Guidance for Industry

Complicated Intra-Abdominal Infections: Developing Drugs for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Joseph G. Toerner, MD, MPH at 301-796-1300.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2012
Clinical/Antimicrobial

Guidance for Industry

Complicated Intra-Abdominal Infections: Developing Drugs for Treatment

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2012
Clinical/Antimicrobial

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 2

III. DEVELOPMENT PROGRAM 3

A. General Considerations 3

1. Early Phase Clinical Development Considerations 3
2. Drug Development Population 3
3. Efficacy Considerations 3
4. Safety Considerations 4

B. Specific Efficacy Trial Considerations 5

1. Trial Design 5
2. Clinical Microbiology Considerations 5
3. Entry Criteria 6
4. Randomization and Blinding 7
5. Special Populations 7
6. Dose Selection 8
7. Choice of Comparators 8
8. Concomitant Antibacterial Drugs and Prior Nontrial Antibacterial Drugs 8
9. Efficacy Endpoints 10
10. Trials in cIAI Patients With Unmet Need 10
11. Trial Procedures and Timing of Assessments 11
a. Entry visit 11
b. On-therapy visits 12
c. End-of-therapy visit 12
d. Visit at day 28 12
12. Statistical Considerations 12
a. Analysis populations 13
b. Noninferiority margins 14
c. Sample size considerations 14
d. Missing data 14
e. Secondary analyses 14
f. Interim analyses and data monitoring committee 15
13. Risk-Benefit Considerations 15

C. Other Considerations 15

1. PK/PD Considerations 15
2. Labeling Considerations 16

APPENDIX A: JUSTIFICATION FOR NONINFERIORITY MARGIN FOR COMPLICATED INTRA-ABDOMINAL INFECTIONS 17

APPENDIX B: LIST OF PUBLICATIONS USED IN THE ESTIMATE OF A PLACEBO/NO TREATMENT RESPONSE 21

Guidance for Industry[1]
Complicated Intra-Abdominal Infections: Developing Drugs for Treatment

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of complicated intra-abdominal infections (cIAIs).[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of cIAI. This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and the public.[3]

This guidance addresses the following topics:

- Definition of cIAI
- Time point of the primary efficacy outcome assessments
- Noninferiority versus superiority clinical trial designs
- Scientific support for an appropriate noninferiority margin
- Use of prior antibacterial drug therapy
- Use of concurrent antibacterial drug therapy

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the clinical development.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[4]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Intra-abdominal infections are common in clinical practice and comprise a wide variety of clinical presentations and differing sources of infection. The infections can involve the entire peritoneal cavity or retroperitoneal spaces, or can be localized with one or more abscesses surrounding diseased or perforated viscera. A wide variety of bacterial pathogens are responsible for cIAIs, including Gram-negative aerobic bacteria, Gram-positive bacteria, and anaerobic bacteria, and there are also mixed infections. *Uncomplicated* intra-abdominal infections or complicated intra-abdominal infections may be difficult to distinguish, but in general cIAIs extend beyond local viscera into peritoneal or retroperitoneal spaces and are associated with systemic signs and symptoms of illness.

The clinical diagnoses and brief descriptions that define cIAIs include, but are not limited to, the following:

- **Intra-abdominal abscess:** one or more abscesses surrounding diseased or perforated viscera, often characterized by nonspecific abdominal pain

- **Perforation of stomach or intestine:** an acute perforation of abdominal viscera associated with diffuse infection of the peritoneum, often characterized by nonspecific abdominal pain

- **Peritonitis:** a diffuse infection of the peritoneum, often characterized by nonspecific abdominal pain

- **Appendicitis with perforation or periappendiceal abscess:** an acute infection of the appendix characterized by colicky abdominal pain often localized to the right lower quadrant

- **Cholecystitis with perforation or abscess:** an acute infection of the gallbladder, often accompanied by right upper quadrant abdominal pain

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- **Diverticulitis with perforation, peritonitis, or abscess:** an acute infection of a diverticula (herniation of mucosa or submucosa through the muscularis propria of the colon), most often characterized by left lower quadrant abdominal pain

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

The wide variety of bacterial pathogens responsible for cIAI represents a challenging aspect for clinical development. Before sponsors start phase 3 clinical trials, an investigational drug's antibacterial activity should be characterized (e.g., information on whether an investigational drug is active against only Gram-negative bacteria and whether the drug is active against anaerobic bacteria). These data inform phase 3 clinical development.

2. Drug Development Population

The intended clinical trial population should be male and female patients with cIAI representative of the general population of patients with cIAI. Sponsors should discuss with the FDA their plans for evaluation of a drug in the pediatric population early in clinical development. Sponsors also should consider clinical development plans for patients with an unmet need (e.g., patients with limited treatment options because of allergy, intolerance to most antibacterial drugs, or who have or are suspected of having a bacterial pathogen with in vitro susceptibility testing that shows resistance to most antibacterial drugs; see section III.B.10., Trials in cIAI Patients With Unmet Need).

3. Efficacy Considerations

The number of clinical trials needed to support an indication for treatment of cIAI depends on the overall development plan for the drug under consideration. A single persuasive adequate and well-controlled trial with supportive information can be provided as evidence of effectiveness in certain circumstances.[5] For sponsors developing a drug for more than one indication for treatment of infections caused by similar bacterial pathogens, a single trial in cIAI and a trial in the other indication can be provided as evidence of effectiveness (e.g., one trial in complicated urinary tract infection and one cIAI trial or one trial in hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and one cIAI trial). Sponsors should discuss with the FDA their overall clinical development plans for cIAI and for other infectious disease indications, and whether other clinical trials might lend support for a single adequate and well-controlled trial in cIAI. Sponsors pursuing clinical development for a drug in which cIAI is the only indication being sought should discuss with the FDA the type and amount of other

[5] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

confirmatory evidence that could support a single trial, or whether two adequate and well-controlled trials in cIAI should be conducted.

We recommend that clinical trials enroll patients with a variety of cIAI diagnoses. We also anticipate that new drugs for treatment of cIAI will be administered intravenously and not orally, because patients with cIAI do not ingest food or drugs orally (i.e., nothing by mouth, or nil per os (NPO)) during the course of their illness.

Currently, we do not recognize any surrogate markers in cIAI. Primary outcome assessments in cIAI are readily measured (see section III.B.9., Efficacy Endpoints). Sponsors who wish to propose alternative outcome assessments should discuss this with the FDA early in the drug development process.

