Abstract
The management of severe intra-abdominal infections remains a major challenge facing surgeons and intensive care physicians, because of its association with high morbidity and mortality. Surgical management and intensive care medicine have constantly improved, but in the recent years a rapidly continuing emergence of resistant pathogens led to treatment failure secondary to infections with multi-drug resistant bacteria. In secondary peritonitis the rate of resistant germs at the initial operation is already 30%. The lack of effective antibiotics against these pathogens resulted in the development of new broad-spectrum compounds and antibiotics directed against resistant germs. But so far no “super-drug” with efficacy against all resistant bacteria exists. Even more, soon after their approval, reports on resistance against these novel drugs have been reported, or the drugs were withdrawn from the market due to severe side effects. Since pharmaceutical companies reduced their investigations on antibiotic research, only few new antimicrobial derivates are available.

In abdominal surgery you may be in fear that in the future more and more patients with tertiary peritonitis secondary to multi-drug resistant species are seen with an increase of mortality after secondary peritonitis.

This article reviews the current treatment modalities for complicated intra-abdominal infections with special reference to the antibiotic treatment of complicated intra-abdominal infections with multi-drug resistant species.

Key words: antibiotic treatment, multi-drug resistance, intra-abdominal infection

Abbreviations:
cIAI Complicated intra-abdominal infection
ESBL Extended spectrum β-lactamase
IAI Intra-abdominal infection
ICU Intensive care unit
MRS A Methicillin resistant staphylococcus aureus
SP Secondary peritonitis
spp. Species
TP Tertiary peritonitis
VRE Vancomycin resistant Enterococcus

Historical Background
One-hundred years ago complicated intra-abdominal infections (cIAIs) were associated with mortality rates of 90% [1]. During the last century more aggressive surgical methods, intensive care management and the availability of a large diversity of differently acting antibiotics have reduced mortality below 25% [2]. But at the end of the first decade of the 21st century cIAIs remain responsible for 20% of severe sepsis in intensive care units (ICU). Thus cIAIs represent the second common cause for infectious morbidity and mortality after pneumonia [3, 4].

The treatment of cIAI is based on a few simple principles, including focus elimination, lavage concepts, intensive care medicine and application of antibiotics [5]. While innovative surgical techniques and intensive care management constantly improved treatment modalities for critical ill patients, the development of new potent antibiotics was unable to follow the rapidly increasing number of resistant germs [6-8]. To assure the high quality in the management of cIAIs, surgeons will need substantial help of new antimicrobial compounds.

Classification
Complicated intra-abdominal infections are usually defined as abscess formation or peritonitis beyond the origin of the perforation of a hollow viscus into the peritoneal cavity, requiring an invasive procedure for source control [9]. Although the term intra-abdominal infection (IAI) is often synonymously used with the term peritonitis, there is a wide variation in the severity of illness for the different forms and origins of peritonitis. The mortality for patients with appendicitis ranges between 5% and 9%, while the mortality for gastric ulcer perforation is 21% and ranges from 45% to 50% for large bowel perforation or peritonitis originating from the biliary tract [1, 10, 11].

Peritonitis includes the local reaction of the organ “peritoneum” and the patients’ systemic inflammatory response to micro-organisms and their toxins. Thus, peritonitis needs a clear differentiation from bacterial contamination, e.g. in acute cholecystitis or gan-
genuous appendicitis, where local spillage of bacteria into the abdominal cavity occurs, but infection is not established.

Usually peritonitis is classified into primary, secondary (SP) and tertiary peritonitis (TP); (Table 1, forms of peritonitis) [12]. Primary peritonitis, also referred to as spontaneous peritonitis, arises without derangement of anatomical barriers and has a low incidence on surgical wards.

The most frequent entity is SP, which is defined as infection of the peritoneal cavity resulting from perforation, breakdown of an intestinal anastomosis, ischamnic necrosis or other injuries of the gastro-intestinal tract [12]. According to the mode of acquisition SP is divided into community-acquired and hospital associated infections. Community-acquired peritonitis is associated with bacterial stains originating from the source of the infection, although today community acquired infections with resistant species are a common and serious problem [13]. Usually patients with health care associated peritonitis have a higher probability of infections with opportunistic nosocomial facultative pathogenic bacteria and fungi. The diversity of different micro-organisms isolated in nosocomial infections is higher, while susceptibility among these strains is lower compared to community-acquired infections [14].

