Perioperative Antibiotic Prophylaxis and Antimicrobial Therapy of Intra-Abdominal Infections

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\textbf{Keywords}\nPerioperative antibiotic prophylaxis · Intra-abdominal infections · Antibiotic resistance

\textbf{Summary}\n
\textbf{Background:} The increase of antimicrobial resistances to first- and second-line antibiotics, especially of Gram-negative bacteria, and the lack of novel antimicrobial substances are a challenge in the treatment of intra-abdominal infections. \textbf{Methods:} Review article. \textbf{Results:} The efficacy and safety of perioperative antibiotic prophylaxis in visceral surgery has been demonstrated by several meta-analyses. Perioperative antibiotic prophylaxis is defined as a single administration of antibiotics shortly before a surgical intervention. A so-called prolonged prophylaxis including the postoperative period (e.g. 1–3 days postoperatively) should be avoided as it does not reduce the number of wound infections and is associated with an increased risk of antimicrobial resistance and side effects. Antimicrobial management of severe intra-abdominal infections involves a delicate balance of optimizing empirical therapy which has been shown to improve outcomes while simultaneously reducing unnecessary use of antimicrobials. \textbf{Conclusion:} Antimicrobial resistance poses a serious threat to human health and requires a rational use of antibiotics to curb further spreading. This applies for perioperative prophylaxis as well as for the treatment of intra-abdominal infections.

\textbf{Schlüsselwörter}\nPerioperative Antibiotikaprophylaxe · Intraabdominelle Infektionen · Antibiotikaresistenz

\textbf{Zusammenfassung}\n
\textbf{Hintergrund:} Die Zunahme von Resistzen gegen «Erst- und Zweitlinien-Antibiotika» (z.B. \(\beta\)-Laktam Antibiotika, Fluorchinolone und Aminoglykoside), vor allem von Gram-negativen Erregern, und das Fehlen neuer Substanzen er schwerten die Behandlung von intraabdominellen Infektio nen und stellen eine zunehmende Herausforderung für den Chirurgen im Alltag dar. \textbf{Methoden:} Übersichtsarbeit. \textbf{Ergebnisse:} Die Wirksamkeit und Sicherheit der perioperativen Antibiotikaprophylaxe in der Viszeralchirurgie ist auf breiter Basis durch Metaanalysen abgesichert. Die peri operative Antibiotikatherapie ist definiert als die einmalige Antibiotikagabe kurz vor einem operativen Eingriff. Die über die Operation hinausgehende, sogenannte verlängerte Prophylaxe (z.B. 1–3 Tage postoperativ) soll unterbleiben, da sie in keiner Weise geeignet ist, die Zahl der Wundinfektionen zu verringern, und mit einem erhöhten Resistenz- und Nebenwirkungsrisiko einhergeht. Die Therapie von intraabdominellen Infektionen erfordert eine breite empirische antimikrobielle Therapie, da eine früh zeitige resistentengerechte Therapie mit einer niedrigeren Mortalität einhergeht. Gleichzeitig sollte jedoch der unkritische breite Antibiotikaeinsatz vermieden werden, um die weitere Entwicklung und Ausbreitung von Antibiotikaresistenzen zu verhindern. \textbf{Schlussfolgerung:} Die Zunahme von Antibiotikaresistenzen stellt eine zunehmende Bedrohung dar und erfordert einen rationalen Umgang mit Antibiotika, um die weitere Ausbreitung zu verlangsamen. Dies trifft sowohl für die perioperative Antibiotikaprophylaxe als auch für die Therapie intraabdomineller Infektionen zu.
Perioperative Antibiotic Prophylaxis

In the second national prevalence study on the frequency of healthcare-associated infections and use of antibiotics in Germany, surgical wound infections were the most frequent type of healthcare-associated infections, accounting for 24% of the cases [1]. The wound infection rate after aseptic interventions is in the range of 5%, while it is as high as 40% after abdominal interventions with contamination (colorectal surgery) [2, 3]. Every postoperative infection increases the risk of further complications and the suffering of the individual patient. The efficacy and safety of perioperative antibiotic prophylaxis to reduce surgical wound infections in visceral surgery has been demonstrated by several meta-analyses. Due to the economic burden of postoperative wound infections, perioperative antibiotic prophylaxis is also of major importance as it reduces the duration of the hospital stay by preventing infections. The necessity of outpatient follow-up treatment can also be reduced.