4. Safety Considerations

The protocol should specify the methods to be used to obtain safety data during the course of the trial. Both adverse event information and safety laboratory data should be collected. All patients should be evaluated for safety at the time of each trial visit or assessment, regardless of whether the investigational drug has been discontinued. Although serious and unexpected adverse events and follow-up information about the events must be reported promptly (21 CFR 312.32(c)(1)(i)(A) and 21 CFR 312.32(d)(1) and (2)), we recommend that in general all adverse events be followed until resolution, even if time on trial has been completed. If the investigational drug has been studied previously, it may be possible to reduce collection of minor adverse events.[6]

A sufficient number of patients, including geriatric patients, should be studied at the exposure (dose and duration) proposed for use to draw appropriate conclusions regarding drug safety.[7] Safety evaluations and assessments should take into consideration the patient populations that are likely to be treated for cIAIs. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. The nonclinical and clinical profiles of the specific drug under study may determine whether additional safety evaluations are needed.[8] Longer term assessment of adverse events after discontinuation or completion of the antimicrobial should be considered depending on the specific drug's potential for long-term or delayed adverse effects. If the same dose and duration of therapy for treatment of cIAI was used in clinical trials for other infectious disease indications, the safety information from clinical trials in other infectious disease indications can contribute to the overall preapproval safety database.

---

[6] See the draft guidance for industry *Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[7] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

[8] See the guidance for industry *Premarketing Risk Assessment* for further discussion on sizes of premarketing safety databases.

We recommend in general that an overall preapproval safety database contain approximately 700 to 1,000 patients treated at the same dose and duration of therapy as for treatment of cIAI. For drugs in development for treatment of an unmet need (e.g., patients with limited treatment options because of allergy, intolerance to most antibacterial drugs, or who have or are suspected of having a bacterial pathogen with in vitro susceptibility testing that shows resistance to most antibacterial drugs (see section III.B.10., Trials in cIAI Patients With Unmet Need)), sponsors should discuss with the FDA the size of an appropriate preapproval safety database.

B. Specific Efficacy Trial Considerations

1. Trial Design

Patients with cIAI for whom there is an effective available therapy would not be eligible for enrollment in placebo-controlled trials even if the placebo period is of a short duration.[9] The clinical trials should be comparative trials designed to show noninferiority or superiority to the active control. Trial populations should be enriched with patients who are likely to have bacterial pathogens isolated on culture from intra-abdominal specimens or from blood.

2. Clinical Microbiology Considerations

An adequate clinical specimen for microbiologic evaluation should be obtained from all patients and sent to the laboratory for microscopic evaluation (e.g., Gram stain), culture, and in vitro antibacterial susceptibility testing performed on appropriate organisms isolated from the specimen. Specimens should be processed according to recognized methods.[10] If the specimen is kept at room temperature, the Gram stain should be performed and the specimen plated for culture within 2 hours from the collection time. Alternatively, these tests can be performed within 24 hours of collection if the specimen is stored at 2 to 8 degrees Celsius before processing. The specimen obtained for culture should be collected during the operative or percutaneous procedure. We recommend aerobic and anaerobic blood cultures taken at two separate venipuncture sites before initiation of antibacterial drug therapy for cIAI.

All isolates considered to be possible pathogens taken from patients enrolled in clinical trials should be saved in the event that additional testing of an isolate is needed (e.g., pulse field gel electrophoresis for strain identification). Sponsors conducting clinical trials outside the United States should characterize the pathogen and describe similarities and differences among isolates identified in the United States. For microbiological assessment, the investigator should collect the following information:

---

[9] The general issue of the ethics of placebo-controlled trials is addressed in ICH E10, section II.A.3., Ethical Issues (2.1.3).

[10] For examples, see the most current editions of the publications from American Society for Microbiology, such as *Manual of Clinical Microbiology* and *Clinical Microbiological Procedures Handbook.*

- The anatomic location of where the specimen was obtained.

- A description of how the sample was obtained, processed, and transported to the laboratory.

- Data from in vitro susceptibility testing of the isolates to both the investigational drug and other antibacterial drugs that may be used to treat cIAI caused by the pathogens targeted by the investigational drug. In vitro susceptibility testing should be performed by using standardized methods unless otherwise justified.[11] Sponsors should describe the exact methodology used for susceptibility testing if a standardized method was not used.

Even though most patients will have a microorganism identified on routine bacteriologic cultures, development of new rapid diagnostic tests may facilitate future clinical trial design and potentially benefit patients by providing earlier diagnosis of causative organisms. Clinical trials of a new antibacterial drug for treatment of cIAI may provide an opportunity to contribute to the evaluation of a new diagnostic test. An FDA-approved or cleared rapid diagnostic test may provide a means of enriching clinical trials by enrolling patients with a bacterial etiology for cIAI caused by a specific type of bacteria. The use of rapid diagnostic tests to determine the presence of the bacterial pathogens should be discussed with the FDA before initiation of clinical trials. Sponsors interested in the development of a new rapid diagnostic test should contact the Center for Devices and Radiological Health.

3. Entry Criteria

Inclusion criteria should include the following characteristics:

- Male or female patients hospitalized for cIAI

- Operative procedure completed or scheduled to occur within 48 hours

  – Procedures include open laparotomy, laparoscopy, and percutaneous drainage of intra-abdominal abscess

- A diagnoses of cIAI including one or more of the following:

  - Intra-abdominal abscess, including splenic or liver abscess
  - Appendicitis complicated by perforation or abscess formation
  - Diverticulitis complicated by perforation or abscess formation
  - Cholecystitis with evidence of perforation or empyema
  - Perforation of large or small intestine with abscess or fecal contamination
  - Gastric or duodenal ulcer perforation
  - Peritonitis accompanied by fecal contamination

[11] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute, Wayne, PA.

- Systemic signs or symptoms of infection that include one or more of the following:
  - Body temperature greater than 38 degrees Celsius or hypothermia (less than 35.5 degrees Celsius)
  - Abdominal pain or flank pain, or pain caused by cIAI that is referred to another anatomic area such as back or hip
  - Nausea or vomiting
  - White blood cell count elevated beyond the upper limit of the normal laboratory range or the proportion of band forms of the white blood cell differential count beyond the upper limit of the normal laboratory range

Exclusion criteria should include the following:

- Receipt of effective antibacterial drug therapy for cIAI for a continuous duration of more than 24 hours during the previous 72 hours (see section III.B.8., Concomitant Antibacterial Drugs and Prior Antibacterial Drugs)
- Concomitant illnesses that may preclude the evaluation of antibacterial drug efficacy (e.g., malignancy, leucopenia, neutropenia)
- Concomitant medications that could interfere with the evaluation of antibacterial drug efficacy (e.g., immunosuppressant therapy)
- Concurrent infectious disease at a site other than the abdomen that may have a potential effect on outcome evaluation in patients with cIAI

4. Randomization and Blinding

Trials should be randomized, multicenter, and double-blind unless there is a compelling reason for single-blind or open-label trials. If trials are single-blind or open-label, sponsors should discuss potential biases with the FDA and how these biases will be addressed.