TP is less common and is defined as a severe or recurrent or persistent IA after apparently successful and adequate surgical source control of SP [12]. TP is always a nosocomial infection, typically associated with high morbidity and mortality due to prolonged systemic inflammation, systemic inflammatory response syndrome, sepsis, severe sepsis or septic shock [15, 16]. While the mortality of SP is less than 25 %, mortality for patients with TP is higher than 50 % [8, 17, 18]. Although the reasons for the development of TP are not completely understood, the high mortality in TP may reflect its association with more virulent species. Figure 1 illustrates the infection source of patients who developed TP after successful treatment of SP (Fig. 1, causes for SP and TP in surgical ICU patients) [18].

**Type of Infection and Mode of Acquisition Indicates Pathogens**

Primary peritonitis is usually a mono-microbial infection with Gram-positive Cocci or Enterobacteriaceae. The etiology implies a conservative management, since primary peritonitis occurs spontaneously without perforation of a hollow viscus [19].

The species in SP and TP most frequently represent mixtures of Gram-positive and Gram-negative aerobes and anaerobes as well as fungi in certain cases of TP or in patients with immune suppression [20, 21]. In community-acquired SP facultative and obligate aerobic Gram-negative and Gram-positive organisms must be considered in infections originating from the stomach, duodenum, biliary system and the small bowel (Table 2, Micro-organisms in peritonitis) [20, 22]. Ulcer perforations are usually associated with infections with E. coli

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**Table 1.** Forms of peritonitis, according to [12].

| Causes of peritonitis                                                                 | Most common bacterial species                                      |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| Primary bacterial peritonitis Peritoneal infection without anatomic barrier disruption; most common in patients with cirrhosis or severe immune dysfunction or early childhood | Gram negative Enterobacteriaceae, Streptococcus spp.                |
| Secondary bacterial peritonitis Peritoneal infection with perforation of the gut wall and spillage of bacteria into the peritoneal cavity. This peritonitis may be health care associated or community-acquired | Polymicrobial infection with Gram-negative Enterobacteriaceae, Gram-positive Enterococci, Staphylococci and anaerobes |
| Tertiary peritonitis Persistent or recurrent infection after "adequate" treatment of primary or secondary peritonitis; most common in patients with severe co-morbidities or compromised immune function | Polymicrobial infections like in secondary peritonitis, but more likely to involve resistant bacteria |

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**Fig. 1.** Causes for SP and TP in surgical ICU patients, modified by [18]. Infection source for patients with SP at the index operation, who further developed TP (n = 15, red bars) and for patients who did not (SP, n = 54, yellow bars).
or Streptococci. Typical bacteria in biliary tract associated SP are E. coli, Klebsiella spp. and Enterococci. In small bowel derived infections gram-negative aerobes and anaerobes are the most frequent pathogens. For infections originating from the colon all kinds of different aerobes and anaerobes must be considered.

The microbial flora encountered in healthcare associated IAs and TP includes the same species as community-acquired SP with a shift towards opportunistic, nosocomial facultative pathogens and fungi. Frequent isolates include Enterobacteriaceae with extended spectrum β-lactamase (ESBL), Pseudomonas aeruginosa, Enterobacter spp., Enterococci, Methicillin resistant staphylococcus aureus (MRSA), Acinetobacter spp., Morganella morganii, Stenotrophomonas, coagulase-negative Staphylococci and different forms of Candida. Compared to community-acquired peritonitis the amount of micro-organisms with resistance mechanisms is higher among these species (Fig. 2, germs in SP and TP) [18].

### Table 2. Micro-organisms in peritonitis, according to [20].

| Micro-organisms       | Gastro-duodenal | Biliary tract | Small or large bowel | Appendicitis | Abscess | Liver | Spleen |
|-----------------------|-----------------|---------------|----------------------|--------------|--------|-------|--------|
| **Common aerobes**    |                 |               |                      |              |        |       |        |
| Gram-positive         |                 |               |                      |              |        |       |        |
| Streptococcus spp.    | X               | O             | Ø                    | Ø            | Ø      | Ø     | X      |
| Enterococcus spp.     | Ø               | X             | Ø                    | Ø            | X      | X     | Ø      |
| Staphylococcus spp.   | Ø               | X             | Ø                    | Ø            | Ø      | Ø     | X      |
| Gram-negative         |                 |               |                      |              |        |       |        |
| E. coli               | X               | X             | X                    | X            | X      | X     | Ø      |
| Enterobacter spp.     | Ø               | O             | Ø                    | Ø            | Ø      | Ø     | Ø      |
| Pseudomonas spp.      | Ø               | X             | X                    | Ø            | X      | X     | Ø      |
| Klebsiella spp.       | Ø               | Ø             | X                    | Ø            | Ø      | Ø     | Ø      |
| Proteus spp.          | Ø               | Ø             | X                    | Ø            | Ø      | Ø     | Ø      |
| Other                 | Ø               | Ø             | Ø                    | Ø            | Ø      | Ø     | Ø      |
| **Common anaerobes**  |                 |               |                      |              |        |       |        |
| Bacteroides spp.      | Ø               | Ø             | Ø                    | X            | X      | X     | (X)    |
| Clostridium spp.      | Ø               | Ø             | Ø                    | Ø            | X      | Ø     | Ø      |
| Anaerobe Cocci        | Ø               | Ø             | Ø                    | (X)          | Ø      | Ø     | Ø      |

