

Data management

Data will be recorded via an electronic Case Report Form. All data will be stored on secured servers at the Study Center of the German Society of Surgery at the University of Heidelberg. On completion of the study, depending on the type of data, it will become available via the corresponding author, on reasonable request.

Sample size

Due to nature of an observational study, no formal sample size calculation was performed. The study will recruit until 300 patients are included. Based on the results of

Table 2 Major endpoints of the REpeat versus Single ShoT Antibiotic prophylaxis in major Abdominal Surgery I study

Primary endpoint	Surgical site infections
Secondary endpoints	Remote infections Bloodstream infections Occurrence of resistant bacteria Postoperative antibiotic treatments General complications Organ-specific complications Length of hospital and intensive care stay Additional diagnostics and interventions Total antibiotic and treatment costs Perioperative volume management

this study, an estimation of effect size for subsequent interventional studies will be possible.

Statistical analysis

Dichotomous variables will be shown as rates with 95% CIs. Continuous variables will be shown as means and SD, when appropriate minimal and maximum values as well as 95% CI will be reported. In case of skewed distribution, continuous variables will be presented as medians with interquartile ranges. The differences among various groups will be analysed with analysis of covariance. Univariate tests in the descriptive statistics will be performed using χ^2 tests for nominal variables and Kruskal-Wallis tests for continuous variables. Statistical significance is set at $p < 0.05$. Statistical analysis will be performed using the software R V.4.00.0 via RStudio. Main comparison will be between single-shot group versus repeat antibiotic prophylaxis during major abdominal surgery.

Ethics and dissemination

RESISTAAS I is conducted in accordance with the Declaration of Helsinki and internal, national and international standards of GCP. Participants receive detailed written and oral information on the study procedures and all participants provide written informed consent. Prior to initiation of the study, an ethical approval of the study protocols was obtained from the Medical Ethics Review Board of Heidelberg University (S-404/2021). The study has been registered on 7 February 2022 at German Clinical Trials Register, with identifier DRKS00027892.

The findings of this study will be submitted for publication to peer-reviewed journals.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

DISCUSSION

RESISTAAS I will be the first study to assess perioperative redosing of antibiotic prophylaxis in major abdominal surgery and its effect on SSI. Comparison of single-shot prophylaxis versus redosing will provide valuable information to be used for further interventional trials within the antibiotic stewardship framework.

There is an exceeding need for improving strategies for antibiotic usage within clinical settings. The growth and spread of antimicrobial resistance in bacteria lead to increased mortality, morbidity and healthcare cost.^{23 24} A major driver of this spread is the sporadic and unnecessary antibiotic use. Various antibiotic stewardship programmes aiming at improving strategies and systematic prescription of antibiotics have led to significant outcome improvements in the ambulatory setting.²⁵ Hospital antibiotic stewardship have been shown to improve patient outcomes as well as present a beneficial economic impact.²⁶ Although antibiotic stewardship

initiatives around the world have led to significant re-evaluations and investigations of antibiotic use, this topic is vastly under-represented in abdominal surgery. The WHO guideline emphasises the need for further studies on the optimal time for antibiotic prophylaxis and the repetition of prophylaxis in abdominal surgery.¹²

Surgery has been made significantly safer through perioperative antibiotic prophylaxis, reducing SSI.²⁷ However, studies on postoperative antibiotic prophylaxis have underlined the need to abandon certain dogmatic practices of prescribing antibiotics out of precaution.^{7 8} Studies show that even if the surgical site is contaminated through intestinal perforations, prolonged use of antibiotics does not bring any advantages.^{7 28} Overall, studies support a restrictive use of antibiotics. However, the pressure to prescribe antibiotics without concrete indications is present as clinicians tend to intervene in cases of uncertainty. An evidence-based approach to antibiotic administration is needed and with this, common, empirically driven practices must be evaluated and verified. Perioperative antibiotic prophylaxis has been introduced empirically but have later been proven an effective method to reduce postoperative infection in certain surgeries.²⁷ Postoperative antibiotic prophylaxis has often been prescribed to further reduce infection but failed to show benefit.⁶ Whether perioperative antibiotic redosing is beneficial has not yet been investigated in major abdominal surgery. Many hospitals developed internal strategies incorporating intraoperative redosing; however, this consideration is largely based on pharmacokinetic considerations of plasma half-time of antibiotic. In view of the increasing spread of resistant skin and intestinal bacteria, which are favoured by unnecessary and sporadic administration of antibiotics, and limited new development of antibiotics, the investigation of redosing of perioperative antibiotic prophylaxis is indispensable.

RESISTAAS I will investigate redosing of antibiotic prophylaxis in major abdominal surgery. Based on findings from this study, clinical trials will be developed. In case no difference of SSI is detected between redosing and single-shot antibiotic prophylaxis, a confirmatory non-inferiority randomised controlled trial will be developed. If a significant difference is detected, a confirmatory superiority randomised controlled trial will be conceptualised. Design of a randomised controlled trial will depend on data acquired from this observational study. Potential confounders such as blood loss and time intervals between antibiotic administration will be assessed in the RESISTAAS I study and incorporated into the design aspects of the future randomised controlled trials.

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Contributors AM-L conceived the idea. AM-L, PP, UC, JL and KH developed the methodology. AM-L, JF, MT, RK, HR, ORF, UC and JL developed patient recruitment, data collection and analysis strategies. AM-L, DH, AB, UC, JL, MAW, PP and KH were involved in intellectual content. AM-L drafted the manuscript. All authors revised and edited the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

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