5. Special Populations

Patients with at least mild to moderate renal impairment and hepatic impairment should be included in drug development programs, and the need for dose adjustment in such patients should be assessed. Patients with unmet need (e.g., patients with limited treatment options because of allergy, intolerance to most antibacterial drugs, or who have or are suspected of having a bacterial pathogen with in vitro susceptibility testing that shows resistance to most antibacterial drugs) can be included in drug development programs (see section III.B.10., Trials in cIAI Patients With Unmet Need). Sponsors are required to conduct trials that support labeling for use in pediatric populations and should discuss the pediatric development plans with the FDA, including the potential extrapolation of adult efficacy data, pharmacokinetic (PK) studies

in pediatric populations to support dose and formulation selection, and appropriate safety studies in pediatrics.[12] A sufficient number of geriatric patients, including patients 75 years of age or older, should be evaluated to draw conclusions regarding drug safety.[13]

6. Dose Selection

The findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics, pharmacodynamics, in vitro susceptibility profiles of target pathogens, safety and tolerability information from phase 1 trials, and safety and antibacterial activity information from phase 2 dose-ranging trials should be integrated for purposes of selecting appropriate doses and duration of doses to be evaluated in phase 3 clinical trials. Nonclinical data should document activity against commonly implicated pathogens for cIAI. An assessment of drug penetration into certain tissues can be used as supportive evidence that the selected doses are likely to achieve drug concentrations sufficient to exert both an antimicrobial and clinical effect for cIAI. In addition, the pharmacokinetics of the drug in specific populations (e.g., pediatric patients, geriatric patients, patients with renal or hepatic impairment) should be evaluated before initiation of phase 3 clinical trials to determine whether dose adjustments are necessary. This evaluation may prevent the exclusion of such patients from phase 3 clinical trials.

In general, patients with cIAI have NPO ordered by their health care providers for certain periods of time, up to 1 week or more depending on the type of cIAI, and drugs are given by intravenous (IV) administration. Guidelines recommend that the total duration of therapy for cIAI be from 4 to 7 days.[14] Therefore, it is likely that the clinical trials will be conducted entirely using IV drugs (i.e., an IV formulation of the investigational drug would be used without a switch to an oral drug).

7. Choice of Comparators

Clinical trials for the evaluation of treatment of cIAI should use an FDA-approved drug for treatment of cIAI as the comparator. In addition, the comparator drug should also be one recommended for use in current treatment guidelines. The dosages, regimens, and infusion rates recommended in the labeling should be used.

8. Concomitant Antibacterial Drugs and Prior Nontrial Antibacterial Drugs

The protocol should specify the use of nontrial concomitant antibacterial drugs that may be permitted in the trial to provide empirical antibacterial coverage against a wide variety of pathogens. Such concomitant treatment is often necessary for initial treatment of patients with

---

[12] The Pediatric Research Equity Act requires the conduct of pediatric studies for certain drug and biological products (see section 505B(b) of the Federal Food, Drug, and Cosmetic Act).

[13] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

[14] Solomkin, JS, JE Mazuski, JS Bradley et al., 2010, Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Disease Society of America, Clinical Infectious Diseases, 50:133-164.

cIAI before the culture results are available. The investigational drug's in vitro antibacterial activity should be well-characterized and the investigational drug may be known not to fully encompass all bacterial pathogens implicated in cIAI. To the extent possible, the nontrial concomitant antibacterial drug should not have antibacterial activity similar to the investigational drug, so that the effect of the investigational antibacterial drug can be assessed.

After bacterial pathogens have been identified on culture and found on in vitro susceptibility testing to be susceptible to the investigational drug (or to the control drug used in the clinical trial), the protocol should provide for discontinuation of the concomitant antibacterial drugs (that were initially used for empirical antibacterial coverage against a wide variety of pathogens but are no longer needed in light of the susceptibility of the organism and the activity of the investigational and control drugs). If the organism is not sensitive to the investigational or control drug, those drugs would be discontinued and replaced with appropriate antibacterial drug therapy.[15] If feasible, the course of treatment should be completed as monotherapy with the investigational drug or its comparator (e.g., active-controlled drug), thereby allowing clearer conclusions about an investigational drug's efficacy during a full course of treatment. The use of concomitant antibacterial drugs with similar antibacterial activity to the investigational drug or continuation of the empirical antibacterial coverage during the entire course of treatment will compromise the ability to evaluate efficacy of an investigational drug.

To the extent possible, the use of nontrial antibacterial drugs for treatment of cIAI immediately before administration of clinical trial drugs should be minimized because of a potential to obscure any difference between treatment arms, potentially biasing conclusions about treatment effects in a noninferiority clinical trial. If a nontrial antibacterial drug must be used for initiating therapy for the current treatment of cIAI, it is preferable for the antibacterial drug to have a short serum half-life and be used for not more than 24 hours during the previous 72 hours. We recognize that patients newly diagnosed with cIAI may require urgent administration of nontrial antibacterial drugs, and that it may be difficult to avoid the use of nontrial antibacterial drugs immediately before enrollment while patients are being considered for enrollment in cIAI clinical trials. For this reason, we examined the role of the administration of an antibacterial drug in placebo-controlled trials that were evaluating prophylaxis of surgical wound infections.

We found three prospective, double-blind, and placebo-controlled trials that evaluated use of antibacterial drugs in prophylaxis of surgical wound infections. In two trials to evaluate the effect of a single dose of an antibacterial drug for prophylaxis of surgical wound infections, the subgroup of patients who were found at surgery to have a gangrenous or perforated appendix had a high rate of subsequent wound infections (greater than 50 percent of patients) regardless of whether they had received the antibacterial drug or placebo.[16] In the third trial, the role of the

---

[15] For example, see the recommendations for refining antimicrobial regimens according to culture and susceptibility results in: Solomkin, JS, JE Mazuski, JS Bradley et al., 2010, Diagnosis and Management of Complicated Intra-Abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Disease Society of America, Clinical Infectious Diseases, 50:133-164.

