Review

Treatment of Complicated Intra-abdominal Infections in the Era of Multi-drug Resistant Bacteria

T. Herzog, A. M. Chromik, W. Uhl

Department of Surgery, St. Josef Hospital, Ruhr University Bochum, Germany

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more, soon after their approval, reports on resistance against these novel drugs have been reported, or the drugs were withdrawn from the market due to severe side effects.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 ß-lactamase
IAI	Intra-abdominal infection
ICU	Intensive care unit
MRSA	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-

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

grenous 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, ischemic 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 IAI 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

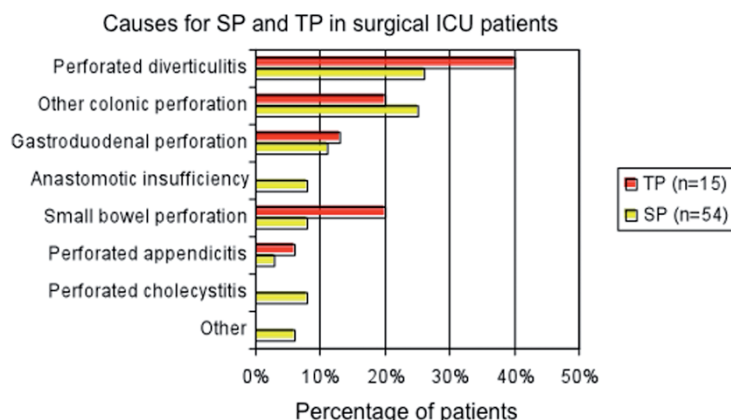Causes for SP and TP in surgical ICU patients

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).

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

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

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

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 health care associated IAIs 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].

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
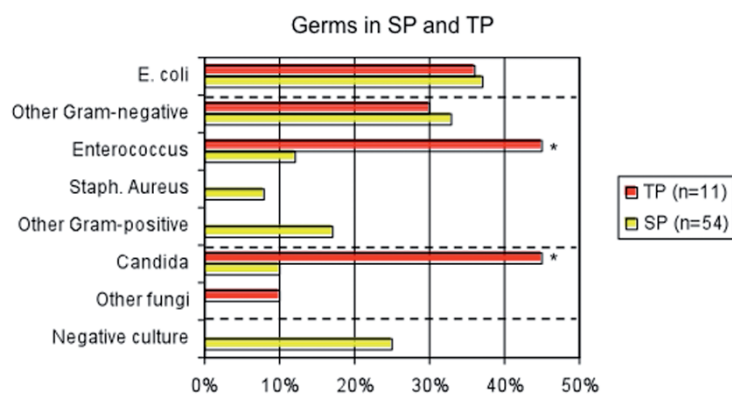

Fig. 2. Germs in SP and TP, modified by [18]. Microbiological isolates in TP (n = 11, red bars), vs. SP (n = 54, yellow bars). The microbial isolates of TP were obtained from the re-laparotomy that was diagnostic for TP. Isolates of SP were obtained at the index operation. The rate of Enterococcus and Candida was significantly higher in TP vs. SP (*$p \leq 0.05$).

Table 3. Risk factors for MDR, modified by [24-27].

Risk factors for multi drug resistance

- High APACHE II score
- Longer preoperative hospitalisation
- Health care associated peritonitis
- Prior antibiotic treatment
- Longer postoperative antibiotic treatment
- Postoperative changes in antibiotic treatment
- Longer postoperative hospitalisation

Table 4. Risk factors for treatment failure or death, modified by [9 20].