**Legends:** X = most frequent species; Ø = usually not present; (X) = rarely present

Resistant Germs

One reason for the progressive amount of antibiotic resistance among bacteria is the inadequate and inappropriate use of antibiotics, as well as an increasing number of patients with severe co-morbidities. Today, patients often have a history of previous hospitalisation and broad-spectrum antibiotic exposure with selection of resistant pathogens [23]. Therefore, the rate of resistant micro-organisms in patients with hospital acquired SP ranges between 37 % and 70 % [24]. Several risk factors for infections with MDR germs have been identified (Table 3, risk factors for multi-drug resistance) [25-28].

At the end of the 20th century most resistant species were found among Gram-positive bacteria, including MRSA and Vancomycin resistant Enterococci (VRE). In the last decade a shift towards a higher frequency of resistant Gram-negative bacteria occurred, especially among Enterobacteriaceae producing ESBL.
Figure 3 illustrates the development of resistant species in a surgical ICU (Fig. 3, surgical ICU resistance development).

A high prevalence for MRSA infections is observed in skin and soft structure infections, as well as in post-operative wound infections, while sepsis secondary to MRSA is most frequent in pneumonia and primary bacteremia [30-32]. Although less common in cIAIs, infections with MRSA should be considered in patients colonized with MRSA, hospital-acquired SP or TP or if risk other factors are present [26, 33].

Enterobacteriaceae are the most frequent isolates in cIAI and usually represent susceptible micro-organisms. Prior antibiotic therapy affects the development of ESBL, which is responsible for MDR, especially among Klebsiella spp., E. coli and Proteus spp. [29, 34, 35].

Enterococci are frequently isolated in patients with cIAIs. The need for specific therapy against Enterococci in SP has been discussed controversially, but isolation in ICU patients with health care associated SP or TP should always imply antibiotic treatment according to resistance analyses [36-40].

Pseudomonas aeruginosa is a common pathogen in pneumonia and in ICUs, but has also been frequently isolated in patients with appendicitis and peritoneal dialysis [4, 41, 42]. Although less frequent, the Gram-negative species Stenotrophomonas maltophilia, Morganella morganii and Acinetobacter spp. are responsible for a substantial part of MDR isolates in cIAIs [43].

Infections with fungi are less common in community-acquired infections, but should always be suspected in patients with immunodeficiency and prolonged antibacterial exposure [44].

**RISK FACTOR ANALYSES**

Infections with MDR pathogens are associated with a higher rate of treatment failure and mortality, but several other factors affect patients’ outcome (Table 4, Risk factors for treatment failure or death) [9, 14, 20, 45, 46]. The only risk factor that is not based on patients’ physiologic constitution is an unsuccessful operation. Thus, the inability to achieve adequate source control is predictive of mortality [2, 45, 47, 48]. Therefore, the fundamental basis in the treatment of cIAIs remains a successful operation, while intensive care management and antibiotic therapy are essential for post-operative stabilisation and final outcome of the individual patient.

The goal of patient adapted individual risk stratification should be to select a suitable antibiotic therapy to avoid the dilemma to be confronted with resistant micro-organisms after the return of the results from the microbiology. Therefore, assuming the patients risk for treatment failure is mandatory to optimise the individual initial treatment plan.