[16] Donovan, IA, D Ellis, D Gatehouse et al., 1979, One-Dose Antibiotic Prophylaxis Against Wound Infection After Appendectomy: A Randomized Trial of Clindamycin, Cefazolin Sodium and a Placebo, Br J Surg, 66:193-196; and Morris, WT, DB Innes, RA Richardson, AJ Lee, and RB Ellis-Pegler, 1980, The Prevention of Post-Appendectomy Sepsis by Metronidazole and Cefazolin: A Controlled Double-Blind Trial, Aust NZ J Surg, 50:429-433.

administration of 5 days of an antibacterial drug for prophylaxis of surgical wound infections was examined. In this trial there were no wound infections in the subgroup that was found to have a gangrenous or perforated appendix and who received 5 days of antibacterial drug, but wound infections were observed among placebo recipients.[17]

Thus, although we recommend that clinical trials attempt to enroll a considerable proportion of patients who have not received prior nontrial antibacterial drugs, we conclude from these data in the subgroup of patients that would fulfill the definition of cIAI that the administration of a nontrial antibacterial drug for not more than 24 hours during the 72 hours preceding trial entry in cIAI trials is not likely to have a large effect and is not an explicit exclusion criterion for a noninferiority trial. However, nontrial antibacterial drug treatments for cIAI longer than 24 hours should be an exclusion criterion. Another circumstance when the use of nontrial antibacterial drugs immediately before the trial may not preclude the patient's enrollment into a trial is among patients who are receiving antibacterial therapy and whose infections have failed to respond to that therapy, provided objective criteria for treatment failures are prespecified and documented.

9. Efficacy Endpoints

The primary endpoint of clinical success is defined as the complete resolution of the baseline signs and symptoms attributable to cIAI at a fixed time point approximately 28 days following randomization, and the absence of clinical failure, including the following types of events or complications of cIAI occurring up to the fixed time point at 28 days following randomization:

- Death
- Persistence of clinical symptoms of cIAI
- Unplanned surgical procedures or percutaneous drainage procedures
- Initiation of rescue antibacterial drug therapy for cIAI

A patient having any of these events before 28 days should not be considered a clinical success.

10. Trials in cIAI Patients With Unmet Need

Patients with cIAI and unmet need (e.g., patients with limited treatment options because of allergy, intolerance to most antibacterial drugs, or who have or are suspected of having a bacterial pathogen with in vitro susceptibility testing that shows resistance to most antibacterial drugs) would not be appropriate patients for enrollment in a noninferiority trial design (see section III.B.9., Efficacy Endpoints). The noninferiority trial design assumes that the drug being used as the active control has a known and reliable treatment effect, which would not be the case for these patients.

An active-controlled trial designed to show superiority can be considered in the setting of cIAI caused by bacteria resistant to multiple antibacterial drugs. Such a trial can also enroll patients with a greater degree of comorbid conditions and could also be appropriate in a setting where the

[17] Gottrup, F, 1980, Prophylactic Metronidazole in Prevention of Infection After Appendectomy: Report of a Double-Blind Trial, Acta Chir Scand, 146:133-136.

risk-benefit profile of the drug only supports a more limited use because of its toxicity. The following three conceptual approaches can be considered for superiority clinical trial designs:

1. Patients would be randomized to receive either the investigational drug or antibacterial drug treatment chosen empirically or based on in vitro susceptibility testing when available and represents standard-of-care therapy. The evaluation of efficacy of the investigational drug would be based on a finding of superiority in the group that received the investigational drug.

2. All patients would receive antibacterial drug treatment chosen empirically or based on the results of in vitro susceptibility testing when available (standard-of-care therapy), and patients would be randomized to receive, in addition, an investigational drug or matching placebo (an *add-on* study). The efficacy of the investigational drug would be shown by a superior outcome in the group that received the added investigational drug.

3. Patients would be enrolled in a dose-response trial where patients are randomized to receive one of two doses of the investigational drug for which there is equipoise. The goal of the trial is demonstration of superiority in one dose group (presumably the higher dose). A potential problem is that the lower dose would need to be plausibly effective based on in vitro susceptibility studies, so that superiority might be difficult to show.

We encourage sponsors considering superiority clinical trial designs in cIAI patients with unmet need (e.g., cIAI caused by bacteria resistant to multiple antibacterial drugs) to discuss the design with the FDA during protocol development. We recommend that a data monitoring committee (DMC) be in place to perform interim effectiveness analyses for success or futility and that such analyses be prespecified in the protocol and in the analysis plan (see section III.B.12.f., Interim analyses and data monitoring committee).

11. Trial Procedures and Timing of Assessments

a. Entry visit

At the entry visit, the following information should be captured and recorded on the case report form:

- History and physical examination
- Prior and concomitant drug therapy
- Baseline clinical signs and symptoms including vital signs
- Radiographic or ultrasound imaging of the abdomen using standard interpretive criteria
- Clinical severity score(s)

- Microbiologic specimens: adequate intra-abdominal specimens as determined by Gram stain, culture of intra-abdominal specimen, and blood cultures (using aseptic techniques, aerobic and anaerobic blood cultures obtained from two separate venipuncture sites)

- Laboratory tests as appropriate

b. On-therapy visits

Patients should be evaluated early in the course of treatment to assess clinical improvement or clinical failure, in which case rescue antibacterial drug therapy would be appropriate. It is important that investigators distinguish patients who are worsening or not improving (i.e., where rescue antibacterial drug therapy is appropriate) from patients who are improving slowly and may still remain on assigned therapy and be potentially considered clinical successes. These visits should capture clinical and laboratory assessments for safety, and should include patient symptoms and clinical observations such as vital signs, physical examination findings, laboratory test results, radiographic or ultrasound imaging results, and microbiology results. Specific objective criteria that would be reason to initiate rescue therapy in patients without clinical improvement or with progression of signs or symptoms of cIAI should be included in the protocol.

c. End-of-therapy visit

Patients should be evaluated at the end of prescribed therapy. Clinical and laboratory assessments for safety should be performed at this visit. If it is possible that the trial drug would need to be continued beyond the protocol-specified duration, objective criteria for extending the therapy should be prespecified in the protocol.

d. Visit at day 28

At approximately day 28 following randomization, patients should be evaluated in the hospital or in the clinic for assessment of the primary clinical endpoint of complete resolution of clinical signs and symptoms of cIAI or the occurrence of an event that characterizes clinical failure (see section III.B.9., Efficacy Endpoints).