The decision for perioperative antibiotic prophylaxis is made according to a number of risk factors, in particular in aseptic interventions (table 1). The degree of potential contamination of the surgical field (clean, clean-contaminated, contaminated, dirty), prolonged duration of surgery, implantation of biomaterials, and comorbidity need to be considered [4, 5]. Perioperative antibiotic prophylaxis is administered in a risk-adapted individualized manner. The antibiotics selected for prophylaxis must cover the expected pathogens for that operative site, and the choice of antibiotic should take local resistance patterns into account. The broadest experience is in the area of β-Lactam antibiotics [4]. For our own practice, we have developed a recommendation scheme based on the recommendations in the current literature (table 2).

For surgical procedures, intravenous prophylactic antibiotics should be given within 60 min before the skin is incised and as close to the time of incision as practically possible. For operative durations up to 3 h, the one-time administration of an antibiotic (‘single shot’) is sufficient. In prolonged surgery (>3 h) or massive blood loss (>1,500 ml), a repeated intra-operative administration is necessary [6]. Any further administration of antibiotics is defined as treatment, not as prophylaxis [7]. Such prolonged administration is not associated with a reduced wound infection rate. Hirokawa et al. [8] randomly assigned patients undergoing scheduled liver resection to either prolonged postoperative antibiotic prophylaxis for 3 days after the operation or single-shot antibiotic prophylaxis. There were no significant differences between the two groups regarding signs of surgical site infection (10.6 vs. 13.8%, p = 0.66) and remote site infection (2.1 vs. 8.5%, p = 0.1) [8]. In fact, prolonged perioperative antibiotic prophylaxis is associated with an increased risk of Clostridium difficile-associated infection (CDI) and correlates with an increased risk of acquired antibiotic resistance. In a retrospective cohort study with 7,600 episodes of perioperative antibiotic prophylaxis, there were 7,600 episodes of perioperative antibiotic prophylaxis, accounting for 3.6% of the cases [1].

### Patient-related factors
- Age (increase per decennium)
- Diabetes mellitus
- Compromised immunity/immunosuppression
- Poor general condition, malnutrition
- Obesity
- ASA score > II
- MRSA/MSSA carrier
- Fever (1 week preoperatively)
- Women: for interventions on the colon and cardiac surgery
- Hemodialysis
- Hepatitis, cirrhosis
- Stoma
- Drug abuse
- Infections in other locations
- Arterial ischemia
- Peripheral edema
- Lymphangitis
- Neuropathy
- Previous antibiotic treatment
- Smoking
- Left ventricular failure after coronary artery bypass graft
- Bacterial translocation in laparotomy

### Surgery-related factors

#### Preoperatively
- Emergency surgery
- Prolonged preoperative hospitalization
- Wrong choice of perioperative antibiotic prophylaxis
- Wrong timing of perioperative antibiotic prophylaxis
- Wound classified as contaminated/dirty
- Previous radiation therapy
- High-risk surgery
- Reinterventions
- Stones in the biliary duct, biliary duct obstruction
- Elevated C-reactive protein
- Biomaterials implantation
- Shave not immediately prior to surgery
- Preoperative urinary catheter

#### Intraoperatively
- Surgeons’ experience
- Duration of surgery > 2 h (increase per hour)
- Infected surgical field
- Contaminated surgical field
- Blood transfusion, albumin administration
- Prolonged duration of anesthesia
- More than one surgical intervention
- Diathermy
- Decreased oxygen saturation
- Hypothermia
- Wound stapler
- Unpredictable complications
- Surgical technique
- Ineffective blood concentration of the drug
- Conversion from laparoscopy to laparotomy
- Wound contamination with Enterococcus, enterobacteria, Bacteroides fragilis