**ANTIBIOTIC TREATMENT OPTIONS**

For the antibiotic therapy of cIAIs a broad coverage against Gram-negative and Gram-positive species is generally recommended, but several treatment regimens lack activity against MDR bacteria. New antibiotics, with a narrower spectrum with special activity...
Table 5. Antimicrobial agents against MDR pathogens, modified by [49].

|                      | MRSA | VRE | ESBL | Acinetobacter | Pseudomonas aeruginosa |
|----------------------|------|-----|------|---------------|------------------------|
| Ampicillin/Sulbactam | Ø    | Ø   | X    | Ø             | Ø                      |
| Piperacillin/Sulbactam| Ø    | Ø   | X    | (X)           | X                      |
| Glycopeptides (Vancomycin) | (X) | Ø   | Ø    | Ø             | Ø                      |
| Streptogramins (Quinupristin) | X   | X   | Ø    | Ø             | Ø                      |
| Lipopeptides (Daptomycin) | X   | X   | Ø    | Ø             | Ø                      |
| Oxazolidinones (Linezolid) | X   | X   | Ø    | Ø             | Ø                      |
| β-lactams (Ceftobiprole) | X   | (X) | X    | Ø             | Ø                      |
| Carbapenemes (Doripenem) | (X) | (X) | X    | (X)           | X                      |
| Glyceleyclene (Tigecycline) | X   | X   | X    | (X)           | Ø                      |
| Quinolones           | Ø    | Ø   | (X)  | (X)           | (X)                    |

Legends: X = effective; Ø = not effective; (X) = partial activity

Table 6. Antibiotic treatment recommendations, according to [65].

| Diagnosis               | Monotherapy                                      | Combination therapy                                      |
|-------------------------|--------------------------------------------------|---------------------------------------------------------|
| Secondary peritonitis   |                                                   |                                                         |
| low risk (localised peritonitis) | Ampicillin/Sulbactam | 2nd generation Cephalosporin + Metronidazol |
|                         | Carbenem                                          | 3rd generation Cephalosporin + Metronidazol             |
| low risk (diffuse peritonitis) | Ampicillin/Sulbactam | 2nd generation Fluoroquinolone + Metronidazol |
|                         | Piperacillin/Tazobactam                           | 3rd or 4th generation Cephalosporin + Metronidazol     |
|                         | Carbenem (group 1/2)                             |                                                         |
|                         | Fluoroquinolone 4th generation                    |                                                         |
|                         | Tigecyclin                                        |                                                         |
| High risk               | Piperacillin/Tazobactam                           | 4th generation Cephalosporin + Metronidazol            |
|                         | Carbenem (group 1/2)                             |                                                         |
|                         | Tigecyclin                                        |                                                         |
| Tertiary peritonitis    | According to resistance from microbiology         | Antifungal therapy in high risk patients                |

against MRSA and VRE have been developed, including quinupristin, daptomycin and oxazolidinones [49-51]. While these drugs offer a new opportunity in the treatment of infections with these difficult to treat organisms, they have no activity against Gram-negative bacteria. But especially among Gram-negative bacteria the amount of resistant microorganisms producing ESBL increases constantly, while the rate of infections with MRSA remains stable (Fig. 3, surgical ICU resistance development).

New drugs with activity against Gram-positive and Gram-negative resistant germs with special coverage of ESBL include Tigecycline and 4th generation β-lactam antibiotics [52-55]. Both derive have broad spectrum activity against most pathogens commonly associated with cIAIs, but they do not have a reliable activity against pseudomonas aeruginosa [56, 57].

Although all these novelties offer an alternative in the presence of MDR species, each derivate has a weak point and no compound is able to cover all resistant pathogens (Table 5; Antimicrobial agents against MDR pathogens) [50, 58, 59]. In high risk patients with nosocomial cIAIs the empiric antimicrobial therapy should therefore be selected after consideration of the likelihood of difficult-to-treat isolates [60].

The only derivatives with broad coverage against the expected flora in SP are Carbapenemes, β-lactam antibiotics and tigecycline, since they provide coverage against both, Gram-negative and Gram-positive species. None of the new derivatives with special activity against infections with MRSA and VRE (daptomycin and linezolid) covers ESBL, while Enterobacteriaceae with ESBL can be treated with Ampicillin/Sulbactam or Piperacillin/Tazobactam. Carbapenemes and 4th generation β-lactam antibiotics have no reliable activity against VRE and MRSA. The only derivate covering MRSA, VRE and ESBL is tigecycline. The weak point of tigecycline is the lacking activity against Pseudomonas aeruginosa, while treatment with Carbapenemes and Piperacillin/Sulbactam is effective against Pseudomonas aeruginosa.

TREATMENT RECOMMENDATION

Guidelines aimed at simplifying the antibiotic choice according to the severity of illness, but in fact most guidelines do not consider that there is a vast diversity of differently acting antibiotics [9, 61]. Most antibiotics are effective in preventing post-operative complications following peritonitis, but there is no evidence
physicians will be confronted with an increasing rate of resistant micro-organisms with a decreasing number of antibiotics. A major concern in the future will be that surgeons and intensive care medicine do not need a substantial change. However, the third part in the treatment of SP, the use of antibiotics, has to be improved. Since the rate of resistant bacteria in SP is 30% - 40%, physicians should use the vast diversity of differently acting antibiotics to optimise the therapy of patients with SP [14]. Therefore, the initial treatment of patients at risk for infections with MDR germs should include a broad spectrum antibiotic, covering the most frequent resistant bacteria in SP.