12. Statistical Considerations

The trial's primary and secondary hypotheses and the analysis methods should be prespecified in the protocol and in the statistical analysis plan, and generally should be finalized before trial initiation, although later changes can be acceptable if blinding is unequivocally maintained. The primary endpoint analysis should be a comparison of clinical success rates at a fixed time point of approximately 28 days following randomization. Trials should be adequately powered to compare clinical success rates between treatment groups. If sponsors choose to test multiple

primary or secondary hypotheses, they should address issues related to the potential inflation of false-positive results and control of overall type I error rate caused by multiple comparisons.[18]

a. Analysis populations

The following definitions apply to various analysis populations in cIAI clinical trials:

- Intent-to-treat (ITT) population — All patients who were randomized.

- The microbiological intent-to-treat population (micro-ITT population) — All randomized patients who have baseline bacterial pathogens that cause cIAI and against which the investigational drug has antibacterial activity. This includes bacterial pathogens associated with cIAI identified in blood or appropriate abdominal specimen. Patients should not be excluded from this population based upon events that occurred after randomization (e.g., loss to follow-up).[19]

- Clinically evaluable or per-protocol populations — Patients who meet the definition for the ITT population and who follow important components of the trial as specified in the protocol.

- Microbiologically evaluable populations — Patients who meet the definition for the micro-ITT population and who follow important components of the trial as specified in the protocol.

- Safety population — All patients who received at least one dose of drug during the trial.

The micro-ITT population with bacterial pathogens in the antibacterial spectrum of the investigational drug should be considered the primary analysis population. For example, the micro-ITT population for an investigational antibacterial drug with activity against Gram-negative bacterial pathogens should consist of the population identified with baseline Gram-negative pathogens; and the micro-ITT population for an investigational antibacterial drug with activity against Gram-positive bacterial pathogens should consist of the population identified with baseline Gram-positive pathogens. Consistency of the results should be evaluated in all populations and any inconsistencies in the results of these analyses should be explored and explanations provided in the final report.

[18] These issues should be discussed with the FDA during protocol development, and if any subsequent changes are considered, they should be discussed with the FDA before incorporation into the statistical analysis plan. See ICH E9.

[19] The attribution of efficacy to an investigational drug would be compromised if a bacterial pathogen has in vitro susceptibility to both the investigational drug and a concomitant drug used for initial empirical antibacterial coverage. Sponsors should address this issue in the protocol, for example, by choosing concomitant antibacterial drugs that do not have overlapping antibacterial activity with an investigational drug, or by excluding patients from the micro-ITT population with baseline pathogens susceptible to both the investigational drug and a concomitant drug.

b. Noninferiority margins

If a noninferiority clinical trial is used in the evaluation of an investigational antibacterial drug for cIAI, the noninferiority margin can be selected and scientifically justified based on historical evidence of the effect of the control antibacterial therapy on clinical event rates in cIAI. Appendix A provides a discussion of the noninferiority margin of 10 percent. Sponsors considering a different noninferiority margin should discuss this with the FDA.

c. Sample size considerations

The appropriate sample size for a clinical trial will be based upon the number of patients needed to answer the prespecified hypothesis posed by the trial. The sample size is influenced by several factors, including the prespecified type I and type II error rates, estimate of the control mortality rate, the noninferiority margin, or the magnitude by which the trial drug is expected to be superior (for a superiority trial). The appropriate sample size should be estimated using a two-sided type I error rate of 0.05 (α=0.05).

The following is an example of sample size estimation for a noninferiority cIAI clinical trial. Using an endpoint of clinical success (complete resolution of the baseline clinical signs and symptoms attributable to cIAI at a fixed time point approximately 28 days following randomization), we assumed that the rate of success in the control group would be 80 percent. We also assumed a two-sided type I error (α) of 0.05 and type II error (β) of 0.2 (power 0.80) and a noninferiority margin of 10 percent (see Appendix A for justification of noninferiority margin). The sample size for the efficacy analysis population is approximately 250 patients per group and patients with microbiologically documented infections were considered the primary analysis population. If 80 percent of enrolled patients have a confirmed bacterial pathogen as the cause of cIAI, approximately 315 patients per group (630 patients per trial) would need to be enrolled in the clinical trial, using a 1:1 randomization to investigational drug or to active-controlled drug, to obtain 250 patients per group with microbiologically documented infection.

d. Missing data

There is no optimal way to deal with missing data in clinical trials. Sponsors should make every attempt to limit loss of patients from the trial, because patients who do not complete the trial may differ substantially from patients who remain in the trial in both measured and unmeasured ways. The method of how missing data will be handled should be specified in the protocol. Missing data should be minimal in clinical trials evaluating hospitalized patients with cIAI and using a primary endpoint at approximately 28 days following randomization.

e. Secondary analyses

Sponsors can present secondary analyses on other endpoints of interest that may include but are not limited to the following:

- Evaluation of consistency of the results among patient subsets based on demographic characteristics, such as age, sex, geographic region, underlying medical conditions, and microbiological etiology

- Time to complete resolution of signs and symptoms analysis by treatment group (e.g., Kaplan-Meier method)

- An analysis of patients who did or did not receive prior antibacterial drug therapy

f. Interim analyses and data monitoring committee

If interim effectiveness analyses for success or futility will be performed, they should be prespecified in the protocol and in the analysis plan along with a justification. Details on the operating procedures also should be provided before trial initiation. The purpose of the interim analysis should be stated along with the appropriate statistical adjustment to control the overall type I error rate. It is important that an appropriate firewall be in place to guarantee that the interim analysis will not affect trial conduct and thereby compromise trial results. This can be accomplished by creating an independent DMC that monitors the protocol with prespecified operational procedures. Such a committee also might be created if there were safety concerns about the drug or the treatment approach. If a DMC is used, a detailed charter with the composition of the committee members, conflicts of interest, decision rules, details on the measures taken to protect operational bias and the integrity of the trial, and the standard operating procedures should be provided for review.[20]

13. Risk-Benefit Considerations

The risk-benefit considerations depend on the population being studied and the safety profile of the drug being investigated. For example, in areas where a drug demonstrates meaningful therapeutic advantage in patients with unmet need, a greater degree of risk may be offset by the benefit provided in an overall evaluation of risk and benefit.

C. Other Considerations

1. PK/PD Considerations

The PK/pharmacodynamic (PD) characteristics of the drug should be evaluated using in vitro models or animal models of infection if not previously performed. The results from PK/PD assessments should be integrated with the findings from phase 1 PK assessments to help identify appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials. A dose-response trial design can be considered as an option in early clinical development. This allows weighing of benefits and risks when selecting doses in an attempt to ensure that suboptimal doses or excessive doses (beyond those that add to efficacy) are not used in phase 3 clinical development, offering some protection against unexpected and unrecognized dose-related toxicity.