#### Postoperatively
- Drainage device > 3 days
- Respiratory sepsis
- Invasive interventions, urinary catheter, chest drain, nasal tube, central venous catheter
- Hemodialysis
- Previous reoperation for hemorrhages

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| Patient-related factors | Surgery-related factors |
|------------------------|-------------------------|
| Age (increase per decennium) | Emergency surgery |
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| Poor general condition, malnutrition | Wrong timing of perioperative antibiotic prophylaxis |
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| ASA score > II | Previous radiation therapy |
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1.5% of the patients who received perioperative antibiotic prophylaxis as their only antibiotic treatment developed CDI [9]. Harbarth et al. [10] compared the effect of short (<48 h) versus prolonged (>48 h) perioperative antibiotic prophylaxis on surgical site infections and acquired antimicrobial resistance in an observational 4-year cohort study in 2,641 patients who underwent coronary artery bypass graft surgery. After adjustment for possible confounding factors, prolonged perioperative antibiotic prophylaxis was not associated with a decreased risk of surgical site infections (adjusted odds ratio (OR): 1.2; confidence interval (CI): 0.8–1.6) but was correlated with an increased risk of isolation of enterobacteriaceae or enterococci with acquired resistance to the administered prophylactic agent (i.e. cephalosporins or vancomycin) (adjusted OR: 1.6; CI: 1.1–2.6) [10]. Although evidence shows that prolonged perioperative antibiotic prophylaxis is ineffective in reducing surgical site infections, increases antimicrobial resistance, and aggravates the risk for CDI, this practice is still widespread. In the above-mentioned European Centre for Disease Prevention and Control (ECDC) point prevalence survey of healthcare-associated infections and antimicrobial use in European hospitals, perioperative antibiotic prophylaxis was administered for more than 1 day in 59% of the cases (country range: 10.7–92.3%). Considering Germany alone, more than 70% of all perioperative antibiotic prophylaxis were administered for more than 1 day [1].

As a consequence, the DGAV (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie/German Society for General and Visceral Surgery) has recently developed the following plan [11]:

- Depending on the operation, the proper antibiotic agent needs to be selected with the correct dosage. Thus, on the basis of local resistance patterns, an interdisciplinary group shall determine the drugs for perioperative antibiotic prophylaxis once per year. Interventions for which no antibiotic prophylaxis is required shall also be clearly defined.
- The administration of the perioperative antibiotic prophylaxis shall be the responsibility of the anesthetist. This safeguards that the drugs are reliably administered 60–30 min prior to the intervention.
- For an operative duration of less than 3 h, a single administration of an antibiotic (‘single shot’) is sufficient. Only prolonged operations or massive blood loss justify the repeated intraoperative administration.
- The so-called prolonged prophylaxis beyond the operation (e.g. 1–3 days postoperatively) shall not be administered as it does not reduce the number of wound infections.

The national clinical guideline SIGN 104 – ‘Antibiotic Prophylaxis in Surgery’ – of the Scottish Intercollegiate Guidelines Network provides a very good current overview of perioperative antibiotic prophylaxis (http://sign.ac.uk/guidelines/index.html).

### Intra-Abdominal Infections

Intra-abdominal infections (IAIs) are frequently a challenge for medical professionals in visceral surgery. In Germany, approximately 150,000 patients are being treated for this condition each year [12]. While the lungs are the most frequent focus of infections, IAIs are the second-most frequent type of infections in patients with severe sepsis and septic shock as well as the second-most frequent cause of death from infections in the intensive care unit [13, 14]. Unfortunately, there is no consensus in the literature with respect to the classification of IAIs, and there are different parallel and in some cases overlapping classification systems. The Anglo-American literature in particular distinguishes between uncomplicated and complicated IAIs. According to the guidelines of the Surgical Infection Society (SIS) and the Infectious Diseases Society of America (IDSA), a complicated intra-abdominal infection (cIAI) extends beyond the hollow organ of origin into the peritoneal space and is associated with either abscess formation or peritonitis. Uncomplicated infection involves intramural inflammation of the gastrointestinal tract and has a substantial probability of progressing to complicated infection if
Infections