Tertiary peritonitis still is a major problem in ICU patients and is associated with unsatisfactory too high morbidity and mortality. Patients at risk for the development of TP have a high Mannheim peritonitis index at the index operation and higher SAPS II scores during ICU stay [18]. The treatment strategy for patients with TP consists in antibiotic and antifungal therapy in accordance to the resistance analyses from the microbiology.

The best description for the antibiotic treatment in the future has been summarized by the “Tarragona strategy” (Table 7, “Tarragona strategy”) [67]. The initial empiric antibiotic therapy should be calculated according to the hospital specific surveillance data. The antibiotic choice should be selected out of the vast diversity of differently acting antibiotic agents to reduce the selection pressure.

The “Tarragona strategy” in detail:

**Hit hard and early.** The initial therapy should include high doses of broad spectrum antibiotics, even if the costs are expensive. Initial therapy should be initiated as soon as possible.

**Look at your patient.** In patients with community-acquired secondary peritonitis antibiotic therapy should cover Enterobacteriaceae and anaerobes. In patients with post-operative SP a shift towards more resistant species has to be expected including Gram-negative and Gram-positive species with MDR (ESBL, VRE, MRSA). The highest risk for infections with MDR pathogens exists in patients with serious co-morbidities, a recent surgical history or prior broad spectrum antibiotic therapy. Therefore, the choice of cheaper antibiotics should be reserved for “healthy” patients without serious co-morbidities.

**Listen to your hospital.** Antibiotic treatment modalities need a regular update according to the hospital specific surveillance data. Use broad spectrum antibiotics with wide coverage.

### Summary and Conclusions

In ICU patients the increasing rate of infections with resistant bacteria and fungi is a serious problem. In addition to the control of vital parameters and organ function during ICU stay, the interpretation of resistance analyses from the microbiology is getting more important than it was in the past. To assure patients’ survival after a successful operation surgeons and intensive care physicians must be aware of the diversity of resistant bacterial species and fungi to choose the best antimicrobial agent out of the different classes of antibiotics. A major concern in the future will be that physicians will be confronted with an increasing rate of resistant micro-organisms with a decreasing number of new antibiotic agents.

At the moment the two principles surgical treatment and intensive care medicine do not need a substantial change. However, the third part in the treatment of SP, the use of antibiotics, has to be improved.

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**Listen to your hospital.** Antibiotic treatment modalities need a regular update according to the hospital specific surveillance data. Use broad spectrum antibiotics with wide coverage.

### Table 7. “Tarragona strategy”, according to [66].

| Tarragona strategy | Antibiotic treatment recommendations |
|--------------------|-------------------------------------|
| **Look at your patient** | The choice for a certain antibiotic treatment should be based on individual patients’ risk factors |
| **Listen to your hospital** | Knowledge of the actual hospital specific surveillance data is essential for the antibiotic choice |
| **Hit hard and fast** | The therapy should be initiated immediately and be broad enough to reach the vast majority of likely pathogens |
| **Get to the point** | Select antibiotics with pharmacokinetic and -dynamic properties to reach effective concentration at the side of infection |
| **Focus, focus, focus** | Re-evaluation of the initial therapy after 3 days, depending on the results from the microbiology, providing the option of de-escalation to reduce selection pressure and costs |

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**Listen to your hospital.** Antibiotic treatment modalities need a regular update according to the hospital specific surveillance data. Use broad spectrum antibiotics with wide coverage.
Focus, focus, focus. De-escalation is indicated in stable patients in accordance to the results from the microbiology to avoid prolonged antibiotic exposure. Use the whole diversity of differently acting antibiotics to reduce the selection pressure among pathogens.

Successful treatment of CIAIs is based on the three important columns: focus elimination, intensive care management and antibiotic therapy. Resistance analyses of microbiological culture results became more important, since the rate of MDR micro-organisms increased rapidly. Intensive care physicians and surgeons must be aware of the diversity of different antibiotic classes to choose an appropriate initial therapy, based on patients’ risk factors and hospital specific resistance rates. Immediate and appropriate application of antimicrobial agents is mandatory to avoid treatment failure and the development of new resistance. Further investigation from the pharmaceutical industry for the development of new antibiotics is essential to assure effective treatment options in the future. Otherwise we will end up in an a-antibiotic time.

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