[20] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

Sponsors should consider a sparse sampling strategy from all patients in phase 2 and phase 3 clinical trials to allow for the estimation of drug exposure in each patient. Collection of PK data in phase 2 clinical trials can be used to explore the exposure-response relationship and to confirm that the proper dose and regimen are selected for further evaluation in phase 3 clinical trials. Collection of PK data in phase 3 clinical trials may help to address potential questions regarding efficacy or safety that might arise from the clinical trials.

A retrospective exposure-response analysis based on the population PK model from patients in phase 3 clinical trials should be performed to assess the relationship between PK/PD indices and observed clinical and microbiologic outcomes. The relationship between drug exposure or different dosing regimens and clinically relevant adverse events should also be explored to identify potential risks. These relationships should also be explored for specific patient populations (e.g., patients with renal impairment).

2. Labeling Considerations

The labeled indication should be for the treatment of cIAI caused by specific bacteria identified in patients in the clinical trials. For example:

> *"Drug X is indicated for the treatment of complicated intra-abdominal infections due to…."*

APPENDIX A: JUSTIFICATION FOR NONINFERIORITY MARGIN FOR COMPLICATED INTRA-ABDOMINAL INFECTIONS

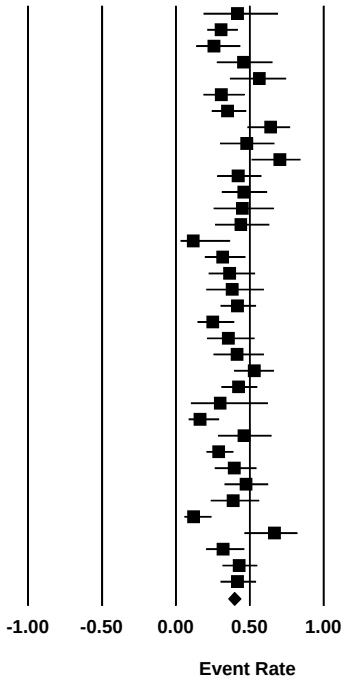
This appendix describes an approach to justify the noninferiority margin for cIAIs. Sponsors should consider the information presented in this appendix when considering active-controlled trials designed for noninferiority.

A literature search was conducted using search terms such as *intra-abdominal infection*, *placebo*, and *antibacterial*. The search found no placebo-controlled trials in patients with cIAI. Next, an attempt was made to describe the rate of complications from cIAI not treated with antibacterial drug therapy. There were numerous observational studies published before the availability of antibacterial drugs. These observational studies described outcomes among patients with cIAI following surgical interventions. In general, the studies summarized the rates of clinical success and clinical failures among consecutive cases at each author's institution, and patient-level data were not presented. When clinical vignettes specified outcomes in a few of the papers, it became clear that outcomes of cIAI labeled as a success might not be considered a true successful outcome today. For example, continued drainage of pus from a catheter to drain an intra-abdominal infection was kept in place for months and was considered a successful outcome. Today the continued drainage of pus for longer than 28 days from a catheter for an intra-abdominal infection would be considered a clinical failure. Therefore, there was uncertainty as to whether events labeled as clinical success before the availability of antibacterial drugs were actual clinical successes and it was not possible to estimate the proportion of patients with a clinical success before the availability of antibacterial drugs.

In the literature search, we found approximately 40 placebo-controlled trials, or trials that randomized patients to antibacterial drug or to no treatment, in patients who were undergoing elective intra-abdominal surgeries to evaluate the effect of antibacterial drugs in the prophylaxis of surgical wound infections. Of these, 36 trials provided enough data to characterize clinical event rates (e.g., wound infections) among placebo recipients or patients that were randomized to receive no treatment. For these trials, we excluded patients undergoing procedures for simple appendicitis without abscess formation. In general, patients were followed postoperatively in a hospitalized setting, and then evaluated in an outpatient clinic setting after completion of antibacterial drug or placebo/no treatment therapy, usually within a 1-month period of time. Therefore, the event rates can be considered as events that occurred within a 1-month time frame. Figure 1 describes the event rates of death or development of an intra-abdominal or surgical wound infection.

Figure 1. Forest Plot of the Event Rates (Death or Intra-Abdominal or Surgical Infection) in the Studies of Antibacterial Drug Prophylaxis Among Recipients of Placebo or Randomized to Receive No Antibacterial Drug Treatment[21]

Study name	#Events / Total	Statistics for each study: Event rate	Lower limit	Upper limit
Bates (1980)	5 / 12	0.417	0.185	0.692
Bauer (1989)	22 / 72	0.306	0.210	0.421
Bjerkeset (1980)	8 / 31	0.258	0.135	0.437
Burdon-trial 1(1977)	11 / 24	0.458	0.275	0.654
Burdon-trial 2 (1977)	13 / 23	0.565	0.363	0.748
Burton (1975)	12 / 39	0.308	0.184	0.467
Clarke (1977)	21 / 60	0.350	0.241	0.478
Eykyn (1979)	25 / 39	0.641	0.481	0.775
Feathers (1977)	12 / 25	0.480	0.296	0.669
Foster (1981)	19 / 27	0.704	0.510	0.844
Galland (1977)	16 / 38	0.421	0.276	0.581
Gillespie (1978)	17 / 37	0.459	0.308	0.619
Glenhill (1983)	9 / 20	0.450	0.253	0.664
Goldring (1975)	11 / 25	0.440	0.263	0.634
Gordon (1965)	2 / 17	0.118	0.030	0.368
Gottrup (1985)	13 / 41	0.317	0.194	0.473
Griffiths (1976)	12 / 33	0.364	0.219	0.537
Hagen (1980)	8 / 21	0.381	0.203	0.598
Hojer (1978)	25 / 60	0.417	0.299	0.544
Hughes (1970)	11 / 44	0.250	0.144	0.397
Hunt (1979)	11 / 31	0.355	0.209	0.534
Keighley (1976)	12 / 29	0.414	0.252	0.596
Kjellgren (1977)	26 / 49	0.531	0.392	0.665
Matheson (1978)	25 / 59	0.424	0.305	0.552
Nichols (1973)	3 / 10	0.300	0.100	0.624
Nygaard (1980)	8 / 49	0.163	0.084	0.294
Persson (1981)	12 / 26	0.462	0.284	0.650
Polk (1969)	26 / 90	0.289	0.205	0.391
Rosenberg (1971)	17 / 43	0.395	0.262	0.546
Rubbo (1965)	19 / 40	0.475	0.327	0.627
Schiessel (1984)	12 / 31	0.387	0.235	0.565
Soderquist (1995)	6 / 50	0.120	0.055	0.242
Ulrich (1981)	16 / 24	0.667	0.461	0.824
Utley (1984)	15 / 47	0.319	0.202	0.464
Washington (1974)	27 / 63	0.429	0.313	0.553
Wetterfors (1980)	25 / 60	0.417	0.299	0.544
Weighted Analysis		**0.392**	**0.351**	**0.434**