Antimicrobial Therapy of Intra-Abdominal Perioperative Antibiotic Prophylaxis and prevention of infections requires early recognition of the causative agents and appropriate antimicrobial treatment. Postoperative peritonitis is a polymicrobial infection with facultative aerobic enterobacteriaceae (e.g. Escherichia coli, Klebsiella spp., Citrobacter spp., Enterococcus spp.) and obligate anaerobic bacteria (e.g. Bacteroides spp., Peptostreptococci, Clostridium spp.). Infections originating from the stomach, duodenum, bile ducts, or proximal small intestine are mostly caused by Gram-positive and Gram-negative facultative aerobic bacteria. Infections originating from the ileum are mainly caused by facultative aerobic and obligate aerobic Gram-negative bacteria (such as e.g. Bacteroides fragilis). In case of the colon being the origin, facultative and obligate anaerobic microbes are predominant (often enterococci, most often E. coli) [16].

Antimicrobial management of severe IAI's involves a delicate balance of optimizing empirical therapy, which has been shown to improve clinical outcomes, while at the same time reducing unnecessary use of antimicrobial drugs. The increase of antimicrobial resistances and the lack of novel antimicrobial substances complicate this process. While Methicillin-resistant Staphylococcus aureus (MRSA) was considered to be the biggest challenge in the 1990s, it is now the multiresistant, Gram-negative bacteria and VRE for which the therapeutic options are limited. The development of a new antibiotic drug from bench to bedside takes 8–10 years so that the number of antibiotics will be limited in the near future. Thus, the term ‘postantibiotic era’ is increasingly used [18].

MRSA (Methicillin-Resistant S. Aureus)

Worldwide, infections with MRSA are decreasing or stagnant. In a current study, Meyer et al. [19] have analyzed data from the German hospital infection surveillance system (KISS) between 2007 and 2012. They found a significant decrease from 33 to 27% of the MRSA proportion in hospital-acquired S. aureus infections. Current data from the USA report about a decrease of 31% of invasive MRSA infections between 2005 and 2011. In the UK, a decrease of 69% could be found and was thus even more pronounced. The reasons for the decrease are unclear. They are possibly due to interventions and/or may be related to the biology of the microbes [19]. As opposed to respiratory and wound infections, MRSA has a minor impact in IAI's. According to the IDSA guideline for IAI's, empiric antimicrobial coverage directed against MRSA should only be provided to patients with healthcare-associated IAI's who are known to be colonized with the organism or who are at risk of having an infection due to this organism because of prior treatment failure and significant antibiotic exposure. Vancomycin is recommended for the treatment of suspected or proven IAI's due to MRSA [14]. Besides vancomycin, tigecycline is approved for IAI's, and there exist several meta-analyses on its efficacy in IAI's (table 3). Practical experience also shows that tigecycline, when given alone or in combination with other antibacterial drugs, appears to be efficacious against multiple pathogens, with clinical response rates in approximately 80% of the patients with cIAI [20].
**ESBL-Expressing Enterobacteriaceae**

Members of the family enterobacteriaceae commonly express plasmid-encoded β-lactamases (e.g. TEM-1, TEM-2, and SHV-1), which confer resistance to penicillins but not to expanded-spectrum cephalosporins (e.g. third-generation cephalosporins). In 1979, however, a new group of enzymes, the extended-spectrum β-lactamases (ESBLs), was first detected. ESBLs are β-lactamas that hydrolyze these expanded-spectrum cephalosporins in addition to other penicillins. Because they are located on plasmids, ESBLs are interchangeable between Gram-negative bacteria. Very broad antibiotic resistance of ESBL-producing bacteria extends to multiple antibiotic classes, including fluoroquinolones and aminoglycosides, has become an increasing problem in Europe as well as worldwide over the last decade. As a result, carbapenems, ticycycline, and colistin are often the only remaining treatment options. The proportion of ESBL-producing *E. coli* and *Klebsiella* spp. has increased from less than 1% to more than 20% in many places. The excess use of third-generation cephalosporins and fluoroquinolones appears to promote the prevalence of ESBL. Risk factors for an ESBL infection are in particular hospitalization and a stay in the intensive care unit, residence at a nursing home, central venous catheter, urinary catheter, and chronic hemodialysis [21].