Independent risk factors for treatment failure or death in patients with cIAIs

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- High APACHE II score
- Advanced age
- Malnutrition (Hypoalbuminemia, Hypocholesterolemia)
- Preoperative organ impairement (Liver disease, Cardiovascular disease, Renal disease)
- Malignancy
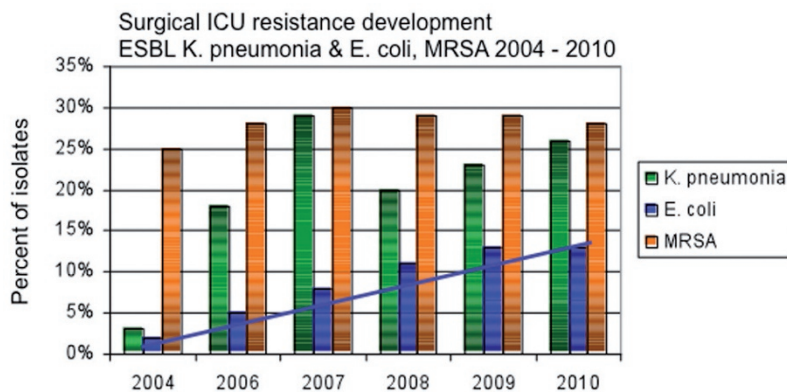- Corticosteroid therapy (Status post transplantation)
- Unsuccesful operation

Fig. 3. Surgical ICU resistance development. Percentage of resistant pathogens among isolates. The blue line indicates the increasing rate of ESBL producing E. coli (blue bars), while the rate of ESBL producing Klebsiella pneumonia (green bars) and MRSA (orange bars) remains stable. (Own data, surgical ICU, St. Josef Hospital Bochum; Department for Medical Microbiology, University of Bochum).

[29]. 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 postoperative 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 affronted 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
Ampicilin/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
ß-lactams (Ceftobiprole)	X	(X)	X	X	Ø
Carbapenemes (Doripenem)	(X)	(X)	X	(X)	X
Glycylcycline (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].

	Monotherapy	Combination therapy
Diagnosis		
Secondary peritonitis		
low risk (localised peritonitis)	Ampicillin/Sulbactam Carbapenem	2nd generation Cephalosporin + Metronidazol 3rd generation Cephalosporin + Metronidazol
low risk (diffuse peritonitis)	Ampicillin/Sulbactam Piperacillin/Tazobactam Carbapenem (group 1/2) Fluorochinolon 4th generation Tigecyclin	2nd generation Fluorochinolon + Metronidazol 3rd or 4th generation Cephalosporin + Metronidazol
High risk	Piperacillin/Tazobactam Carbapenem (group 1/2) Tigecyclin	4th generation Cephalosporin + Metronidazol
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 micro-organisms 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 derivates 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 derivates with broad coverage against the expected flora in SP are Carbapenems, β-lactam antibiotics and tigecycline, since they provide coverage against both, Gram-negative and Gram-positive species. None of the new derivates 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/Tazobac. Carbapenems 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 Carbapenems 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

Table 7. "Tarragona strategy", according to [66].

Tarragona strategy	
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

to support that one regimen is superior to another. Controversially, regularly changes between the different compounds according to the hospital specific epidemiology are essential to avoid the development of resistant germs [62]. The initial empiric antibiotic therapy should be initiated immediately. Any delay of appropriate antibiotic treatment increases the probability of mortality [63-65].

Low risk patients with community-acquired SP still represent the largest group of patients with cIAIs. According to the intra-operative findings these patients should receive "narrow spectrum" agents, e.g. ampicillin/sulbactam or a 3rd generation cephalosporines/fluorochinolones and metronidazol for one or two days, if the peritonitis is localized and source control is assured. When peritonitis is diffuse, piperacillin/tazobactam, 3rd generation cephalosporines/fluorochinolones and metronidazol, 4th generation cephalosporines, a carbapenem or tigecycline should be admitted for 5 to 7 days.

In high risk patients and health care associated peritonitis with a higher suspicion of resistant pathogens, an antibiotic therapy of 10 to 14 days with e.g. piperacillin/tazobactam, a 4th generation cephalosporin and metronidazol, a carbapenem or tigecycline is recommended.

In TP the antibiotic choice should be based on microbial resistance analysis with inclusion of candida spp. (Table 6; Antibiotic treatment recommendations) [9, 66].

SUMMARY AND CONCLUSIONS

In ICU patients the augmenting 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. 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 individual patients' risk factors, with respect 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.

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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Address for correspondence:
Prof. Waldemar Uhl, M.D., FRCS
Department of Surgery
St. Josef Hospital Bochum
Hospital of the Ruhr-University
Gudrunstr. 56
D-44791 Bochum
Germany
Phone: + 49 234 509 2211
Fax: + 49 234 509 2209
E-mail: w.uhl@klinikum-bochum.de