A random effects meta-analysis was performed using the methods described by DerSimonian and Laird.[22] The point estimate for the event rate among placebo/no treatment recipients was 39.2 percent, with a two-sided 95 percent confidence interval of 35.1 percent and 43.4 percent. The rate of a clinical success outcome was computed by 1 minus the event rate. Thus, an estimate of the placebo/no treatment response rate is 60.8 percent, with a two-sided 95 percent confidence interval of 56.6 percent and 64.9 percent.

We evaluated the rate of clinical success outcomes among recently conducted active-controlled clinical trials in cIAI. All trials evaluated patients during antibacterial drug treatment for cIAI and observed patients for differing periods of time after completion of antibacterial drugs (e.g., observations from day 14 to day 60). Table 1 shows the classification we used to define clinical success or clinical failure at day 28 based on the available data.

[21] A list of these references can be found in Appendix B.

[22] DerSimonian, R and N Laird, 1986, Meta-Analysis in Clinical Trials, Control Clin Trials, 7:177-187.

Table 1. Classification Scheme for Clinical Cure and Clinical Failure

Last Assessment Before or On Day 28	Earliest Assessment After Day 28	Clinical Response at Day 28
Cure, improvement	Cure	Cure
Cure, improvement	Failure	Cure
Cure, improvement	Indeterminate or missing	Cure
Failure	All possible outcomes	Failure
Indeterminate, missing	Cure	Failure
Indeterminate, missing	Failure, indeterminate, missing	Failure

The results from the datasets available for review at the FDA are displayed in Table 2.

Table 2. Clinical Response Cure Rate at Day 28 in the Micro-ITT Population

Trial	Study Group	Clinical Response Rate at Day 28 n/N (%)
1	A	157/194 (80.9)
1	B	159/191 (83.2)
2	C	157/199 (78.9)
2	D	157/186 (84.4))

The DerSimonian and Laird meta-analysis for the clinical response rates among patients treated with an antibacterial drug showed a point estimate of 81.7 percent and a two-sided 95 percent confidence interval of 78.8 percent and 84.3 percent.

An estimate of the treatment effect of a successful clinical response during treatment and period of observation following completion of treatment at day 28 can be derived from the results of recently conducted clinical trials and results of placebo or no treatment among patients undergoing intra-abdominal surgery. Using an approach of the lower bound two-sided 95 percent confidence interval for antibacterial drug treatment estimate minus the upper bound of the two-sided 95 percent confidence interval for the placebo/no treatment estimate, a treatment difference is estimated to be 13.9 percent (78.8 percent minus 64.9 percent).

There are strengths and limitations associated with this approach to justify the noninferiority margin. The limitations of the available data are outlined as follows:

- There was a large amount of heterogeneity among the patients enrolled in the 36 antibacterial drug prophylaxis trials

- Cross-study comparisons result in a greater amount of uncertainty and the patient populations among the two comparison groups were clearly different

The strengths of this approach are outlined as follows:

- Most patients did not have an intra-abdominal infection at the beginning of therapy in the placebo-controlled or no-treatment surgical prophylaxis studies; the rate of clinical

success (point estimate of 60.8 percent) thus probably represents an over-estimate of the rate of successful outcomes among patients who would present with an intra-abdominal infection and would receive placebo

- The definition of clinical success and clinical failure was clear in most of the studies and trials that were evaluated

- The more recently conducted phase 3 trials had patient-level data reviewed by FDA medical and statistical reviewers

- The endpoints of clinical success and clinical failure are consistent with the current framework for clinical endpoints because they represent how a patient feels, functions, or survives (e.g., death, unplanned surgical intervention, continuation or worsening of symptoms attributable to cIAI)

The comparison of the lower bound 95 percent confidence interval for antibacterial drug therapy and the upper bound of the 95 percent confidence interval for placebo/no treatment is a conservative approach to an estimate of the treatment difference. Moreover, as noted, the placebo/no treatment response is probably overestimated (i.e., is conservative) because most patients at the start of a surgical prophylaxis trial did not have evidence of an intra-abdominal infection and success rates are likely to be lower for patients with evidence of intra-abdominal infection and would receive placebo. Therefore, there is little reason to consider discounting the treatment difference and M_1 is at least 13.9 percent. Because it is important to preserve a reasonable portion of an important treatment effect when selecting a noninferiority margin, there is support for a 10 percent noninferiority margin for active-controlled trials of cIAI for an endpoint of clinical success or clinical failure at 28 days following initiation of antibacterial drug therapy, in the micro-ITT population.

APPENDIX B: LIST OF PUBLICATIONS USED IN THE ESTIMATE OF A PLACEBO/NO TREATMENT RESPONSE

Bates, T, VLR Touquet, MK Tutton, SE Mahmoud, and WA Reuther, 1980, Prophylactic Metronidazole in Appendectomy: A Controlled Trial, BrJ Surg, 67:547-50.

Bauer, T, BO Vennits, B Holm et al., 1989, Antibiotic Prophylaxis in Acute Nonperforated Appendicitis, Ann Surg, 209(3):307-11.

Bjerkeset, T and A Digranes, 1980, Systemic Prophylaxis With Metronidazole (Flagyl) in Elective Surgery of the Colon and Rectum, Surgery, 87(5):560-6.

Burdon, JGW, PJ Morris, P Hunt, and JM Watts, 1977, A Trial of Cephalothin Sodium in Colon Surgery to Prevent Wound Infection, Arch Surg, 112:1169-73-Trial 1.

Burdon, JGW, PJ Morris, P Hunt, and JM Watts, 1977, A Trial of Cephalothin Sodium in Colon Surgery to Prevent Wound Infection, Arch Surg, 112:1169-73-Trial 2.

Burton, RC, ESR Hughes, and AM Cuthbertson, 1975, Prophylactic Use of Gentamycin in Colonic and Rectal Surgery, Med J Aust, 2:597-9.