**Carbapenemase-Producing Bacteria**

The spread of carbapenem-non-susceptible bacteria, more specifically of carbapenemase-producing enterobacteriaceae and carbapenem-resistant *Acinetobacter baumannii*, is a threat to healthcare and patient safety worldwide. In particular, *Klebsiella pneumoniae* carbapenemases (KPC) have spread globally in countries where carbapenemase-producing bacteria are endemic (e.g. Greece, Italy, Israel) it is well known that especially *K. pneumoniae* has a high potential for transmission within hospitals. This is confirmed by a recently terminated outbreak at the university hospital in Leipzig. There, the largest KPC outbreak reported in Germany so far occurred between July 2010 and June 2013 when a total of 103 patients were either colonized (58%) or infected (42%) with KPC-2-producing *K. pneumoniae* (KPC-2-KP). The outbreak was caused by the admission of a 66-year-old patient who was transferred from a hospital in Rhodes (Greece) where he had contracted a hospital-acquired pneumonia. There, KPC-producing *Klebsiella* species are highly endemic. Molecular genetic testing suggested that in individual cases a single night in a room with multiple patients of whom one was later tested positive for KPC was sufficient for microbe transmission to other patients. In a matched-pair analysis, the clinical data of 9 KPC-positive liver transplant recipients (LTR) have been compared with the data from 18 KPC-negative LTRs. 89% of the KPC-positive LTRs developed infections with KPC-2-KP (pneumonia: 4/9, peritonitis: 2/9, postoperative wound infection: 2/9), and 56% (5/9) had a positive blood culture. The univariate analysis showed a significant difference in in-hospital mortality, with increased mortality in the KPC-positive LTRs (78 vs. 11%, p = 0.001) and a relative risk of death related to KPC-2-KP infection of 7.0 (95% CI: 1.8–27.1) [24, 25].

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**Table 3. Overview of new antibiotics effective against MRSA**

| Class                  | Linezolid          | Tigecyclin       | Daptomycin      | Ceftarolin       |
|------------------------|--------------------|------------------|-----------------|-----------------|
| Bioavailability after oral application | oxazolidinone almost 100% | glycyclcline i.v. only | lipopeptides i.v. only | group 5 cephalosporin i.v. only |
| Mechanism of action | protein synthesis | protein synthesis | membrane pores | blocking of cell wall synthesis |
| Effect                  | bacteriostatic     | bacteriostatic   | bacterialid     | bacterialid      |
| Spectrum                | Gram-positive      | Gram-positive and Gram-negative (not Pseudomonas spp. and Proteus spp.) | Gram-positive | Gram-positive (not ESBL and non-fermter, such as Pseudomonas aeruginosa) |
| Side effects            | thrombocytopenia, polynepathy | nausea, vomiting | rhabdomyolysis, eosinophilic pneumonia | nausea, vomiting |
| Approved indications    | pneumonia, cSSSIa  | cSSSIa, intra-abdominal infections | cSSSIa, (right ventricular) endocarditis from MRSA, MRSA bacteremia | community-acquired pneumonia (non-MRSA), cSSSIa |

*Complicated skin and skin structure infections.*
Vancomycin-Resistant Enterococci (VRE)

The clinical relevance of detection of enterococci in patients with IAI is discussed controversially. In general, enterococci are less virulent than enterobacteriaceae. Detection of enterococci in tracheal aspirate, for example, is generally considered as colonization only. However, detection of the species in sterile samples should generally lead to targeted therapy. In most cases, only linezolid, tigecycline, and daptomycin can be used against VRE (usually Enterococcus faecium). Table 4 shows clinical constellations requiring calculated treatment that is effective against enterococci [14].

Candida Species

Similar to enterococci, Candida is not to be considered necessarily as a pathogen in IAI. Candida spp. are cultured from 20% of the patients with acute perforations of the gastrointestinal tract. Even when there is evidence of fungi, antifungal agents are unnecessary in adults unless the patient has recently received immunosuppressive therapy for a neoplasm, has a perforation of a gastric ulcer on acid suppression, or shows malignancy, inflammatory disease, or postoperative or recurrent IAI. Fluconazole is an appropriate choice for treatment if Candida albicans is isolated. For fluconazole-resistant Candida species, treatment with an echinocandin (caspofungin, micafungin, or anidulafungin) is appropriate. For the critically ill patient, initial treatment with an echinocandin instead of a triazole is recommended [14]. In case of candidemia, all catheters should be changed, a fundoscopy should be performed in all cases as there are frequently septic abscesses, and treatment should be continued for at least 14 days after the first negative blood culture. In the case of organ involvement, a 12-week treatment is the standard [26].

Calculated Treatment

It is impossible to give general recommendations concerning the selection of a certain class of antimicrobial chemotherapeutics since all available clinical trials were designed to prove noninferiority to the comparator product and because of heterogenous clinical study data [16]. Nevertheless, several societies developed guidelines and recommendations based on the multitude of clinical trials investigating antimicrobial chemotherapeutics. Amongst others, the Paul Ehrlich Society/Infektliga have developed recommendations for antibiotic treatment based on American guidelines [21]. For secondary peritonitis, there are the following scenarios:

- Locally contained situation, sterile or low number of microbes, clear or slightly frothy secretions (e.g. acute gastric perforation, acute cholecystitis, acutely perforated appendicitis): aminopenicillin/BLI or acylaminopenicillin/BLI; alternatives: cephalosporin group 2 + metronidazole, cephalosporin group 3a + metronidazole, carbapenem group 2. Duration of treatment: Short-term treatment (1–2 days) often sufficient.
- Diffuse peritonitis, duration of the peritonitis >2–4 h, medium number of microbes, frothy/fecal secretions: acylaminopenicillin/BLI, cephalosporin group 2, cephalosporin group 3/4, or fluoroquinolone group 2, each with metronidazole; fluoroquinolone group 4; tigecycline. Duration of treatment: 5–7 days depending on clinical and microbiological findings and organ function (bowel).
- Postoperative peritonitis: carbapenem group 1/2, acylaminopenicillin/BLI, cephalosporin group 4, with metronidazole; tigecycline. Duration of treatment: 10–14 days.

Patient-specific risk factors including severe comorbidities, previous antibiotic treatment (last 3 months), duration of preoperative hospitalization, travel history, known colonization with multiresistant microbes, and local resistance patterns have to be considered when making individual choices in the initial empiric treatment. The risk of developing resistance should be reduced by a so called de-escalation treatment: following initial broad, calculated antibiotic treatment, this will be changed to a narrow-spectrum antibiotic according to the microbiological findings. Empiric coverage of Enterococcus and empiric antifungal therapy for Candida are both not recommended in patients with community-acquired IAI. Antifungal therapy for patients with severe community-acquired or healthcare-associated infection is recommended if Candida is grown from intra-abdominal cultures. For the critically ill patient, initial therapy with an echinocandin instead of a triazole is recommended [14].

Table 4. Clinical constellations requiring calculated treatment effective against enterococci (modified according to [14])

| Clinical constellation                                           | Calculated treatment                                      |
|----------------------------------------------------------------|------------------------------------------------------------|
| Enterococcus faecalis                                           | amoxicillin/ampicillin; piperacillin (/tazobactam); imipenem |
| + VRE                                                           | linezolid, tigecycline, daptomycin                          |

VRE = Vancomycin-resistant enterococci.
Conclusion

Antimicrobial management of severe IAIs involves a delicate balance of optimizing empirical therapy, which has been shown to improve clinical outcomes, while at the same time reducing unnecessary use of antimicrobial drugs to curb further spreading of antimicrobial resistance. For the same reason, prolonged perioperative antibiotic prophylaxis should be particularly avoided as it is not associated with a reduced wound infection rate but an increased risk for CDI and acquired antibiotic resistance.

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