Clarke, JS, RE Condon, JH Bartlett, SL Gorbach, RL Nichols, and S Ochi, 1977, Preoperative Oral Antibiotics Reduce Septic Complications of Colon Operations: Results of Prospective, Randomized, Double-Blind Clinical Study, Ann Surg, 186:251-9.

Eykyn, SJ, HE Lockhart-Mummery, BT Jackson, and II Phillips, 1979, Prophylactic Preoperative Intravenous Metronidazole in Elective Colorectal Surgery, Lancet, 2(8146):761-4.

Feathers, RS, AAM Lewis, GR Sagor, ID Amirak, and P Noone, 1977, Prophylactic Systemic Antibiotics in Colorectal Surgery, Lancet, 2:761-4.

Foster, GE, JB Bourke, J Bolwell et al., 1981, Clinical and Economic Consequences of Wound Sepsis After Appendicectomy and Their Modification by Metronidazole or Povidone Iodine, Lancet, 1(8223):769-71.

Galland, RB, JH Saunders, JH Mosley, and JH Darrell, 1977, Prevention of Wound Infection in Abdominal Operations by Preoperative Antibiotics or Povidone-Iodine: A Controlled Trial, Lancet, 2:1043-5.

Gillespie, G and W McNaught, 1978, Prophylactic Oral Metronidazole in Intestinal Surgery, J Antimicrob Chemother, 4(suppl c):29-32.

Gledhill, T, A Odurny, and PC Weaver, 1983, A Controlled Study of Single Dosage Cefamandole in the Prophylaxis of Wound Infections in Appendectomy, Surg Gynaecol Obstetr, 156(3):295-7.

Goldring, J, A Scott, W McNaught, and G Gillespie, 1975, Prophylactic Oral Antimicrobial Agents in Elective Colonic Surgery: A Controlled Trial, Lancet, 2:997-1000.

Gordon, HE, DW Gaylor, DM Richmond et al., 1965, Operations on the Colon: The Role of Antibiotics in Preoperative Preparation, Calif Med, 103:243-6.

Gottrup, F, P Diederich, K Sorensen et al., 1985, Prophylaxis With Whole Gut Irrigation and Antimicrobials in Colorectal Surgery: A Prospective, Randomized Double-Blind Clinical Trial, Am J Surg, 149(March):317-22.

Griffiths, DA, RA Simpson, BA Shorey, DCE Speller, and NB Williams, 1976, Single-Dose Preoperative Antibiotic Prophylaxis in Gastrointestinal Surgery, Lancet, 2(7981):325-8.

Hagen, TB, T Bergan, I Liavag, 1980, Prophylactic Metronidazole in Elective Colon-Rectal Surgery, Acta Chir Scand, 146:71-5.

Hojer, H and J Wetterfors, 1978, Systemic Prophylaxis With Doxycycline in Surgery of the Colon and Rectum, Ann Surg, 187(4):362-8.

Hughes, ESR, KJ Hardy, AM Cuthbertson, and SD Rubbo, 1970, Chemoprophylaxis in Large Bowel Surgery. 1. Effect of Intravenous Administration of Penicillin on Incidence of Postoperative Infection, Med J Aust, 1:305-8.

Hunt, PS, JK Francis, G Peck et al., 1979, Tinidazole in the Prevention of Wound Infection After Elective Colorectal Surgery, Med J Aust, 1:107-9.

Keighley, MRB, AR Crapp, DW Burdon et al., 1976, Prophylaxis Against Anaerobic Sepsis in Bowel Surgery, Br J Surg, 63:538-41.

Kjellgren, K and H Sellstrom, 1977, Effect of Prophylactic Systemic Administration of Cephalothin in Colorectal Surgery, Acta Chir Scand, 143:473-7.

Matheson, DM, Y Arabi, D Baxter-Smith et al., 1978, Randomized Multicentre Trial of Oral Bowel Preparations and Antimicrobials for Elective Colorectal Operations, Br J Surg, 65:597-600.

Nichols, RL, P Broido, RE Condon et al., 1973, Effect of Preoperative Neomycin-Erythromycin Intestinal Preparation on the Incidence of Infectious Complications Following Colon Surgery, Ann Surg, 178:453-9.

Nygaard, K and J Hognestad, 1980, Infection Prophylaxis With Doxycycline in Colorectal Surgery, A Preliminary Report, Scand J Gastroenterol Suppl, 59:37-9.

Persson, S and H Gnarpe, 1981, Tinidazole as Preventive Treatment in Elective Colonic Surgery, Scand J Infect Dis, 13:137-40.

Polk, HC Jr and JF Lopez-Major, 1969, Postoperative Wound Infection: A Prospective Study of Determinant Factors and Prevention, Surgery, 66:97-103.

Rosenberg, IL, NG Graham, FT deDombal, and JC Goligher, 1971, Preparation of the Intestine in Patients Undergoing Major Large-Bowel Surgery, Mainly for Neoplasms of the Colon and Rectum, Br J Surg, 58:266-9.

Rubbo, SD, ESR Hughes, B Blainey, and IS Russell, 1965, Role of Preoperative Chemoprophylaxis in Bowel Surgery, Antimicrob Agents Chemother, 5:649-58.

Schiessel, R, I Huk, M Wunderlich et al., 1984, Postoperative Infections in Colonic Surgery After Enteral Bacitracin-Neomycin-Clindamycin or Parenteral Mezlocillin Oxacillin Prophylaxis, J Hosp Infect, 5:289-97.

Söderquist-Elinder, C, K Hirsch, S Bergdahl et al., 1995, Prophylactic Antibiotics in Uncomplicated Appendicitis During Childhood — A Prospective Randomised Study, Eur J Pediatr Surg, 5:282-285.

Ulrich, C, 1981, 24-hour Systemic Antibiotic Prophylaxis in Large-Bowel Surgery, The Netherlands Journal of Surgery, 33(1):3-9.

Utley, RJ and WAAG Macbeth, 1984, Peroperative Cefoxitin, A Double-Blind Prospective Study in the Prevention of Wound Infection, J R Coll Surg Edinb, 29(3):143-6.

Washington, JA, WH Dearing, ES Judd, LR Elveback, 1974, Effect of Preoperative Antibiotic Regimen on Development of Infection After Intestinal Surgery, Prospective, Randomized, Double-Blind Study, Ann Surg, 180(4):567-71.

Wetterfors, J and H Hoejer, 1980, Prophylaxis With Doxycycline (Vibramycin) in Colorectal Surgery, Scand J Gastroenterol, Suppl 59:12–6.